Cow's milk allergy overdiagnosis: prevalence, characteristics and risk factors

Dr. Hilary Allen (CID: 01298487)

National Heart and Lung Institute, Imperial College London

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Primary Supervisor: Dr. Robert Boyle, Imperial College London

Co-Supervisors: Prof. Miriam Santer, University of Southampton

Prof. Andrew Murphy, National University of Ireland, Galway

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1 Statement of originality of the project:

I declare that the research undertaken and content of this thesis is original and my own work. All assistance received has been acknowledged or referenced, as applicable.

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3 Abstract

3.1 Background

Cow's milk allergy (CMA) affects about 1% of European infants but overdiagnosis is common. Concern has been raised about promotion of CMA overdiagnosis by formula milk companies. However, the extent and nature of CMA overdiagnosis and its relationship with formula sponsorship have not been formally evaluated.

3.2 Aims

This thesis characterised CMA overdiagnosis by estimating prevalence, describing triggers and identifying risk factors. To explore the impact of formula sponsorship, independent clinical practice guidance for CMA was developed through Delphi consensus, and compared with diagnosis and management recommendations from formula-funded guidelines.

3.3 Methods

Three independent studies were performed. First, analysis of national prescribing databases to document low-allergy formula prescribing. Second, analysis of primary care records for a cohort of English children characterised for CMA. Third, a Delphi consensus study to develop independent CMA clinical practice guidance.

3.4 Results

Low-allergy formula prescriptions in England, Norway and Australia increased 2-3-fold over 11 years, with prescribed volumes ~10-fold greater than expected.

In a clinical trial cohort, parent-reported CMA overdiagnosis affected 16.1% infants compared with 1.4% true confirmed CMA. CMA overdiagnosis occurred at median 49 days old, mainly for gastrointestinal symptoms. Half of those over diagnosed were prescribed low-

allergy formula. In this cohort, high primary care practice prescribing of low-allergy formula in the year prior to birth was associated with increased CMA overdiagnosis. Exclusively formula-fed infants had increased low-allergy formula prescription.

Non-conflicted guidance for CMA diagnosis and management was more supportive of breastfeeding women, included narrower criteria for CMA and more limited recommendations for specialised formula, compared with formula-funded guidance.

3.5 Conclusions

CMA overdiagnosis is common and ~90% of infants with a CMA diagnosis probably don't have CMA. Primary care practice prescribing habits are a risk factor for CMA overdiagnosis. Independent CMA guidance may protect mothers and infants from CMA overdiagnosis better than formula industry-funded guidance.

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4 List of Abbreviations

AAF	Amino acid formula
AAI	Adrenaline auto-injectors
AAP	American Academy of Paediatrics
ADHD	Attention deficit hyperactivity disorder
APC	antigen-presenting cells
BEEP	Barrier Enhancement for Eczema Protection clinical trial
CBC	Canadian Broadcasting Corporation
CCG	Clinical Commissioning Group
CI	Confidence Interval
CKD	Chronic kidney disease
CMA	Cow's milk allergy
CREDES	Conducting and REporting DElphi Studies
DBPCFC	Double-blind, placebo-controlled food challenge
DHSC	Department of Health and Social Care
EC	European Commission
EFSA	European Food Standards Agency
EHF	Extensively hydrolysed formula
FDA	Food and Drug Administration
FPIAP	Food protein-induced allergic proctocolitis
FPIES	Food Protein-Induced Enterocolitis Syndrome
GINI	German Infant Nutrition Intervention study
GMC	United Kingdom General Medical Council
GP	General Practitioner

HF	Hydrolysed formula
IBCLC	International Board Certified Lactation Consultants
IgE	Immunoglobulin-E
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ITT	Intention to treat
Kr	Norwegian Krone (currency)
MeSH	Medical subject headings
NCTU	Nottingham Clinical Trials Unit
NHANES	National Health and Nutrition Examination Survey, United States
NHS	National Health Service
NHSBSA	NHS Business Service Authorities
NLM	United States National Library of Medicine
OR	Odds ratio
PATCH	Prevention of allergy through cow's milk hydrosylate
PBS	Pharmaceutical Benefits Scheme Australia
pHF	Partially hydrolysed formula
PP	Per protocol
PPI	Patient and public involvement
SPSS	Statistical Package for Social Sciences
SPT	Skin Prick Test
STAR-PU	Specific Therapeutic group Age-Sex Related Prescribing Unit
UK	United Kingdom
USA	United States of America
WAO	World Allergy Organisation

WHO	World Health Organisation

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7 Peer reviewed thesis publications:

Mehta S, **Allen HI**, Campbell DE, Arntsen KF, Simpson MR, Boyle RJ. Trends in use of specialized formula for managing cow's milk allergy in young children. Clin Exp Allergy. 2022 Jul;52(7):839-847. doi: 10.1111/cea.14180. PMID: 35643986. [Joint first named author]

Allen HI, Pendower U, Santer M, Groetch M, Cohen M, Murch SH, Williams HC, Munblit D, Katz Y, Gupta N, Adil S, Baines J, de Bont EGPM, Ridd M, Sibson VL, McFadden A, Koplin JJ, Munene J, Perkin MR, Sicherer SH, Boyle RJ. Detection and management of milk allergy: Delphi consensus study. Clin Exp Allergy. 2022 Jul;52(7):848-858. doi: 10.1111/cea.14179. Epub 2022 Jun 10. PMID: 35615972.

Allen HI, Wing O, Milkova D, Jackson E, Li K, Bradshaw LE, Wyatt L, Haines R, Santer M, Murphy AW, Brown SJ, Kelleher M, Perkin MR, Jay N, Smith TDH, Moriarty F, Montgomery AA, Williams HC, Boyle RJ. Prevalence and risk factors for milk allergy overdiagnosis in the BEEP trial cohort. Allergy. 2024 Jun 20. doi: 10.1111/all.16203. PMID: 38899450.

8 Other publications:

Allen HI, Boyle RJ. Clinical Question. Dietary management of breastfed children with food allergy. *Clin Exp Allergy*; 2022. 52:29-32. http://doi.org/10.1111/cea.14073

Allen HI, Gupta A, Mundell A, Gupta N, Thakur A, Nagarajan S, Munblit D, Baker P, Boyle RJ. Formula milk companies and allergy healthcare professionals in India. Clin Exp Allergy. 21st June 2023. https://doi.org/10.1111/cea.14355

Bradshaw LE, Wyatt LA, Brown SJ, Haines RH, Montgomery AA, Perkin MR, Sach TH, Lawton S, Flohr C, Ridd MJ, Chalmers JR, Brooks J, Swinden R, Mitchell EJ, Tarr S, Jay N, Thomas KS, **Allen H**, Cork MJ, Kelleher MM, Simpson EL, Lartey ST, Davies-Jones S, Boyle RJ, Williams HC. Emollient application from birth to prevent eczema in high-risk children: the BEEP RCT. Health Technol Assess. 2024 Jul;28(29):1-116. doi: 10.3310/RHDN9613. PMID: 39021147; PMCID: PMC11261424.

Bradshaw LE, Wyatt LA, Brown SJ, Haines RH, Montgomery AA, Perkin MR, Lawton S, Sach TH, Chalmers JR, Ridd MJ, Flohr C, Brooks J, Swinden R, Mitchell EJ, Tarr S, Jay N, Thomas KS, **Allen H**, Cork MJ, Kelleher MM, Simpson EL, Lartey ST, Davies-Jones S, Boyle RJ, Williams HC. Emollients for prevention of atopic dermatitis: 5-year findings from the BEEP randomized trial. Allergy. 2023 Apr;78(4):995-1006. doi: 10.1111/all.15555. Epub 2022 Nov 3. PMID: 36263451.

Li KHT, Wing O, **Allen HI**, Smith TDH, Moriarty F, Boyle RJ. Time Trends, Regional Variation and Associations of Low-Allergy Formula Prescribing in England. Clin Exp

Allergy. 2024 Nov;54(11):909-918. doi: 10.1111/cea.14570. Epub 2024 Sep 27. PMID: 39328036.

9 Presentations to date:

- BSACI Milk allergy webinar. Presented and chaired. 30th November 2020
- St. Mary's Hospital London Paediatric Trainees weekly teaching. 2nd September 2021
- BSACI annual conference. 8th October 2021. Invited speaker. *Can we safely de-label penicillin allergy patients in primary care?*
- NIHR SPCR skin and allergy workshop. *Developing an intervention to prevent inappropriate prescription of specialised low-allergy formula in primary care.* 5th November 2021.
- Paediatric Grand Rounds. St. Mary's Hospital, London. Oral presentation. *Cow's milk allergy*. 12th October 2022.
- Association of University Departments in General Practice in Ireland. Annual Conference. Oral presentation. *Patterns of specialised formula prescriptions for cow's milk allergy in young children.* 4th March 2022
- Paediatric Western Regional Education Network. Galway, Ireland. Invited speaker. *Milk Allergy overdiagnosis in children.* 2nd April 2022
- WAO BSACI Conference. 26th April 2022.
    - Poster and Oral presentation. *An international Delphi consensus study on the detection and management of milk allergy.*
    - Poster presentation. *Trends in use of specialised formula for managing CMA in young children*
- Society of Academic Primary Care, UK. Annual Conference. Oral presentation. *Guidance for primary care practitioners on the safe detection and management of milk allergy in children.* 4th July 2022.

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- Preventing Overdiagnosis Conference 2023, Copenhagen. Oral presentation. *Overdiagnosis of cow's milk allergy in children: causes and consequences.* 15th August 2023.
- World Public Health Nutrition Congress 2024. Poster presentation. *Prevalence and nutritional consequences of milk allergy misdiagnosis.* June 2024
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Contributions by others:

Author contributions: Trends in use of specialised formula for managing cow's milk allergy in young children

Dr Boyle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Robert Boyle, Shriya Mehta, Hilary Allen.

Acquisition, analysis or interpretation of data: Shriya Mehta (England, Australia, Norway), Hilary Allen (Scotland, Wales, Northern Ireland), Karoline Fagerli Arntsen (Norway), Melanie Rae Simpson, Dianne E Campbell, Robert J. Boyle

Drafting of the manuscript: Shriya Mehta, Hilary Allen, Robert Boyle.

Critical revision of the manuscript for important intellectual content: Shriya Mehta, Hilary Allen, Dianne E Campbell, Karoline Fagerli Arntsen, Melanie Rae Simpson, Robert J. Boyle

Statistical analysis: Shriya Mehta, Hilary Allen, Robert Boyle.

Administrative, technical or material support: Shriya Mehta, Hilary Allen, Dianne E Campbell, Karoline Fagerli Arntsen, Melanie Rae Simpson, Robert J. Boyle

Supervision: Robert Boyle.

For this project, Shriya Mehta collected and analysed the data for England and Australia. Karoline Fagerli Arntsen and Melanie Rae Simpson collected the data for Norway which was then analysed by Shriya Mehta. Hilary Allen collected and analysed the data for Scotland, Wales and Northern Ireland. Shriya Mehta and Hilary Allen are joint first authors of the published manuscript. All authors reviewed the manuscript. Dianne Campbell and Melanie Rae Simpson advised on interpretation of the Australian and Norwegian data respectively. Dr. Boyle supervised the project.

Author contributions: Prevalence and risk factors for milk allergy overdiagnosis in the BEEP trial cohort

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Concept and design: Robert Boyle, Hilary Allen, Lucy Bradshaw, Frank Moriarty

Acquisition, analysis or interpretation of data: Hilary Allen, Emilia Jackson, Dara Milkova, Olivia Wing, Karen Li, Lucy Bradshaw, Frank Moriarty, Robert Boyle

Drafting of the manuscript: Hilary Allen, Robert Boyle

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Supervision: Robert Boyle, Lucy Bradshaw, Frank Moriarty

For this project, the primary care records were initially collected and analysed by Emilia Jackson as part of a BSc student project. A research nurse was subsequently employed to

collect more primary care records for this project. Dara Milkova undertook a second BSc student project further analysing the primary care records. Hilary Allen undertook an independent analysis of all of the primary care records received, extracted and cleaned all data, developed a data dictionary to ensure consistency of data collection and analysed all primary care record data for this thesis. Olivia Wing and Karen Li extracted the GP practice data and each undertook a BSc student project analysing this data. Hilary Allen extracted any further GP practice data that was available building on the students initial data collection, and re-analysed the GP practice data merging it with the BEEP participant data. Hilary Allen independently analysed the GP practice data. Hilary Allen undertook all statistical analysis for the BEEP participant and GP practice data with advice from Dr. Boyle, Frank Moriarty and Lucy Bradshaw. Hilary Allen wrote the first draft of the manuscript which was reviewed and edited by Dr. Boyle.

Author contributions: Detection and management of milk allergy: Delphi consensus study

Dr Robert Boyle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Robert Boyle, Hilary Allen, Una Pendower, Miriam Santer,

Acquisition, analysis or interpretation of data: Hilary Allen, Una Pendower, Robert Boyle

Drafting of the manuscript: Hilary Allen, Robert Boyle

Critical revision of the manuscript for important intellectual content: All Delphi panel participants, Hilary Allen, Una Pendower, Robert Boyle, Michael Perkin

Statistical analysis: Hilary Allen, Robert Boyle

Administrative, technical or material support: Hilary Allen, Una Pendower, Robert Boyle, Michael Perkin

Supervision: Robert Boyle, Miriam Santer

For this project, Hilary Allen researched the most appropriate consensus method before deciding on a Delphi consensus study. Hilary Allen applied for research ethics, and wrote the Delphi study protocol including participant information leaflets. Hilary Allen and Una Pendower (BSc student) researched and found Delphi participants meeting the inclusion criteria, researched the initial Delphi statements, and recruited the Delphi patient panel under the supervision of Dr. Boyle and Miriam Santer. Una Pendower designed the Qualtrics survey with supervision from Hilary Allen. Hilary Allen and Una Pendower invited the Delphi participants, analysed Round 1 of the Delphi survey and produced the Round 2 statements. Hilary Allen collected and analysed Round 2 Delphi responses, organised the Delphi face to face meeting, presented the Round 2 consensus statements, analysed all final Delphi responses and collated the final Delphi statements. Hilary Allen interviewed non-attendees at the Delphi meeting and piloted the final Delphi statements along with Dr Boyle. Hilary Allen wrote the first draft of the manuscript which was edited and supervised by Dr Boyle.

11 Introduction

Cow's milk allergy (CMA) affects approximately 1% of children under age 2 years old. (1) CMA overdiagnosis appears to be increasing and has not been well-characterised. (2,3) Overdiagnosis is increasingly recognised as a harmful phenomenon of modern medicine, with most studies involving cancer screening programmes. (4) CMA in children may be vulnerable to overdiagnosis. This literature review aims to understand the broader concept of overdiagnosis in medicine, the reasons why paediatric CMA may be vulnerable to overdiagnosis and the potential consequences of such overdiagnosis.

11.1 Overdiagnosis in medicine

11.1.1 Introduction

The term over-diagnosis can be confusing, due to variation in the way it is used. The task of any doctor is to interpret patient reported symptoms, reach a diagnosis aided by appropriate investigations, and recommend a prescribed or non-prescribed treatment to improve patient well-being – or at the very least, give advice to empower the patient to self-manage their symptoms. (5) In some cases, ruling out a diagnosis is as important as confirming a diagnosis, because it alleviates the uncertainty surrounding 'unexplained symptoms' from a patient perspective. In general, making a diagnosis or excluding a diagnosis is an important aim of medical consultations. Therefore, the concept of overdiagnosis is counterintuitive – how does one overdiagnose? And what does overdiagnosis actually mean? Overdiagnosis can mean different things depending on the context in which it occurs, and the presence or absence of disease or illness. (5,6) Overdiagnosis is recognised as a problem in modern medicine affecting clinicians, patients and healthcare systems. (5,7-10) For more than a decade, there

has been a movement within medicine that includes special edition medical journals, conferences, and initiatives by policy makers and regulatory bodies all dedicated to the prevention of overdiagnosis. (7-14) This is in response to recognition of its prevalence and associated harms. In this section, I will examine what overdiagnosis means and discuss related concepts, drivers and harms.

11.1.2 Definition

Researchers have attempted to define overdiagnosis and other related concepts in order to enable a methodological approach to researching the subject, with much disagreement on the definition. (5,6,15) In 2022, the United States National Library of Medicine (NLM) included 'overdiagnosis' as a new term within the medical subject headings (MeSH) where all related information is filed. They define overdiagnosis as:

"the labelling of a person with a disease or abnormal condition that would not have caused harm if left undiscovered, creating new diagnoses by medicalizing ordinary life experiences, or expanding existing diagnoses by lowering thresholds or widening criteria without evidence of improved outcomes. Individuals derive no clinical benefit from overdiagnosis, although they may experience physical, psychological or financial harm." (16,17)

Overdiagnosis needlessly turns well people into patients seeking healthcare. (6) It does this through overdetection or overdefinition. (6) Overdetection means identifying abnormalities that are harmless and do not develop into illness during a person's life. (4-6) This can be a consequence of using modern imaging techniques where high quality imaging identifies incidental findings that don't require treatment. (5,6,18) Overdetection is also driven by an increasing array of laboratory and self-testing now available. (5,6,19) Overdefinition means broadening the criteria for diagnosing a condition either by lowering the threshold for

inclusion criteria or expanding the disease definition to include more symptoms or mild symptoms. (5,6,19-21)

Other concepts related to overdiagnosis are overselling, disease mongering, overutilisation, overtesting, overmedicalisation, overtreatment, misdiagnosis and false-positive results. Although there is overlap, it is best to consider each separately with examples described in the literature to allow a clearer definition of overdiagnosis. (5,6)

Overselling encourages overdefinition. (6) It refers to the interpretation of symptoms commonly experienced by many people as a disease. Some people with severe symptoms may reasonably require medical attention but overselling encourages people with very mild symptoms or symptoms unrelated to a medical condition, to be diagnosed with a medical condition. (6) For example, many people experience low mood at times or poor concentration but overselling encourages a formal diagnosis such as depression or attention deficit hyperactivity disorder (ADHD). (6) Disease mongering has a similar meaning to overselling but has historically been used to refer to a marketing tactic to encourage healthcare and medication utilisation for profit. (5,6) In disease mongering, new ‘diseases’ are created or disease definitions are expanded and promoted to the public, for example ’low testosterone in older men’ and ’female sexual dysfunction’ in women with low libido. (5,6) Overutilisation and overtesting refers to healthcare practices routinely undertaken without any benefit such as routine imaging for lower back pain or recall systems for annual pelvic examination in women. (5,6) Overmedicalisation means changing the interpretation of normal human experiences and considering them as medical conditions requiring diagnosis and medical treatment without benefit; described examples of this include using medications to treat undisciplined children or medical interventions used to treat the natural losses experienced in life. (5,22) Overtreatment is the provision of treatment for a particular condition despite evidence-based medicine suggesting treatment is not beneficial; an example of this as

described by Carter et al is antibiotics which are often prescribed inappropriately for otitis media in children. (5,6)

Misdiagnosis occurs when the wrong diagnosis is attributed to a person's symptoms, for example, an appendectomy for abdominal pain but the appendix is subsequently normal on histological diagnosis. (5,6) False positives refer to abnormal results that initially suggest a disease but on further investigation, the disease is ruled out. (5,6) An example of false positive are women recalled on breast cancer screening but who have normal results on re-imaging. (5,6)

In summary, overdiagnosis is caused by overdetection or overdefinition, which in turn can be caused by overselling and disease mongering. (5,6) Overtesting and overutilisation may lead to overdiagnosis but not always. (5,6) The consequence of overdiagnosis can also be overtesting, overutilisation and overtreatment. (5,6) False positives and misdiagnosis are not overdiagnosis but they can be difficult to distinguish from it and can also lead to overtreatment and overutilisation. (5,6)

11.1.3 Types of overdiagnosis

Evidence for overdiagnosis is found in many medical specialities. It is useful to consider examples from the literature to better understand the multiple concepts related to overdiagnosis.

Overdiagnosis through overdetection

In Korea, thyroid cancer incidence increased 15-fold between 1993 and 2011 on a background of a national cancer screening programme introduced in 1999. (6,23,24) Although the government did not include thyroid cancer in the screening programme, healthcare providers offered thyroid ultrasounds in addition to the programme at low cost to

patients. (6,23,24) Mortality from thyroid cancer remained stable during the same timeframe, suggesting overdiagnosis caused by overdetection through screening. (6,23,24)
This overdiagnosis led to overtreatment with almost all undergoing surgical removal of the thyroid. (6,23,24)

Overdiagnosis through overdefinition

In 2002 in the US, guidelines for diagnosing chronic kidney disease (CKD) were introduced based on laboratory assessments of decreased renal function (albuminuria or glomerular filtration rate <60mL/min per 1.73m^2 present for at least 3 months). (25,26) The purpose of this refined definition of disease was to prevent more severe forms of kidney disease. (25,26) These new guidelines generated controversy due to overdiagnosis of chronic kidney disease in older patients with age-appropriate 'abnormal' renal function.
The prevalence of childhood ADHD in the US was reported as 6.1% in late 1990's, increasing to over 10% in 2017-2022. (27,28) A Canadian study of almost 1 million children found that boys born in December were 30% more likely to be diagnosed with ADHD than their peers who were born in January and girls were 70% more likely to be diagnosed with ADHD when born in December. Boys were 41% more likely to be prescribed medication to treat ADHD and girls 77% more likely when born in December. This implies that the most immature children received a diagnosis and treatment for ADHD, raising concerns of overdiagnosis. (29) Broadening diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and interpretation of those criteria by healthcare practitioners are thought to contribute to overdiagnosis of ADHD, particularly as ADHD diagnosis is often reliant on reported clinical features rather than an objective measure (30,31)

11.1.4 Harms of overdiagnosis

Overdiagnosis has consequences for patients, healthcare professionals, health systems and society. While there may be specific benefits, particularly for clinicians and manufacturers of tests or treatments, overdiagnosis can cause significant harms.

Impact on patients and their carers

Overdiagnosis by definition harms patients as there is no benefit from the diagnosis or medical intervention. (5,6) Direct harms can result from over treatment such as scarring or wound infection from unnecessary surgery or adverse effects from medications. (5,32) However, other indirect harms can occur as a consequence of overdiagnosis. These include the psychological impact of being labelled with a disease and the impact that this can have on future employment or potential for insurance. (5,32) This can also lead to effects on other family members, for example offspring may be perceived as being 'more at risk' of the disease. (5) Loss of income can occur during recovery from surgery and other direct and indirect costs of unnecessary healthcare can be significant. (32) Qualitative research has shown the psychological impact of receiving a prostate cancer diagnosis despite a low risk of mortality from the disease: (33,34) men reported a sense of uncertainty towards their future, powerlessness and increased awareness of their own mortality. (33)

Impact on healthcare professionals

Although healthcare practitioners can be viewed as gatekeepers for overdiagnosis, and in some circumstances may profit through increased activity, profile and income, they are also harmed by overdiagnosis. Overdetection inevitably leads to further testing and monitoring of patients with increased workload for healthcare practitioners. (35) If this is not accompanied by increased income then it can be a significant strain on healthcare practitioners and the

systems that they work in. Ageing populations and an increased burden from chronic disease management are already creating additional demands on healthcare professionals. (35,36) A recent report identified difficulties recruiting and retaining healthcare staff across all European countries independent of a country's income level. (35,36) This problem pre-dates the Covid-19 pandemic although was likely exacerbated by it. (35,36) Excessive workload risks healthcare practitioner burnout and overdiagnosis contributes to this. (35,36) Beyond the immediate impact of overdiagnosis on workload, overdiagnosis can lead to confusion and misunderstanding in the practice of healthcare practitioners. (3) This can lead to conflict and uncertainty in practice, regulatory action and dismissals. When a culture of overdiagnosis becomes embedded, then clinical practice which deviates from the norm of excessive testing or treatment can be perceived as erroneous, creating unnecessary friction between clinicians. In the realm of scientific research, dominant narratives which support overdiagnosis can lead to scientific uncertainty and confusion, conflict between researchers and inappropriate prioritisation of research resources. An example of this will be described later in the introduction, under the 'hydrolysed formula story'.

Impact on health systems and society

Health systems are experiencing increased demand for services and some of that demand is related to low-value care. For example, in Australia, analysis of national cancer registry data for 2012 estimated that just under one-fifth of cancers in women and almost one-quarter of cancers in men were overdiagnosis. (35,37) The use of healthcare for low-value care diverts resources away from more necessary care. (32,35,38,39) Excessive healthcare represents poor value for money through direct costs of unnecessary medical interventions but also indirect costs related to burden on patients and healthcare staff. (32,35-37) A Canadian study ruled out asthma through formal guideline-recommended diagnostic assessment which included

objective airway testing in one-quarter of adults who reported being diagnosed with asthma by their doctor. (40) Costs related to this asthma diagnosis included outpatient visits, primary care physician visits and medications with medication accounting for half of direct healthcare costs. (40)

Overdiagnosis impacts other aspects of society through loss of work productivity due to work absence, such as from patient recovery or healthcare staff burnout. (32,35,36) Claims for social support such as disability living allowances or early retirement and pension can also potentially be impacted, leading to workforce and wider economic issues.

Environmental Impact

Another easily over-looked harm of overdiagnosis is the environmental impact. For example, healthcare is responsible for 4.4% of global carbon emissions. (41) There is an association between a country's healthcare spending and carbon footprint. (41) The production, transport and disposal of pharmaceuticals, medical devices, hospital equipment and medical instruments contribute significantly to a country's emissions. (41) Tackling overdiagnosis, overutilisation and overtreatment will improve the sustainability of healthcare particularly when climate change will inevitably lead to increased demand for healthcare resources to treat increased diseases and consequences of extreme weather events such as heatwaves. (41-44)

In this context, more prudent use of healthcare resources has benefits not only for human society but also for the environment we live in.

11.1.5 Drivers of overdiagnosis

Drivers of overdiagnosis include patients, healthcare professionals, health systems, technology, industry and society. (45,46)

Patients, patient advocacy groups, cultural beliefs and society

It is suggested that patients are potential drivers of overdiagnosis due to difficulty living with uncertainty, expectations of treatment and dependence on testing for assurance of good health. (32,45,47,48) Patients' expectations of healthcare are also influenced by cultural beliefs and for many, there is a belief system that early detection of disease is worthwhile without an understanding of the potential harms. (32,45,47,48) Patients are limited by their own experiences and can lack the medical or scientific knowledge to fully understand the implications of incidental findings or the natural history of disease. (32,45,47,48) Patient advocacy groups may also be part responsible for overdiagnosis as they endeavour to create awareness about less well-known conditions, often in response to perceived diagnostic delays or undertreatment. (32,45-48)

An example of this as highlighted by Woloshin et al is a high profile breast cancer charity in the US which was heavily involved in promoting breast screening to all women through use of inaccurate survival data which over-estimates the benefits of screening. (49) Their public advertisements aimed to encourage women to undertake breast mammography, without reference to possible harms of screening. (49)

Healthcare professionals

Healthcare professionals may be drivers of overdiagnosis depending on their medical training, confidence in their diagnostic ability and the context they work in. (32,45,47,48) Defensive medicine and fear of blame is reported to influence healthcare practitioner

behaviour. (32,45,47,48) It is also suggested that doctors are influenced by their own experiences and this can make them less rigorous in applying scientific evidence when making clinical decisions. (32,45,47,48) In this manner, they are more trusting of their own experience and less likely to accept opposing evidence. (32,45,47,48) Doctors may habitually diagnose certain conditions and over-estimate the benefits of a diagnosis or treatment for their patient. (32,45,47,48)

Although supported clinical decision making may be a potential solution for healthcare professional driven overdiagnosis, guidelines have also been identified as a driver of overdiagnosis through commercial influence or conflicts of interest amongst authorship. (2,3,45,50) Guidelines are usually written by experts within a particular field of medicine. It has been reported that general practitioners were more likely to follow the practice of a trusted local colleague considered an 'expert' than guidelines. (51,52) However, in some health systems, reimbursement of primary care may be dependent on making a diagnosis, referral or prescribing a particular treatment and following a particular local guideline. (13,45,48). Healthcare professionals and the clinics that they work in may benefit from overdiagnosis, through increased income and profile, driven by increased patient numbers. This may be a conscious or unconscious factor in some healthcare professional research, education and practice activities that promote overdiagnosis. (3)

Health systems and technology

Technological advances have led to precision diagnostics such as highly sensitive diagnostic imaging. (32,45,47,48,53) The consequences of this are abnormal findings of undetermined clinical significance in radiological reports. (32,45,47,48,53) The responsibility then falls on the healthcare practitioner to clinically interpret the significance of the finding which may lead to either further investigation or erring on the side of caution with diagnosis or treatment,

depending on their aptitude for risk. (32,45,47,48,53) Hospitals may benefit financially from performing investigations, procedures and follow-up of patients. (32,45,47,48,53) A pressurised health system lacks the capacity for longer consultations which may be required for adequate explanations and discussions with patients in order to prevent overdiagnosis, overtesting and overtreatment. (32,45,47,48,53) High quality care takes time and health systems that use quantitative measures as a marker of quality may inadvertently encourage overdiagnosis. (32,45,47,48,53)

Industry

Industry plays an important role as a driver of overdiagnosis through multiple channels. Sponsorship of guidelines, educational events and patient advocacy groups represents indirect marketing opportunities for industry to promote their products and encourage healthcare utilisation. (32,45,47,48,53) Industry advertisements take advantage of the fear and uncertainty surrounding disease, illness and dying and encourage patients to seek testing as a preventative measure. (32,45-48,53) Guidelines authored by experts with commercial conflicts of interest are also considered a driver of overdiagnosis through overdefinition of disease (lowering of thresholds for diagnosis or expanded disease definitions) and is an indirect marketing strategy commonly adopted by industry. (32,45,47,48,53)

11.1.6 Definition of conflicts of interest

Relationships between healthcare professionals and industry are necessary and often beneficial in medicine, as seen during the Covid-19 pandemic where healthcare professionals, scientists and pharmaceutical industry collaborated to rapidly develop a vaccine. (54) However, a conflict of interest arises when this relationship benefits the clinician through industry-sponsored financial or non-financial rewards and influences clinical-decision

making to favour that particular industry. (55,56) Policies exist in Europe and the US to promote transparency in reporting of payments to healthcare practitioners and healthcare organisations but regardless, receipt of industry-sponsored rewards is known to create bias in clinical practice, often unconscious bias. (56-58) The United Kingdom General Medical Council (GMC) provides guidelines for doctors on avoiding conflicts of interest as it is recognised to undermine patient care and is associated with poor professional standards. (55) The GMC defines a conflict of interest as *"a medical professional's interests (financial or otherwise) compete with their professional responsibilities, and there's a risk (real or perceived) that the medical professional will prioritise these interests above the care of patients."* (55)

Financial conflicts of interest include financial remuneration for an advisory role to pharmaceutical companies selling drugs for a condition that is treated by the healthcare practitioner, for writing guidelines, educational materials or other journal articles. (59,60) Other examples include remuneration for lectures on a medical condition from the company who sells drugs to treat that condition. (59,60)

Non-financial conflicts of interest also exist. These can contribute to publication bias: positive research findings are more likely to be published in medical journals despite undergoing peer-review which intends to protect against bias. (61) Researchers may be prejudiced by their own prior research findings and may develop non-commercial relationships that promote their work; or researchers may have academic biases based on their own personal research or experiences. (61)

11.1.7 Relevance of conflicts of interest

The relevance of conflicts of interest is that it is reported to introduce unconscious bias into decision-making and healthcare practitioner relationships with industry may benefit industry

while disadvantaging patients. Studies show that physician receipt of funding from the pharmaceutical industry is associated with increased prescribing of marketed drugs and more favourable research findings. (62,63)

In 2011, the United States Institute of Medicine recommended that guideline panel members should be non-conflicted and conflicted experts should serve only as guideline consultants or reviewers, but guideline authors commonly have relevant conflicts of interest. (26,64-66)

A 2013 study of guidelines for diagnosis of common diseases identified that the majority of panel members had benefited financially from pharmaceutical industry and that these guidelines commonly promoted disease diagnosis, which in-turn benefits the pharmaceutical industry. (66) Another study found that even a single pharmaceutical-sponsored meal (mean value under $20) to physicians influenced their prescribing habits in favour of the particular brand of drug sold by that company (OR 1.18 for rosuvastatin, 1.70 for nebivolol, 1.52 for olmesartan, 2.18 for desvenlafaxine). (67)

Conflicts of interest also plays a role in overdiagnosis. An Australian study investigated the relationship between industry sponsorship of physician educational events over a 4-year period of three conditions where there was evidence for overdiagnosis: depression, osteoporosis and over-active bladder syndrome. (68) They found that the companies sponsoring these events promoted less cost-effective drugs for treatment of these conditions and mainly to primary care physicians. (68) Authors concluded that these companies intended to reach a broader patient population by promoting their products to primary care physicians. (68)

11.1.8 Best practice relating to conflicts of interest

The British Medical Journal introduced a policy in 2015 requiring authorship of editorials and clinical education articles to be free of financial ties to industry for the preceding 3 years. (59) They defined conflicts of interest as:

"A conflict of interest arises when a person has a personal or organisational interest that may influence or appear to influence the work they are doing. Usually this is a financial interest, but it may also be non-financial." (59)

Factors influencing the journal's decision to adopt this approach was a concern about harms associated with commercially biased information (as had occurred with the diabetic drug Rosiglitazone) and a reported lack of confidence amongst readership in manuscripts with declared financial competing interests. (59,69,70) In 2010, GlaxoSmithKline (the company that manufactured Rosiglitazone) were accused of attempting to downplay the cardiovascular risks identified with Rosiglitazone and led to a spotlight on industry relationships with medical experts. (69)

Although the BMJ have created awareness about conflicts of interest and have adopted a best practice standard to limit the influence on clinical decision making, the same is not true for many guidelines which continue to include authors with declared industry-related conflicts of interest contrary to best practice. (3,71-73) Paediatric professional bodies have also attracted criticism for close relationships with formula industry with two-thirds surveyed reporting financial sponsorship. (74)

In conclusion, overdiagnosis is a complex problem with many drivers and associated harms. It is important for healthcare practitioners to understand their role in overdiagnosis as well as the indirect contribution of conflicts of interest to overdiagnosis, in order to mitigate against the potential harms.

In the next section, we will consider the clinical condition of cow's milk allergy - epidemiology, pathophysiology, diagnosis and management before moving on to the evidence for overdiagnosis of this condition.

11.2 Cow's milk allergy

11.2.1 Introduction

Food allergy commonly affects children and adults but is less common than perceived food allergy. (75-79) Distinguishing allergy from non-allergic reactions is essential in clinical practice to avoid unnecessary elimination of foods from a child or adult's diet and requires a clear definition of allergy and understanding of allergy mechanisms. (75,80) The World Allergy Organisation (WAO) (2003) defined allergy and associated terminology to aid with this distinction. (80)

The WAO define hypersensitivity as *"objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons"*.

Allergy is described as a type of *"hypersensitivity reaction initiated by specific immunological mechanisms"*. (80) Atopy is defined as "*a personal and/or familial tendency usually in childhood or adolescence, to become sensitised and produce Immunoglobulin-E (IgE) antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema*". (80) It is important to distinguish atopy from allergy – the former refers to the ability to produce IgE antibodies in response to allergens (known as sensitisation) and which is pre-determined genetically but does not necessarily result in a clinical reaction. (80) In contrast, allergy refers to a hypersensitivity reaction which is initiated by immune mechanisms and produces clinical symptoms. (80) An allergen is an antigen (usually

proteins) which triggers allergy. (80) The pathophysiology of CMA and allergic mechanisms is discussed later in this section.

11.2.2 Epidemiology of cow's milk allergy

Milk allergy is estimated to affect up to 1% of children under 2 years old. (1) This is based on the most comprehensive epidemiological data available at the time of writing – a Europrevall birth cohort study of 12,000 European children which used double blind, placebo-controlled food challenges to confirm or refute each case of suspected IgE-mediated and non-IgE-mediated milk allergy or other food allergies. (1)

The estimated incidence of IgE-mediated CMA was 0.59% (95% CI 0.43-0.80) with very little geographical variation. (1) Non-IgE-mediated CMA was only identified in the UK (adjusted incidence 0.72%; 0.3-1.5%), the Netherlands, Poland and Italy (adjusted incidence 0.13%; 0.0-0.6%). (1) Approximately half of children in the UK and Netherlands, and a quarter of children in Poland presenting with suspected non-IgE-mediated CMA were confirmed through food challenge, although the numbers were small. (1) In the UK, non-IgE-mediated CMA (56.3%) was more prevalent than IgE-mediated CMA (43.7%). (1)

Although a previous small Chinese study suggested challenge-proven CMA doubled between 1999 (3.5%) and 2009 (7.7%), (81) the more rigorous Europrevall-INCO study estimated very low prevalence of CMA in children living in China (0.00%), India (0.00%) and Russia (0.05%). (82) Europrevall-INCO had higher numbers of participants and although limited to diagnosis of probable allergy based on patient reported symptoms, skin and serum IgE testing, it is likely that confirmed CMA would be even less if participants had undergone oral challenge. (82)

11.2.3 Pathophysiology of cow's milk allergy

The immune system incorporates three layers of protection: physical and physiological barriers (skin, gastric acid, lung cilia), innate immunity (cellular and humoral) and adaptive immunity (cellular and humoral). (83)

The innate immune system is composed of cells residing in tissues to allow an immediate response (e.g. macrophages and mast cells) and leukocytes circulating in the bloodstream that are recruited during an immune response (eg. neutrophils, eosinophils, basophils, natural killer cells and natural killer T cells). (83)

The innate immune system also has humoral features (eg. complement) which responds rapidly to infection without antigen-specificity and lacks immunological memory. (83)

The adaptive immune system comprises T-lymphocyte and B-lymphocyte cells (cellular) which respond more slowly to infection (several days) and antibodies (humoral). The adaptive immune system is antigen-specific and has immunological memory. (83)

Atopic sensitisation

On first exposure to an allergen, the immune system initiates a process culminating in sensitisation to that allergen. The allergen is initially taken up by antigen-presenting cells (APC), internally digested by the cell and the resultant peptide fragments are presented on the surface of the APC. (83) T-lymphocyte cells possessing an antigen cell surface receptor unique for that allergen peptide engage with the APC and become activated. (83) If an allergic immune response develops, these activated T-cells become helper T cells that express Th2 cytokines. (83) Th2 cytokines induce B-lymphocytes to switch class and express Immunoglobulin-E (IgE), induce eosinophil production in the bone marrow and activate adhesion molecules on blood vessels which allows circulating inflammatory cells (eosinophils and basophils) to infiltrate tissues. (83) The allergen-specific IgE produced on

initial exposure to the allergen binds to IgE-receptors on mast cells and basophils, a process known as sensitisation. (83) IgE sensitised mast cells in tissue, or basophils in circulation, are activated on subsequent exposure to the allergen resulting in release of histamine and other inflammatory mediators producing the clinical features of an IgE-mediated allergic reaction. (83) Non-IgE mediated allergic reactions occur through a variety of mechanisms, but these are also usually initiated by Th2 cytokines. Non-IgE mediated allergic inflammation is often cell-mediated, with eosinophils, T cells and other cell types implicated. However, the mechanisms of non-IgE mediated allergic reactions are not as well characterised as IgE mediated allergy. (83)

Immune basis of cow's milk allergy

Hypersensitivity reactions continue to be categorised according to the original classification system proposed by Gell and Coombs although modifications have been proposed. (84-86)

Type 1: IgE-mediated immune reaction presenting with immediate symptoms (eg. anaphylaxis)

Type 2: cytotoxic reactions where an antigen binds to a cell surface producing antibodies which induce cell death (eg. drug induced cytopenia)

Type 3: (immune complex-mediated) immune complexes of antigens, antibodies and complement block small blood vessels (eg. drug induced vasculitis or serum sickness)

Type 4: T-lymphocyte-mediated immune reaction causing delayed symptoms (eg. Stevens Johnson syndrome)

CMA may be caused by any of these 4 immunological mechanisms but is broadly considered in 2 distinct categories – IgE-mediated (Type 1) and Non-IgE-mediated (Type 2, 3 and 4 hypersensitivity reactions). (85) In IgE-mediated CMA, the immune system initially becomes sensitised to cow's milk by producing IgE antibodies specific for cow's milk protein antigen

that attach to mast cells and basophils. (85) On subsequent exposure through ingestion of cow's milk protein and contact with mucosal surfaces, the primed mast cells and basophils release histamine and other inflammatory mediators. (85) The immune mechanisms underlying non-IgE-mediated CMA are poorly understood but are thought to be caused by other antibodies, immune complexes or T-cell mediated reactions. (85)

Cow's milk protein allergens

Cow's milk is comprised of 80% casein and 20% whey protein. (71,85) Caseins (e.g. Bos d 8 allergen) include alpha-caseins (37%), beta-casein (27%), g-caseins (6%) and k-casein (10%). (71,85) Whey protein is composed of alpha-lactalbumin (Bos d 4) (5%), beta-lactoglobulin (Bos d 5) (10%), immunoglobulin (Bos d 7) (3%), bovine serum albumin (Bos d 6) (1%) and lactoferrin. (71,85) Beta-lactoglobulin is not present in human milk. Bos d 6 is responsible for allergy to beef as well as milk. (71,85) Sensitisation to alpha-caseins and k-casein is common. (71,85) All of these milk proteins are implicated in IgE mediated CMA but Bos d 7 rarely triggers reactions. (71,85)

Crossreactivity occurs when two allergens are structurally similar in their amino-acid sequence or have similar affinity for specific antibodies. (71,85) Cow's milk proteins are similar to goat and sheep milk proteins and so ingestion of goat's or sheep's milk will trigger an allergic reaction in a cow's milk allergic individual. (71,85)

Immune basis of oral tolerance

The defence mechanisms of the gastrointestinal tract include physiological barriers (e.g. gastric acid and an epithelial layer with tight junctions) and innate immunity (e.g. macrophages, mast cells, neutrophils, natural killer cells) to protect against harmful agents entering the body following food ingestion. (85,87,88) However, gastrointestinal immunity

has the ability to accept unfamiliar antigens by down-regulating immune responsiveness, a process called ‘oral tolerance’ which involves regulatory T Cells and antigen presenting cells. (85,87,88) Oral tolerance is necessary for normal digestion and intestinal health. (85,87,88) In allergy, oral tolerance is defective and the immune system misinterprets food antigens as harmful. Acquisition of oral tolerance is influenced by the size of the antigen, frequency of antigen exposure, as well as individual characteristics such as atopic status and age at initial exposure. (85,87,88)

11.2.4 Clinical presentation of cow’s milk allergy

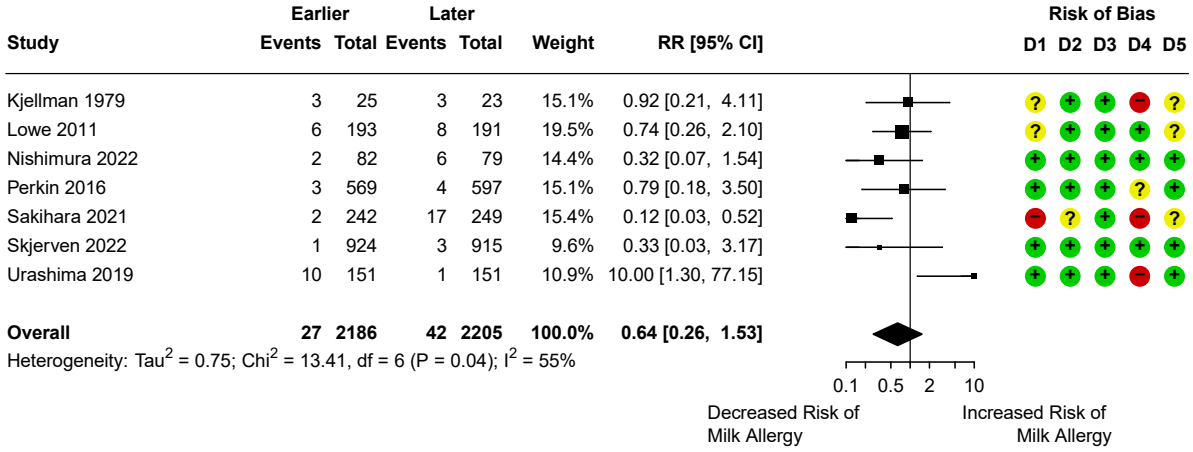
The clinical presentation of cow’s milk allergy is dependent on the nature of the immune reaction. (75,85) Symptoms may be cutaneous, gastrointestinal, or respiratory and in more severe cases, may affect the cardiovascular system. (75,85,89) CMA presents on introduction of cow’s milk protein into the diet, usually at the time of formula-feeding or introduction of solids containing cow’s milk protein. (75,85,89)

Risk factors for cow’s milk allergy

Atopic dermatitis affects approximately one-fifth of children and confers increased risk for development of food allergy, particularly if more severe or early onset. (78,90-92)
The integrity of the skin barrier is impaired in atopic dermatitis, sometimes due to genetic mutation, and food sensitisation is thought to occur through this defective skin barrier. (93-96)
Cow’s milk formula supplementation early in life of an exclusively breastfed infants is thought to be a risk factor for CMA, thought to result from non-sustained exposure to cow’s milk antigen interfering with immune-tolerance. (97,98) However, data from prospective cohort studies and intervention trials are inconclusive, so it is not clear whether avoidance or

early introduction of cow's milk in the early months of life promotes or prevents CMA development. (Figure 11.1). For Non-IgE CMA, there is even less conclusive evidence, partly due to the difficulty of robustly classifying Non-IgE CMA status in epidemiological studies.

Figure 11.1. Forest plot of the effect of early versus late introduction of cow's milk on development of IgE-mediated cow's milk allergy.



Taken from Scarpone et al 2023 with kind permission of the authors. This is a meta-analysis of randomised controlled trials of timing of milk protein introduction for preventing milk allergy. The analysis includes the SPADE study data (Sakihara et al 2021) which was excluded from the primary meta-analysis in Scarpone et al 2023, because the age of outcome assessment was under 1 year, but is captured in this sensitivity analysis. Squares indicate risk ratios (RRs), horizontal lines indicate 95% confidence intervals and size of squares indicate weight; diamond indicates the pooled estimate with the outer points of the diamond indicating 95% CI. Green circles indicate low risk of bias, yellow circles indicate some concerns of bias and red circles indicate a high risk of bias. (99)

IgE-mediated cow's milk allergy

IgE-mediated CMA is characterised by an immediate onset within minutes but can occur up to 2 hours after ingestion of the allergen. (75,85) Anaphylaxis is the most severe form of IgE-mediated reaction and can be life-threatening. (75,85,100,101) Criteria for diagnosing anaphylaxis requires a sudden onset illness involving the skin and/or mucosa with at least one of: respiratory compromise, hypotension, collapse, severe gastrointestinal symptoms, or sudden onset of hypotension/bronchospasm/laryngeal involvement after exposure to a likely allergen even if skin symptoms are absent. (100) European data shows CMA is commonly implicated in paediatric anaphylaxis particularly in younger children and in severe or fatal anaphylaxis. (101) However, the majority of allergic reactions to cow's milk are relatively mild, with skin and gastrointestinal symptoms most common. Cutaneous symptoms commonly occur in children, mainly urticaria but may also include maculopapular rash and angioedema. (75,85) Oral mucosal symptoms include lip swelling, tongue swelling, pruritis or throat tightness. (75,85) Gastrointestinal symptoms include nausea, vomiting, abdominal pain, diarrhoea and occasionally haematochezia. (75,85) Respiratory symptoms occur less commonly but indicate more severe allergy and include wheezing, dyspnoea and chest tightness. (75,85)

Non-IgE-mediated cow's milk allergy

Non-IgE-mediated CMA is characterised by delayed onset of symptoms occurring greater than 2 hours after ingesting cow's milk protein. (75,85) Symptoms are mainly gastrointestinal but may also be cutaneous in the form. (75,85) Gastrointestinal symptoms include nausea, vomiting, abdominal pain, constipation, diarrhoea, failure to thrive, proctocolitis and rarely, CMA-protein-induced enteropathy. (75,85) Eosinophilic oesophagitis is an uncommon condition affecting less than 1 in 1000 children and adults, characterised by dysphagia,

retrosternal chest discomfort and food impaction. (75,85) Food protein-induced enterocolitis syndrome (FPIES) is often caused by cow's milk and is estimated to affect approximately 0.3% of infants although epidemiological data is limited. (75,85,102,103) It presents with repeated projectile vomiting occurring approximately 1-3 hours after cow's milk protein ingestion accompanied by pallor, lethargy and occasionally diarrhoea with the risk of dehydration. (75,85,103) Symptoms of all types of IgE and non-IgE mediated CMA tend to resolve spontaneously within a few hours. (75,85,103)

11.2.5 Diagnosis of cow's milk allergy

Diagnosis of CMA relies on a comprehensive history to assess likelihood of cow's milk protein as the index allergen, quantity consumed, timing of symptom onset, nature of symptoms, severity, co-factors augmenting the reaction such as exercise, and overall risk. (75,85) A detailed diet history is also required to assess if cow's milk is being consumed in other forms. (75,85) The purpose of the history is for the clinician to assess the probability that the symptoms were an allergic reaction, that cow's milk was the culprit food, to assess the risk of future reactions and guide appropriate investigations. (75,85)

Skin prick testing (SPT) is performed usually using commercial extracts on the forearm to assess an IgE-antibody response to a particular food through release of histamine and is only reliable as part of the diagnostic work-up for IgE-mediated allergy. (75,85)

A negative (saline) and positive (histamine) control are used as a quality measure and comparator. (75,85) A positive SPT is defined as an average wheal diameter exceeding the negative saline control by 3mm. (75,85)

Fresh milk can be used with greater sensitivity than commercial extracts but carries a small increased risk of a clinical reaction and a higher rate of false positive response. (75,85)

The accuracy of skin prick testing is influenced by the skill of the person performing the test, the standardised dilution of the commercial extracts, age of the patient, skin site used for testing and the allergen food being tested. (75,85,88,104) The threshold wheal size that predicts a clinical reaction may be smaller in younger children. (75,85,88,104,105)

Negative SPT are more accurate at outruling IgE-mediated with negative predictive value exceeding 90%. (75,85,88,104,105) A positive SPT does not confirm diagnosis of allergy but confirms sensitisation to the food allergen, providing further information to aid diagnosis. (75,85,88,104,105) Many studies have examined the accuracy of skin prick tests in predicting the likelihood of a clinical allergic reaction using wheal sizes and comparing with positive oral food challenges. (75,85,88,104,105) These studies inform us that a positive SPT does not predict the severity of a clinical reaction but rather confirms the likelihood that a reaction would occur on ingestion of the food tested, particularly with larger wheal diameters. (75,85,88,104,105) A previous study found 100% correlation with a clinical allergic reaction to cow's milk for wheal size >8mm and >6mm for children older and younger than 2 years old respectively. (105)

Serum-specific IgE blood testing is another means of assessing IgE-mediated allergy but is more expensive than SPT. (75,85) The likelihood of a clinical allergic reaction correlates with higher levels of serum-specific IgE. (75,88,106) The serum-specific IgE level that determines a 95% positive predictive value for a clinical reaction to cow's milk is >/=5 kIU/L for age <2 years old and >/=15 kIU/L age >2 years old derived from paediatric studies. (75,88,106,107)

The gold standard for diagnosing food allergy is a double-blind, placebo-controlled food challenge (DBPCFC) following dietary elimination of the food. (75,85) This follows a standardised approach of ingesting increasing amounts of food protein over several hours in a

controlled hospital environment with close monitoring of the patient, and access to emergency medication if required. (75,85)

Antihistamines must be avoided for at least 5 days prior to SPT as they interfere with testing which is dependent on histamine release and similarly for DBPCFC where they could mask symptoms. (75,85)

No scientifically validated diagnostic test exists for non-IgE-mediated food allergy beyond the burdensome DBPCFC test. Diagnosis depends on a clinical history suggestive of non-IgE allergy, followed by a period of elimination of the suspected culprit food and re-introduction. (75,85) The length of food elimination is dependent on the age, nature of reaction and culprit food; in the case of FPIES, elimination is undertaken for a few years and re-introduction may be done following oral challenge. (75,85) For children with milder symptoms and in the context of diagnostic work-up, a period of elimination may be undertaken for 2-6 weeks before reintroduction to confirm or refute the diagnosis. (75,85,108)

In summary, diagnosis of food allergy is made through a combination clinical history, targeted SPT and if needed, serum-specific IgE testing when the history suggests IgE-mediated allergy, and oral food challenge.

11.2.6 Dietary exclusions and substitutions for managing cow's milk allergy

The treatment for cow's milk allergy is dietary avoidance of cows, sheep and goat's milk products for at least 6 months or until age 9-12 months old, with dietician assessment to ensure adequate dietary calcium. (85,89)

Breastfeeding for at least 2 years and beyond is recommended by the World Health Organisation as optimal for infants and should be encouraged for all children including those

with CMA. (72,85,89,109) Maternal dietary elimination of dairy as a treatment for milk-allergic breastfed children features in many guideline recommendations. (72,110) Hypoallergenic infant formulas contain smaller proteins with less allergenicity than normal cow's milk formula. (89,111,112) They are produced by heat or enzymatic hydrolysis. (89,111,112) Infant formulas that meet the criteria of 90% tolerance in studies of milk-allergic children can only be considered hypoallergenic and so partially hydrolysed formula is excluded from this definition. (89,111,112) Extensively hydrolysed and amino acid formulas are the two main categories of hypoallergenic formulas. (89,111,112) Extensively hydrolysed formulas are usually based on either casein or whey cow's milk proteins and do not cause allergic reactions in most milk-allergic children due to peptides with molecular weight under 3000 Daltons. (89,111-113) Amino-acid formula contain amino-acids only without proteins or peptide fragments rendering them non-allergenic but they are more expensive so use is generally reserved for severe cases of CMA, multiple food allergies, or malabsorption conditions. (89,111-113)

Other cow's milk substitutes

Soya formula may also be used as a cow's milk substitute except in cases of co-existing soya allergy which affects 10% of milk-allergic children. (85,89) Phytoestrogens which are oestrogenic occur naturally in soya bean and at significantly higher levels than breastmilk and therefore soya formula is not advised for infants under 6 months old. (85,89,114,115) Other plant milk alternatives are available but not advised as a sole form of nutrition in young children. (114,115) They can be used as cheese and yoghurt substitutes and in older children as a drink but nutritional adequacy is variable amongst different plant protein sources and they are expensive. (114,115)

11.2.7 Prognosis of cow's milk allergy

The natural course of CMA is resolution by school age in most patients and re-assessment of children for tolerance is advised at least annually. (85,89) Cow's milk protein becomes less allergenic with heat treatment and therefore, milk protein in baked products may be tolerated by milk-allergic children. (85,89) This forms the basis of milk ladders used to reintroduce cow's milk protein and improve tolerance. (116)

Oral immunotherapy

Oral immunotherapy involves initial graded introduction of cow's milk protein under supervision to a maximum tolerated dose, followed by continued regular home feeding at a maintenance dose. (117) The aim of immunotherapy is to modify the host immune response to induce tolerance. (117) A study of baked milk oral immunotherapy successfully desensitised 11/15 children aged 3-18 years old with severe CMA after 1 year of treatment. (118) Non-baked cow's milk immunotherapy seems to improve tolerance but is also associated with increased risk of severe adverse reactions. (117) Systematic reviews and guideline recommendations cite oral immunotherapy as a treatment option for people with persistent IgE-mediated cow's milk allergy. (119)

11.2.8 Limitations of diagnosis and management of cow's milk allergy

The limitations of SPT and serum-specific IgE testing are that neither are entirely sensitive or specific. (75,85) Both modalities have a high false positive rate, with only about half of those with a positive test reacting on food challenge. There are also some patients who will have clinical reactions despite having results falling below the lowest threshold value that usually

determines allergy. (75,85) Positive tests determine sensitisation to a food but do not confirm allergy and so have to be interpreted in the context of the clinical history. (75,85)
Serum-specific IgE concentrations are affected by cross-reactivity with pollens and foods, for example, people with pollen-allergy may be sensitised to many foods through serum-specific IgE testing but are consuming those foods without difficulty. (75) An exaggerated response in both SPT and serum-specific IgE testing may be seen in people with pollen allergy due to cross-reactivity. (75)
DBPCFC are time-consuming and costly, requiring a hospital setting and experienced nursing staff. (75) Variations of DBPCFC may be undertaken which include open challenges where food is not blinded but this risks subjective symptoms due to fear of allergic reaction which can be difficult to interpret. (75) There are no convenient, reliable tools for non-IgE CMA diagnosis, meaning that many with a non-IgE CMA diagnosis have significant uncertainty about the need to avoid cow's milk.

Having considered cow's milk allergy epidemiology, pathophysiology, diagnosis, management and prognosis, I will now consider overdiagnosis of this condition in the next section.

11.3 Milk allergy overdiagnosis

11.3.1 Introduction

Self-reported food hypersensitivity is common in adults and children but few studies have undertaken formal assessment of self-reported cow's milk allergy. (78,82,85) In a clinical trial cohort of English children born between 2014-2016, parental reported cow's milk allergy (15%) was 10-fold higher than diagnostically confirmed CMA (1.4%). (78) In this

section, I will review the evidence for milk allergy overdiagnosis and the potential factors that make CMA, especially non-IgE CMA, vulnerable to overdiagnosis.

11.3.2 Evidence to support milk allergy overdiagnosis

Overdiagnosis often leads to overtreatment and for conditions that are difficult to diagnose (such as CMA), evidence of overtreatment can raise suspicions of overdiagnosis. (2,5,6) An Australian study reported a 41% rise in amino-acid formula (AAF) prescribing between 2002-2004 with a concomitant 9% increase in extensively hydrolysed formula (EHF) prescriptions. (2,113) Munblit et al reported a 10-fold increase in amino-acid formula prescriptions in England from 2005-2018. (2) In general, AAF is used second-line to EHF, CMA the most common condition treated by hypoallergenic infant formula. (2,113) Epidemiological data does not show a similar increase in prevalence of CMA, which suggests that increased prescribing of low-allergy formula is a marker of overdiagnosis of CMA. (2,113) Sensitisation rates to cow's milk protein in Australia assessed at 12 months old in high-risk children have remained stable between 1990-1994 (2.4%; 95% CI 1.6-3.1; n=541) and 2006-2010 (2.6%; 95% CI 2.0-3.4; n=1893). (2,113,120) In the United States, moderate level sensitisation rates to cow's milk protein in children aged 6-19 years old have also remained stable between 1988-1994 (0.4%; 95% CI 0.1-0.7) and 2005-2006 (0.5%; 95% CI 0.1-0.9), and similarly 'any sensitisation' to cow's milk protein using a lower cut-off was similar in the two NHANES surveys at 8.3% and 8.1%. (2,121) In the Isle of Wight study, 1.1% of children were milk sensitised at age 4 years old in 1989 and 0.5% at age 3 years old in 2001. (122,123) This again suggests no obvious change in CMA or milk sensitisation in recent years. If CMA is relatively stable in the populations studied, then prescribing patterns of low-allergy infant formula used to treat CMA over time can be used as a surrogate for trends in CMA overdiagnosis. (2,5,6,113)

11.3.3 Milk allergy and commercially-driven overdiagnosis

Cow's milk allergy may be vulnerable to commercially-driven overdiagnosis for several reasons.

Lack of robust diagnostics

IgE-mediated cow's milk allergy presents rapidly with characteristic symptoms and can be verified with testing. (2,75,85) Non-IgE-mediated cow's milk allergy presents several hours after ingestion of the culprit food with non-specific symptoms including vomiting, abdominal pain, constipation, diarrhoea or eczema (also referred to as atopic eczema and atopic dermatitis throughout this thesis). (2,75,85) Blood in the stool or symptoms of FPIES may be more obviously CMA when there has been a recent introduction of cow's milk into the diet but for other symptoms, correct diagnosis can be difficult to ascertain. (2,75,85) No validated diagnostic test exists for non-IgE-mediated CMA and diagnosis relies on trial elimination and re-introduction of dietary cow's milk. (2,75,85) Blinded oral challenges are not practical which makes CMA vulnerable to overdiagnosis. (2,75,85) A Dutch study compared home re-introduction of cow's milk with DBPCFC performed in primary care following a standard protocol adopted by the health system as a response to CMA overdiagnosis. (1,124) CMA was outruled in 12/50 (24%) children with home re-introduction and 33/50 (66%) children with DBPCFC. (124) In the home re-introduction group, 36/50 (72%) of children were reported milk-allergic compared with 13/50 (25%) children who had DBPCFC. (124) The authors concluded that home introduction overestimated CMA (124) This study also illustrates the significant parental concern about allergy as 4/33 children failed to re-introduce cow's milk into their child's diet due to perception of continued allergy despite a negative DBPCFC. (124)

Potential link with symptoms which affect large numbers of people

Symptoms of non-IgE CMA are not unique to the condition. Gastroesophageal reflux is common in infancy but problematic in about one-fifth of infants. (2,125) Colic affects approximately 16% of infants and eczema in up to 20% of infants. (2,126,127) Non-eczematous rashes are common in infancy and not necessarily indicative of disease. (2) Non-IgE-mediated CMA symptoms are similar to symptoms which affect many infants but most infants presenting with these symptoms do not have cow's milk allergy which occurs in only 1% of children under 2 years old. (1,2) Participants (n=650) in the Early Acquisition of Tolerance study comprising the control group who were all exclusively breastfed had vomiting (22% infants), colic (22% infants) and eczema (43% infants) reported by parents on at least one occasion under 1 year old. (2,128) IgE-mediated CMA was diagnosed by oral food challenge in 0.7% of infants in EAT, and 13% infants had symptoms related to cow's milk as reported. (2,128)

Linked prescribable and over-the-counter commercial opportunities

Prescriptions of adrenaline autoinjectors increased by about 10% annually in England and Wales over a decade to 2018, despite no known increase in fatal anaphylaxis or the conditions which trigger fatal anaphylaxis, such as food allergy and drug allergy. (129,130) This may represent increased awareness and concern about severe allergy with associated over-prescribing of autoinjectors.

A recent study found over-prescribing of low-allergy formula in England was associated with prescribing of milk feed thickeners (Gaviscon Infant and Carobel Instant) and anti-reflux medications for young children. (131) This may represent over-prescribing behaviours amongst primary care practitioners, which might be commercially-driven. (2,131) Prescribers and parents may be encouraged to consider products aimed at treating infant gastrointestinal

symptoms through marketing of these products despite little evidence for their use and despite these symptoms not usually being caused by CMA. (2,132)

Parental / societal concern about allergy

The global rise in allergic conditions awareness with a paucity of specialist services has created a culture of uncertainty in the diagnosis and management of these conditions. However, concern about possible allergy far exceeds true allergy and this is well-documented for paediatric penicillin allergy. (78,133) Self-reported penicillin allergy and parental reported milk hypersensitivity exceeds true allergy approximately ten-fold. (78,133) In one study investigating possible CMA in formula-fed infants <6 months old presenting with colic, constipation or GORD, all 6208 children screened failed to meet inclusion criteria, leading authors to conclude that these symptoms are mainly self-limiting, and not related to underlying CMA. (134)

11.3.4 Stakeholders and beneficiaries of milk allergy overdiagnosis

All problems require consideration of possible solutions but complex problems demand new perspectives. (135) The problem of milk allergy overdiagnosis requires an understanding of the actors, stakeholders and beneficiaries of the condition (Figure 11.2). (135) There is overlap between these roles but also distinctions. (135) Actors are individuals or organisations who may or may not have an interest in the problem or its resolution but have a role to play ('act') in resolving the problem. (135) Stakeholders are individuals or organisations who are impacted by the problem or it's resolution but may not act to resolve the problem. (135) Beneficiaries are individuals or organisations who benefit from the problem and are reluctant to change. (135) Beneficiaries of problem resolution also exist but they are considered stakeholders. (135)

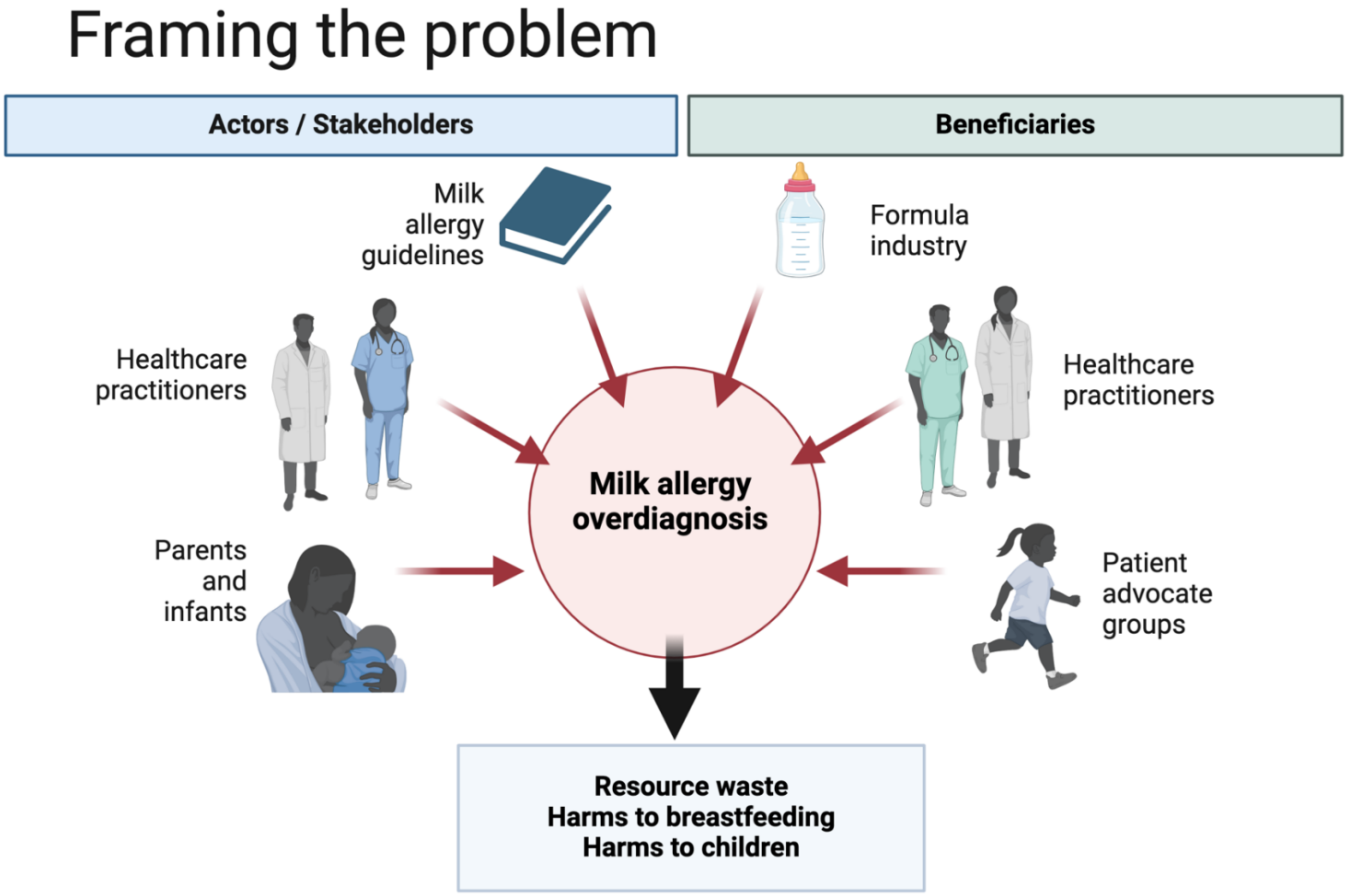


Figure 11.2 Framing the problem of milk allergy overdiagnosis. (Adapted from Problem Framing Canvas, Griffith Centre for Systems Innovation). Created with Biorender.com https://BioRender.com/k02b482 (135)

Parents and patient advocacy groups

Excessive allergy awareness may also interfere with the recognition and management of other infant health issues such as infectious gastroenteritis, malrotation and immune deficiency. (2,50,136) There is also growing evidence that excessive concern about infant allergy in high-income countries is serving to undermine mother-infant bonding, breastfeeding and child nutrition. (137) Allergy charities may overpromote allergy awareness inadvertently in response to a fear of under-diagnosis. (38,45,46)

Healthcare practitioners

In some high-income countries, the growth of paediatric allergy as a specialty in the early 21st century coincided with sharp increases in sales of low-allergy formula milk, to levels that exceed population requirements by 10-fold. (2) Allergy healthcare professionals have also attracted criticism for close relationships with the formula industry, which appear to have contributed to excessive use of specialised formula products and undermining of breastfeeding. (3) In recent years, the allergy community have shifted the focus of allergy prevention efforts to tolerance induction. (138) There is therefore increased pressure within the field of allergy that solid food introduction should occur earlier than 6 months old, in order to allow earlier allergenic food introduction to reduce risk of food allergy. (139) Currently WHO recommends exclusive breastfeeding for the first 6 months. (109) Yet commercial dietary products containing allergenic food for infants aged under 6 months are increasingly marketed in high income countries. Promotion of early dietary interventions to prevent the development of food allergies may therefore directly undermine WHO recommendations for optimal infant feeding. (99,109)

The issue of hydrolysed formula for allergy prevention has been constrained at a regional level by a European Directive prohibiting health claims for hydrolysed formula products.

(140) However, there is provision within the Directive for future claims of milk allergy prevention being included in labelling of these products, if these can be appropriately substantiated. (140) The message of allergy prevention being important in child nutrition can be exploited by promotional activities which co-opt the allergy community and undermine breastfeeding.

Milk allergy guidelines authorship

There is evidence that formula industry marketing has played an important role in reframing normal infant symptoms as possible milk allergy, although wider changes in cultural attitudes to health and overdiagnosis of food allergy as a whole may also be relevant. (2,3,32,130) Through several decades of close partnerships between the formula industry and allergy professionals in high-income countries, milk allergy overdiagnosis has become widely promoted in guidelines. (3) For example, constipation was considered a sign of Non-IgE milk allergy in a recent survey of all 70 United Kingdom primary care milk allergy guidelines. (141) There is significant potential commercial gain in pathologising normal symptoms as milk allergy and formula industry funding of guidelines and educational events reflects this. (3) A recent analysis of one milk allergy guideline in primary care disseminated by formula companies found recommendations labelled 74% of healthy infants as having symptoms of milk allergy. (50) A two-third increase in prescriptions for low-allergy formula in Northern Ireland followed targeted implementation of this milk allergy guideline in primary care. (142) A common recommendation in such guidelines is for breastfeeding women to restrict their diet, a practice which has little or no empirical evidence base and can undermine breastfeeding confidence as reported in a recent systematic review. (137,143)

Concern has been raised regarding relationships between allergy professionals and the formula industry. (3) Most milk allergy guidelines declare direct or indirect financial ties with formula industry. (2,3)

Formula industry

Conflictive relationships between formula milk companies and the allergy community have caused controversy due to breaching World Health Organization guidance on sponsorship of health professional meetings. (3,144) For example, in South Africa the formula industry sponsors allergy societies and allergy education initiatives. These include an Allergy in Africa webinar series with potential to drive allergy overdiagnosis on the African continent and foster clinical practices which undermine breastfeeding. (145) Specialised formula has been used unnecessarily for preventing allergy, based on fraudulent and selectively reported science; and for managing normal infant symptoms which are mislabelled as milk allergy. (2,146-149) This forms part of a broader formula industry corporate strategy to widen the boundaries of illness in order to expand sales and markets.

11.3.5 Commercially-driven allergy practice recommendations: the hydrolysed formula story

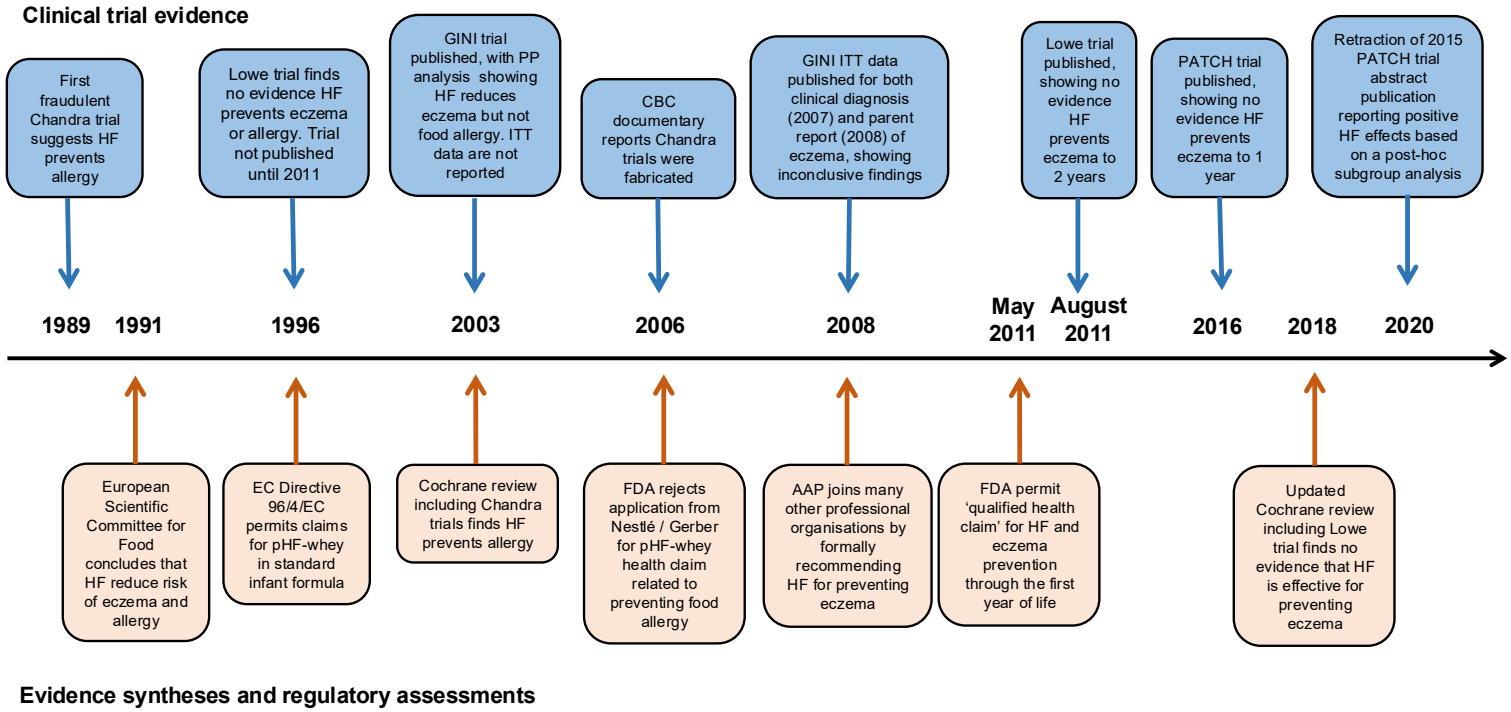
Commercially influenced allergy practice is not unique to CMA overdiagnosis. Indeed, the same infant formula industry has promoted hydrolysed formula products for allergy prevention until recently. The 'hydrolysed formula story' provides some lessons and understanding of formula industry activity in promoting unnecessary use of higher-priced formula products based on allergy concerns Figure 11.3. Hydrolysed infant formula originated in the 1940s and was investigated in the 1980s for its potential to prevent allergy in healthy infants. (146) Researchers hypothesised that consumption of hydrolysed proteins in

infant formula would prevent cow's milk allergy and atopic eczema by reducing sensitisation to milk protein. (150) Preliminary studies in the late 1980s and 1990s further corroborated this hypothesis and it appeared hydrolysed formula may prevent allergy. (146-148) In 1989, an influential study by Dr Ranjit Chandra confirmed maternal dietary avoidance of cow's milk protein and use of hydrolysed infant formula prevented atopic eczema. (147) A television documentary raised concerns about fabricated results and scientific fraud in 2006 but the study was not retracted until 2015. (149)

The findings of these early studies led to statements from European gastroenterology and allergy societies and a 1991 European Report of the Scientific Committee for Food that hypoallergenic infant formula prevented allergy in children at high risk of atopy. (150,151) Dissemination of the allergy prevention concept at educational meetings was promoted through formula industry relationships with healthcare professionals. (152) An independent Cochrane review which used the fraudulent Chandra studies and the German Infant Nutrition Intervention (GINI) study further validated the concept. (153) In the GINI study, a beneficial effect reported through per protocol analyses was not confirmed through intention to treat analyses. (154,155) Subsequent published studies have also not found hydrolysed formula effective in preventing cow's milk allergy. (154-157) However, it was widely accepted by the allergy community for decades that hydrolysed formula prevented allergy. (158) Hydrolysed formula as an intervention to prevent allergy is no longer recommenced in milk allergy guidelines from Europe, North America, Japan and Australasia due to a lack of reliable evidence. (159-162) This case study illustrates how close educational and research relationships between formula industry and allergy healthcare professionals, along with fabricated and selective reporting of research study findings profoundly influenced allergy clinical practice. (158) Guideline recommendations for allergy prevention became dominated

by formula marketing messages that hydrolysed formula could prevent eczema or milk allergy development, despite little credible scientific evidence to support these claims.

Figure 11.3. Timeline of hydrolysed formula story and allergy prevention



Adapted from Genuneit et al 2021. (158) Summary of evidence for allergy and eczema prevention using hydrolysed formula. Timeline of data availability from the main clinical trials, along with timing of the main European and North American regulatory assessments, allergy guideline recommendations and Cochrane systematic review findings.

AAP, American Academy of Pediatrics; CBC, Canadian Broadcasting Corporation; EC, European Commission; FDA, Food and Drug Administration; GINI, German Infant Nutritional Intervention trial; HF, hydrolysed formula; ITT, intention to treat; pHF-whey, partially hydrolysed whey formula; PATCH, prevention of allergy through cow's milk hydrolysate; PP, per protocol

11.4 Public health implications of milk allergy overdiagnosis

11.4.1 Introduction

Milk allergy overdiagnosis has direct and in-direct public health consequences through inappropriate use of resources but also through its negative impact on breastfeeding and child health.

11.4.2 Financial implications and resource waste

The cost of specialised infant formula used to treat CMA to England's national health service exceeded £60 million sterling in 2016, compared with £8 million in 2006. (2,3) Amino-acid formula accounted for most spending and is more expensive than extensively hydrolysed formula. (2,3) A Dutch study identified suspected CMA in 7% of patients attending primary care, exceeding the expected prevalence of 1%. (163) Almost three-quarters of suspected cases were prescribed an alternative milk formula. (163) Authors concluded that suspected CMA created additional burden for primary care. (163)

11.4.3 Burden of milk allergy overdiagnosis on maternal health

Impact on maternal health

Women have reported psychological distress and early cessation of breastfeeding when milk allergy is diagnosed in their child. (137) Advice to restrict maternal diet, which often accompanies CMA overdiagnosis, can potentially lead to maternal weight loss, nutritional deficiencies and anxiety related to uncertainties around the adequacy of the exclusion diet. (137)

Maternal dietary restriction

From the early 20th century, acute allergic reactions in breastfed, food-allergic infants have been reported due to maternal ingestion of specific foods. (164) Early reports focussed on vegetables, milk, egg, codfish and chocolate as a cause of allergic and non-allergic symptoms in the infant through breastmilk. (164) Opinions differ on the role of maternal dietary restriction in managing food allergy in the 21st century.

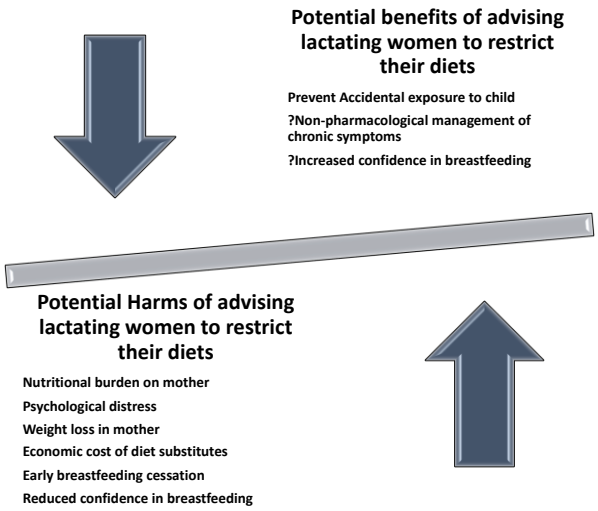
In clinical practice, lactating mothers commonly report symptoms of crying, gastrointestinal disturbance or eczema in their child which they attribute to their own dietary ingestion of specific foods. Differentiating between significant maternal observations and normal infant behaviour is a diagnostic challenge for healthcare practice (2) Acute or delayed reactions to breastmilk in food-allergic infants exist in case reports but blinded food challenge studies suggest a low prevalence of reactions when there is a documented allergy to a relevant food in the maternal diet. (165)

Mechanistic studies show that food allergens ingested by lactating women often become detectable in breastmilk. (2) However, studies of cow's milk, egg, peanut and wheat have shown that detectable food allergen levels in breastmilk are in the range of nanograms per ml, meaning that infant ingestion of typical threshold doses for triggering acute reactions is almost impossible. (2) Acute or delayed allergic reactions in an exclusively breastfed infant are rare, and although proctocolitis can occur in breastfed infants, this is not always caused by a specific, identifiable food allergy. (165) Similarly, the evidence that eczema can be managed via maternal dietary restriction is not strong. (166)

One of the few double-blind clinical trials in this field evaluated 37 infants with eczema which was thought to be related to maternal diet. In 6/37 (16%) infants, authors reported that maternal egg and milk exclusion was associated with an improvement in eczema which relapsed on reintroduction, while dietary manipulation was not helpful for most participants. (167) The findings were statistically inconclusive. Studies in this field have often failed to identify a statistical association between specific food allergy in the child and apparent response to maternal exclusion of the same food. So, the evidence for advising maternal dietary restriction when their child has a diagnosed food allergy is low-level evidence, relying largely on case reports and small case series. (165)

Historically, guidelines have widely recommended lactating mothers eliminate allergens from their own diet, but this advice is controversial, with some reporting that maternal dietary restrictions can undermine breastfeeding. (2,3) Strong evidence for this advice is lacking, and the risks and benefits of advising maternal dietary restrictions should probably be carefully considered on a case by case basis (Figure 11.4).

Figure 11.4. Potential benefits and harms of healthcare professional advice for a lactating mother to restrict her diet when breastfeeding her food-allergic child.



Possible reasons to advise dietary exclusions include safeguarding against accidental, direct exposure of the child to the food allergen when the mother or family members continue to consume the food. Anecdotal evidence suggests benefit of maternal dietary restriction for some children with chronic symptoms associated with food allergy, such as eczema. (165) Eczema is the most burdensome skin condition worldwide, with a high prevalence during the first two years of life (168) and limited non-pharmacological options for management. Some families may feel that maternal dietary restriction is safer than using medical products such as skin creams, wash products and topical anti-inflammatories. Offering a solution by restricting the maternal diet may empower some families, giving them a sense of control and potentially increasing confidence that they can safely breastfeed their child. Maternal dietary restrictions may also be used to manage symptoms which are not food allergy. Although the science underpinning this practice is largely derived from case reports and historical and cultural

records, controlled trials have suggested that infants do respond to some specific maternal dietary exposures, often through a change in flavour or smell of breastmilk. (169)

The potential harms of advising maternal dietary restriction are magnified when the child's diagnosis of food allergy is uncertain. Exclusion diets can be difficult to adhere to, especially without a clear understanding of which foods should be avoided. Symptoms may persist, leading to ever more restrictive diets, and families advised to use maternal dietary exclusion may suffer adverse nutritional, emotional and economic outcomes. (137) Women using dietary exclusions to manage food allergy in their child were reported in one study to have increased depression and anxiety symptoms, and over three-quarters of mothers reported weight loss and two-thirds a reduction in breastmilk supply. (137) Larger and more representative studies are needed to better understand the impact of dietary exclusions on breastfeeding women; however, these preliminary findings of adverse effects are supported by anecdotal reports of such diets undermining confidence in breast feeding. (3)

11.4.4 Potential harms of milk allergy overdiagnosis on children

Growth and micronutrient deficiencies

Amino acid formula has been associated with micronutrient deficiencies when used as a sole source of nutrition. For example, case reports document hypophosphataemia and rickets detected during investigation for bone disease in children who were consuming amino-acid formula as their only form of nutrition; with improvement in levels of phosphate and bone health on transition to an alternative formula. (170,171) Some types of specialised low-allergy formula have also been associated with altered taste perception and growth trajectories in young children. (172,173)

Potential impact on obesity and dental health

Prescriptions of specialised formula in England (2009-2018) grossly exceed expected requirements to treat CMA, a condition only affecting up to 1% of the population. (2) This apparent overuse of specialised formula may have significant implications for child health. Dietary carbohydrates are necessary for energy but can also be harmful for health depending on the form of carbohydrate, whether it has been artificially processed and if it has been added to food or is naturally occurring. (174-178) Identified potential harms of carbohydrate sources such as glucose syrups, present in some specialised low-allergy formulas, include effects on post-prandial metabolism and dental health. (175)

Carbohydrates found in human milk have nutritional benefits and are considered important for infant gut health, acting as prebiotics amongst other possible immune effects. (178) Free sugars is the term given to all sugars that are added to food either by the individual when eating or cooking (eg. honey or syrups) or by the manufacturer during food processing (eg. glucose syrup or malt extract). (176,178) Lactose is a milk sugar that naturally occurs in human breastmilk and cow's milk and is not considered a free sugar. (176,178) However, lactose that is added to foods as an ingredient, such as lactose in whey powder, is considered a free sugar. (176,178) The WHO (2015) recommends restricting dietary free sugars to less than 5% of total carbohydrate intake in both adults and children due to the risks to dental health. (179) This recommendation is based on evidence that suggests dietary harms in childhood can determine dental caries in adulthood. (179,180)

Glucose syrups and maltodextrins are produced in manufacturing by the hydrolysis of starch, such as corn, maize, wheat or potato. (176,178) Glucose syrup has shorter glucose chains and is essentially liquid glucose oligomers. (174,176,178) Maltodextrins are not classified as free sugars but are commonly used in food manufacturing as a carbohydrate replacement without taste or odour. (174-176,178) Maltodextrins are commonly used in infant formula and food,

energy drinks and non-alcoholic beverages, and use of corn syrup which is a glucose syrup is increasing. (174-176,178) Dextrose equivalent (DE) is one measure used to categorise carbohydrates and is used to differentiate between maltodextrins (DE <20) and glucose syrups (DE>20) (174-176,178) The relevance of this distinction is their cariogenic potential, with higher DE indicative of a greater potential to cause dental caries. (174,181) The mechanism of dental caries appears to be fermentation of these carbohydrates by dental plaque microorganisms, resulting in an acidic environment which promotes enamel demineralisation and dental decay (174,175,181,182) Children are more susceptible as the enamel is less robust. (175,182) In vitro and animal studies have identified an association between dental caries and both maltodextrins and glucose syrups (181)

A review of evidence found an association between higher dietary intake of sugars, mainly through beverages containing sugar, and increased weight in children (OR 1.55; 95% CI 1.32-1.82). (183) The quality and source of early childhood nutrition is associated with risk of obesity. (184) Starch derivatives such as maltodextrin and glucose syrup are typically rapidly digested, leading to a high glycemic index and potential for promoting adiposity and insulin resistance compared with less refined carbohydrate sources (185,186) Normal cow's milk infant formula contains lactose as its main carbohydrate source. In specialised infant formula, milk lactose is partially or completely replaced by other carbohydrate sources such as maltodextrin, dried glucose syrup or sucrose, leading to increased free sugars intake, a risk factor for dental decay and obesity (Table 11.1). (115,179,187-189) Lactose naturally present in dairy products is not considered a risk factor for dental decay or obesity. (174-177,179)

Table 11.1. Carbohydrate content of prescribed specialised formula (PSF) and non-prescription formula marketed in England

Product	Carbohydrate sources	Non-lactose sugars content per 100mls	Free sugars content per 100mls	Typical daily free sugars intake*
Prescribed Specialised Formula (PSF)				
Infantrini Peptisorb	Glucose syrup, maltodextrin	10.1	10.1	60.6
Nutramigen 2	Glucose syrup, fructose, modified corn starch	7.7	7.7	46.2
Aptamil Lactose Free	Glucose syrup, maltodextrin	7.6	7.6	45.6
SMA Lactose Free	Glucose syrup	7.6	7.6	45.6
Alfamino	Glucose syrup, starch	7.5	7.5	45.0
Nutramigen 1	Glucose syrup, modified corn starch	7.4	7.4	44.4
SMA Althera	Lactose, maltodextrin	3.6	7.3	45.8
Elecare	Glucose syrup, oligosaccharides	7.2	7.2	43.2
Neocate	Glucose syrup, oligosaccharides	7.2	7.2	43.2
Peptijunior	Glucose syrup, maltodextrin	7.1	7.1	42.6
Pregestimil	Glucose syrup, modified corn starch	6.9	6.9	41.4
Puramino	Glucose syrup, modified tapioca starch	6.9	6.9	41.4
SMA Soya	Maltodextrin	6.8	6.8	40.8
Alimentum	Maltodextrin, sucrose, modified starch	6.6	6.6	39.6
Aptamil Pepti 1 and 2	Maltodextrin, lactose, oligosaccharides	4.8	4.8	28.8
Standard Infant and Follow-on Formula available without prescription				
Aptamil Comfort	Glucose syrup, oligosaccharides, maltodextrin, starch, lactose	4.3	4.3	25.8
SMA Little Steps	Lactose	0	3.5	21.0
SMA Preterm	Lactose, maltodextrin	2.4	3.3	19.8
SMA Anti-reflux	Lactose, potato starch	0	2.9	17.4
SMA Comfort	Lactose, potato starch, oligosaccharides	0.26	2.8	16.8
SMA Advanced	Lactose, oligosaccharides	0.17	2.8	16.8
Cow and Gate	Lactose, oligosaccharides	0.28	2.7	16.2
SMA Pro	Lactose, oligosaccharides	0.03	2.7	16.2
Aptamil Advanced	Lactose, oligosaccharides	0.66	2.5	15.0
Aptamil	Lactose, oligosaccharides	0.56	2.5	15.0
Aptamil Anti-reflux	Lactose, oligosaccharides	0.3	2.5	15.0
Kendamil	Lactose, oligosaccharides	0.27	2.4	14.4
Similac Gold	Lactose, oligosaccharides	0.22	2.0	12.0
Standard Toddler Formula available without prescription				
Paediasure shake	Corn syrup, sucrose, maltodextrin	8.5	8.5	34.0
Alpro Soya Growing Up	Maltodextrin, sucrose, fructose	7.9	7.9	31.6
SMA Pro 3 Growing Up	Lactose, maltodextrin, oligosaccharides	2.4	4.4	17.6
Oatly	Free sugars released from oat starch	4.1	4.1	16.4
Aptamil 3 Toddler	Lactose, maltodextrin, oligosaccharides	2.2	4.1	16.4
SMA Little Steps Growing Up	Maltodextrin, lactose	3.1	4	16.0
Cow & Gate 3 Growing Up	Lactose, maltodextrin, oligosaccharides	1.8	3.9	15.6

Aptamil 4 Toddler	Lactose, maltodextrin, oligosaccharides	1.9	3.3	13.2
SMA Advanced Growing Up	Lactose, oligosaccharides	0.04	3.3	13.2
Kendamil Classic Toddler	Lactose, oligosaccharides	0.21	2.8	11.2
Cow & Gate 4 Growing Up	Lactose, maltodextrin	1.4	1.9	7.6

Data shown are from analyses conducted by collaborating charity First Steps Nutrition Trust (FSNT), published in 2024. (190,191) They are representative of the market leading formula products, rather than a comprehensive analysis of all products available in 2024. *Daily free sugars intake is calculated assuming 600mls per day consumption during infancy and 400mls per day consumption for toddler milks.
Public health recommendations are to limit free sugars to <5% of total energy intake (DHSC), <10% of energy intake (WHO) or 'as low as possible' (EFSA). 1g free sugars = 4kcal, and infants consume about 100kcal per kg per day in the first year and about 1100-1200kcal per day in the second and third years of life. So DHSC free sugar limits are ~14g free sugars in the second and third years of life. No limits yet for first year, but 5% for an 8kg baby would be 10g free sugars

A US study of children (n=15246) receiving infant formula as part of a state-subsidised nutrition support programme found a significant association between children receiving formula containing little or no lactose and obesity. (192) The carbohydrate source in these lactose-reduced formula was corn syrup. (192) The study population included infants who were formula-fed only from 3 months old, and controlled for duration of breastfeeding and duration of formula-feeding. (192) There was a 10% higher risk of obesity by the age of 2 years old for those children receiving any duration of corn syrup-based formula. (192) Children who received corn syrup-based formula (n=3548) were more obese at school-age compared to those children who received standard infant formula (n=11698), 26.9% and 24.6% respectively and this was significant (p value=0.007). (192) Duration of exposure to corn syrup-based formula was also relevant. (192) The risk of obesity increased for each additional month of use and children aged 2 years old had a 16% increased risk of obesity following 12 months of exposure compared to those without exposure to corn syrup-based formula. (192)

The same research group subsequently reported on differences in eating behaviours up to 2 years old in a cohort of Hispanic children fed standard formula, corn syrup-based formula or breastmilk. (193) Early life consumption of corn syrup-based formula was associated with

increased food fussiness and reduced food enjoyment which worsened over time, although this finding was not confirmed in a subsequent study where type of formula carbohydrate was not associated with food preferences at age 1-5 years. (193,194)

Previous work has shown that taste preferences are influenced by type of early feeding, with differences observed between breastmilk, standard cow's milk formula and hydrolysed formula (172) Consumption of lactose-free and reduced lactose formula appears to be increasing in the US and the longer term implications of this on child health are unknown. (195,196)

Another study compared the nutrient content of lactose-free, lactose-reduced and standard lactose infant formula. (197) Lactose was replaced with alternative carbohydrates such as sucrose, glucose syrup or maltodextrin. (197) They found that the sugar content increased by almost one-fifth for every gram of lactose that was substituted per 100 gram of formula. (197) The medical indication for lactose-free formula is limited to certain conditions such as prematurity or galactosemia when breastfeeding is not possible. (197) The authors hypothesised that the unwarranted use of lactose-free formula could be harmful for children who do not have these specific medical conditions, (197) particularly as evidence shows that early-life feeding can have implications for infant neurodevelopment and immunity. (198,199)

11.5 Rationale for this PhD

Milk allergy overdiagnosis in children has been highlighted by others with significant cost implications for NHS England. It is unknown if this problem exists outside of England and what the potential harms are to children misdiagnosed as milk-allergic. The factors leading to children acquiring an unnecessary milk allergy diagnosis or receiving an unnecessary prescription of specialised formula are also unknown. Most milk allergy guidelines or their

authorship have commercial ties and are mainly written by specialists leading to concerns that commercial influences are contributing to milk allergy overdiagnosis. The rationale for this PhD is to characterise the problem of milk allergy overdiagnosis in children by:

1. assessing the extent of specialised formula prescribing nationally and internationally
2. identifying the prevalence and symptoms associated with milk allergy overdiagnosis, and
3. understanding the patient risk factors for acquiring a false label of milk allergy.

This thesis will also identify risk factors associated with GP prescribing habits that may lead to milk allergy overdiagnosis. Finally, this thesis will compare GP prescribing behaviours with independent guidance on milk allergy diagnosis and management, developed as part of this PhD. This PhD is focussed on primary care as most patient contact occurs in primary care and research to date shows overprescribing of low-allergy formula in the community in England.

11.6 Research Questions

How common is milk allergy overdiagnosis?

Population: Children aged under 1 year old, resident in the United Kingdom, Norway or Australia during the study period

Outcome: Volume and cost of prescribed specialised infant formula and, where available, proportion of the child population prescribed such a formula, as a measure of milk allergy overdiagnosis

How do children acquire a false label of milk allergy?

Population: Children in a clinical trial cohort who underwent formal evaluation for CMA

Exposures explored: Symptoms documented in primary care record, including age at documentation and type of practitioner documenting symptoms and labelling

Outcome: Milk hypersensitivity label reported by parent, documented in primary care record, or suggested by documented prescription of specialised low-allergy formula

Are there particular patient features that increase the risk of being misdiagnosed milk-allergic?

Population: Children in a clinical trial cohort who underwent formal evaluation for CMA

Exposures explored: Patient data including sociodemographic details and maternal pre-birth health-related quality of life data collected as part of original BEEP trial

Outcome: Milk hypersensitivity label reported by parent, documented in primary care record, or suggested by documented prescription of specialised low-allergy formula

Are there particular healthcare practitioner features which are associated with risk of a child being misdiagnosed milk-allergic?

Population: Children in a clinical trial cohort who underwent formal evaluation for CMA

Exposures explored: GP Practice prescribing patterns; GP practice socioeconomic status; GP practice local CMA guidelines

Outcome: Milk hypersensitivity label reported by parent, documented in primary care record, or suggested by documented prescription of specialised low-allergy formula

Is guidance on milk allergy diagnosis and management different when developed by multidisciplinary healthcare practitioners without conflicts of interest to formula industry, and with parental involvement?

Population: Infants aged under 24 months evaluated by any healthcare practitioner in any setting, for possible CMA

Intervention: Delphi consensus method with Multidisciplinary healthcare practitioners without conflicts of interest to formula industry

Control: Current milk allergy guidelines

Outcome: Guidance for diagnosing and managing CMA

11.7 Hypothesis

Overdiagnosis of milk allergy is preventable by identifying the factors leading to healthcare practitioner diagnosis of milk allergy and providing non-conflicted guidance for healthcare practitioners who manage infants and young children with possible milk allergy.

11.8 Overall aims of this thesis

To characterise the problem of milk allergy overdiagnosis in children by estimating prevalence, describing triggers and identifying risk factors.

To develop non-conflicted guidance for detection and management of milk allergy and compare with diagnosis and management recommendations from formula industry-sponsored guidelines thus evaluating the impact of formula industry sponsorship.

11.9 Specific Research Objectives

i. To identify the volume and cost of prescribed specialised infant formula used to treat milk allergy in the United Kingdom, using this as a surrogate marker for CMA overdiagnosis nationally
ii. To identify a primary care record of reaction to milk and/or prescription of specialised infant formula used to treat milk allergy, using this as an estimate of CMA prevalence
iii. To identify the factors in primary care records that lead to children acquiring a false milk allergy label from healthcare practitioners.
iv. To identify the volume and cost of prescribed specialised infant formula used to treat milk allergy in Norway and Australia, using this as a surrogate marker for CMA overdiagnosis internationally
v. To identify healthcare practitioner prescribing patterns that may be associated with CMA overdiagnosis
vi. To identify whether guidance from a wide range of stakeholders who are independent of formula industry influence differs from current, mainly conflicted guidance.

12 Methods

12.1 Overall approach

The specific aims and objectives of this thesis were addressed in 3 main projects: a cross-sectional analysis of national and international prescribing databases, a retrospective analysis of the primary care records of a clinical trial cohort of English children where milk allergy was well-characterised and a Delphi consensus study. Data analysis is presented in 7 results chapters. (Table 12.1) This layout was chosen to first illustrate the evidence for CMA overdiagnosis in the UK (chapter 13-15) followed by the international evidence for CMA overdiagnosis (chapter 16). Chapter 17 and 18 presents the evidence for risk factors for CMA overdiagnosis. Finally, chapter 19 presents independent guidance for diagnosing and managing CMA overdiagnosis.

Methodology

The methodology for this thesis was chosen at the time of writing the research proposal. The first research objective was to identify the prevalence of milk allergy overdiagnosis using a retrospective analysis of prescription databases. This method was chosen as the best method of analysing trends in milk allergy diagnosis and management over time, building on previous work. (2)

To address the second research objective, how children acquire a false label of milk allergy and what risk factors exist, the method chosen was a retrospective analysis of the primary care records from a cohort of 1400 infants in England. Here, parents reported a high rate of CMA (14%) but careful phenotyping documented a 10-times lower rate of CMA; and parent-reported use of a specialised formula milk was high (6% of participants during the second

year of life). (78) This methodological approach was adopted in order to confirm the rate of specialised formula use in the primary care records compared to parent-reported use, and evaluate by whom, where, when and why this was initiated. This approach also incorporated evaluation of the infants with parent-reported CMA, in order to understand symptom patterns and risk factors for development of a false CMA diagnosis.

A Delphi consensus method was chosen to address the third research objective whether guidance on milk allergy diagnosis and management is different when developed by multidisciplinary healthcare practitioners without conflicts of interest to formula industry, and with parental involvement. This method was chosen as it facilitates amalgamation of anonymous expert opinion independently in order to reach a consensus on the management of a difficult problem where there is insufficient evidence to provide scientific certainty. (200-202)

Public involvement

The extent of public involvement in this thesis was limited within the constraints of a PhD. However, I used insights from my clinical practice working in primary care as a GP with a special interest in allergy to inform elements of the thesis.

Parents were involved in the Delphi consensus study as described in Section 12.6.5.

Table 12.1: Overall approach to thesis

Research Question	Projects	Chapter
How common is milk allergy overdiagnosis?	National trends in use of specialised formula for managing cow's milk allergy in young children	13
	Prevalence of cow's milk overdiagnosis in the BEEP trial cohort	14
	International trends in use of specialised formula for managing cow's milk allergy in young children	16
How do children acquire a false label of milk allergy and what are the risk factors?	Consultation features of cow's milk overdiagnosis in the BEEP trial cohort	15
	Patient risk factors for milk allergy overdiagnosis in the BEEP cohort	17
	GP Practice-level risk factors for milk allergy overdiagnosis in the BEEP cohort	18
Is guidance on milk allergy diagnosis and management different when developed by multidisciplinary healthcare practitioners without conflicts of interest to formula industry, and with parental involvement?	Delphi consensus study for the detection and management of milk allergy in children	19

12.2 National trends in use of specialised formula for managing cow's milk allergy in young children

The overuse of specialised formula to treat CMA has previously been reported for England. (2) The aim of this project was to complete the analysis in more detail, for the whole United Kingdom, in order to identify national prescribing trends of specialised formula.

12.2.1 Study design

This was a cross-sectional analysis of national prescription databases of reimbursed specialised infant formula in England, Scotland, Wales and Northern Ireland. Inclusion criteria were complete national prescription databases for more than one type of specialised formula for at least one year. Exclusion criteria were incomplete national prescription databases, databases without a breakdown of specialised infant formula brands and quantities reimbursed or sold, or regions without public records of reimbursed or sold specialised infant formula volumes. We included breastmilk substitutes marketed for children with cow's milk allergy and excluded food supplements and products designed for malabsorption or eosinophilic oesophagitis from our analysis (Tables S1-2, Appendix 22.3).

The primary outcome assessed was volume of specialised formula prescribed to children under 1 year old in each country. Secondary outcomes were the annual total cost of specialised formula reimbursement, and the comparison between actual volumes re-imbursed and expected volumes estimated according to a 1% incidence of CMA and based on national infant feeding data. (1)

12.2.2 Data collection

Data collection was undertaken by myself (Scotland, Wales and Northern Ireland) and by a BSc medical student, Ms. Shriya Mehta (England). Quantity and cost of specialised formula reimbursements were obtained from national prescription databases (Tables S1-2, Appendix 22.3). Product information was reported as total quantity of powdered formula reimbursed (in grams) or number of items (tins of specialised formula). (203-208) Total quantity of specialised formula (grams) reimbursed was recorded. Where relevant, the number of items prescribed was multiplied by the product size (usually 400gm formula tin) specified on the database or from the manufacturers website to calculate the total grams of powdered formula reimbursed.

Relevant specialised formula products re-imbursed in England by the National Health Service (NHS) were obtained from hard copy (1991-1997) Prescription Cost Analysis reports held at the British Library, digital reports held at the National Archives (1998-2003) and NHS Digital Prescription Cost Analysis website (2003-2020). (203-205) Prescription data were obtained from Public Health Scotland Community Dispensing Prescription Cost Analysis website (2001-2019), from the Health and Social Care Business Services Organization Prescription Cost Analysis website (2000-2020) for Northern Ireland, and from NHS Wales Prescription Cost Analysis website (2017-2020). (206-208) The total grams of specialised formula reimbursed was calculated by multiplying the quantity reimbursed (items) by the product size. Annual live birth rates were obtained from the national statistics website for each country. (209-214)

12.2.3 Data analysis

The quantity of specialised formula (grams) was converted to volume (litres) to standardise the data, using the British National Formulary (UK). (215) Total reimbursement costs were calculated in pounds sterling and converted to United States Dollars (USD) and euros (EU) using mid-2020 currency conversion rates.

The number of infants expected to consume specialised formula was calculated assuming that 1% of annual live births had a true diagnosis of milk allergy. (1) The proportion of milk-allergic infants receiving formula milk was estimated using national infant feeding survey data. (216,217) The volume of specialised formula consumed was estimated using reference daily formula consumption values of 780ml for 0- to 5.9-month-old and 600ml for 6- to 11.9-month-old infants. (218)

The estimated volume of specialised formula expected to be prescribed was calculated based on a cumulative incidence of 1% of annual live births diagnosed with milk allergy and national infant feeding survey data.

12.3 Prevalence and consultation features for cow's milk allergy overdiagnosis in the BEEP trial cohort

In this study, we analysed a clinical trial birth cohort where milk allergy was formally assessed, in order to estimate the prevalence of CMA overdiagnosis, describe the typical patterns of occurrence and to identify potential risk factors.

12.3.1 Study design

We retrospectively analysed the primary care records of children with a parent-reported reaction to milk during participation in the Barrier Enhancement for Eczema Protection (BEEP) clinical trial. (78) BEEP was a prospective, community-based randomised clinical trial of a skincare intervention in 1394 infants enrolled at birth in England in 2014-2016, who had an increased risk of eczema defined by a family history of atopy (first-degree relative with eczema, allergic rhinitis or asthma). During the BEEP trial, participants were assessed for milk allergy at age 12 months and 24 months with 3 screening questions: "in the last year, has your baby had a reaction to any foods containing cow's milk protein?" (asked at 12 months), "has your child had a reaction to foods containing cow's milk?" (asked at 24 months) and "in the last year, has your child been prescribed special low allergy formula milk?" (asked at 24 months). Children whose parents answered yes to any of the three screening questions underwent formal diagnostic assessment for milk allergy as part of the BEEP clinical trial.

12.3.2 Study procedure

The Nottingham Clinical Trials Unit (NCTU) (who were responsible for the original BEEP clinical trial) created a secure online database with the original BEEP study ID numbers for eligible participants. Three members of our research team had access to this secure database. A standardised letter was designed by the NCTU and included in the database to inform parents about this study and the research team's request for the children's medical records (Appendices 22.6). The purpose of this letter was to allow parents to "opt-out" of the study, which was a condition of ethical approval. A similar standardised letter was designed for the

GP practice the participants were registered to during the BEEP clinical trial. The purpose of this letter was to request a copy of the participant's primary care record.

Letters downloaded from the database were pre-populated with the relevant contact details for each participant from the BEEP trial and saved under their study ID. The database also facilitated a record of the date the letter was sent to the parent/GP under each individual study ID and the response from the parent if they requested to "opt-out". Parents who did not respond within the required 2-week opt-out timeframe were considered to have consented to participation in this study.

Each GP practice was emailed from the study email address to request a copy of the primary care records for those participants whose parents did not opt-out and a copy of the parent letter attached. The email subject included the participant's name and date of birth for ease of identification for GP administrative staff. Each participant's study ID was included in the email to assist the research team on receipt of the primary care records. A single email request containing information for all participants was sent to those practices who had more than one participant registered.

GP practice email addresses were initially identified by online search of the GP practice name and address. The email address was then taken from the GP practice website or facebook page. This initial search strategy proved ineffective and so was modified to searching for GP practice email addresses using the NHS study email account or entering the GP practice code from the NHS Digital ODS portal (https://odsportal.digital.nhs.uk) into the NHS study email. Finally, GP practices were telephoned to ask the most suitable email address to use when no email address could be identified. In some cases, GP practices could not be found (likely due

to these practices closing or merging with other practices since the BEEP clinical trial) and the new GP practice was identified using the BEEP study ID and mother's NHS number.

12.3.3 Data protection protocol

Each research team member was mandated to complete the NIHR Good Clinical Practice online training course in advance of this study. (219) Each research team member responsible for downloading the letters to the parents/GPs emptied their computer downloads folder and recycling bin on a daily basis as these letters contained personal information. A secure study email address was created (imperial.beepstudy@nhs.net) to facilitate GP practices emailing the medical records. Medical records were initially saved to the University of Nottingham Microsoft Teams Onedrive under the study ID number and analysed in Teams rather than downloaded as the initial analysis was undertaken by a University of Nottingham medical student. Records were deleted from Teams once the medical student had extracted the data. All electronic medical records were saved within the BEEP study email address. Subsequent analysis was undertaken on the Children's Clinical Research Facility at Imperial College Healthcare NHS Trust, London on an NHS computer by an Imperial College London medical student. Paper records were stored and analysed at the NCTU, Nottingham and subsequently at the Children's Clinical Research Facility at Imperial College Healthcare NHS Trust, London. I completed further data extraction of both electronic and paper records at the Children's Clinical Research Facility at Imperial College Healthcare NHS Trust, London. The procedures for analysing the records electronically were adopted as the research study commenced in 2021 during the Covid pandemic when remote working was required and were discussed in advance by NCTU team members (L.B and L.W) responsible for the BEEP clinical trial.

12.3.4 Email protocol

An Excel spreadsheet was created to monitor responses from the GP practices for request of medical records using the anonymised study ID numbers. If the GP practice responded that the patient was no longer registered, the new practice was found by a research team member (RJB) using the mother's NHS number via NHS Spine. In some cases, this search strategy confirmed that the mother was still registered at the same GP practice and the practice was re-emailed to confirm the child was still registered at their practice. In cases where the practice could not be located (likely due to a family leaving without registering elsewhere or moving overseas), the original registered practice was emailed again to request any archived medical records. Administrative fees requested by GP practices in this scenario were paid accordingly.

Practices who responded requesting parental consent were emailed advising them to locate their copy of the original parental consent form signed during the BEEP trial. In cases where the GP practice could not locate this consent form, the NCTU contacted the site administrator for the participant's BEEP clinical trial site to provide a copy of the original signed parental consent form to the research team and this in turn was forwarded to the GP practice. In some cases, GP practices contacted the parents directly for more recent consent or forwarded the medical records only after clarification from the research team that the original BEEP parental signed consent included consent for future review of medical records.

Primary care records were email from the GP practices to the study email address (imperial.beepstudy@nhs.net) or the BEEP trial email address (beep@nottingham.ac.uk) and forwarded by the NCTU to the study email address. Some medical records were posted to the NCTU office initially and forwarded to the Children's Clinical Research Facility at Imperial College Healthcare NHS Trust, London. Records were checked initially by a member of the research team (EJ, DM, SP) to check they related to the correct participant and for

completeness. If records were incomplete (for example, missing consultation notes, prescription records or outpatient letters), the practice was contacted again via email or telephone to request the missing information.

12.3.5 Non-responder protocol

The protocol for follow-up was to phone or email the GP practice within 2 weeks of the initial email request for the medical records. Primary care was under immense pressure at the time due to the Covid-19 pandemic and we observed that email was more time-efficient than phone as GP practice phone lines were extremely busy with long waiting times. Phonecalls were limited to clarifying GP practice email addresses.

12.3.6 Outcome data protocol

The research team discussed the datapoints of most interest in advance of data extraction and agreed the definitions of these datapoints as it was a retrospective analysis. (Datasheet dictionary Appendix 22.7) Ten patient records were separately analysed by 2 members of the research team initially to evaluate concordance and discuss any areas of uncertainty. Concordance was assessed using a Kappa score which is a standardised statistical method used to measure consistency of agreement between two data analysers. (220) Kappa is calculated using a standardised formula comparing the observed agreement between two analysers and considers agreement likely to occur by chance. (220) Data analysis could proceed when the kappa score was ≥ 0.8 compared with my own assessments, indicating strong agreement between both analysers. (220) If the kappa score was <0.8, there was a period of training and a further 10 records were evaluated until each researcher had good concordance with my own assessments. This procedure was repeated when a new researcher

joined the team to undertake further data extraction and analysis. All information within the primary care records was analysed which included consultation notes, prescription records and outpatient letters. The datapoints of interest were extracted and recorded on an anonymised Excel spreadsheet under the relevant study ID numbers. Primary care records were analysed independently by three investigators (HA, DM, EJ).

12.3.7 Primary care record data collection and classification

Primary outcome data collected was primary care record of milk reaction and prescription or documented use of a low allergy formula. Other data collected included the most definitive diagnosis given by a healthcare professional, age of child at initial symptoms and diagnosis, nature of initial symptoms and diagnosis, role of person who raised initial concern of a reaction to milk, role of healthcare professionals who diagnosed milk allergy and who prescribed low-allergy formula, indication for low-allergy formula prescription, infant feeding status at diagnosis and at prescription of low-allergy formula, documentation of advice for maternal or infant dietary restriction, presence or absence of dietician review, type(s) of low-allergy formula, age at initial and final prescription, duration, volume and cost of low-allergy formula, other prescribed medicines, and primary care record of any formal diagnostic assessment for CMA. Data was recorded on an anonymised Excel spreadsheet using the Study ID's only as a means of identification.

12.3.8 Cow's milk allergy diagnosis

For this study, true CMA diagnosis was defined as participants confirmed milk-allergic, through formal diagnostic assessment (skin prick testing, oral food challenge and expert panel review) undertaken in the original BEEP study at 2 years old and participants who met

BEEP criteria but were beyond the age 2 years old window for diagnosis in the original study. BEEP criteria for diagnosis of CMA were allergic reaction to cow's milk on supervised oral food challenge at age 2 years or expert panel consensus diagnosis, based on available information from clinical history and skin prick testing undertaken as part of BEEP, and additional information collected from primary care and/or secondary care records and/or supplementary telephone interview with participating families. Expert panel consensus followed published guidance. (78,221) In BEEP, IgE-mediated CMA at age 2 years was diagnosed in 17 participants (1 by oral food challenge and 16 by expert panel consensus). For this study of CMA overdiagnosis, a further 2 participants were identified who had CMA, but didn't have IgE-mediated CMA at the age of 2 years. One participant had non-IgE CMA proven by oral food challenge, and one participant had IgE-mediated CMA which resolved before age 2 years.

12.3.9 Cow's milk allergy overdiagnosis

CMA overdiagnosis was defined in three ways, each analysed separately. For all three evaluations, participants with proven IgE-mediated or non-IgE mediated CMA through BEEP trial assessments were excluded from analysis. The first definition was 'parent-reported milk reaction', categorised as present for participants whose parent/carer answered yes to at least one of the 3 milk allergy screening questions used at 1 and 2 years in the original BEEP clinical trial, shown in Table 14.3 (Section 14.3). The second definition was 'primary care record of milk hypersensitivity', categorised as present for participants whose primary care record included description of a reaction or possible reaction attributed to cow's milk ingestion. The third definition was 'low-allergy formula prescription', categorised as present for participants whose primary care record indicated that a soya, extensively hydrolysed or amino-acid formula had been prescribed.

Participants who did not answer yes to any screening question were considered not to have CMA and those who did not answer any of the screening questions were considered non-responders.

12.3.10 Statistical analysis methodology

Analyses were performed using Statistical Package for Social Sciences (SPSS version 29, IBM). (222) Visual inspection of histograms was used to assess distribution of data and parametric or non-parametric statistical tests were used accordingly.

12.4 International trends in use of specialised formula for managing cow's milk allergy in young children

The overuse of specialised formula to treat CMA has previously been reported for England, (2) but it is unknown if a similar problem exists globally. The aim of this project was to identify prescribing patterns of specialised formula in countries outside the United Kingdom in order to confirm whether milk allergy overdiagnosis is an issue internationally.

12.4.1 Study design

This was a cross-sectional analysis of national prescription databases of reimbursed specialised infant formula. Inclusion criteria were complete national prescription databases for more than one type of specialised formula for at least one year. Exclusion criteria were incomplete national prescription databases, databases without a breakdown of specialised infant formula brands and quantities reimbursed or sold, or regions without public records of reimbursed or sold specialised infant formula volumes. We initially reviewed Euromonitor,

an industry database of global and national infant milk formula sales data, but comprehensive global, regional or national data for specialised formula for managing milk allergy were not available. Colleagues in 23 countries covering 54% of the world population were contacted to assess suitability of national prescription records but only Norway and Australia met the inclusion criteria (Appendix 22.2). We reviewed breastmilk substitutes marketed for children with cow's milk allergy in each country and excluded food supplements and products designed for malabsorption or eosinophilic oesophagitis from our analysis (Tables S1-2, Appendix 22.3).

The primary outcome assessed was volume of specialised formula prescribed to children under 1 year old in each country. Secondary outcomes were the annual total cost of specialised formula reimbursement, and the comparison between actual volumes re-imbursed and expected volumes estimated according to a 1% incidence of CMA and based on national infant feeding data. (1)

12.4.2 Data collection

Data collection was undertaken in Australia by a BSc medical student (Ms. Shriya Mehta) with support and advice from Prof. Dianne Campbell (Professor of Allergy, University of Sydney) who provided advice on interpretation of the Australian data. Data collection was undertaken in Norway by a masters student (Ms. Karoline Fagerli Arntsen) under the supervision of Dr. Melanie Rae Simpson (postdoctoral researcher, Norwegian University of Science and Technology).

The two variables collected from national databases were quantity and cost of specialised formula reimbursements, obtained from national prescription databases. (Table S1-S2;

Appendix 22.3) Total quantity of specialised formula (grams) reimbursed was recorded. Where relevant, the number of items prescribed was multiplied by the product size (usually 400gm formula tin) specified on the database or from the manufacturers website to calculate the total grams of powdered formula reimbursed.

Annual live birth rates and national formula-feeding rates were collated from relevant public databases, in order to estimate expected quantity of specialised formula consumption.

For Norway, products reimbursed for infants aged 0-11 months and 12-23 months old were requested from the Norwegian Directorate for Health and reported as number of items. The unique number of users of these specialised formula products was also collected. The total grams of specialised formula reimbursed was calculated by multiplying the quantity reimbursed (items) by the product size (grams). Annual live birth rate was obtained from Statistics Norway. (223)

For Australia, products reimbursed under the Pharmaceutical Benefits Scheme (PBS) and Repatriation PBS were obtained from the Services Australia website. (224) The prescription data was reported as number of prescriptions, which was multiplied by the maximum number of items claimed per prescription to calculate the total grams of powdered formula reimbursed. Annual live birth rates were obtained from the Australian Bureau of Statistics website. (225)

12.4.3 Data analysis

Data was analysed in the same was as for the United Kingdom data, described in Section 12.2.3. The quantity of specialised formula (grams) was converted to volume (litres) to standardise the data, using the manufacturer recommended weight-to-volume for preparation

of liquid formula feeds, in grams per litre (Norway and Australia). (215) Total reimbursement costs were calculated in the local currency and converted to United States Dollars (USD) and euros (EU) using mid-2020 currency conversion rates.

The number of infants expected to consume specialised formula was calculated assuming that 1% of annual live births were diagnosed with milk allergy. (1) The proportion of milk-allergic infants receiving formula milk was estimated using national infant feeding survey data. (226-231) The volume of specialised formula consumed was estimated using reference daily formula consumption values of 780ml for 0- to 5.9-month-old and 600ml for 6- to 11.9-month-old infants. (218)

The estimated volume of specialised formula expected to be prescribed was calculated based on a cumulative incidence of 1% of annual live births diagnosed with milk allergy and national infant feeding survey data. (Table S3, Appendix 22.4)

12.5 Risk factors for milk allergy overdiagnosis in the BEEP cohort

12.5.1 Study design

We undertook a secondary analysis of data from the BEEP clinical trial to assess if there were particular participant characteristics associated with CMA overdiagnosis. We further explored the relationship between general practice prescribing behaviours, practice socioeconomic status and practice milk allergy guidelines with CMA overdiagnosis in the BEEP cohort to understand if practice features were associated with CMA overdiagnosis. Participant characteristics and sociodemographic data were collected as part of the original BEEP clinical trial. The research team agreed 9 participant risk factors which could be associated with CMA overdiagnosis, based on literature review and clinical experience.

These risk factors included: maternal age and ethnicity, antenatal use of antibiotics, family history of atopy, first child, infant feeding, maternal psychological state and health state at birth using and participant socioeconomic status. Maternal psychological state and health state was assessed using a standardised measure of health-related quality of life (EQ-5D) and entailed a questionnaire completed by the mother on enrolment in the BEEP clinical trial.

12.5.2 Participant-level risk factors data collection

The extracted primary care record data was merged with the original BEEP clinical trial characteristics and sociodemographic data and new anonymised study IDs created to protect the identity of the participants whose data had been extracted. This resulted in a new merged Excel sheet which included anonymised data for the 1394 BEEP participants to facilitate risk factor data analysis.

12.5.3 GP practice-level data collection

Practice-level prescribing data for practices in England in 2014 were extracted for specialised low-allergy formula, junior adrenaline auto-injectors (AAI) and anti-reflux medications used in infants and young children. Data were extracted from NHS Business Service Authorities (NHSBSA) using R code (Supplementary material). (232-234) Data for 2014, prior to birth of the first BEEP study participants, were chosen to ensure BEEP participant prescribing data were not included. Data were linked to the individual BEEP participant practice codes. Total quantity (grams) of low-allergy formula was converted to volume (litres) using British National Formulary for children (BNFc) weight-to-volume conversion rates. ((215) AAI quantity was determined by number of items prescribed. Specific anti-reflux medications, formulations and doses used for managing reflux symptoms in infants were identified through

a survey of primary and secondary care practitioners with an interest in allergy and gastroenterology, and total items prescribed was calculated. Since most of these anti-reflux medications are also used beyond the first two years of life, we separately analysed quantity of Alginate infant sachets (Gaviscon®) infant prescribing (Appendix 22.13). Gaviscon® infant is only indicated for use in the first two years of life. Practice antibiotic prescribing data were extracted from NHSBSA Catalyst public database (235) as an indicator of practice over-prescribing, based on previous evidence that antibiotics are over-prescribed in primary care. (236,237) Total antibiotic items and antibiotic items per Specific Therapeutic group Age-Sex Related Prescribing Unit (STAR-PU) were recorded from Catalyst. STAR-PU is an indicator which adjusts for age and gender distribution within a practice population for antibiotic prescribing. (235,238,239)

Other practice-level data extracted were decile of English index of multiple deprivation 2019 based on the GP practice postcode, as a marker of practice socioeconomic status; practice demographics from the NHS Digital patient registry; Clinical Commissioning Group (CCG) characteristics from the Office for National Statistics database; and a categorisation of local CCG milk allergy guideline recommendations in relation to a recent Delphi consensus study (Appendix 22.13). (141,240-243)

12.5.4 Statistical analysis methodology

Logistic regression was used to explore the association between participant level risk factors and CMA overdiagnosis. This is a commonly used statistical method to explore individual exposures on an outcome and was deemed most appropriate for this dataset. Multivariate logistic regression analyses was used to find the risk factors most strongly associated with CMA overdiagnosis, using a backward elimination procedure with variables remaining in the model at each step if p-value <0.10. This method was chosen as it eliminated those risk

factors which were least associated with the outcome at each step, allowing only the strongest associations to be identified in the final step of the model. Alternative methods were not used, due to the lack of prior hypothesis about which of the studied risk factors was likely to be most strongly associated with CMA overdiagnosis. Mixed-effects logistic regression with complete case analysis was used to assess practice-level risk factors and adjust for clustering of participants within practices. Sensitivity analyses were conducted substituting antibiotic items for antibiotic items/STAR-PU and using multiple imputation for logistic regression to account for missing data. Results from regression analyses are summarised as odds ratio (OR) and 95% CI. A p-value <0.05 was considered statistically significant. Statistical tests for significance between confirmed CMA and CMA overdiagnosis included Mann-Whitney U test for non-parametric data, Chi-squared and Fishers exact test for categorical data and we used Benjamini-Hochberg method to control the false discovery rate at 5%. (222,244) Benjamini-Hochberg is a standardised statistical method to control for the possibility that statistically significant p-values may occur by chance and so reduces the risk of false-positive results in the data analysis.

12.5.5 Sensitivity analyses for logistic regression

Sensitivity analyses were performed for logistic regression analysis of associations between participant features and CMA overdiagnosis. Due to a relatively large amount of missing data for EQ5D measurements in the BEEP trial dataset (Tables S10-S12, Appendix 22.11), we repeated multivariate logistic regression analyses excluding EQ5D (Tables S13-S15, Appendix 22.11). We also undertook multiple imputation analysis for variables with significant missing data (Tables S16-S18, Appendix 22.11). For logistic regression analysis of associations between practice characteristics and CMA overdiagnosis, we undertook a sensitivity analysis where antibiotic items per STAR-PU was substituted in place of total

antibiotic items per 1000 practice population, in order to understand whether practice population demographic structure was likely to influence relationships seen between antibiotic prescription rates and CMA overdiagnosis (Tables S21-S24, Appendix 22.14).

12.5.6 Clustering

The mixed models function within SPSS was used to adjust for clustering within practices when assessing associations between practice-level characteristics and CMA overdiagnosis. This method employed generalised linear mixed models using GP practice code to identify clusters (Tables S21-S24, Appendix 22.14).

12.5.7 Multiple imputation for missing data

Multiple imputation details are reported following previous published guidance. (245) Data were missing in the BEEP cohort for the predictor and outcome variables of interest shown in Table S10, Appendix 22.11. Table S11 (CMA overdiagnosis) and Table S12 (confirmed CMA) in Appendix 22.11 outline the number of complete and missing values for each predictor and outcome variable. Participants with missing predictor variables were broadly similar to participants with complete predictor variables in terms of the predictors and outcomes. Although complete case analysis excluding the missing values can be undertaken, it reduces statistical power, and the risk of bias is reported with missing values approaching 30%. (246) Multiple imputation is suggested as a method of managing missing data. (245,247) Multiple imputation was performed using the automatic multiple imputation function in SPSS. The imputation method was fully conditional specification, Markov chain Monte Carlo (MCMC) which is suitable for data with a random pattern of missing values. The following predictor variables were imputed into the model: EQ5D health state at baseline

(answered antenatally or shortly after birth), EQ5D anxiety at baseline (answered antenatally or shortly after birth), Infant feeding status from birth to 6 months, Decile of English Index of Multiple Deprivation 2015, Maternal use of antibiotics in pregnancy. The following outcome variables were imputed into the model: Parent reported reaction to milk, Primary care record of milk reaction, Primary care record of low-allergy formula prescription. It has been suggested that a high number of imputations should be performed to improve statistical power. (248) One hundred datasets were imputed for both predictor and outcome variables, to reduce possible attenuation of the association by only imputing for missing predictor variables (Tables S16-S18, Appendix 22.11). (245,248) The percentage of participants in the imputed and complete dataset were similar for each of the 3 CMA overdiagnosis outcomes (Table S10, Appendix 22.11). Logistic regression analysis was performed on the imputed dataset in the same manner as the complete dataset (Tables S16-S18, Appendix 22.11). Multiple imputation was used for the missing participant-level characteristics only as missing data for practice-level characteristics was minimal and considered to be 'missing completely at random' (n=19/1375) (Tables S22-S24, Appendix 22.14).

12.6 Delphi consensus study for the detection and management of milk allergy in children

Current milk allergy guidelines or their authors often report financial ties to the formula industry raising concerns that this contributes to milk allergy overdiagnosis. (2,3) Diagnosing milk allergy in children can be difficult, particularly non-IgE milk allergy which lacks an objective test and relies on clinical interpretation of symptoms. No non-conflicted milk allergy guidance currently exists. This study aims to develop independent guidance for detection and management of milk allergy, and to compare if guidance developed by

multidisciplinary experts without commercial influence and with parental involvement differs from current conflicted guidelines.

12.6.1 The Delphi method

A Delphi consensus method was used due to the lack of scientific certainty in this area. (201,202,249-251) We designed a detailed study protocol following an initial literature search of Delphi consensus methods (Appendix 22.15). (201,202,249-251) We included 2 rounds of anonymous consensus building to minimise potential drop-out of participants, followed by an online meeting between January and July 2021. (201,202,249-251) We followed the Conducting and REporting DElphi Studies (CREDES) guidance for reporting of this Delphi study (Appendix 22.16). (252,253)

12.6.2 Participants

Geographically-diverse expert participants were identified through literature search of Medline and Embase using the MeSH term 'Milk Hypersensitivity', contacting experts affiliated with relevant allergy and infant feeding professional organisations such as the World Allergy Organization, World Health Organisation (WHO) and International Board Certified Lactation Consultants (IBCLC) and by asking enrolled experts to nominate other experts meeting the inclusion criteria.

Inclusion criteria were clinical and/or research expertise in general practice, dietetics, infant nutrition, health visiting, midwifery, lactation support, general paediatrics, paediatric allergy, paediatric gastroenterology, paediatric dermatology, paediatric allergy nursing or food allergy and a good command of the English language. Exclusion criterion was a recent conflict of interest related to the formula (breastmilk substitute) industry, i.e. a conflict related to activities in the previous three years or anticipated to occur in the next year, similar to the

Cochrane Conflict of Interest policy. (59,254) We defined relevant conflict of interest as: personal financial support for speaking, travel, consultancy or other activities including research grants, employment or institutional support from a company that develops or markets breastmilk substitutes. Each potential expert participant's publication record was examined for a relevant conflict of interest. Not all enrolled participants had publication records as their expertise was entirely clinical. All enrolled participants were asked to confirm they had no relevant conflict of interest as part of the written informed consent process and again when answering the Round 1 Delphi survey.

Identified experts were invited to participate in the Delphi study via an individual invitation email to maintain participant anonymity, along with the participant information leaflet and study protocol (Appendices 22.13, 22.15-22.16). Email invitation was chosen to encourage participation and reduce any additional administrative burden of this study, which was mainly completion of questionnaires.

12.6.3 Study procedure

A literature search of Medline and Embase databases focussing on milk allergy epidemiology, guidelines and overdiagnosis defined the scope of the study and identified three key questions for the Delphi consensus study:

1. What aspects of milk allergy detection are important to ensure the condition is not overdiagnosed or underdiagnosed?

2. In a fully or partially breastfed child who has milk allergy, what aspects of management are important to ensure breastfeeding is not undermined?

3. What aspects of milk allergy management are important to prevent unnecessary use of specialised formulas such as amino acid formula, extensively hydrolysed formula, soya or rice-based infant formula?

The initial Delphi Questionnaire addressed these three key questions and was designed by the research team based on literature review, relevant clinical experience and interview of individual parents to provide insight into the aspects of milk allergy diagnosis and management that are important to parents. Formal diagnosis of milk allergy through oral food challenges and skin prick testing was considered beyond the scope of this study and so the questionnaires concentrated on the clinical interpretation of children presenting with symptoms that concern parents and which might be interpreted as milk allergy by healthcare practitioners.

Delphi questionnaires were piloted among research team members and three independent assessors with expertise in survey methodology, general practice and allergy.

The Delphi method involved 2 rounds of anonymous electronic survey using Qualtrics XM electronic software (Qualtrics, London, England). Each survey round lasted three weeks. Participants ranked the importance of each statement using a 9-point scale (Table 12.2). (255) In Round 1, participants were invited to comment on the survey statements and to suggest modifications or new statements. One-to-one calls were made with participants by the research team to better understand their views where participant responses were unclear or it was apparent that participants failed to fully understand a question. In Round 2, no new statements could be proposed. For each round, the research team applied the classification of consensus as “Essential”, “Recommended” and “No Consensus” to the participant scored statements (Table 12.2). (153)

Table 12.2. Definition of consensus

	Description	Definition
Essential	Consensus that statement is essential for the safe detection or management of milk allergy	≥70% participants scoring as 7-9 and <15% participants scoring 1-3
Recommended	Consensus that statement is recommended for the safe detection or management of milk allergy	≥70% participants scoring as 4-6 and <15% participants scoring 1-3
Statement excluded	Consensus that statement is not important for the safe detection or management of milk allergy	≥70% participants scoring as 1-3 and <15% participants scoring 7-9
No consensus	Uncertainty about importance of the statement	Anything else

Consensus classification used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) method. (153,255) A score of 1-3 indicates that the participant considers the statement is not important for the safe detection and management of cow's milk allergy; a score of 4 to 6 is 'important but not critical' and a score of 7 to 9 is 'critical'.

In the second round, comments and scoring from the first round were included in the questionnaire, with comments attributed to each participant's field of expertise while retaining anonymity. Following the two survey rounds, provisional recommendations were sent for comments from external experts and the parent panel, described below. The summary recommendations, external comments received and outstanding issues which had not yet reached consensus were then emailed to all participants.

A consensus meeting was held to resolve any areas where consensus had not yet been achieved, chaired by an independent, non-voting paediatric allergist. Participants unable to attend the consensus meeting were interviewed individually by the research team prior to the meeting so their views could be represented. At the consensus meeting, participants discussed statements where no consensus had yet been reached and were given the opportunity to

comment on statements which had reached consensus. The meeting was recorded and carefully reviewed by the research team in order to update the recommendations. Flowcharts were developed by the research team based on the final consensus recommendations and piloted by the participants, independent paediatric allergists, community and hospital-based dietitians, general practitioners, health visitors and community midwives resulting in minor modifications. Flowcharts and the study recommendations were subsequently finalised by the study participants. See Appendix 22.19 for detailed responses from the Delphi process.

12.6.4 External consultation

The views of experts excluded from the study due to conflicts of interest were represented by inviting five authors of high profile existing guideline to comment on the scope of the study and the draft recommendations prior to the consensus meeting. (85,89,116,256) Experts provided written feedback on the provisional scope, key questions and protocol prior to initiation of the first Delphi round, and again provided written feedback on the provisional recommendations prior to the consensus meeting. They were not invited to attend the consensus meeting, but their feedback was summarised and included in the information sent to study participants prior to the consensus meeting (Appendix 22.19).

12.6.5 Parental involvement

We invited 7 mothers with a range of experiences related to cow's milk allergy diagnosis and management from the practices of the research team to form an anonymous parental panel. Prior to the first Delphi round, the panel were individually invited to comment on the scope of the study and suggest additional aspects for healthcare professionals to consider for the safe detection and management of milk allergy. They were also emailed a copy of the initial draft of the first-round survey and follow-up one-to-one telephone interviews were conducted with four panel members. Prior to the consensus meeting, we invited each mother to

comment on the provisional recommendations by email and one-to-one telephone interviews. We specifically asked the panel whether the recommendations captured all the early signs of milk allergy in their child, and whether the role of healthcare practitioners in providing support, diagnosis and management including maternal dietary advice and breastfeeding promotion was fully addressed. Parental feedback was summarised for the consensus meeting and two parent panel members attended the Consensus meeting and contributed to discussions (Appendix 22.19).

12.7 Ethics and consent

Ethics approval for the Delphi consensus study was given by the Imperial College Research Governance and Integrity Team (reference 21IC6572).

Ethical approval for the BEEP milk allergy study was granted by the West Midlands Ethics Committee, UK (14/WM/0162). (Appendix 22.8)

13 National trends in use of specialised formula for managing cow's milk allergy in young children

13.1 Introduction

Cow's milk allergy affects up to 1% of children before age two years. (1) Most infant formula is derived from cow's milk, so for infants with milk allergy who are not fully breastfed, specialised formula products have been developed as alternatives to cow's milk-based formula.

Increasing specialised formula use has been interpreted as evidence for milk allergy overdiagnosis, leading to use of specialised formula for managing common infant symptoms. (2,3,50) This is because there is little evidence in high-income countries for a change in milk allergy incidence to explain rises in specialised formula prescription. (2) While specialised formula is reasonably well tolerated by most infants, and supports infant nutrition and growth, there are significant differences from standard cow's milk based infant formula or human breast milk. (115,257) In specialised formula products, the lactose naturally present in breastmilk or cow's milk is partially or completely replaced by alternative carbohydrate sources, often free sugars such as glucose syrup. (115) High free sugars intake is an important risk factor for obesity and dental decay, and a major public health issue. (179) Indeed, there is some direct evidence that prolonged consumption of glucose syrup based formula during infancy is associated with early-onset obesity. (192) Thus, it is conceivable that unnecessary use of specialised formula may have important public health consequences that have not been studied to date. (115,179,258,259)

We therefore undertook a cross-sectional survey of national prescription databases recording reimbursement of specialised formula for managing formula-fed infants with cow's milk

13.2 Methods

A detailed description of methods is outlined in Section 12.2. In brief, we analysed trends in community prescription of specialised formula for managing cow's milk allergy in infants in the United Kingdom. We evaluated changes in prescribing over time, including comparison with expected consumption rates based on national infant feeding data and an assumed cow's milk allergy rate of 1%. We identified publicly available electronic data but also searched paper library records for historical community prescribing, and included all available data up to 2020. Data availability varied by product type and nation.

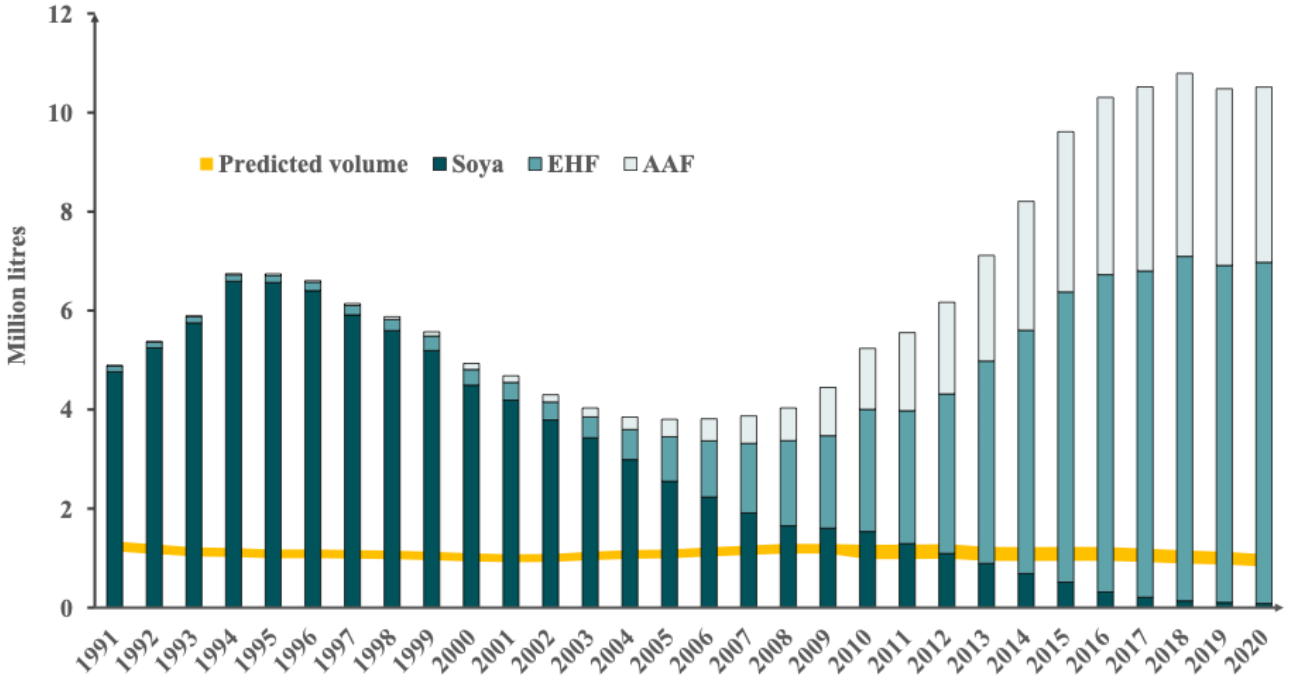
13.3 Results

Community prescription data for children under 1 year old were available from England (1991-2020), Scotland (2001-2019), Northern Ireland (2000-2020), and Wales (2017-2020). Data was also retrieved for children over 1 year old in England from 2006-2020. Data extracted was for extensively hydrolysed formulas (EHF), amino-acid formulas (AAF) and soya formula. The specific eligible products available for public reimbursement in each country are summarised in Table S1, and products excluded from analysis are listed in Table S2. (Appendix 22.3)

Trends in volume of reimbursed specialised formula

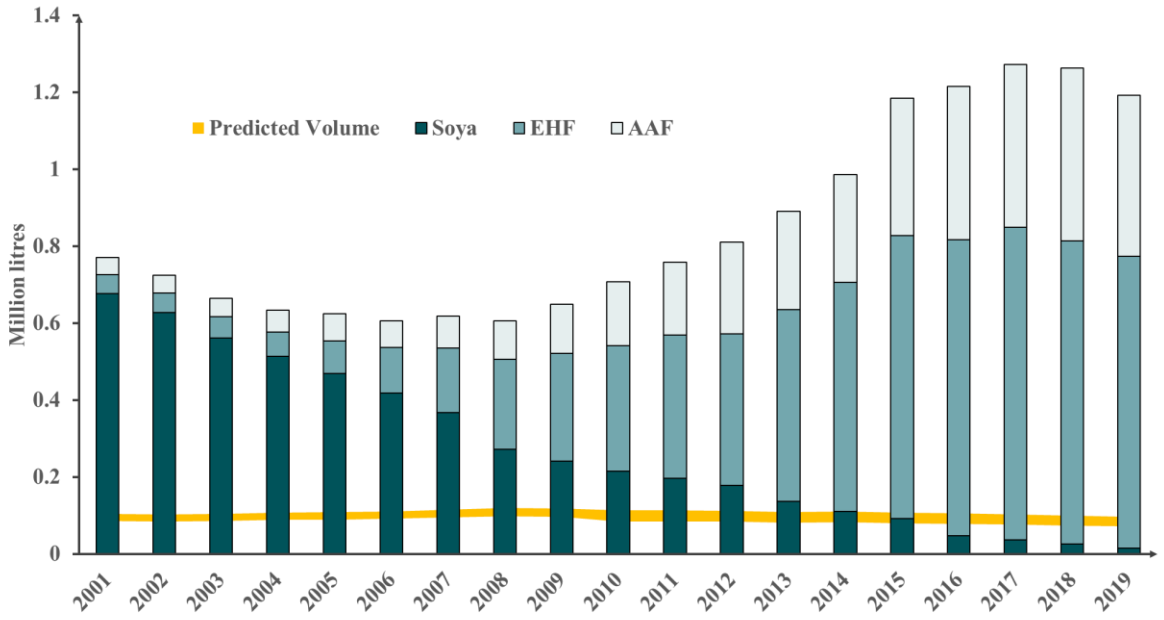
Data for specialised formula products marketed for infants less than one year in England are shown in Figure 13.1. Prescribed volumes rose 2.8-fold between 2007 and 2018 without any subsequent rise. This represents a 4.9-fold increase in EHF and a 6.7-fold increase in AAF for those years, accompanied by a decline in soya formula. There was an earlier rise in volumes of reimbursed soya formula, peaking in 1994 at 5.5 to 6.4 times greater than expected volume. In 2020, soya represented less than 1% of reimbursed specialised formula volumes, but the total volume of reimbursed specialised formula was 9.7 to 12.6-fold greater than expected. Data for other regions of the United Kingdom showed similar trends (Figures 13.2 to 13.4). Volumes of reimbursed specialised formula marketed for children over one year in England increased to 2019, mainly AAF, without a further rise in 2020, at less than one-tenth the volumes for infants under one year (Figure 13.5).

Figure 13.1. Volume of reimbursed specialised infant formulas for under 1 year olds with milk allergy in England.



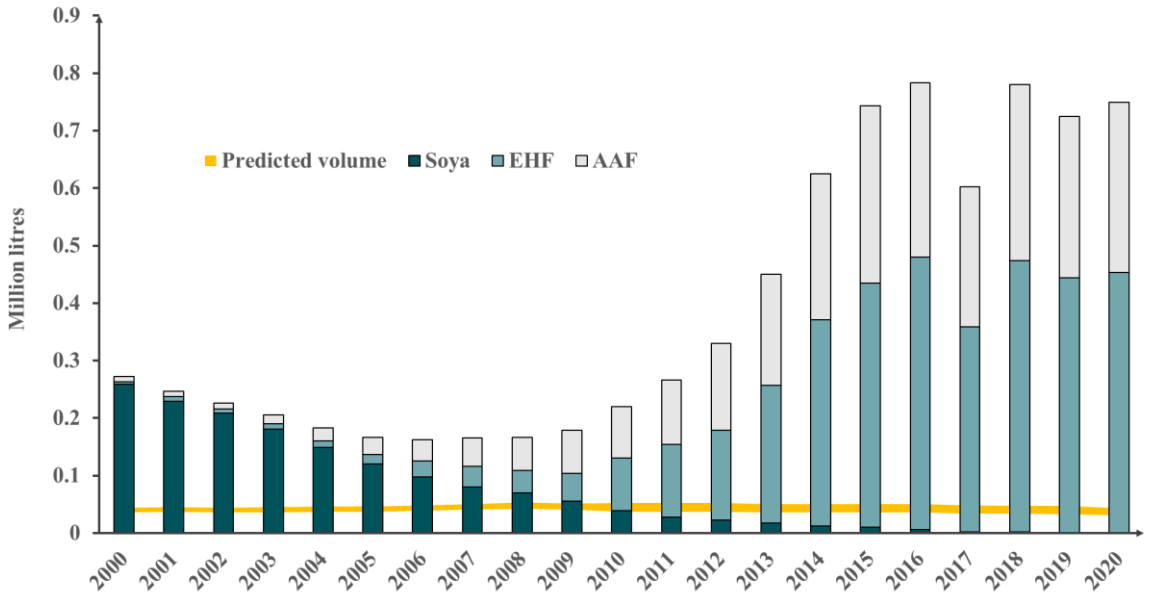
Data on the number of community prescriptions of reimbursed powdered amino acid formulas (AAF), extensively hydrolysed formulas (EHF) and soya formula products were obtained from the annual England National Health Service Prescription Cost Analysis reports. Volumes were calculated using product details in the British National Formulary for Children. Predicted volumes are the lower to upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2005 and 2010 United Kingdom National Infant Feeding Survey and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (216-218) In 2020, prescribed volumes were an estimated 9.7 to 12.6-fold higher than expected.

Figure 13.2. Volume of reimbursed specialised infant formulas for under 1-year olds in Scotland.



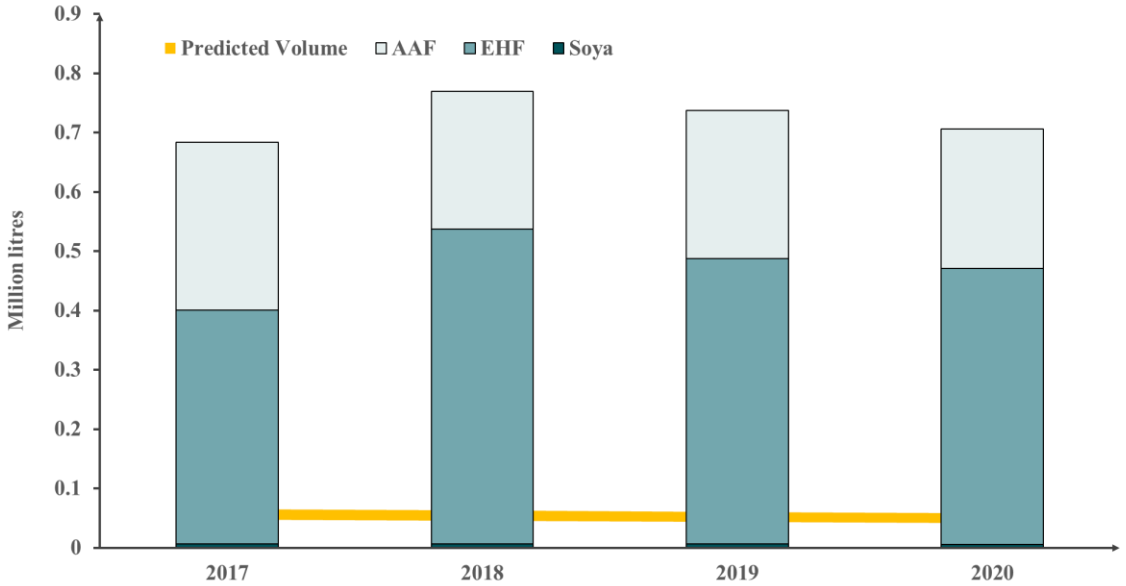
Data on the number of community prescriptions of reimbursed powdered amino acid formulas (AAF), extensively hydrolysed formulas (EHF) and soya formula products were obtained from the annual Public Health Scotland Community Dispensing Prescription Cost Analysis reports. Volumes were calculated using product details in the British National Formulary for Children. Predicted volumes are the lower to upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2005 and 2010 United Kingdom National Infant Feeding Survey (Table S3) and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (216-218) In 2019, prescribed volumes were an estimated 10.0 to 13.4 fold higher than expected.

Figure 13.3. Volume of reimbursed specialised infant formulas for under 1-year olds in Northern Ireland.



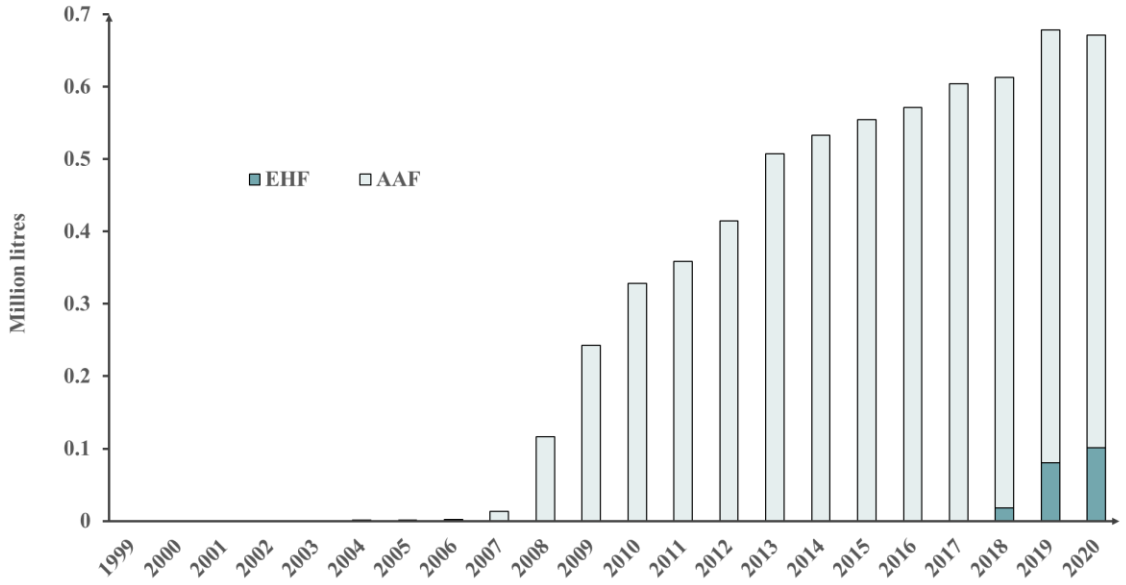
Data on the number of community prescriptions of reimbursed powdered amino acid formulas (AAF), extensively hydrolysed formulas (EHF) and soya formula products were obtained from the annual Health Services Executive Business Services Organization Prescription Cost Analysis reports. Volumes were calculated using product details in the British National Formulary for Children. Predicted volumes are the lower to upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2005 and 2010 United Kingdom National Infant Feeding Survey (Table S3) and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (216-218) The method of reporting prescription quantities changed part-way through 2017, which is likely to explain the inaccurate volume estimate in 2017. In 2020, prescribed volumes were an estimated 17.3 to 24.4 fold higher than expected.

Figure 13.4. Volume of reimbursed specialised infant formulas for under 1-year olds in Wales.



Data on the number of community prescriptions of reimbursed powdered amino acid formulas (AAF), extensively hydrolysed formulas (EHF) and soya formula products were obtained from the monthly NHS Wales Prescription Cost Analysis reports. Volumes were calculated using product details in the British National Formulary for Children. Predicted volumes are the lower to upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2005 and 2010 United Kingdom National Infant Feeding Survey (Table S3) and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (216-218) In 2020, prescribed volumes were an estimated 12.1 to 16.9-fold higher than expected.

Figure 13.5. Volume of reimbursed specialised infant formulas for over 1-year olds in England.

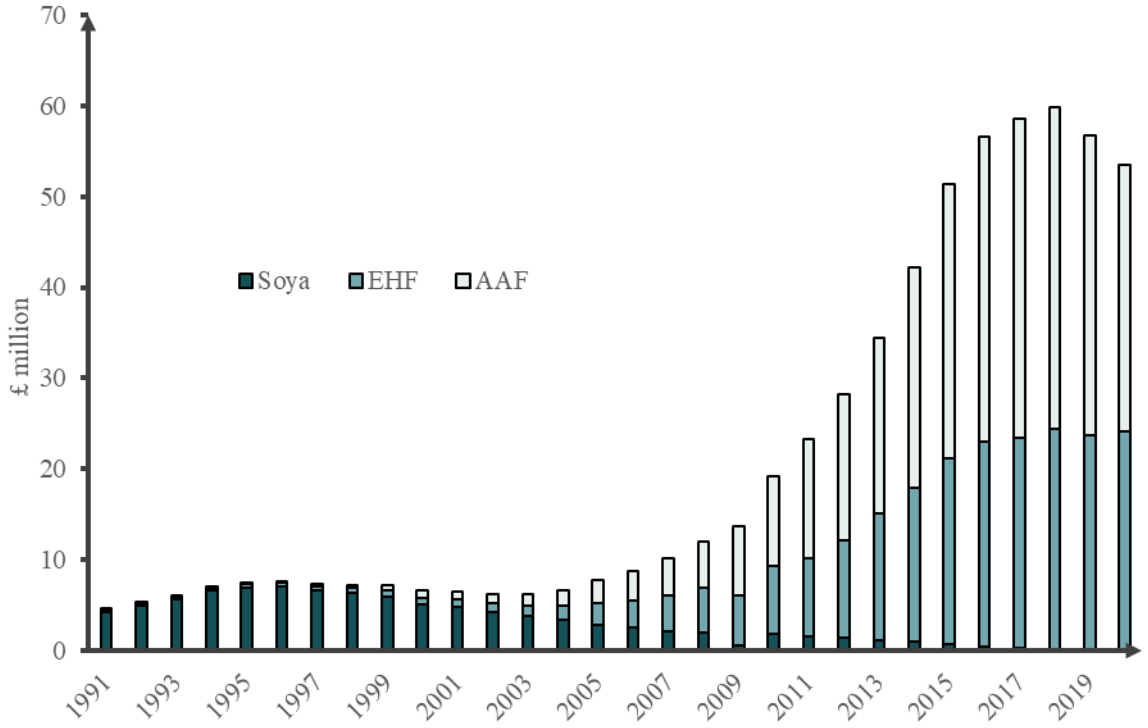


Data on the number of community prescriptions of reimbursed powdered amino acid formulas (AAF), extensively hydrolysed formulas (EHF) were obtained from the annual England National Health Service Prescription Cost Analysis reports. Volumes were calculated using product details in the British National Formulary for Children. The only products specifically marketed for over 1 year olds in England were AAF and EHF, and no products were marketed for this age group prior to 1999.

Trends in expenditure on reimbursed specialised formula

Data for expenditure on specialised formula products marketed for infants less than one year in England are shown in Figure 13.6. Prescription costs rose from £4.6 million per annum in 1991 to £59.8 million in 2018 with a fall to £53.5 million in 2020. At the peak of soya formula reimbursement in 1994, the total cost of specialised formula was £7.1 million. AAF accounted for 55% of expenditure in 2020. In 2020 England's public expenditure on specialised formula for managing milk allergy equated to £91 (US$117; €103 euros) per infant born in that year.

Figure 13.6. Total reimbursement cost of specialised infant formula for under 1 year olds in England.



Data on the reimbursement costs (in UK pounds, £) of all amino acid formulas (AAF), extensively hydrolysed formulas (EHF), and soya formulas marketed for infants under age 1 year with cow's milk allergy were obtained from the annual England National Health Service's Prescription Cost Analysis reports.

13.4 Discussion

In this national survey we identified comprehensive, publicly available databases of specialised formula prescription for infants with cow's milk allergy in the United Kingdom. In all four regions, there was a marked rise in volumes of specialised formula reimbursed by public health systems in the early 21st century, in the absence of any concurrent evidence for a rise in milk allergy. (122) The data suggest that by 2020 there was 10-fold excess use of specialised formula for managing milk allergy in the United Kingdom. An increase in specialised formula prescriptions in England was reported in 2018 and 2020. (2,3) However, this is the first comprehensive evaluation of trends in the United Kingdom. AAF prescriptions in 2012 were 1.4-1.9 fold for England whereas by 2020 AAF rates were up to 4-fold higher than expected in England. In the last year analysed, the percentage of specialised formula volume prescribed to infants under 12 months old comprising amino acid formula was 34% for England in 2020, 40% for Northern Ireland in 2020, 33% for Wales in 2020, and 34% in Scotland in 2019. Although EHF has been available since the 1940s, soya formula appears to have been the dominant specialised formula in the late 20th century in England. In the late 1990s, concerns were raised about phytoestrogens in soya formula affecting endocrine development, especially thyroid and reproductive functions. (260) These concerns led national governments to recommend against use of soya formula in the early years of the 21st century, which likely accounts for the decline in soya formula prescriptions and replacement with EHF and AAF. (261)

Levels of specialised formula prescription now significantly exceed expected levels in the UK. The long-term consequences of this change in early nutrition for a significant minority of the population are unknown. Standard infant formula products derive most of their sugar content from lactose naturally present in cow's milk, which is not considered a free sugar. Although free sugars are added to standard formula products, especially those marketed for

children aged over one year, free sugars are present in higher quantities in specialised formula products, especially AAF, than in standard infant formula. (115) A young infant drinking 780mls per day of AAF might consume up to 55g of dried glucose syrup per day, which compares to United Kingdom Department of Health and Social Care recommended upper limits of 14g free sugars per day for children aged 2 to 3 years and 30g per day for adults. (179) Free sugars intake has been linked with dental decay and obesity, which has led the World Health Organization (WHO) and others to recommend limiting total free sugars consumption for both children and adults. (115,179,181,188,189)

Limitations

This study is limited to data analysis of public health system reimbursements from community prescriptions only and does not include direct to consumer, non-reimbursed sales, hospital prescriptions or private practice prescribing. Our calculations are based on some estimations which may attenuate the findings. For example, although the most robust estimate of challenge-proven milk allergy incidence in the first two years is less than 1%, (1) studies using less stringent criteria for diagnosing milk allergy tend to report higher rates. (262) We also assumed that formula feeding rates and volumes would be similar in infants with milk allergy to the general population, and there is little empirical evidence for or against this assumption. We have assumed that milk allergy overdiagnosis is mainly responsible for this observed increase in use of specialised formula. It is possible that there has been an increase in milk allergy incidence, as recently reported in one Chinese study. (263) However, epidemiological studies do not suggest any increase in milk allergy in England in recent decades. (122)

Conclusion

This study provides evidence of increased and excessive prescription of specialised formula for managing cow's milk allergy in formula-fed infants in the United Kingdom. The data show an important shift in early childhood nutrition which is likely to increase early years free sugars consumption and may promote the development of non-communicable disease.

14 Prevalence of milk allergy overdiagnosis in the BEEP trial cohort

14.1 Introduction

Cow's milk allergy (CMA) affects about 1% of children under 2 years. (1) In England and the USA, prescription rates of specialised low-allergy formula are higher than expected, suggesting CMA overdiagnosis. (2,196) The consequences of unnecessary exposure of large numbers of non-allergic infants to prescription formula designed to manage CMA are unknown. (110,115,179,196) Low-allergy formulas partially or completely substitute lactose with alternative carbohydrate sources, such as glucose syrup and maltodextrin, and these 'free sugars' may carry risks to child health and development. (115,188,189,192,196) The World Health Organisation and other public health bodies recommend limiting exposure to free sugars due to concerns about obesity and dental health. (179,264) Glucose syrup based infant formula provision was associated with increased early childhood obesity in the USA. (192) Other potential consequences of CMA overdiagnosis include resource waste, maternal psychological distress and early cessation of breastfeeding. (137) Milk allergy overdiagnosis has not been well-characterised and appears to be increasing worldwide. (81,196) In this study, we used a clinical trial birth cohort with prospective evaluation of CMA diagnosis to describe prevalence of CMA overdiagnosis. (78)

14.2 Methods

We analysed data from 1394 children born in England in 2014-2016 (BEEP trial, ISRCTN21528841). Participants underwent formal CMA diagnosis at ≤2 years. CMA overdiagnosis was defined in three separate ways: parent-reported milk reaction; primary care record of milk hypersensitivity symptoms; and primary care record of low-allergy formula prescription. A detailed description of methods is outlined in Section 12.3.

14.3 Results

Data collection is summarised in Figure 14.1. In BEEP, 214 participants reported a milk reaction and/or low-allergy formula prescription. Primary care records were successfully obtained and analysed for 171/214 (80%) of these. Nineteen of 214 had confirmed CMA, 18 IgE-mediated and 1 non-IgE mediated (Table 14.1). (78)

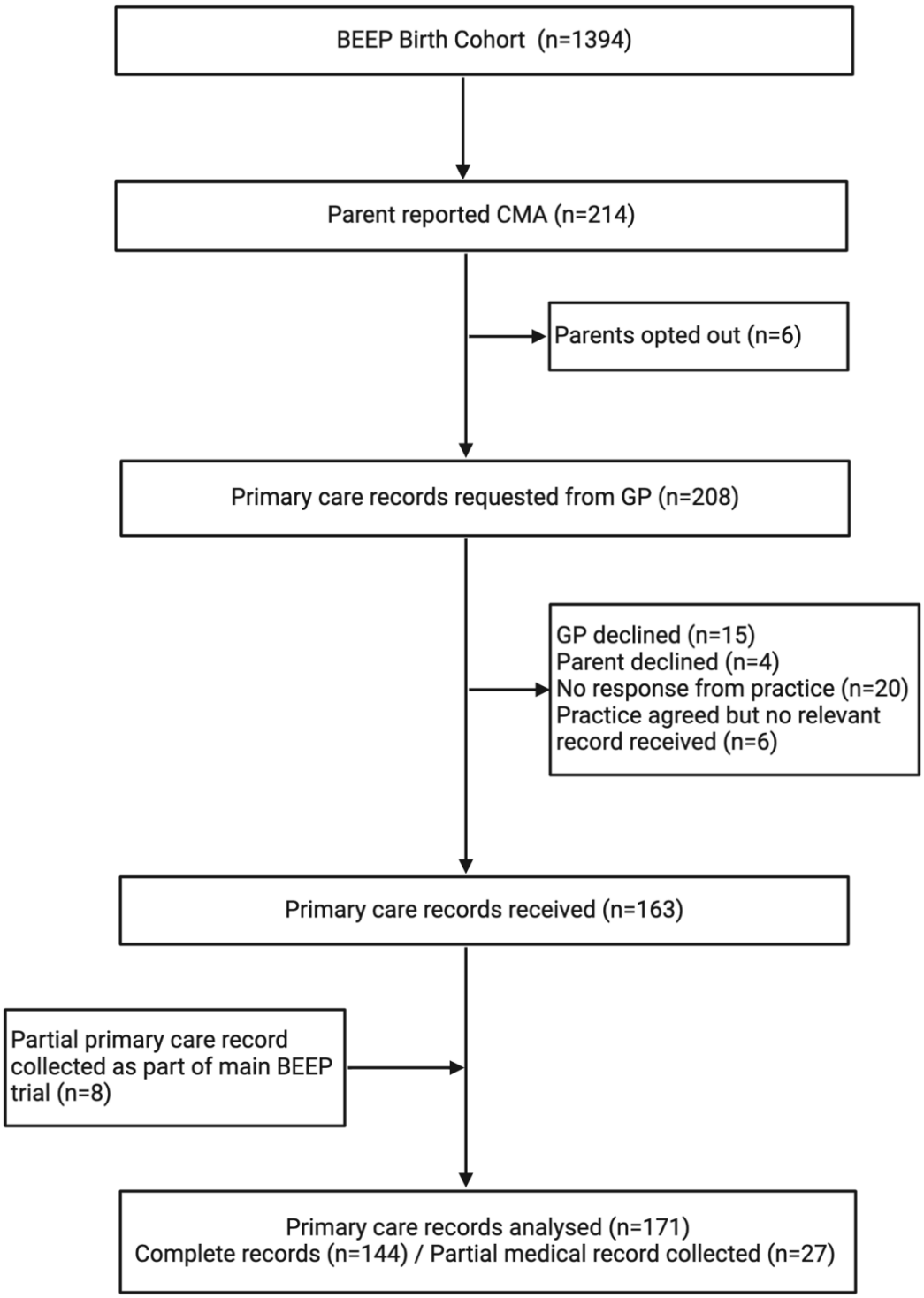


Figure 14.1. Flowchart of data collection. Primary care records were requested for 208/1394 (14.9%) BEEP participants. Of these, 171/1394 (12.3%) were successfully analysed for a reaction to cow's milk and/or low-allergy formula prescription. BEEP = Barrier Enhancement for Eczema Prevention. GP = General Practitioner. Although only six participants opted out of the primary care record review, a further four opted out after the primary care practitioner (General Practitioner, GP) independently contacted the family to confirm their consent for analysis of the child's primary care records.

Table 14.1. Clinical details for participants with confirmed CMA

Participant	Reaction(s) reported	Cow's milk skin prick test result at aged 2	Consumption of cow's milk at age 2 years without reaction	Diagnosis
1	Reaction at oral food challenge. Hives, lip angioedema and diarrhoea within 30 minutes of third dose.	5mm	No	IgE CMA
2	More than two episodes of skin symptoms within 30 minutes of exposure to cow's milk	10mm	No	IgE CMA
3	Reaction to a biscuit containing cow's milk. Hives, vomiting, cough and wheeze within 30 minutes	20mm	No	IgE CMA
4	Delayed vomiting reaction following oral food challenge, consistent with previous delayed vomiting reactions to cow's milk	2mm	Tolerating baked milk	Non-IgE CMA
5	Repeated hives within 30 minutes of exposure to cow's milk	4mm	Tolerating baked milk	IgE CMA
6	Repeated skin rashes within 30 minutes of exposure	9mm	No	IgE CMA
7	Vomiting, hives, drowsy within 30 minutes of consuming cow's milk	7mm	No	IgE CMA
8	Repeated episodes of hives with or without gastrointestinal symptoms within 30 minutes of exposure to cow's milk, including after baked milk challenge	7mm	No	IgE CMA
9	Repeated skin symptoms within 30 minutes of exposure to cow's milk	8mm	Tolerating baked milk	IgE CMA
10	Repeated episodes of hives and vomiting within 30 minutes of exposure to cow's milk, including baked milk	12mm	No	IgE CMA
11	Repeated episodes of hives within 30 minutes of exposure to cow's milk	10mm	Tolerating baked milk	IgE CMA
12	Repeated episodes of hives within 30 minutes of exposure to cow's milk	10mm	Tolerating baked milk	IgE CMA

13	Hives, angioedema, pruritus, diarrhoea and wheezing within an hour of exposure to cow's milk	7mm	No	IgE CMA
14	Repeated episodes of hives, sometimes with abdominal pain and diarrhoea, after cow's milk exposure	11mm	No	IgE CMA
15	Never exposed to cow's milk. Avoided based on family history of cow's milk allergy and personal history of other IgE mediated food allergies	11mm	No	IgE CMA
16	Repeated episodes of hives after exposure to cow's milk	17mm	No	IgE CMA
17	Episode of pruritus after skin contact with cow's milk, but never directly consumed due to other food allergies, eczema and positive allergy tests	13mm at age 1 year	No	IgE CMA
18	Repeated episodes of hives with exposure to cow's milk	8mm	No	IgE CMA
19	Repeated episodes of rash within 30 minutes of exposure to cow's milk	6mm	Tolerating baked milk	IgE CMA

Incidence of CMA overdiagnosis

We estimated 16.1% of children without CMA in BEEP had a parent-reported milk reaction by age 2 years, with 11.3% having a primary care record of milk hypersensitivity and 8.7% prescribed low-allergy formula (Table 14.2, Figure 14.2). At age 12 months, 105 participants reported a milk reaction, 80% of whom had documented cow's milk hypersensitivity. (Table 14.3) Similarly, 85% of participants who reported a milk reaction at 24 months had a documented primary care record of cow's milk hypersensitivity. (Table 14.3) While 94% of participants who reported low-allergy formula use had ≥1 documented prescription, 36% of those reporting a milk reaction but no low-allergy formula use also had a documented prescription. (Table 14.3)

Table 14.2. Prevalence of cow's milk hypersensitivity and low-allergy formula prescription in BEEP study cohort

	Total BEEP Cohort		**BEEP excluding participants with confirmed CMA**	
	Documented rate n/N (%)	Estimated rate n/N (%)	Documented rate n/N (%)	Estimated rate n/N (%)
Parent report of milk reaction	214/1394 (15.4%)	243/1394 (17.4%)	195/1375 (14.2%)	222/1375 (16.1%)
Primary care record of milk hypersensitivity	140/1394 (10.0%)	175/1394 (12.6%)	124/1375 (9.0%)	156/1375 (11.3%)
Low-allergy formula prescription	91/1394 (6.5%)	133/1394 (9.6%)	81/1375 (5.9%)	119/1375 (8.7%)

Cow's milk hypersensitivity refers to any concern about hypersensitivity to cow's milk. Low-allergy formula prescription includes extensively hydrolysed, amino acid and soya formula. Documented rate is the number of identified cases in the available records and assumes all other participants did not have reported cow's milk hypersensitivity or low-allergy formula prescription. Estimated rate assumes the same proportion of parent-reported milk reaction, primary care record of cow's milk hypersensitivity or primary care record of low-allergy formula prescription in the unavailable records. Of 91 participants who were prescribed low-allergy formula, number of prescriptions was available for 72 participants, of which 14 (19%) were one-off prescriptions and the others had repeat prescriptions.

Figure 14.2. Overlap between categories of CMA overdiagnosis

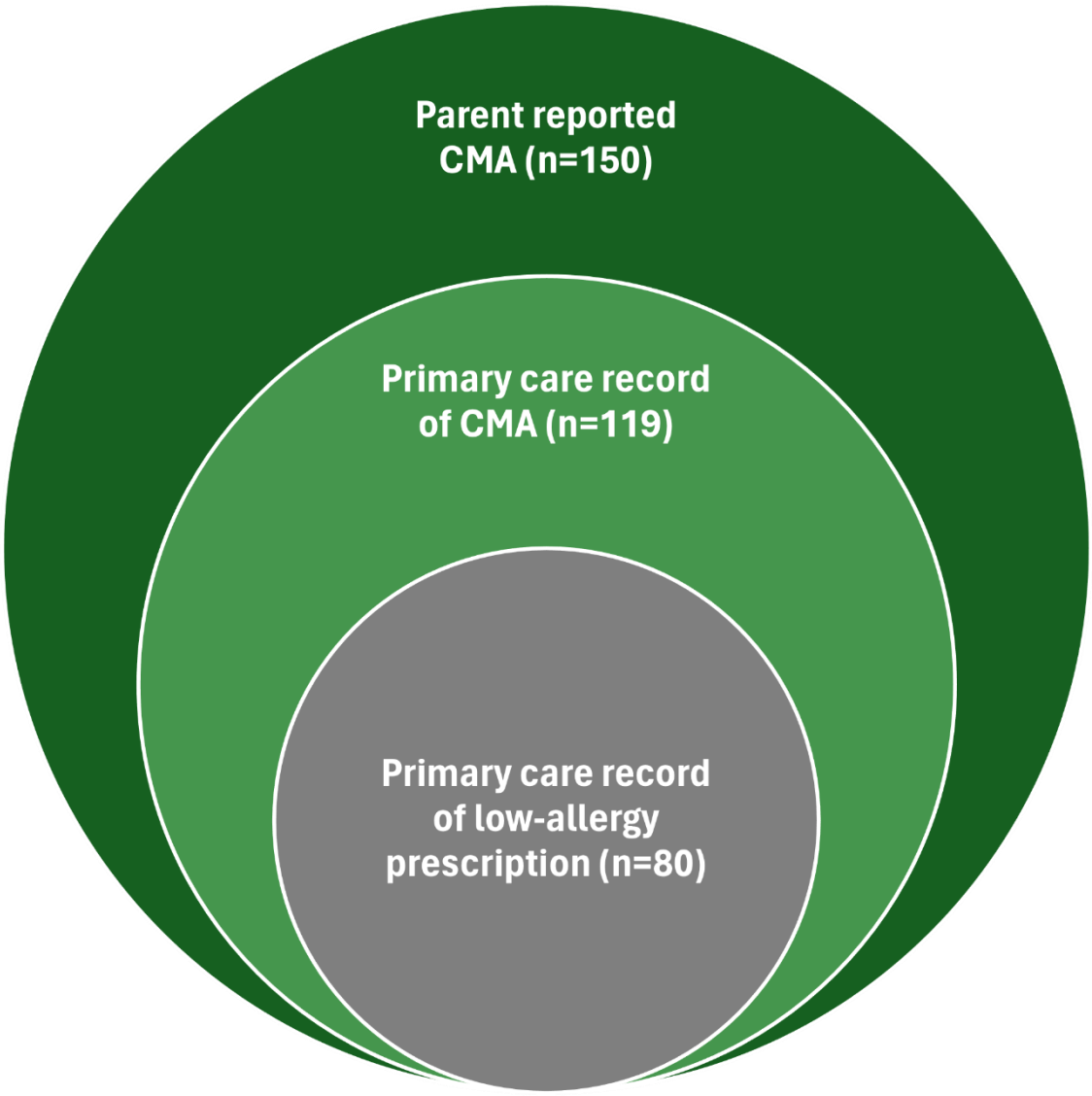


Diagram showing the overlap between parent-reported CMA, primary care record of documented CMA and primary care record of documented low-allergy formula prescription. One further child had a low-allergy formula prescribed without a primary care record of CMA diagnosis (diagnosis was protein-losing enteropathy). Data is for participants with complete data for all 3 parameters, but excluding those who had proven CMA.

Table 14.3 Performance of screening questions in relation to confirmed primary care medical record of cow's milk hypersensitivity

BEEP Trial Screening Questions		Primary care record of cow's milk hypersensitivity	Primary care record of cow's milk hypersensitivity at <12 months	Low-allergy formula prescription recorded	Low-allergy formula prescription at <12 months
Answered 'Yes' to any of the 3 questions in records available for analysis (n=171)		140/171 (82%)	110/162 (68%)	91/166 (55%)	79/163 (48%)
Question 1: In the last year, has your baby had a reaction to any foods containing cow's milk protein? Asked at 12 months.	Yes (n=105) No (n=34)	91/105 (87%) 22/34 (65%)	78/98 (80%) 9/34 (26%)	61/102 (60%) 6/34 (18%)	55/102 (54%) 5/34 (15%)
Question 2: Has your child ever had a reaction to foods containing cow's milk? Asked at 24 months.	Yes (n=137) No (n=27)	116/137 (85%) 17/27 (63%)	91/131 (69%) 13/24 (54%)	78/134 (58%) 8/25 (32%)	67/130 (52%) 7/26 (27%)
Question 3: In the last year, has your child been prescribed special low allergy formula milk (e.g. Nutramigen, Aptamil Pepti, Althera, Neocate)? Asked at 24 months.	Yes (n=54) No (n=115)	52/54 (96%) 86/115 (75%)	46/52 (88%) 62/108 (57%)	51/54 (94%) 40/110 (36%)	44/50 (88%) 35/111 (32%)

Comparison of parental responses to the 3 BEEP study screening questions with the information recorded in the analysed primary care records (n=171) related to primary care concern of reaction to milk and prescription of low-allergy formula (extensively hydrolysed, amino acid and soya). Denominators differ due to different numbers of participants with missing information for different variables

14.4 Discussion

In this analysis of a clinical trial birth cohort with prospective assessment of CMA diagnosis, we found that in those participants who did not have confirmed CMA, about 16% of parents reported a reaction to milk in their child by age 2 years, 11% had primary care records documenting a milk hypersensitivity and 9% of children were prescribed a low-allergy formula during the first two years of life.

The high rates of CMA overdiagnosis in BEEP are consistent with other studies suggesting that CMA is over-reported by parents, perhaps more so than other food allergies, and many low-allergy formula prescriptions are for children without CMA. (2,79,265) The findings build on recent evidence that 4.9% of United States store purchases of formula were low-allergy formula for CMA in 2017, rising to 7.6% in 2019. (196)

Study strengths and limitations

The main strength of this study is the unique dataset it presents, where confirmed CMA and over-reporting of CMA by parents was well-characterised. Limitations of these findings include the specific clinical trial population studied, where families had a history of atopic disease. Clinical trial populations tend to differ from the general population, and for BEEP we found higher rates of white maternal ethnicity and higher socioeconomic status than the general population of England (Table 14.4). Prescription rates for low-allergy formula were also estimated to be higher than the general population, especially for AAF, and the reasons for this are not completely clear.

Table 14.4. BEEP participant characteristics compared to general population England 2014

	Livebirths England 2014 n=661,496	All BEEP participants n=1394	BEEP excluding infants with confirmed CMA n=1375
Maternal age at randomisation / birth	30.2	31.65 (28, 35)	31.62 (28, 35)
White maternal ethnicity	479,567 (72.5%)†	1190 (85.4%)	1177 (85.6%)
Family decile of English Index of Multiple Deprivation 2015 (based on Integer 1-10, where 1 is the most deprived)	4 (2, 6)‡	5.85 (3, 8.75)	5.85 (3, 9)
Exclusive formula feeding from birth	24%§	165 (11.8%)	164 (11.9%)
FLG genotyping¶			
No mutation	677/789 (86%)	691/816 (84.7%)	683/805 (84.8%)
One FLG null mutation	103/789 (13%)	122/816 (15%)	119/805 (14.8%)
Two FLG null mutations	9/789 (1%)	3/816 (0.4%)	3/805 (0.4%)

†Reported as ethnicity of infant defined by the mother. (266) ‡ NHS Maternity statistics 2013-15 (267) §Source: Table 1: Initiation of breastfeeding, England Trend. 2013/2014. (268) ¶Filaggrin (FLG) null mutation rate was based on a population-based study in England as comparator. (269) BEEP study participants included in analysis for FLG genotyping (n=816).

Missing outcome data for some participants means that estimates for CMA overdiagnosis rates in the BEEP population are approximate. The process for identifying confirmed CMA is unlikely to have identified all cases of non-IgE mediated CMA. For example, cow's milk food protein induced enterocolitis syndrome (FPIES) is estimated to affect 0.34% of infants yielding an expected incidence of 4-5 cases within the BEEP cohort, whereas only one case was identified. (102) Robust elimination and re-introduction procedures were not well documented in primary care records and were not undertaken routinely in the BEEP trial for all participants with concerns about CMA and negative skin prick tests. The health impact on mother and child, and the impact on public health systems resources, of the labelling by parents and healthcare practitioners of possible milk hypersensitivity needs further exploration.

In conclusion, CMA overdiagnosis affected up to 16% of young children in this clinical trial cohort, with approximately half of those affected being prescribed a low-allergy formula.

15 Consultation features of milk allergy overdiagnosis in the BEEP trial cohort

15.1 Introduction

In this study, we used a clinical trial birth cohort with prospective evaluation of CMA diagnosis to describe features of CMA overdiagnosis. (78)

15.2 Methods

We analysed data from 1394 children born in England in 2014-2016 (BEEP trial, ISRCTN21528841). Participants underwent formal CMA diagnosis at ≤2 years. CMA overdiagnosis was defined in three separate ways: parent-reported milk reaction; primary care record of milk hypersensitivity symptoms; and primary care record of low-allergy formula prescription. A detailed description of methods is outlined in Section 12.3.

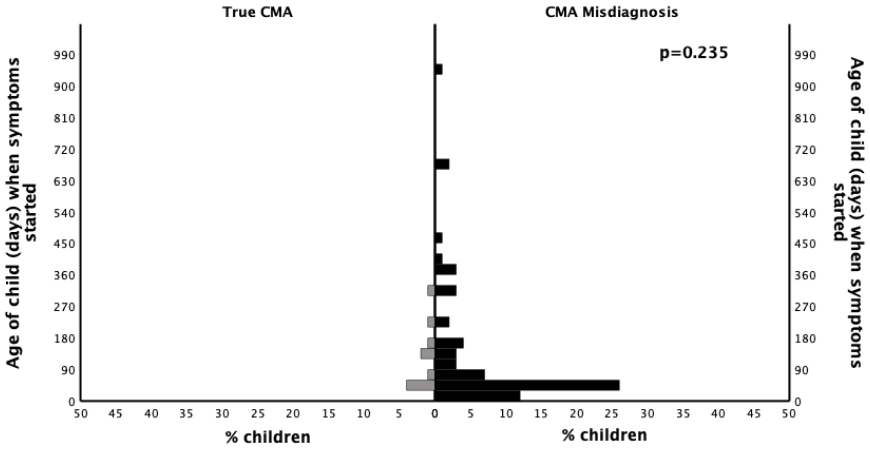
15.3 Results

Timing of CMA overdiagnosis

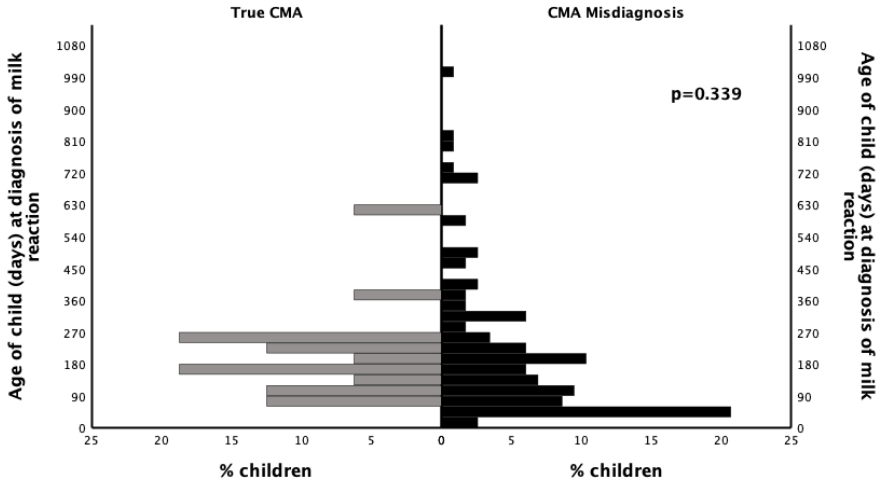
Median age at documented symptom onset and first primary care record documentation of milk hypersensitivity diagnosis was 49 days (IQR 34, 160) and 163 days (IQR 61, 284) for participants CMA overdiagnosis, and 102 days (IQR 47, 184) and 181 days (IQR 125, 249) for participants with confirmed CMA (Figure 15.1). Median time between documented symptom onset and diagnosis was 37 days (IQR 14, 91) for CMA overdiagnosis, and 56 days (IQR 39, 109) for confirmed CMA.

Figure 15.1. Timing of initial symptoms and diagnosis of possible cow's milk hypersensitivity

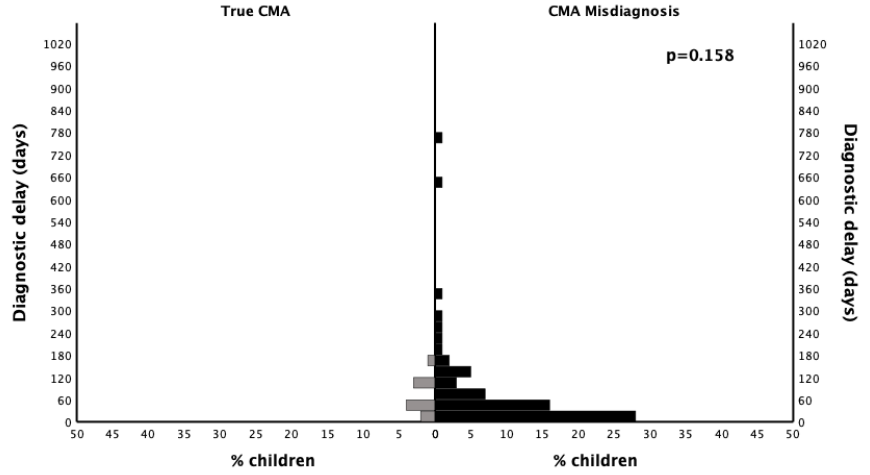
(A)



(B)



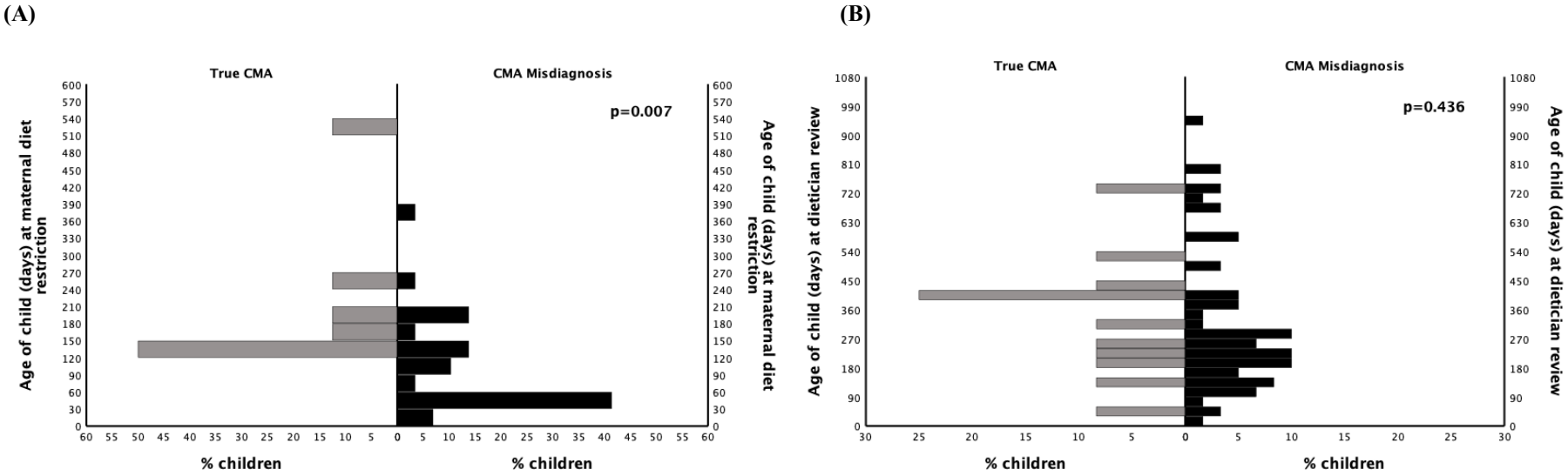
(C)



Histograms showing (A) age of child (days) when symptoms relevant for diagnosis first started (CMA overdiagnosis, n=68 ; confirmed CMA, n=10) and (B) age of child (days) at diagnosis of reaction to cow's milk (CMA overdiagnosis, n=116; confirmed CMA, n=16). Histogram C (CMA overdiagnosis, n=68 ; confirmed CMA, n=10) compares the time delay (days) between when symptoms relevant for diagnosis first started and diagnosis of reaction to cow's milk (diagnostic delay). Number of participants differ due to missing information for different variables. A Mann-Whitney U test was undertaken to determine differences between the CMA overdiagnosis and confirmed CMA group for age at symptom onset, age at diagnosis or diagnostic delay. No statistically significant difference was found.

Timing (measured as age of child) of first mention of maternal dietary exclusion and first dietetic review is shown in Figure 15.2, for participants who had timing of maternal dietary exclusion or dietetic review documented in primary care records. Maternal dietary restriction advice was documented earlier in CMA overdiagnosis (median 76 days, IQR 45, 156) than in confirmed CMA (median 156 days, IQR 135, 236; P=0.007). First dietitian review occurred at median 261 days (IQR 159, 399) in CMA overdiagnosis and 350 days (IQR 214, 435) in confirmed CMA. Timing of symptom onset, diagnosis and dietitian review were all earlier in CMA overdiagnosis than in confirmed CMA, but differences were not statistically significant.

Figure 15.2. Timing of dietary interventions for possible cow's milk hypersensitivity

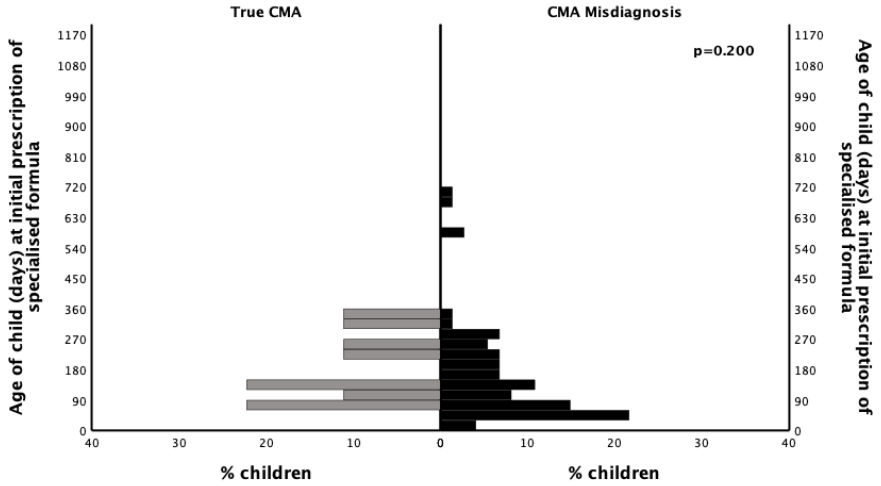


Histograms showing (A) age of child (days) when maternal dietary restriction was undertaken or advised (CMA overdiagnosis, n=29; confirmed CMA, n=8) and (B) age of child at time of Dietician review (CMA overdiagnosis, n=60; confirmed CMA, n=12). One BEEP participant without confirmed milk allergy attended a Dietician at 5 years old. Number of participants differ due to missing information for different variables. A Mann-Whitney U test was undertaken to determine differences between CMA overdiagnosis and confirmed CMA for maternal dietary restriction and dietician review. There was a significant difference in timing of maternal dietary restriction, but not for timing of dietician review.

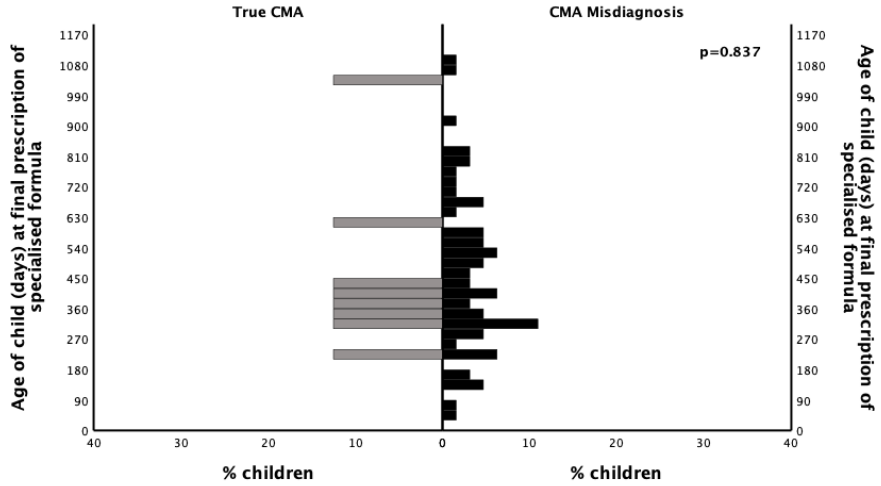
Timing of low-allergy formula prescription is shown in Figures 15.3-15.4, for the subset of 83 participants where timing was clearly documented in the primary care record. First formula prescription occurred at median 121 days (IQR 57, 225) in CMA overdiagnosis and 139 days (IQR 95, 283) in confirmed CMA. Final prescription occurred at median 429 days (IQR 304, 633) in CMA overdiagnosis and 388 days (IQR 318, 576) in confirmed CMA. There were no significant differences between the two groups in these timings.

Figure 15.3. Timing of low-allergy formula prescription for possible cow's milk hypersensitivity

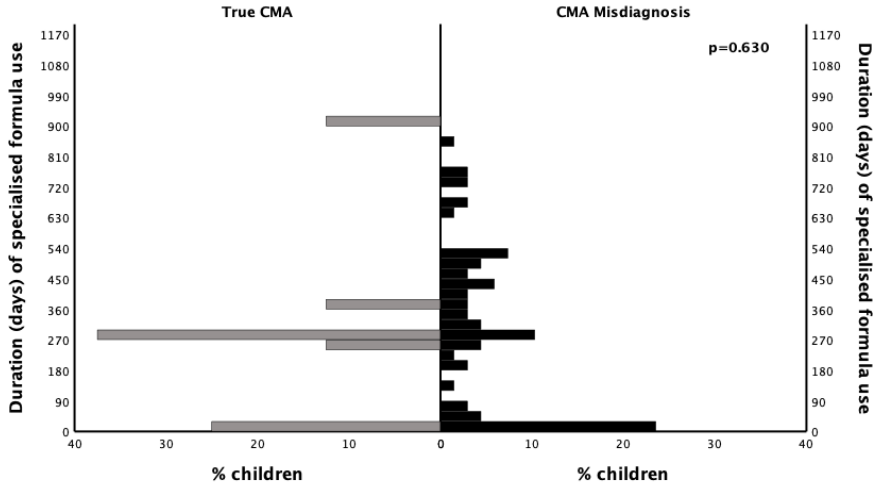
(A)



(B)

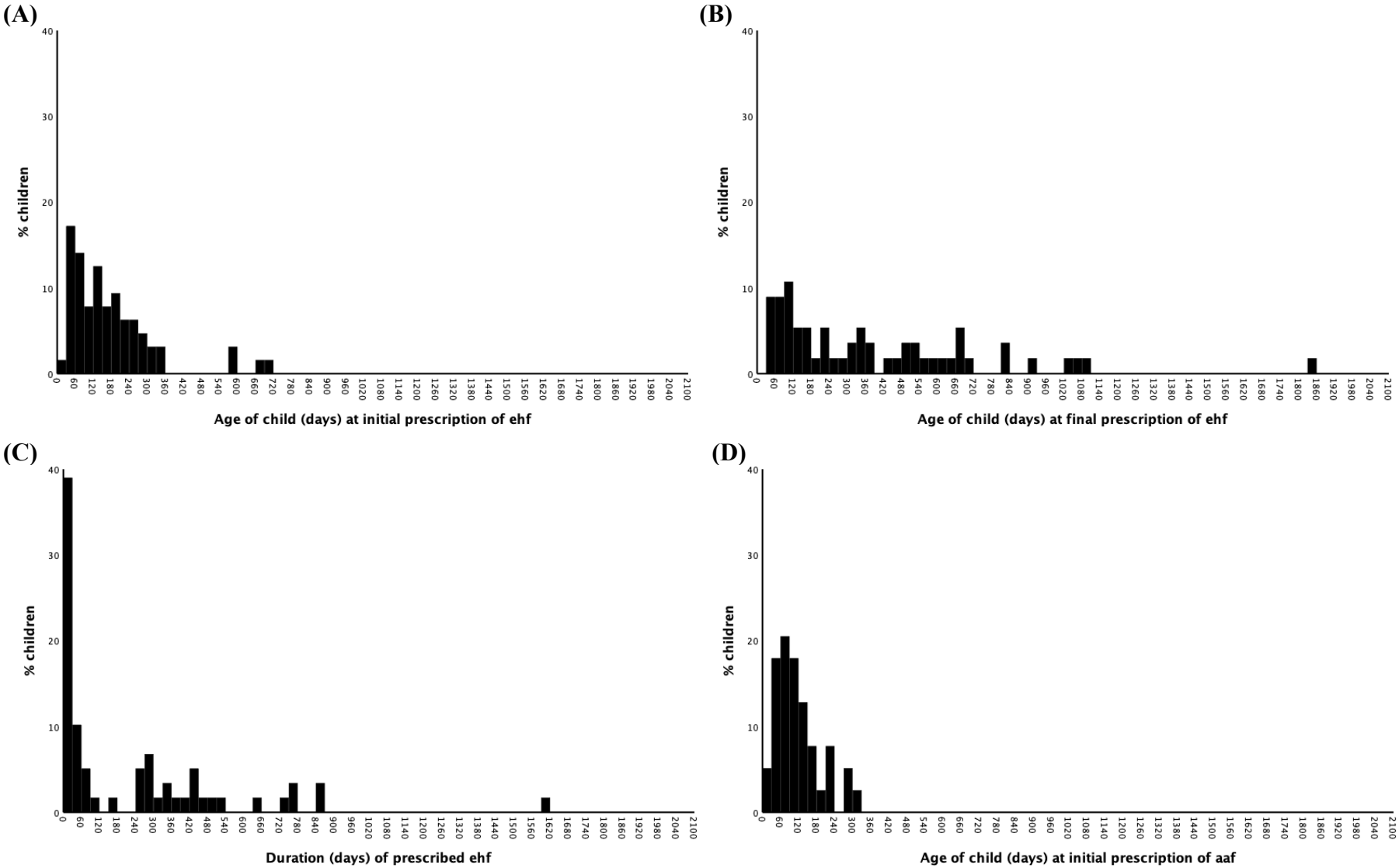


(C)

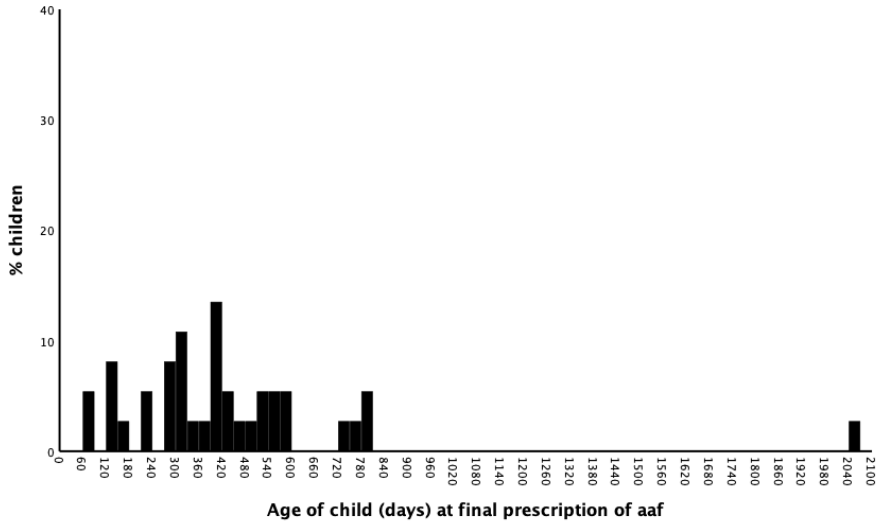


Histograms compare the age of child (days) at (A) first prescription (CMA overdiagnosis, n=74; confirmed CMA, n=9) and (B) final prescription (CMA overdiagnosis, n= 64; confirmed CMA, n=8) of low-allergy formula. Two participants without confirmed milk allergy received their final prescription of low-allergy formula at age 5 years. Number of participants differ due to missing information for different variables. Low-allergy formula refers to extensively hydrolysed (ehf), amino acid (aaf) and soya formula and excludes products designed for over 1 year old. Histogram C (CMA overdiagnosis, n=68; confirmed CMA, n=8) compares the time (days) from initial to final prescription of low-allergy formula (duration of low-allergy formula use). For those participants with missing age at final prescription (n=4) and those with a single prescription only (n=14), duration of low-allergy formula use was estimated according to volume of low-allergy formula prescribed and expected daily infant formula consumption of 780ml for infants aged <180 days old, 600ml for >/=180 days old at time of prescription of formula. (218) A Mann-Whitney U test was undertaken to determine differences between CMA overdiagnosis and confirmed CMA group for age at first and final prescription, and duration of prescribed formula. No statistically significant differences were found.

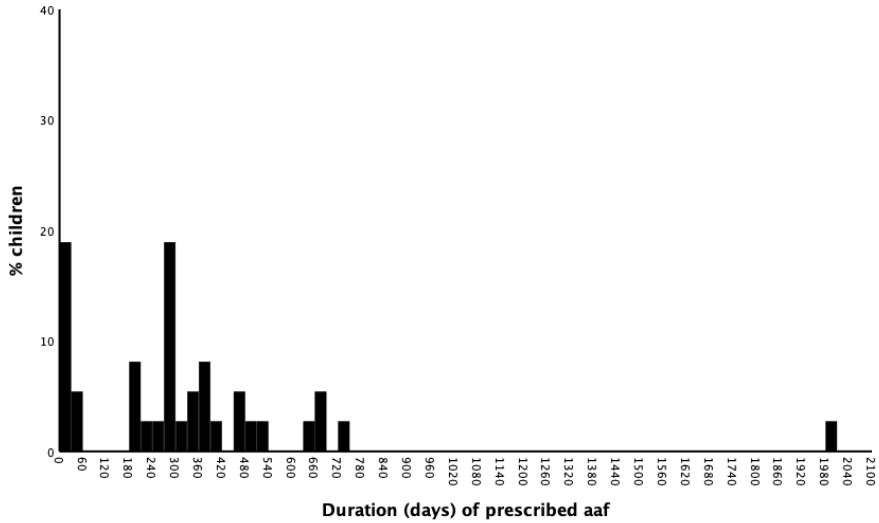
Figure 15.4. Timing of extensively hydrolysed and amino acid formula prescription for possible cow's milk hypersensitivity



(E)



(F)



Histograms showing age at initial prescription of ehf (n=64), final prescription of ehf (n=56), duration (days) of ehf (n=59), age at initial prescription of aaf (n=39), final prescription of aaf (n=37) and duration (days) of aaf (n=37). Products designed for age >1 year old were excluded from analysis. Participants with confirmed CMA and CMA overdiagnosis were included in analysis. For those participants with missing age at final prescription, duration was calculated according to volume of low-allergy formula prescribed and expected daily infant formula consumption of 780ml for infants aged <180 days old, 600ml for >/=180 days old at time of prescription of formula.
(218)

Characteristics of CMA overdiagnosis

Characteristics of CMA overdiagnosis in BEEP are summarised in Table 15.1. Primary care records suggest the possibility of cow's milk hypersensitivity was most commonly raised by primary care physicians (General Practitioner, GP), but in >20% parents raised the initial concern. Definitive clinical diagnosis was most frequently given in secondary care, with 'allergy' the most common diagnostic label. Symptoms were most commonly lower gastrointestinal (58% (72/124)) (Figure 15.5), and skin symptoms were less common than in confirmed CMA (40% vs 94%, $p<0.001$, adjusted for false discovery $p=0.006$; Figure 15.6). (244)

Table 15.1. Diagnostic process in the BEEP cohort

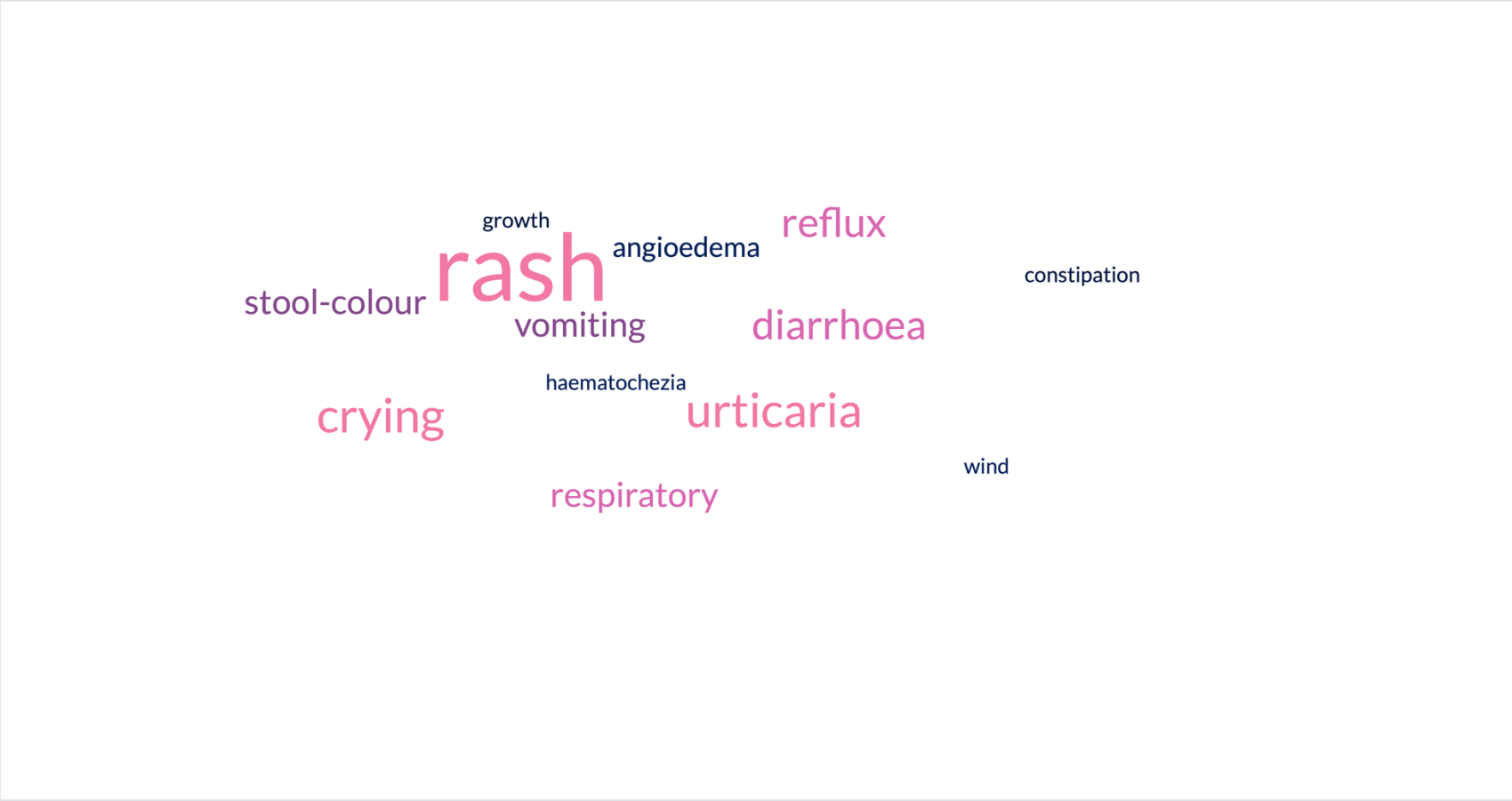
		No confirmed CMA (n=124) N (%)	Confirmed CMA (n=16) N (%)
Role of person who raised the initial concern of cow's milk hypersensitivity	General Practitioner	39 (31.5%)	8 (50%)
	Parent†	37 (29.8%)	4 (25%)
	Unclear	14 (11.3%)	-
	Secondary care specialist	13 (10.5%)	1 (6.3%)
	Community HCP	11 (8.9%)	1 (6.3%)
	Multiple	10 (8.1%)	2 (12.5%)
Role of person who made the most definitive diagnosis of cow's milk hypersensitivity	Secondary care specialist	44 (35.5%)	7 (43.8%)
	General Practitioner	40 (32.3%)	1 (6.3%)
	Multiple	17 (13.7%)	8 (50%)
	Dietician	11 (8.9%)	-
	Unclear	9 (7.2%)	-
	Parent	2 (1.6%)	-
	Community HCP	1 (0.8%)	-
Classification of diagnostic label given	Allergy	54 (43.5%)	9 (56.3%)
	Non IgE-mediated	27 (21.8%)	-
	Intolerance	26 (21%)	-
	Unclear	11 (8.9%)	-
	IgE-mediated	3 (2.4%)	7 (43.8%)
	Hypersensitivity	3 (2.4%)	-
Nature of symptoms at initial concern of cow's milk hypersensitivity‡	Lower gastrointestinal	72 (58.1%)	7 (43.8%)
	Upper gastrointestinal	62 (50%)	6 (37.5%)
	Skin	49 (39.5%)	15 (93.8%)
	Behavioural	29 (23.4%)	4 (25%)
	Faltering Growth	12 (9.7%)	1 (6.3%)
	Respiratory	8 (6.5%)	3 (18.8%)
Diagnostic assessments performed outside of the BEEP trial protocol	None	89 (71.8%)	-
	Negative SPT/SIgE	23 (18.5%)	2 (12.5%)
	Positive SPT/SIgE	6 (4.8%)	8 (50%)
	Unknown	6 (4.8%)	6 (37.5%)
	Supervised OFC	0	0

HCP, healthcare practitioner (usually health visitor); SPT, skin prick test.
†In just two primary care records (no confirmed CMA) a parent raised an initial concern of cow's milk hypersensitivity but was advised by the GP that this diagnosis was unlikely. ‡Cutaneous symptoms alone were recorded for 17/124 (13.7%) no confirmed CMA and 6/16 (37.5%) confirmed CMA children, gastrointestinal symptoms alone 44/124 (35.5%) no confirmed CMA and 1/16 (6.3%) confirmed CMA, mixed symptoms in 61/124 (49.2%) no confirmed CMA and 9/16 (56.3%) confirmed CMA and unclear for 2 (1.6%) no confirmed CMA children. Mixed symptoms included symptoms from more than one system: gastrointestinal, cutaneous, faltering growth, respiratory and behavioural. Lower gastrointestinal symptoms included diarrhoea, constipation, mucus in stools, blood in stools, wind, and abdominal pain. Upper gastrointestinal symptoms included reflux and vomiting. Skin symptoms included rash, eczema, hives, urticaria, angioedema, and itch. Faltering growth included weight loss or drop in centiles. Respiratory symptoms included hoarseness, cough, floppy larynx, phlegm, breathing changes, wheeze, and choking. Behavioural symptoms included crying, colic, unsettled, food aversion, and sleep disturbance.
There was a statistically significant association between skin symptoms and CMA diagnosis (Chi-squared test, $p<0.001$, or $p<0.006$ adjusted for false discovery). No statistically significant difference was found between confirmed CMA and no confirmed CMA participants for lower gastrointestinal symptoms ($p=0.246$), upper gastrointestinal symptoms ($p=0.288$), behavioural (Fisher's exact test, $p=1.00$), faltering growth ($p=1.00$) and respiratory symptoms (0.12).

Figure 15.5. Symptoms recorded at time of first reaction to milk in children with CMA overdiagnosis
Symptoms recorded in the primary care record at time of first mention of a reaction to cow's milk in children who did not have confirmed CMA. Size of words represents the frequency of individual symptoms leading to a diagnosis of possible milk reaction. Word cloud was generated using https://www.freewordcloudgenerator.com.



Figure 15.6. Symptoms recorded at time of first reaction to milk in children with confirmed CMA
Symptoms recorded in the primary care record at time of first mention of a reaction to cow's milk in children who had confirmed CMA. Size of words represents the frequency of individual symptoms leading to a diagnosis of possible milk reaction. Word cloud was generated using https://www.freewordcloudgenerator.com.



For most cases, no formal diagnostic process was undertaken, and where undertaken, test results were usually negative (23/29, 79%). In contrast, for confirmed CMA, tests were usually positive (8/10, 80%), when undertaken. At the time when concern about cow's milk hypersensitivity was first documented, 43% of those with CMA overdiagnosis and 75% confirmed CMA were partially or fully breastfed, and rates were similar at the time of first low-allergy formula prescription (Table 15.2). Most participants with CMA overdiagnosis (66%) or confirmed CMA (75%) had maternal dietary restriction of dairy, usually parent-initiated; although in almost half, a healthcare practitioner also suggested maternal dietary restriction. Most CMA overdiagnosis or confirmed CMA participants were referred for dietetic review.

Table 15.2. Diet and Feeding in the BEEP cohort

		No confirmed CMA n/N (%)	Confirmed CMA n/N (%)
Feeding status at initial concern of cow's milk hypersensitivity	Breastfed, fully or partially	53/124 (42.7%)	12/16 (75%)
	Not breastfed	52/124 (41.9%)	4/16 (25%)
	Unclear	19/124 (15.3%)	-
Feeding status at time of initial prescription of low-allergy formula	Breastfed, fully or partially	38/81 (47%)	7/10 (70%)
	Formula fed	36/81 (44%)	3/10 (30%)
	Unclear	7/81 (9%)	-
Maternal dietary restriction of dairy†	Undertaken or advised	35/53 (66.0%)	9/12 (75%)
	No record of relevant discussion	16/53 (30.2%)	3/12 (25%)
	Unclear	2/53 (3.8%)	-
Role of person who initiated or advised maternal dietary restriction	Parent	18/35 (51.4%)	3/9 (33.3%)
	Secondary Care Specialist	6/35 (17.1%)	1/9 (11.1%)
	General Practitioner	4/35 (11.4%)	-
	Multiple	4/35 (11.4%)	2/9 (22.2%)
	Community HCP	2/35 (5.7%)	-
	Unclear	1/35 (2.9%)	-
	Dietician	-	3/9 (33.3%)
Other dietary exclusion advised from maternal diet	No record of soya exclusion	26/35 (74.3%)	8/9 (88.9%)
	Soya exclusion	7/35 (20.0%)	-
	Unclear	2/35 (5.7%)	1/9 (11.1%)
Other dietary exclusion advised from child's diet	No record of soya exclusion	106/124 (85.5%)	15/16 (93.8%)
	Soya exclusion	9/124 (7.3%)	1/16 (6.3%)
	Unclear	9/124 (7.3%)	-
Dietician review of child with possible milk reaction	Yes	70/124 (56.5%)	12/16 (75%)
	No	44/124 (35.5%)	4/16 (25%)
	Unclear	10/124 (8.1%)	-

†No record of advice against maternal dietary restriction. Denominators differ due to different numbers of participants with missing information for different variables. Unclear refers to missing information. **No confirmed CMA BEEP cohort with a primary care concern of reaction to milk (n=124):** For role of person who initiated or advised maternal dietary restriction of dairy: Community healthcare practitioner (HCP) refers to Health Visitor (n=2); Multiple refers to GP and Health Visitor (n=1), GP and Paediatrician (n=1), Parent, Paediatrician and Paediatric Allergist (n=1), and Dietician, Paediatrician, and Paediatric Gastroenterologist (n=1); secondary care Specialist refers to Paediatrician (n=2), Paediatric Allergist (n=2), Dermatologist (n-1) and Paediatric Gastroenterologist (n=1). †One record of parental initiated maternal dietary restriction advised unnecessary by Paediatric Allergist. One record of initial GP advising maternal dietary restriction and another GP subsequently advising against maternal dietary restriction. **Confirmed CMA BEEP cohort (n=16):** For role of person who initiated or advised maternal dietary restriction of dairy: Multiple refers to parent and GP (n=1), and parent and paediatrician (n=1); secondary care Specialist refers to Paediatrician (n=1).

Patterns of low-allergy formula prescription

Low-allergy formula was usually initiated by GPs, for a documented indication of CMA, or less commonly, intolerance (Table 15.3). EHF was usual as a first prescription (69% CMA overdiagnosis, 50% confirmed CMA), but similar numbers used an alternative EHF or AAF where a second prescription was provided.

Table 15.3: Low-allergy formula prescribed during the first year of life

		No confirmed CMA (n=81) N (%)	Confirmed CMA (n=10) N (%)
Type of low-allergy formula first prescribed	Extensively hydrolysed	56/81 (69%)	5/10 (50%)
	Amino acid	17/81 (21%)	4/10 (40%)
	Soya	8/81 (10%)	1/10 (10%)
Role of person who initially advised, requested or prescribed low-allergy formula	General Practitioner	43/81 (53%)	4/10 (40%)
	Secondary care specialist	21/81 (26%)	2/10 (30%)
	Dietician	7/81 (9%)	2/10 (20%)
	Parent	4/81 (5%)	-
	Multiple	3/81 (4%)	1/10 (10%)
	Unclear	3/81 (4%)	-
Indication for first low-allergy formula prescription	Allergy	47/81 (58%)	6/10 (60%)
	Intolerance	22/81 (27%)	1/10 (10%)
	Non IgE-mediated	4/81 (5%)	1/10 (10%)
	Other†	4/81 (5%)	-
	IgE-mediated	2/81 (2%)	2/10 (20%)
	Unclear	2/81 (2%)	-
	Hypersensitivity	-	-
Nature of symptoms at time of first low-allergy formula prescription‡	Lower gastrointestinal	44/81 (54%)	4/10 (40%)
	Upper gastrointestinal	37/81 (45%)	5/10 (50%)
	Skin	34/81 (42%)	9/10 (90%)
	Behavioural	25/81 (31%)	2/10 (20%)
	Faltering Growth	9/81 (11%)	1/10 (10%)
	Respiratory	1/81 (1%)	2/10 (20%)
Second low-allergy formula prescribed	No second formula	47/81 (58%)	7/10 (70%)
	Amino Acid	17/81 (21%)	1/10 (10%)
	Extensively hydrolysed	14/81 (17%)	2/10 (20%)
	Soya	3/81 (4%)	-

Third low-allergy formula prescribed	No third formula	68/81 (84%)	10/10 (100%)
	Amino acid	9/81 (11%)	-
	Extensively hydrolysed	4/81 (5%)	-
Other prescriptions used in participants prescribed low-allergy formula§	Gaviscon® infant	35/81 (43%)	3/10 (30%)
	Histamine 2 blocker	24/81 (30%)	1/10 (10%)
	Proton Pump Inhibitor	12/81 (15%)	1/10 (10%)
	Lactose free formula	10/81 (12%)	1/10 (10%)
	Thickening agent	7/81 (9%)	1/10 (10%)
	Colic medication	6/81 (7%)	-

†Other refers to gastroesophageal disease (n=1), parent request (n=2), and primary intestinal lymphangiectasia (n=1).
‡Cutaneous symptoms only occurred in 12/81 (15%) participants, gastrointestinal symptoms only occurred in 20/81 (25%) participants, and mixed symptoms occurred in 44/81 (54%) participants. No symptoms were recorded at time of first prescription for 5/81 (6%) participants.
§ Antireflux medication only was prescribed to 8/81 (10%) participants without confirmed CMA, 2/10 (20%) confirmed CMA, multiple agents were prescribed to 33/81 (41%) participants without confirmed CMA, no additional medicines were prescribed to 33/81 (41%) participants without confirmed CMA and 5/10 (50%) confirmed CMA. Skin symptoms were significantly more common in participants with confirmed CMA at time of first low-allergy formula prescription, compared with participants without confirmed CMA (p=0.006, or p=0.036 after adjustment for false discovery). No association was seen for frequency of lower gastrointestinal symptoms (p=0.308), upper gastrointestinal symptoms (p=1.00), behavioural (p=0.495), faltering growth (p=1.00) and respiratory symptoms (0.061; Fisher's exact test).

Low-allergy formula was prescribed for median 10 months (1, 16) and 272 litres (26, 448) in CMA overdiagnosis or 9 months (3, 22) and 182 litres (28, 389) in confirmed CMA (Table 15.4). Total cost was median £1214 (104, 2649) for CMA overdiagnosis versus £854 (164, 1908) for confirmed CMA.

Table 15.4: Volume and cost of low-allergy formula prescribed to BEEP trial participants

	No confirmed CMA (n=195)			Confirmed CMA diagnosis (n=19)		
	Participants included in analysis, n	Total, N	Median (Q1, Q3)	Participants included in analysis, n	Total, N	Median (Q1, Q3)
Total duration of low-allergy formula use (months)†	68	792	10 (1,16)	8	96	9 (3, 22)
Total volume of low-allergy formula (litres)	68	20053	272 (26, 448)	8	1748	182 (28, 389)
Total volume of ehf, aaf and soya (litres)	ehf (n=53)	7982	42 (12, 248)	ehf (n=6)	1329	182 (47, 418)
	aaf (n=34)	11951	334 (122, 470)	aaf (n=4)	419	46 (10, 259)
	soya (n=2)	119	60 (7, -)	soya (n=0)	-	-
Total cost of low-allergy formula (£ sterling)	68	119934	1214 (104, 2649)	8	8497	854 (164, 1908)
Total cost of ehf, aaf and soya prescribed (£ sterling)	ehf (n=53)	29790	160 (42, 864)	ehf (n=6)	4952	689 (175, 1565)
	aaf (n=34)	89898	2504 (907, 3792)	aaf (n=4)	3545	520 (75, 2064)
	soya (n=2)	246	123 (14, -)	soya (n=0)	-	-

Low-allergy formula includes soya, extensively hydrolysed formula (ehf) and amino acid formula (aaf). Q1, 25th centile. Q3, 75th centile. Data analysis includes all ehf and aaf suitable for <1 year old and aaf suitable for >1 year old (Neocate Advance, Neocate Active and Neocate Junior). Volume in litres was calculated using product recommended dilution (%weight/volume equated to grams per 100mls).

†For those participants with missing data (age at final prescription) and once-off prescriptions, duration (in days, divided by 30 to convert to months) of low-allergy formula use was estimated according to volume of low-allergy formula prescribed and expected daily infant formula consumption of 780ml for infants aged <180 days old, 600ml for >/=180 days old at time of formula prescription. (218)

We compared patterns of low-allergy formula prescription in BEEP with national data for England in 2015 (Table 15.5-15.6, Table S6-S7). (Our method of calculating estimated data can be found in Appendix 22.9) These show that documented prescribing in BEEP occurred at a similar level (15.5 litres/birth) to England data (14.5 litres/birth) or to prescriptions in the BEEP primary care practices in the previous year (13.6 litres/birth). However, there was increased prescription of AAF in BEEP- 8.8 litres/birth, compared with 4.9 litres in England and 4.8 litres in the BEEP primary care practices – and less prescribing of soya formula. Assuming similar rates of prescribing for participants with missing data as in those with available primary care records, prescribing rate for EHF was 33% higher in the BEEP cohort than in England (11.7 litres/birth versus 8.8 litres) and for AAF >3-fold higher in BEEP than in England (15.4 litres/birth versus 4.9 litres). For all participants with repeated low-allergy formula prescriptions, estimated volume consumed per day was median 1.01 litres (0.86, 1.20) for AAF compared with 0.64 litres (0.42, 0.89) for EHF (p=0.001) (Table S8-S9).
In those prescribed low-allergy formula, skin symptoms were more commonly recorded at time of low-allergy formula prescription in confirmed CMA (90%) compared with CMA overdiagnosis (42%). Prescription of other medications was common in this sub-group, especially Gaviscon® infant (43% CMA overdiagnosis, 30% confirmed CMA).

Table 15.5. Documented and estimated volume and cost of low-allergy formula in BEEP study cohort

	Documented volume (litres)	Estimated volume of low-allergy formula in participants without information on CMA, prescription or volume†	Total estimated volume of low-allergy formula	Total low-allergy formula volume per BEEP participant	Documented cost (sterling)	Estimated cost of low-allergy formula in participants without information on CMA, prescription or volume†	Total estimated cost of low-allergy formula	Total low-allergy formula cost per BEEP participant
Total BEEP cohort								
Any low-allergy formula suitable < 1 year old	21654	16290	37944	27.22	125874.00	94689.67	220563.67	158.22
eHF	9311	7005	16316	11.70	34742.38	26135.21	60877.59	43.67
AAF	12223	9195	21418	15.36	90885.90	68369.59	159255.49	114.24
Soya	119	90	209	0.15	245.74	185.86	431.60	0.31
BEEP cohort excluding confirmed CMA								
Any low-allergy formula suitable < 1 year old	19942	15179	35121	25.54	118003.30	89817.95	207875.25	151.14
eHF	7982	6076	14058	10.22	29790.00	22674.60	52464.60	38.16
AAF	11840	9012	20852	15.17	87967.44	66956.24	154923.68	112.67
Soya	119	91	210	0.15	245.74	187.04	432.78	0.31

Excluding products designed for age > 1 year old

†Calculated by estimated number of participants without information on CMA, prescription or volume who had a low-allergy formula prescription from Table 8b above (56.9 for total BEEP cohort and 51.64 for BEEP cohort excluding confirmed CMA) and considering the number of participants who had a documented volume prescribed in the primary care records. See Appendix 22.9 for detailed method of calculation.

Table 15.6. Volume and cost of low-allergy formula per infant born

	England 2015†		BEEP Primary Care Practices 2014		BEEP cohort		BEEP excluding infants with confirmed CMA	
	Volume (‘000 litres)	Volume per birth (L)	Volume (‘000 litres)	Volume per birth (L)	Documented volume per birth (L)	Estimated volume per birth (L)	Documented volume per birth (L)	Estimated volume per birth (L)
Any prescribed low-allergy formula suitable for <1 year old ‡	9,611	14.47	837	13.56	15.53	27.22	14.50	25.54
Extensively hydrolysed formula	5,863	8.82	487	7.88	6.68	11.70	5.81	10.22
Amino acid formula	3,234	4.87	297	4.81	8.77	15.36	8.61	15.17
Soya formula	513	0.77	53	0.86	0.09	0.15	0.09	0.15
	Cost (£ thousand)	Cost per birth (£)	Cost (£ thousand)	Cost per birth (£)	Documented cost per birth (£)	Estimated cost per birth (£)	Documented cost per birth (£)	Estimated cost per birth (£)
Any prescribed low-allergy formula suitable for <1 year old‡	51,424	77.40	-	-	90.30	158.22	85.82	151.14
Extensively hydrolysed formula	20,468	30.81	-	-	24.92	43.67	21.67	38.16
Amino acid formula	30,228	45.50	-	-	65.20	114.24	63.98	112.67

Soya formula	728	1.10	-	-	0.18	0.31	0.18	0.31

†Data for quantity (grams) and cost (UK pounds sterling) of low-allergy formula prescribed in England in 2015 was obtained from the National Health Service Prescription Cost Analysis reports; live birth rate for England for 2015 (664,399 births) was obtained from the UK Office of the National Statistics; volumes in litres were calculated using product recommended dilution. ‡Products excluded from analysis include Neocate Advance, Neocate Active and Neocate Junior. One participant from the no confirmed CMA cohort who had quantity of formula recorded in the notes was prescribed aaf over the age of 12 months, but all products included in both the 2015 national analysis and the BEEP study analysis are products designed for use in infants age <12 months Products marketed for children over age 12 months were prescribed to five BEEP participants with CMA overdiagnosis (Neocate Advance n=2, Neocate Junior n=2, Neocate Active n=1) and one BEEP participant with confirmed CMA (Neocate Active) over 12 months old. Estimations assume the same proportion of parent-reported milk reaction, primary care record of cow's milk hypersensitivity or primary care record of low-allergy formula prescription in the participants with unavailable records or missing information

15.4 Discussion

In those without confirmed CMA, we identified primary care practitioners as initiating CMA overdiagnosis and low allergy formula prescription most commonly. Gastrointestinal symptoms were the most common concern triggering CMA overdiagnosis and unnecessary prescription. CMA overdiagnosis presented at median 49 days old and was diagnosed in median 37 days from symptom onset. Low-allergy formula exposure occurred for a median 10 months, at a median estimated consumption of 272 litres. Daily low-allergy formula consumption appeared to be greater for AAF (median 1 litre per day) then EHF (median 0.64 litres per day), something which requires further exploration.

Our findings suggest that low-allergy formula is being used for managing gastrointestinal symptoms, especially diarrhoea, vomiting and reflux, and that multiple healthcare practitioners and parents are all contributing to this process. Maternal dietary restrictions are commonly undertaken and advised. This is something which is commonly advised in milk allergy guidelines, but is not evidence based and may be harmful. (2,50,137,143,265) The increased daily volume of AAF consumption compared with EHF may reflect a safety issue related to a failure AAF to induce normal satiety mechanisms, and requires further confirmation. (270) Ultraprocessed foods are thought to promote obesity due to inadequate induction of satiety. (271) AAF, which is glucose syrup based and contains no peptides, may have a similar effect. Previous work has suggested there is a dose-response relationship between glucose-syrup based formula consumption during infancy and increased early childhood obesity. (115,188,189,192,196) Finally, it is possible that CMA overdiagnosis in breastfed infants may actually promote the development of IgE-mediated CMA through delayed introduction of cow's milk antigen to the infant diet. (272) However, evidence for early cow's milk introduction and CMA prevention is currently inconclusive. (99) Our findings have implications for strategies such as prescribing restrictions, to prevent CMA

overdiagnosis and excessive prescribing of specialised low-allergy formula products. One important target for interventions could be primary care practitioners caring for families who are concerned about gastrointestinal symptoms in young infants.

Study strengths and limitations

Primary care records did not consistently document who raised an initial concern about milk hypersensitivity. Therefore, in some cases where we judged the primary care physician as being most likely to have raised the initial concern, this had not been explicitly stated in the record. This may be an important limitation when considering targets for intervention, although it is also relevant that records only documented primary care practitioners refuting milk hypersensitivity in two cases. These data were acquired in a clinical trial setting, which as discussed previously may not be representative of the general population. Thus, key findings need confirmation in a representative dataset.

In conclusion, CMA overdiagnosis in young children is mainly triggered by gastrointestinal symptoms which start in the first weeks of life. Half of infants with parent-reported milk reactions are prescribed a low-allergy formula, for a median duration of 10 months. CMA overdiagnosis carries a significant financial burden, can adversely affect breastfeeding and carries long-term health risks for children associated with exposure to high levels of free sugars in low-allergy formula.

16 International trends in use of specialised formula for managing cow's milk allergy in young children

16.1 Introduction

Prescriptions for specialised formula are thought to have risen in England, and a 2006 report from Australia documented increasing prescriptions of amino-acid formula, but no comprehensive analysis of all specialised formula products across multiple countries has yet been undertaken. (2,3,113) Specialised infant formula is mainly prescribed for cow's milk allergy and therefore, prescribing trends can be used as a surrogate marker for milk allergy overdiagnosis. (2) We sought to understand if a similar pattern of milk allergy overdiagnosis existed in other countries, to that seen in the United Kingdom.

16.2 Methods

A detailed description of methods is outlined in Section 12.4. In brief, we surveyed countries to identify any nationwide prescribing datasets which included specialised infant formula. For countries with available data, we documented trends in prescribing over time, and compared these with expected prescribing rates based on national infant feeding data and an estimated cow's milk allergy incidence of 1%.

16.3 Results

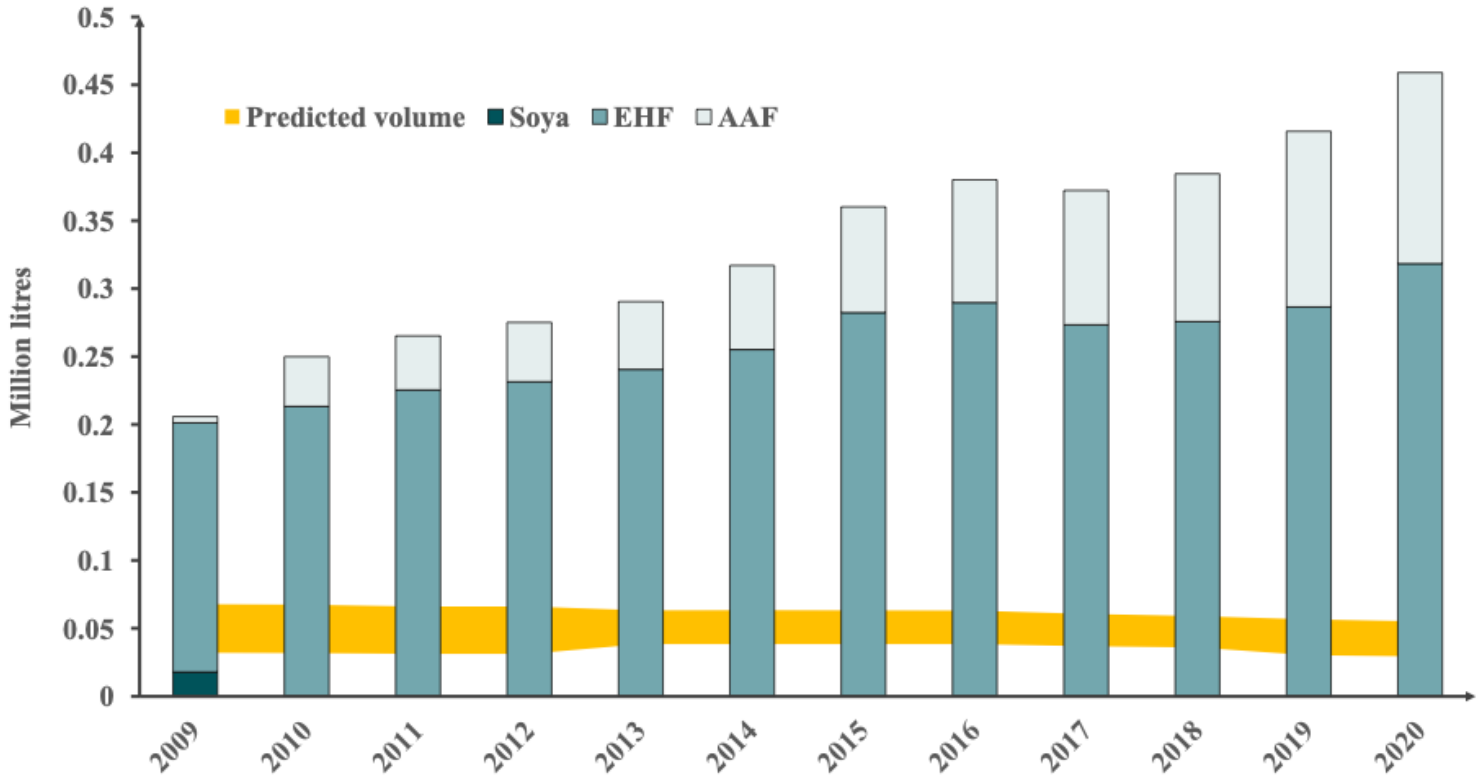
We surveyed 23 countries covering over half of the world's population, to identify any suitable databases. Most countries did not reimburse specialised formula or did not publish an accessible dataset including reimbursed specialised formula prescribing. Community prescription data were available from Norway (2009-2020) and Australia for years 1992 to 2020. Data for extensively hydrolysed formulas (EHF) and amino-acid formulas (AAF) were

available from both countries and data for soya formula from Norway only. Data for the number of infants prescribed a specialised formula were only available from Norway. The specific eligible products available for public reimbursement in each country are summarised in Table S1, and products excluded from analysis are listed in Table S2. (Appendix 22.3)

Trends in volume of reimbursed specialised formula

Data for specialised formula products marketed for infants less than one year in Norway are shown in Figure 16.1. Prescribed volumes rose 2.2-fold between 2009 and 2020. This represents a 1.7-fold increase in EHF and 30.8-fold increase in AAF for those years, with cessation of soya prescription from 2010 onwards. In 2020 the total volume of reimbursed specialised formula was 8.3 to 15.6-fold greater than expected.

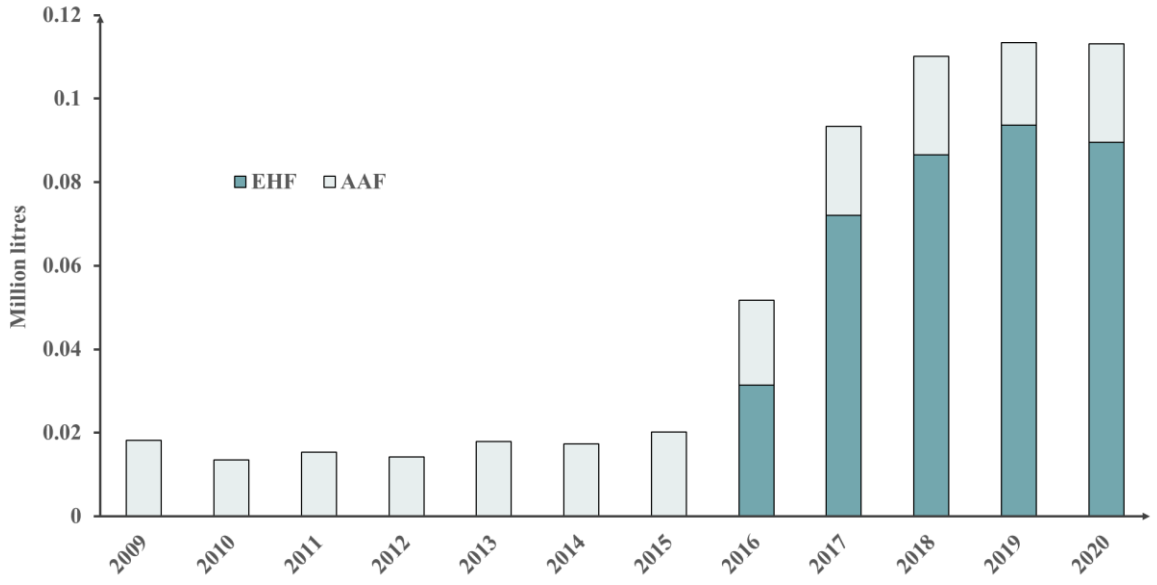
Figure 16.1. Volume of reimbursed specialised infant formulas for under 1 year olds with milk allergy in Norway.



Data on the number of tins of all amino acid formulas (AAF), extensively hydrolysed formulas (EHF) and soya formulas were obtained from the Norwegian Directorate of Health. Volumes were calculated using product details from manufacturer websites. Predicted volumes are the lower to upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2007 and 2019 Norwegian National Dietary Surveys among 6 and 12-month-old infants and the 2013 Norwegian National Survey (Appendix 22.4) and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (218) In 2020 the total volume of reimbursed specialised formula was 8.3 to 15.6-fold higher than expected.

Volumes of reimbursed specialised formula marketed for children over one year in Norway increased to 2019, mainly EHF, without a further rise in 2020, at approximately one-quarter the volumes for infants under one year (Figure 16.2).

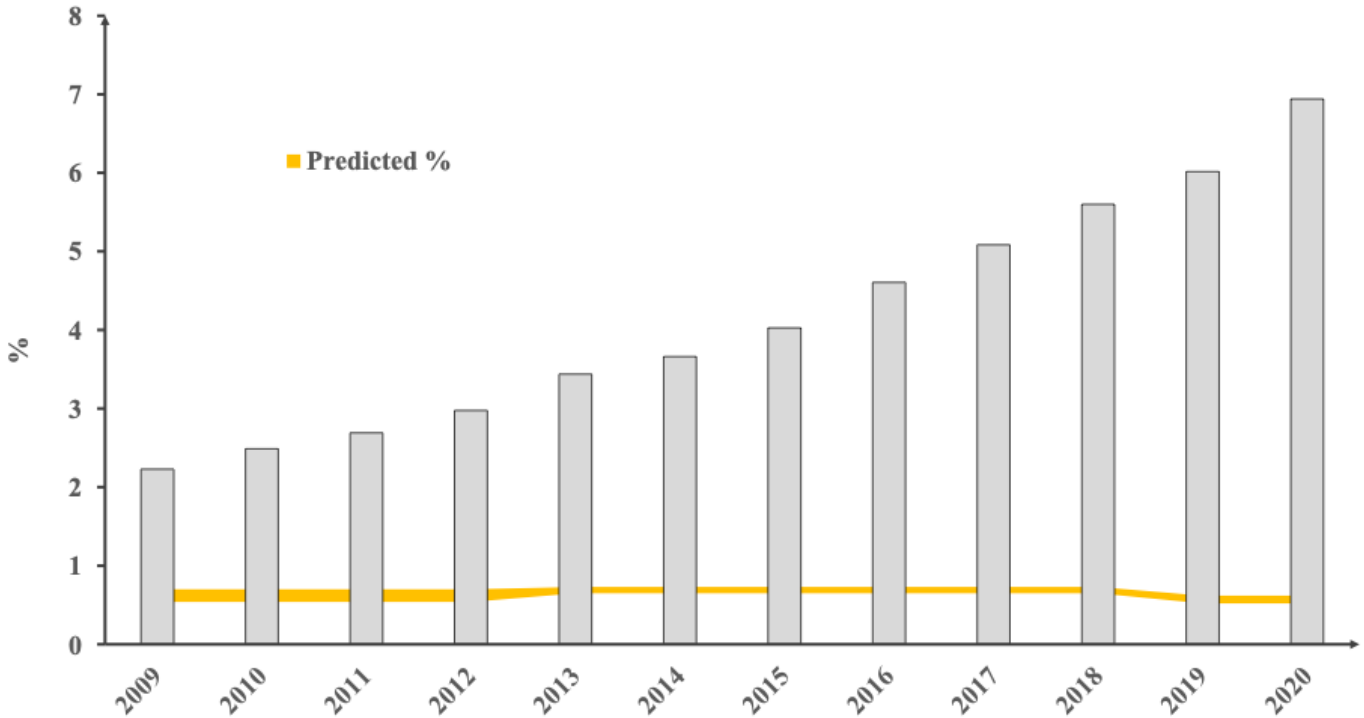
Figure 16.2. Volume of reimbursed specialised infant formulas for 12- to 23-month-olds in Norway.



Data on the number of tins of all amino acid formulas (AAF) and extensively hydrolysed formulas (EHF) were obtained from the Norwegian Directorate of Health. Volumes were calculated using product details from manufacturer websites.

For Norway, data were available on the number and age of children who had received at least one prescription of at least one of the included specialised formula products. These data in relation to total number of live births are shown in Figure 16.3. The proportion of infants prescribed specialised formula rose from 2.2% in 2009 to 6.9% in 2020. In 2020, the proportion of Norwegian infants less than one year prescribed a specialised formula was 11.2- to 13.3-fold greater than expected.

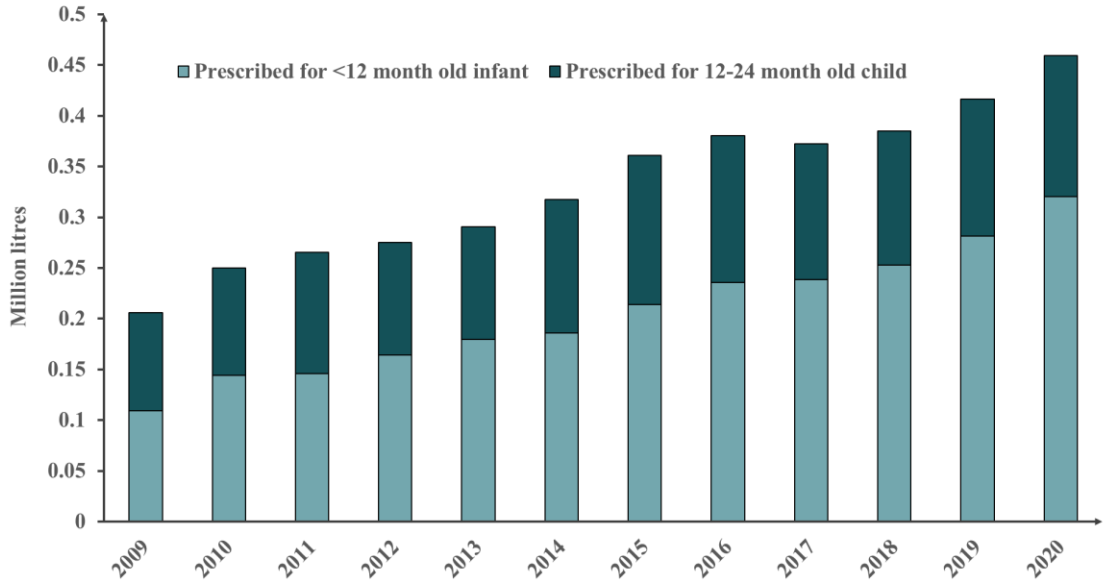
Figure 16.3. Percentage of infants under 1 year old prescribed a specialised infant formula in Norway



Data on the number of infants under 1 year prescribed a specialised formula for infants were obtained from the Norwegian Directorate of Health. Data are expressed as % annual live births for the same calendar year, obtained from Statistics Norway. Predicted lower and upper bound estimates for % of infants who have milk allergy and are formula-fed is based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2007 and 2019 Norwegian National Dietary Surveys among 6 and 12-month-old infants and the 2013 Norwegian National Survey. (218) In 2020, the proportion of Norwegian infants less than one year prescribed a specialised formula was 11.2- to 13.3-fold higher than expected.

In 2020, 69.7% of specialised formula marketed for infants under one year was prescribed for this age group, but 30.3% was prescribed for older children (Figure 16.4).

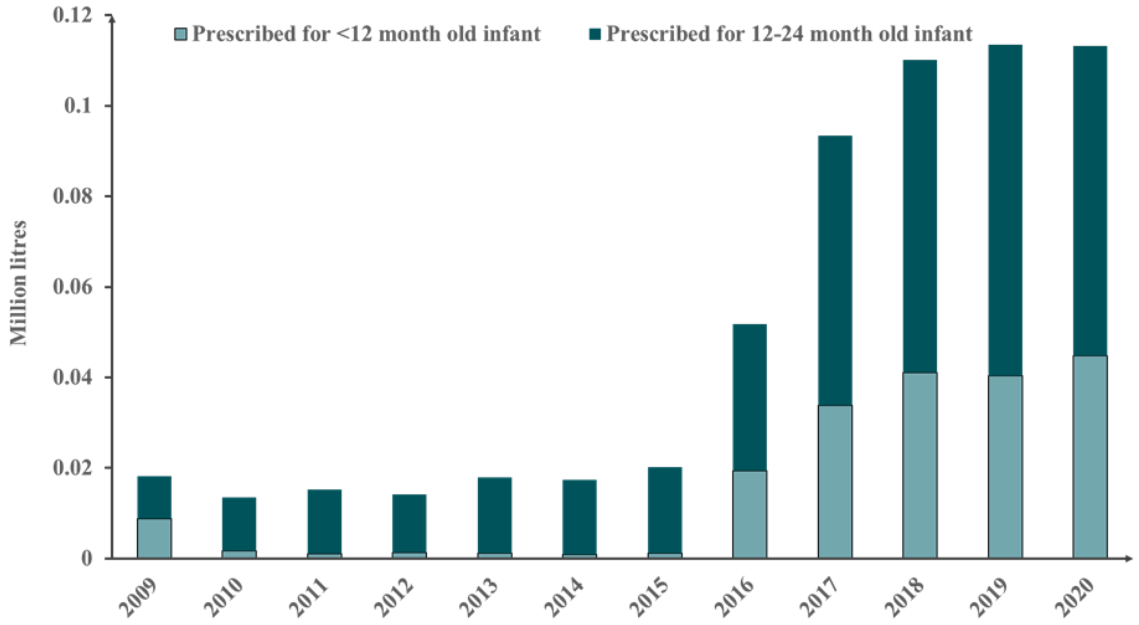
Figure 16.4. Age of children prescribed specialised infant formulas for under 1-year olds in Norway



Data were obtained from the Norwegian Directorate of Health. Volumes were calculated using product details from manufacturer websites. In 2020, 70% of the total volume of specialised infant formulas for under one year olds was consumed by this age group and 30% by children aged between 12 and 23 months.

Similarly, 60.4% of specialised formula marketed for children over one year was prescribed for this age group, but 39.6% was prescribed for infants under one (Figure 16.5).

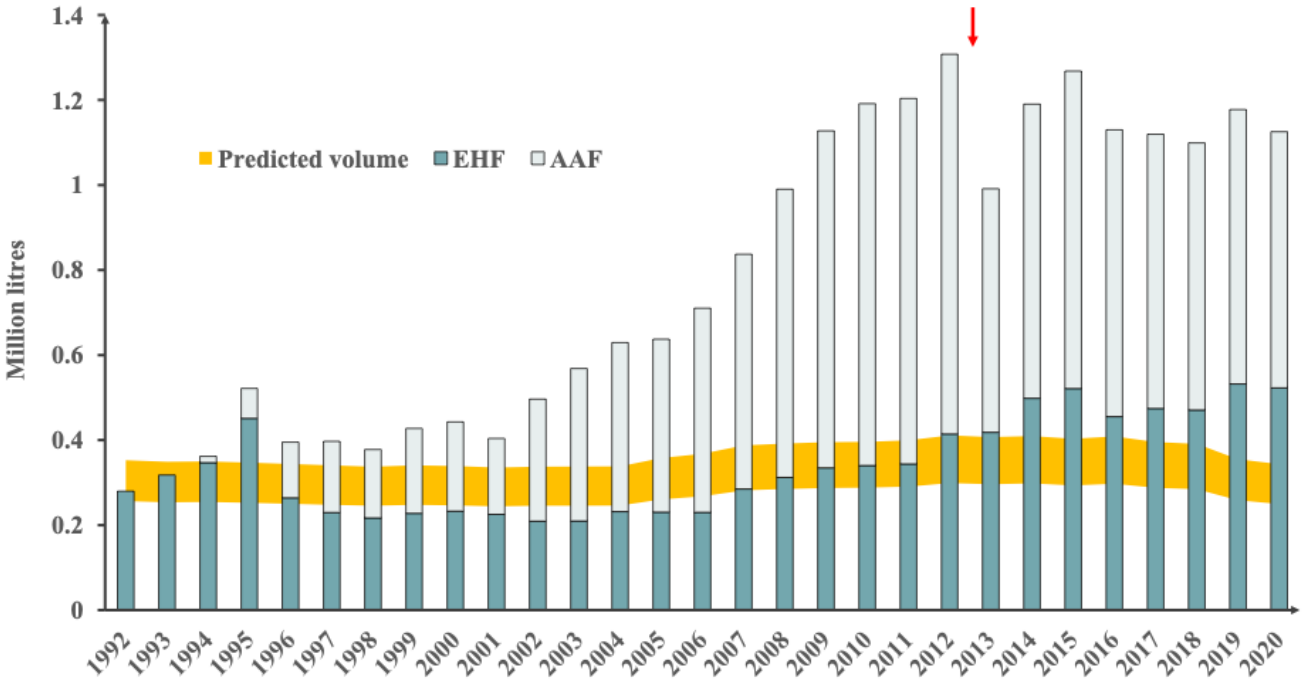
Figure 16.5 Age of children prescribed specialised infant formulas for 12- to 23-month-olds in Norway



Data were obtained from the Norwegian Directorate of Health. Volumes were calculated using product details from manufacturer websites. In 2020, 60% of the total volume of specialised infant formulas for children aged 12 to 23 months was consumed by this age group, and 40% by under one year old infants.

Data for specialised formula products marketed for infants less than one year in Australia are shown in Figure 16.6. Prescribed volumes rose 3.2-fold between 2001 and 2012. This represents a 1.8-fold increase in EHF and a 5.0-fold increase in AAF for those years. Prescribing restrictions were introduced in late 2012 which mandated specialist consultation for prescription of AAF. Direct sale of EHF and rice-based formula to the public was introduced in 2013 which may also have limited any further rise in reimbursed specialised formula volumes after 2012. Despite increased availability of EHF outside of the PBS system, reimbursed volumes of EHF continued to increase from 2013 to 2020. In 2012, the last year where data are likely to be complete, the total volume of reimbursed specialised formula was 3.2 to 4.4-fold greater than expected. In 2020, where data are likely to be incomplete due to availability of EHF and rice infant formula without prescription (i.e. over the counter), the total volume of reimbursed specialised formula was 3.3 to 4.5-fold greater than expected.

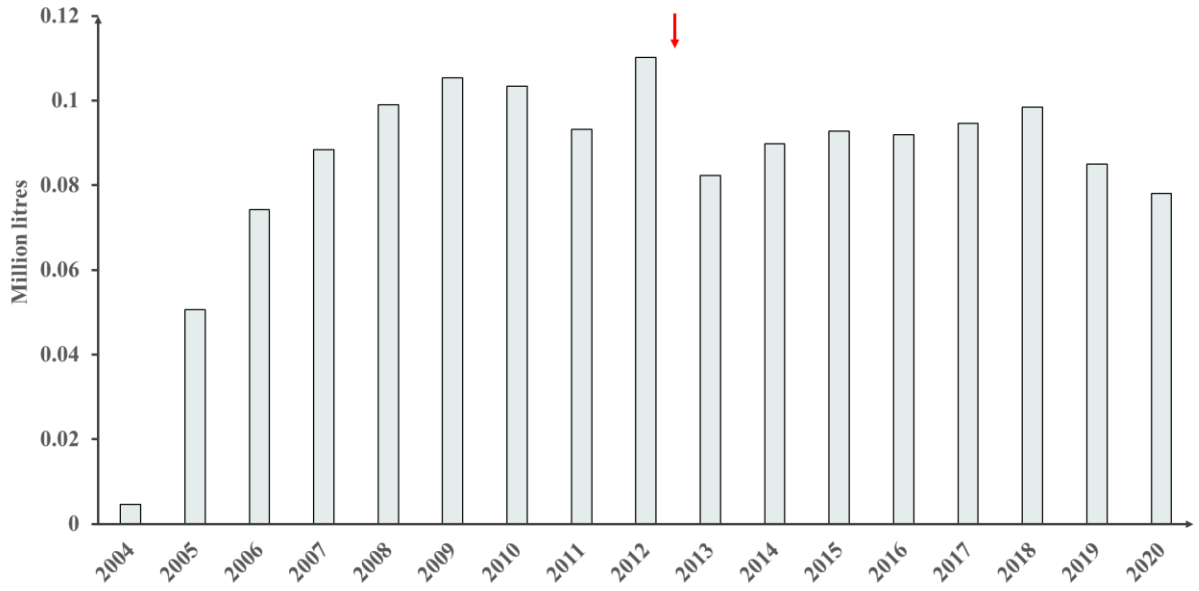
Figure 16.6. Volume of reimbursed specialised infant formulas for under 1 year olds with milk allergy in Australia



Data on the number of community prescriptions reimbursed by the Pharmaceutical Benefits Schedule and Repatriation Pharmaceutical Benefits Schedule for powdered amino acid formula (AAF) and extensively hydrolysed formula (EHF) products were obtained from Services Australia. Volumes were calculated using product details from manufacturer websites. Predicted volumes are the lower and upper bound range of expected total specialised formula consumption, based on 1% of live births each year with milk allergy, population-based formula feeding rates from the 2010 Australian National Infant Feeding Survey (Appendix 22.4) and estimated daily formula consumption of 780ml at 0-5.9 months and 600ml at 6-11.9 months. (218) The Pharmaceutical Benefits Advisory Committee mandated specialist consultations prior to approval of AAF prescriptions products from July 2012 onwards (red arrow) and direct to customer sales of EHF and rice-protein-based formulas were introduced from 2013. Direct to customer sales data and sales of soya formula could not be included in this analysis. In 2020, the total volume of reimbursed specialised formula was 3.3 to 4.5-fold higher than expected.

Volumes of reimbursed specialised formula marketed for children over one year in Australia increased to 2012, exclusively AAF, but were also stable between 2013 and 2020 at approximately one-tenth the volumes for infants less than one year (Figure 16.7). In 2020, AAF accounted for 33.7% of prescribed specialised formula in England, 30.6% in Norway and 53.5% in Australia.

Figure 16.7: Volume of reimbursed specialised infant formulas for over 1-year olds in Australia

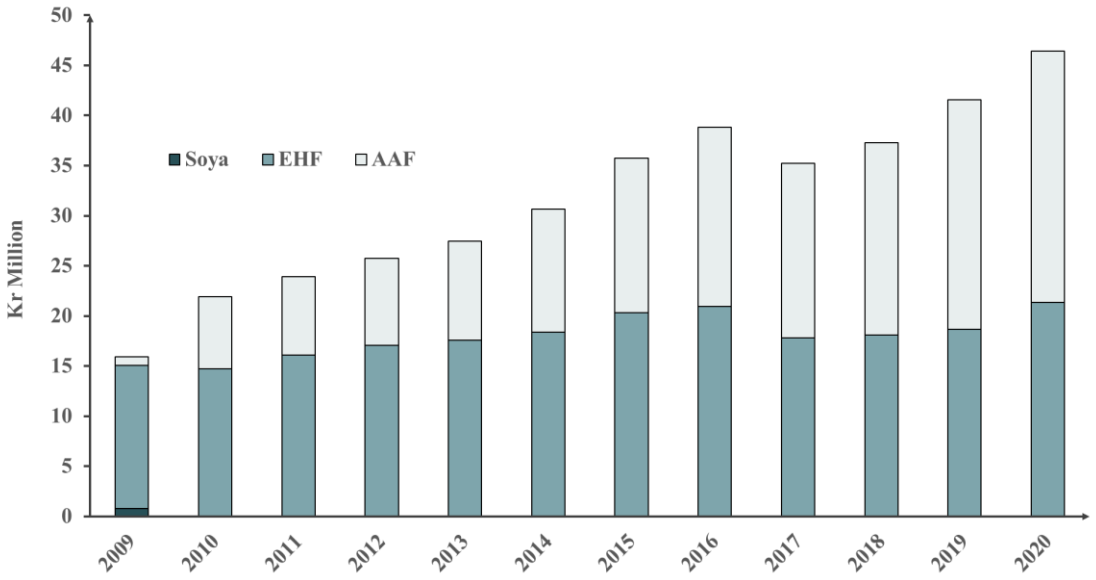


Data on the number of community prescriptions reimbursed by the Pharmaceutical Benefits Schedule and Repatriation Pharmaceutical Benefits Schedule were obtained from Services Australia. The only products marketed specifically for over 1 year olds in Australia were amino acid formula (AAF) products, first introduced in 2004. Volumes were calculated using product details from manufacturer websites. The Pharmaceutical Benefits Advisory Committee mandated specialist consultations prior to approval of AAF prescriptions products from July 2012 onwards (red arrow) and direct to customer sales of EHF and rice-protein-based formulas were introduced from 2013. Direct to customer sales data and sales of soya formula could not be included in this analysis.

Trends in expenditure on reimbursed specialised formula

Data for expenditure on specialised formula products marketed for infants less than one year in Norway are shown in Figure 16.8. Prescription costs rose from Kr15.9 million per annum in 2009 to Kr46.4 million per annum in 2020. AAF accounted for 54% of expenditure in 2020. In 2020 Norway's public expenditure on specialised formula for managing milk allergy equated to Kr880 (US$93; €82 euros) per infant born in that year.

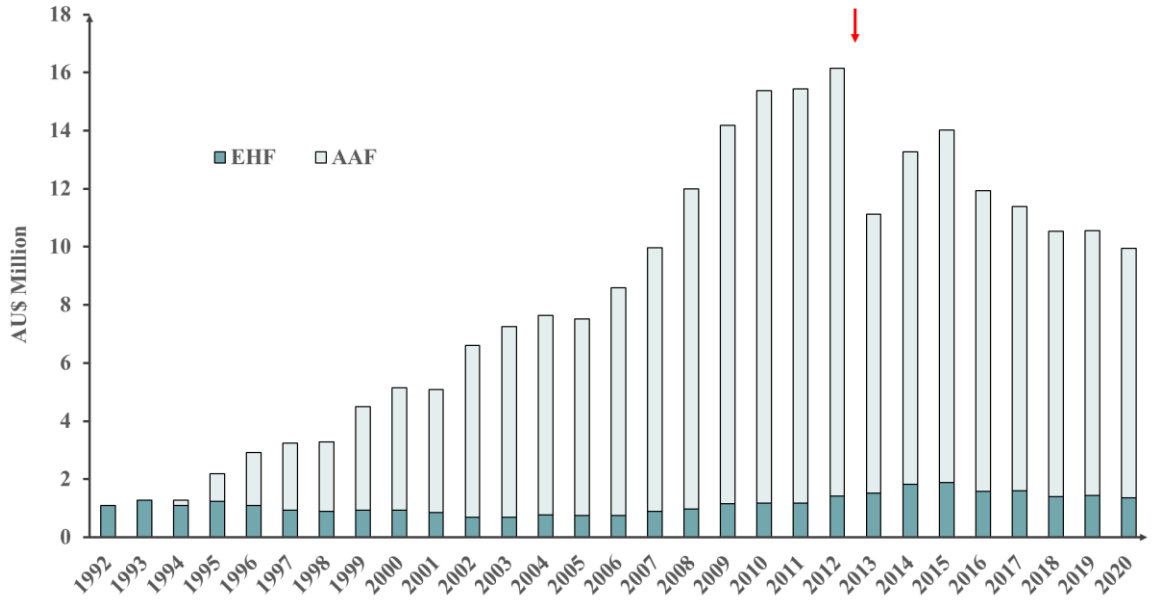
Figure 16.8. Total reimbursement cost of specialised infant formula for under 1-year olds in Norway



Data on the reimbursement cost (in Norwegian krone, (kr) of all amino acid formulas (AAF), extensively hydrolysed formulas (EHF), and soya formulas marketed for infants under age 1 year with cow's milk allergy were obtained from the Norwegian Directorate of Health.

Data for expenditure on specialised formula products marketed for infants less than one year in Australia are shown in Figure 16.9. Prescription costs rose from AU$1.1 million per annum in 1992 to AU$16.2 million in 2012. Following prescribing restrictions introduced in late 2012, costs fell to AU$10.0 million by 2020. AAF accounted for the majority of specialised formula expenditure from 1996 onwards and 86% in 2020. In 2020, Australia's public expenditure on specialised formula for managing milk allergy equated to AU$39 (US$27; €23 euros) per infant born in that year.

Figure 16.9. Total reimbursement cost of specialised infant formula for under 1 year olds in Australia



Data on the reimbursement costs (in Australian Dollars, $) of all amino acid formulas (AAF) and extensively hydrolysed formulas (EHF) marketed for infants under age 1 year with cow's milk allergy were obtained from Services Australia. The Pharmaceutical Benefits Advisory Committee mandated specialist consultations prior to approval of AAF prescriptions products from July 2012 onwards (red arrow) and direct to customer sales of EHF and rice-protein-based formulas were introduced from 2013. Direct to customer sales data and sales of soya formula could not be included in this analysis.

16.4 Discussion

In this international survey we identified two countries with comprehensive, publicly available databases of specialised formula prescription for infants with cow's milk allergy. In both countries, there was a marked rise in volumes of specialised formula reimbursed by public health systems in the early 21st century, similar to the United Kingdom, and also without evidence of increased prevalence of milk allergy. (120-122,130)

The data suggest that by 2020 there was 10-fold excess use of specialised formula by volume for managing milk allergy in Norway and at least three-fold excess use in Australia, where non-recorded specialised formula use is likely to be greater than in the United Kingdom and Norway. In Norway, the proportion of infants prescribed specialised formula was also at least 10 times expected levels. These data suggest high levels of milk allergy overdiagnosis and mark a potentially important shift in early child nutrition. The findings fit within a wider picture of global increases in per capita consumption of infant formula, which itself represents an important shift in early child nutrition. (273) Rapid increases in AAF reimbursement were first noted in Australia in 2006. (2,3,113) However, this is the first comprehensive evaluation of trends in Australia and the first report of trends in Norway. The lack of further increase in AAF prescription in Australia since 2013 is likely due to prescribing restrictions put in place at that time. AAF prescriptions were 2.2-3.0 fold higher than expected total specialised infant formula prescriptions in Australia in 2012, compared with 0.7-1.4 fold for Norway; whereas by 2020 AAF rates were up to 4-fold higher than expected in Norway, but only up to 2.4-fold higher in Australia.

Limitations

This study included reimbursements from community prescriptions only and did not consider other sources of specialised formula prescriptions, such as secondary care or direct consumer

purchase such as through online sales. In Australia, these are likely to have been higher than in Norway since 2013, which may partly explain the lower rates of specialised formula use in Australia. There is some uncertainty about the assumptions underlying our calculations as outlined in the limitations section of Chapter 13; in particular, we estimated CMA incidence as 1% based on a European epidemiological study, and used general population infant formula feeding rates. However, the Norwegian data on number of infants prescribed a specialised formula show a similar level of overtreatment to the data for prescribed volumes, suggesting that formula consumption may be similar to population norms in those using specialised formula, at least in Norway. It is also possible that there has been an increase in milk allergy incidence although the most recent epidemiological evidence in Australia does not suggest this. (120,263) There may also be other reasons to account for the increased use of specialised formula that we have not considered. Finally, data are limited to two, high-income countries and trends in specialised formula consumption may differ in other settings - other methodologies may be needed to develop a complete understanding of global patterns of specialised formula use.

Conclusion

There is excessive specialised formula prescribing in Australia and Norway, with increases in the early 21st century. Excessive specialised formula use has been interpreted as a consequence of cow's milk allergy overdiagnosis, which in turn has been associated with adverse effects on maternal quality of life and breastfeeding confidence. (2,3,113,137) Further work is needed to understand the risk factors for acquiring milk allergy overdiagnosis and the role of patient charities, healthcare professionals, the formula industry and milk allergy guidelines in contributing to milk allergy overdiagnosis. (3,50)

17 Patient risk factors for acquiring a milk allergy label in the BEEP trial cohort

17.1 Introduction

In this study, we used a clinical trial birth cohort with prospective evaluation of CMA diagnosis to explore potential patient risk factors associated with CMA overdiagnosis. (78)

17.2 Methods

We analysed data from 1394 children born in England in 2014-2016 (BEEP trial, ISRCTN21528841). Participants underwent formal CMA diagnosis at ≤2 years. CMA overdiagnosis was defined in three separate ways: parent-reported milk reaction; primary care record of milk hypersensitivity symptoms; and primary care record of low-allergy formula prescription. A detailed description of methods is outlined in Section 12.5.

17.3 Results

Evaluation of participant-level risk factors for CMA overdiagnosis

We evaluated potential participant-level risk factors for CMA overdiagnosis (Tables 17.1-17.4). Participants with true CMA (n=19) were excluded from these analyses. In multivariate analysis, maternal report of antenatal use of antibiotic prescription during pregnancy (included as a potential marker of healthcare-seeking behaviour), (274-276) was significantly associated with all three definitions of CMA overdiagnosis (parent-reported OR 1.79, 95% CI 1.19-2.70, p<0.006; primary care record OR 2.11, 95% CI 1.30-3.42, p<0.003; low-allergy formula prescription OR 2.36 95% CI 1.33-4.18, p<0.003). Exclusive formula feeding from birth was significantly associated with low-allergy formula prescription (OR 2.50 95% CI 1.31-4.75, p<0.005) but not with other measures of CMA overdiagnosis. These associations were apparent in both adjusted and unadjusted analysis.

Table 17.1. Overview of participant characteristics and CMA overdiagnosis

	Parent-reported milk reaction				Primary care record of cow's milk hypersensitivity				Primary care record of low-allergy formula prescription			
	Adjusted (n=777)†		**Adjusted** (n=777)‡		**Adjusted** (n=758)†		**Adjusted** (n=758) ‡		**Adjusted** (n=757) †		**Adjusted** (n=757) ‡	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Maternal Age	0.99 (0.95-1.03)	0.67	-	-	0.99 (0.94-1.04)	0.68	-	-	0.96 (0.91-1.02)	0.24	-	-
White maternal ethnicity	0.85 (0.45-1.63)	0.64	-	-	0.61 (0.30-1.24)	0.17	-	-	0.78 (0.31-1.97)	0.60	-	-
Antibiotics used in pregnancy	1.70 (1.12-2.59)	0.01	1.79 (1.19-2.70)	0.006	2.00 (1.22-3.28)	0.006	2.11 (1.30-3.42)	0.003	2.25 (1.25-4.05)	0.007	2.36 (1.33-4.18)	0.003
More than one first degree relative with atopic disease	0.92 (0.59-1.43)	0.71	-	-	0.89 (0.53-1.51)	0.67	-	-	1.11 (0.59-2.09)	0.76	-	-
No other children in household	0.91 (0.59-1.40)	0.66	-	-	0.83 (0.49-1.40)	0.48	-	-	1.10 (0.59-2.04)	0.77	-	-
Maternal anxiety/depression on EQ-5D (at baseline)	0.70 (0.41-1.20)	0.19	-	-	0.81 (0.43-1.52)	0.52	-	-	0.87 (0.41-1.84)	0.72	-	-
Maternal EQ-5D health state at baseline	0.99 (0.97-1.00)	0.11	-	-	0.98 (0.97-1.00)	0.09	-	-	0.99 (0.97-1.01)	0.46	-	-
Exclusive formula feeding from birth to 6 months old	1.50 (0.89-2.52)	0.13	-	-	1.79 (0.98-3.25)	0.06	1.72 (0.96-3.09)	0.07	2.51 (1.30-4.86)	0.006	2.50 (1.31-4.75)	0.005
Family decile of English Index of Multiple Deprivation 2015	1.00 (0.93-1.08)	0.97	-	-	1.03 (0.94-1.13)	0.56	-	-	1.02 (0.91-1.15)	0.68	-	-

Logistic regression analysis comparing participant characteristics with CMA overdiagnosis, excluding the 19 confirmed milk-allergic participants. CMA overdiagnosis was defined by parent-reported milk reaction (n=195), positive mention of reaction to milk in the primary care records (n=124) and prescription of low-allergy formula in the records (n=77). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk whose prescription records were missing (n=5) were excluded from analysis. Remaining BEEP study participants who did not answer yes to any of the screening questions, and participants who did not have a mention of a milk reaction in the primary care records or prescription of low allergy formula were considered not to have CMA overdiagnosis. Values were adjusted to consider the association of all participant variables together on each outcome. Odds ratio (OR) > 1 shows a positive association between each variable and the outcome. Confidence intervals are 95% and p-value <0.05 indicates statistical significance. †Step 1 of backward stepwise regression including all co-variates ‡ Final step of backward stepwise regression

Table 17.2: Participant characteristics and parent-reported cow's milk reaction

	Unadjusted		**Adjusted** (n=777)†		**Adjusted** (n=777)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1209)	0.99 (0.96-1.02)	0.35	0.99 (0.95-1.03)	0.67	-	-
White maternal ethnicity (white, n=1037; non-white, n=172)	1.04 (0.67-1.62)	0.87	0.85 (0.45-1.63)	0.64	-	-
Antibiotics used in pregnancy (yes, n=345; no, n=854)	1.58 (1.15-2.19)	0.005	1.70 (1.12-2.59)	0.01	1.79 (1.19-2.70)	0.006
More than one first degree relative with atopic disease (two or more, n=767; one, n=442)	1.04 (0.75-1.42)	0.83	0.92 (0.59-1.43)	0.71	-	-
No other children in household (only child, n=506; other children, n=703)	0.96 (0.70-1.31)	0.80	0.91 (0.59-1.40)	0.66	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=188; no anxiety, n=709)	0.89 (0.57-1.39)	0.59	0.70 (0.41-1.20)	0.19	-	-
Maternal EQ-5D health state at baseline (n=891)	0.99 (0.98-1.00)	0.08	0.99 (0.97-1.00)	0.11	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=157; all other feeding, n=837)	1.53 (1.00-2.35)	0.05	1.50 (0.89-2.52)	0.13	-	-
Family decile of English Index of Multiple Deprivation 2015 (n=1185)	0.97 (0.92-1.03)	0.34	1.00 (0.93-1.08)	0.97	-	-

Logistic regression comparing participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort who answered the screening questions (n=1014). BEEP participants who did not answer the screening questions were excluded from analysis (n=166). Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome).

Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=777) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

Table 17.3: Participant characteristics and primary care record of cow's milk hypersensitivity

	Unadjusted		**Adjusted** (n=758)†		**Adjusted** (n=758)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1169)	0.99 (0.95-1.02)	0.45	0.99 (0.94-1.04)	0.68	-	-
White maternal ethnicity (white, n=1002; non-white, n=167)	0.98 (0.58-1.67)	0.94	0.61 (0.30-1.24)	0.17	-	-
Antibiotics used in pregnancy (yes, n=331; no, n=828)	1.91 (1.30-2.80)	<0.001	2.00 (1.22-3.28)	0.006	2.11 (1.30-3.42)	0.003
More than one first degree relative with atopic disease (two or more, n=742; one, n=427)	1.14 (0.77-1.69)	0.52	0.89 (0.53-1.51)	0.67	-	-
No other children in household (only child, n=486; other children, n=683)	0.84 (0.57-1.24)	0.38	0.83 (0.49-1.40)	0.48	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=184; no anxiety, n=686)	0.98 (0.58-1.65)	0.94	0.81 (0.43-1.52)	0.52	-	-
Maternal EQ-5D health state at baseline (n=863)	0.99 (0.97-1.01)	0.17	0.98 (0.97-1.00)	0.09	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=151; all other feeding, n=814)	1.78 (1.09-2.93)	0.02	1.79 (0.98-3.25)	0.06	1.72 (0.96-3.09)	0.07
Family decile of English Index of Multiple Deprivation 2015 (n=1146)	0.97 (0.90-1.04)	0.35	1.03 (0.94-1.13)	0.56	-	-

Logistic regression comparing potential risk factors associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have a reaction to milk (n=1045). Participants who did not answer any of the screening questions (n=166) and the primary care records that were not received (n=40) were excluded from analysis. Odds ratio (OR) >1 shows a

positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=758) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

Table 17.4: Participant characteristics and primary care record of low-allergy formula prescription

	Unadjusted		Adjusted (n=757)†		Adjusted (n=757)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	
Maternal Age (n=1164)	0.97 (0.92-1.01)	0.10	0.96 (0.91-1.02)	0.24	-	-
White maternal ethnicity (white, n=999; non-white, n=165)	1.19 (0.60-2.35)	0.63	0.78 (0.31-1.97)	0.60	-	-
Antibiotics used in pregnancy (yes, n=330; no, n=824)	2.05 (1.30-3.26)	0.002	2.25 (1.25-4.05)	0.007	2.36 (1.33-4.18)	0.003
More than one first degree relative with atopic disease (two or more, n=738; one, n=426)	1.24 (0.77-2.01)	0.38	1.11 (0.59-2.09)	0.76	-	-
No other children in household (only child, n=486; other children, n=678)	0.96 (0.60-1.51)	0.85	1.10 (0.59-2.04)	0.77	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=184; no anxiety, n=684)	1.00 (0.54-1.85)	1.00	0.87 (0.41-1.84)	0.72	-	-
Maternal EQ-5D health state at baseline (n=861)	0.99 (0.97-1.01)	0.46	0.99 (0.97-1.01)	0.46	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=150; all other feeding, n=811)	2.32 (1.31-4.13)	0.004	2.51 (1.30-4.86)	0.006	2.50 (1.31-4.75)	0.005
Family decile of English Index of Multiple Deprivation 2015 (n=1142)	0.97 (0.89-1.05)	0.39	1.02 (0.91-1.15)	0.68	-	-

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription (n=1086). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk

whose prescription records were missing (n=5) were excluded from analysis. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=757) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression.

CMA overdiagnosis was not associated with maternal age, maternal ethnicity, family history of atopic disease, being an only child, maternal psychological health and wellbeing in the antenatal and early postnatal period or socioeconomic status.

We explored the same participant-level risk factors for low-allergy formula prescription within the population who had a primary care record of milk hypersensitivity (n=124) (Table 17.5). Maternal age (OR 0.85 95% CI 0.74-0.97, p=0.02) and age of child at diagnosis (OR 0.97 95% CI 0.94-1.00, p=0.02) were associated with reduced odds of low-allergy formula prescription. This means that children with an older mother or a child who was older at the time of CMA overdiagnosis were less likely to be prescribed low-allergy formula.

Table 17.5: Participant characteristics and primary care record of a low-allergy formula prescription in participants with a primary care record of cow's milk hypersensitivity

	Unadjusted		**Adjusted** (n=72)†		**Adjusted** (n=72)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=119)	0.96 (0.89-1.03)	0.24	0.84 (0.71-0.99)	0.03	0.85 (0.74-0.97)	0.02
White maternal ethnicity (white, n=103; non-white, n=16)	1.27 (0.42-3.80)	0.67	1.01 (0.16-6.44)	0.99	-	-
Antibiotics used in pregnancy (yes, n=50; no, n=68)	1.09 (0.50-2.37)	0.84	0.87 (0.19-4.01)	0.86	-	-
No other children in household (only child, n=47; other children, n=72)	1.07 (0.49-2.34)	0.87	0.94 (0.20-4.51)	0.94	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=20; no anxiety, n=74)	1.05 (0.36-3.09)	0.93	3.96 (0.42-37.47)	0.23	-	-
Maternal EQ-5D health state (at baseline) (n=94)	1.01 (0.98-1.05)	0.52	1.01 (0.96-1.06)	0.76	-	-
Family decile of English Index of Multiple Deprivation 2015 (n=115)	0.97 (0.84-1.12)	0.66	0.86 (0.65-1.14)	0.29	-	-
Age of child when symptoms were first considered related to milk (weeks) (n=113)	0.96 (0.94-0.98)	<0.001	0.97 (0.95-1.00)	0.04	0.97 (0.94-1.00)	0.02
Formula fed only at first mention of milk related symptoms (formula only, n= 49; all other feeding, n=55)	0.77 (0.32-1.86)	0.57	1.30 (0.31-5.38)	0.72	-	-

Parent only raised the initial concern about reaction to milk (parent only, n=36; healthcare practitioner with/without parent, n=72)	0.62 (0.27-1.41)	0.25	1.32 (0.30-5.81)	0.72	-	-

Multivariate logistic regression comparing potential risk factors associated with a prescription of low-allergy formula within the cohort who have a positive mention of a reaction to milk in the primary care records, excluding the 19 confirmed milk allergic participants (n=124). Prescription records were missing for 5 participants with a reported reaction to milk in the primary care records. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=72) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

We undertook further analyses to investigate the potential impact of missing data on findings. We compared characteristics of participants with and without missing values in the risk factors (Tables S10-S12, Appendix 22.11), undertook a sensitivity analysis excluding EQ5D variables, which had the highest rate of missingness (Tables S13-S15, Appendix 22.11) and undertook multiple imputation (Tables S16-S18, Appendix 22.11). Findings continued to support an association between maternal report of antibiotic prescription during pregnancy and all CMA overdiagnosis outcomes (parent reported / primary care record / low-allergy formula prescription); and between exclusive formula feeding from birth and low-allergy formula prescription.

17.4 Discussion

We identified maternal report of antibiotic prescription during pregnancy as a risk factor for CMA overdiagnosis. Exclusive formula feeding from birth was associated with increased risk of low-allergy formula use but was not consistently associated with other markers of CMA overdiagnosis – indeed, CMA overdiagnosis commonly occurred in breastfed infants. The reason for this might be that changing formula in an exclusively formula fed infant is perceived as a relatively straightforward intervention. In contrast, using specialised formula in a fully or partially breastfed infant may be seen as a more complex intervention with potential to undermine breastfeeding. Maternal use of antibiotics in pregnancy was included in these analyses as a potential marker for increased healthcare-seeking behaviour, (274-276) and further work is needed to identify whether the healthcare-seeking behaviour of some mother/infant dyads puts them at increased risk for CMA overdiagnosis. It is interesting to note that the participant characteristics associated with CMA overdiagnosis are all potentially determined by human behaviour – maternal use of antibiotics in pregnancy requires attendance at a doctor, prescription of antibiotics by a doctor and maternal willingness to take

the antibiotics. In the same manner, exclusive formula feeding from birth may sometimes be a feeding choice, although this may be subject to external factors for example, lack of enabling environments and socioeconomic vulnerabilities. There are of course cases when antibiotics are needed in pregnancy and breastfeeding is not possible. However, it appears that the participant characteristics that cannot be directly determined through human choice or behaviour are not associated with CMA overdiagnosis – that is, family history, socioeconomic status, maternal health, maternal age and ethnicity. This suggests that there may be particular participant vulnerabilities associated with CMA overdiagnosis which are modifiable and requires further qualitative research. Such research may lead to improved understanding of parental perspectives and how parents can be better supported with symptoms of concern in their child.

Limitations

The participants in this study were from a clinical trial and therefore, healthcare seeking behaviour, especially in relation to allergy issues, may be different in the BEEP cohort from the general population. Antenatal prescription of antibiotics was not verified from prescription records and relied on maternal recollection which may affect the validity of this risk factor for CMA overdiagnosis. Maternal EQ-5D assessment was undertaken at the time of enrolment in the BEEP study which meant that some assessments were done in the antenatal period and some in the early postnatal period. It is possible that the finding of lack of association between EQ-5D and measures of CMA overdiagnosis would be different if the EQ-5D assessment was done consistently in either the antenatal period or early postnatal period for all participants.

18 GP Practice-level risk factors for acquiring a milk allergy label in the BEEP trial cohort

18.1 Introduction

In this study, we used a clinical trial birth cohort with prospective evaluation of CMA diagnosis to explore potential GP practice-level risk factors associated with CMA. (78)

18.2 Methods

We analysed data from 1394 children born in England in 2014-2016 (BEEP trial, ISRCTN21528841). Participants underwent formal CMA diagnosis at ≤2 years. CMA overdiagnosis was defined in three separate ways: parent-reported milk reaction; primary care record of milk hypersensitivity symptoms; and primary care record of low-allergy formula prescription. A detailed description of methods is outlined in Section 12.5.

18.3 Results

Evaluation of practice-level risk factors for CMA overdiagnosis

We evaluated potential primary care practice-level risk factors for CMA overdiagnosis (Tables 18.1, S21-S24. Appendix 22.14). Practice low-allergy formula prescribing rate (litres/infant aged <1 year) was significantly associated with CMA overdiagnosis (parent-reported OR 1.03, 95% CI 1.02-1.05, p<0.001; primary care record OR 1.04, 95% CI 1.02-1.06, p<0.001; low-allergy formula prescription OR 1.04, 95% CI 1.02-1.07, p<0.001). Practice antibiotic prescribing rate (a marker of overprescribing) (236,237,239) was not positively associated with CMA overdiagnosis. Indeed, there was a weak inverse association between practice antibiotic prescribing and the three measures of CMA overdiagnosis; which remained when antibiotic prescribing was adjusted based on the demographic structure of the

practice population (STAR-PU). Other practice features such as prescribing rates for AAI and reflux treatments, deprivation and local guideline recommendations were not associated with CMA overdiagnosis (Table 18.1).

Table 18.1: Overview of Practice-level variables comparing participants with and without CMA overdiagnosis

	Parent-reported milk reaction				Primary care record of cow's milk hypersensitivity				Primary care record of low-allergy formula prescription			
	Adjusted (n=1193)†		**Adjusted** (n=1193)‡		**Adjusted** (n=1153)†		**Adjusted** (n=1153)‡		**Adjusted** (n=1148)†		**Adjusted** (n=1148)‡	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population)	1.03 (1.01-1.05)	0.002	1.03 (1.02-1.05)	<0.001	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.07)	0.001	1.04 (1.02-1.07)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population)	0.995 (0.99-1.00)	0.05	0.996 (0.992-1.00)	0.09	0.998 (0.997-1.00)	0.02	0.999 (0.997-1.00)	0.03	0.998 (0.996-1.00)	0.02	0.998 (0.997-1.00)	0.03
Practice Decile of English Index of Multiple Deprivation (IMD) 2019	0.97 (0.91-1.03)	0.33	-	-	0.96 (0.89-1.04)	0.3	-	-	0.96 (0.88-1.05)	0.36	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population)	1.03 (1.00-1.05)	0.06	-	-	1.03 (1.00-1.06)	0.09	-	-	1.02 (0.99-1.06)	0.23	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population)	1.00 (0.99-1.01)	0.85	-	-	1.00 (0.99-.01)	0.60	-	-	1.00 (0.99-1.01)	0.98	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population)	1.00 (1.00-1.01)	0.67	-	-	1.00 (1.00-1.01	0.64	-	-	1.00 (0.99-1.01)	0.69	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis	1.59 (0.96-2.63)	0.07	-	-	1.57 (0.86-2.86)	0.14	-	-	1.64 (0.81-3.32)	0.17	-	-
Antibiotic Items/STARPU (Average of 4 quarters for 2014)§	0.97 (0.01-1.58)	0.10	0.10 (0.01-1.30)	0.08	0.16 (0.00-0.52)	0.02	0.03 (0.00-0.72)	0.03	0.01 (0.00-0.49)	0.02	0.02 (0.00-0.73)	0.03

Logistic regression comparing practice-level variables of those participants with CMA overdiagnosis with the remaining BEEP study cohort without CMA overdiagnosis, excluding the 19 confirmed milk-allergic participants. CMA overdiagnosis was defined by parent-reported milk reaction (n=195), positive mention of reaction to milk in the primary care records (n=124) and prescription of low-allergy formula in the records (n=77). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk whose prescription records were missing (n=5) were

excluded from analysis. Remaining BEEP study participants who did not answer yes to any of the screening questions, and participants who did not have a mention of a milk reaction in the primary care records or prescription of low allergy formula were considered not to have CMA overdiagnosis. No data was available for 15 GP practices. Odds ratio (OR) >1 shows a positive association between each variable and each outcome. Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Adjusted values consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. §Antibiotic Items/STARPU was substituted for practice antibiotic prescription items as a predictor variable to adjust for gender and sex effect on antibiotic prescribing in the practice.

When practice-level and participant-level variables were combined (Tables 18.2-18.5), associations were similar, including when multiple imputation was used to account for missing data (Tables S25-S27. Appendix 22.14). These analyses found practice low-allergy formula prescribing rates in the previous year and maternal report of antibiotic prescription during pregnancy were associated with all three measures of CMA overdiagnosis; and exclusive formula feeding from birth with low-allergy formula prescription.

Table 18.2: Combined participant and practice-level variables comparing participants with and without parent-reported cow's milk hypersensitivity

	Parent-reported cow's milk hypersensitivity				Primary care record of cow's milk hypersensitivity				Primary care record of low-allergy formula prescription			
	Adjusted (n=529)†		**Adjusted** (n=529)‡		**Adjusted** (n=515)†		**Adjusted** (n=515)‡		**Adjusted** (n=514)†		**Adjusted** (n=514)‡	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Maternal Age	0.96 (0.91-1.01)	0.12	-	-	0.97 (0.91-1.03)	0.31	-	-	0.95 (0.88-1.02)	0.15	-	-
White maternal ethnicity	0.56 (0.23-1.35)	0.20	-	-	0.36 (0.14-0.95)	0.04	0.43 (0.17-1.06)	0.07	0.41 (0.13-1.22)	0.11	-	-
Antibiotics used in pregnancy	1.95 (1.17-3.27)	0.01	1.97 (1.19-3.26)	0.008	2.09 (1.12-3.88)	0.02	2.17 (1.19-3.97)	0.01	2.10 (1.02-4.29)	0.04	2.42 (1.22-4.82)	0.01
More than one first degree relative with atopic disease	1.11 (0.64-1.92)	0.72	-	-	1.33 (0.67-2.64)	0.42	-	-	1.50 (0.67-3.34)	0.32	-	-
No other children in household	1.00 (0.58-1.71)	0.99	-	-	0.92 (0.48-1.78)	0.80	-	-	1.15 (0.54-2.45)	0.71	-	-
Maternal anxiety/depression on EQ-5D (at baseline)	0.64 (0.32-1.29)	0.21	-	-	0.91 (0.41-2.02)	0.81	-	-	0.74 (0.28-1.96)	0.54	-	-
Maternal EQ-5D health state at baseline	0.98 (0.96-1.00)	0.03	0.98 (0.96-1.00)	0.06	0.98 (0.96-1.01)	0.10	0.98 (0.96-1.00)	0.07	0.98 (0.95-1.01)	0.12	-	-
Exclusive formula feeding from birth to 6 months old	1.80 (0.96-3.37)	0.07	1.73 (0.94-3.18)	0.08	2.52 (1.23-5.19)	0.01	2.39 (1.19-4.78)	0.01	3.16 (1.42-7.02)	0.005	2.87 (1.35-6.10)	0.006
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population)	1.03 (0.96-1.05)	0.11	1.03 (1.00-1.05)	0.05	1.03 (1.00-1.06)	0.08	1.04 (1.01-1.07)	0.007	1.04 (1.02-1.07)	0.001	1.04 (1.02-1.07)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population)	1.00 (0.99-1.00)	0.78	-	-	0.99 (0.99-1.00)	0.59	-	-	0.998 (0.996-1.00)	0.02	-	-

Practice Decile of English Index of Multiple Deprivation (IMD) 2019	1.04 (0.95-1.15)	0.41	-	-	1.06 (0.94-1.19)	0.38	-	-	0.96 (0.88-1.05)	0.36	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population)	1.00 (0.95-1.05)	0.99	-	-	1.00 (0.94-1.07)	0.94	-	-	1.02 (0.99-1.06)	0.23	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population)	1.00 (0.99-1.01)	0.81	-	-	1.00 (0.99-1.02)	0.63	-	-	1.00 (0.99-1.01)	0.98	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population)	1.00 (0.99-1.01)	0.94	-	-	1.01 (1.00-1.01)	0.32	-	-	1.00 (0.99-1.01)	0.69	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis	1.91 (1.01-3.63)	0.05	1.86 (0.99-3.46)	0.05	1.60 (0.73-3.53)	0.24	-	-	1.64 (0.81-3.32)	0.17	-	-

Logistic regression comparing combined participant and practice-level variables of those participants with CMA overdiagnosis with the remaining BEEP study cohort without CMA overdiagnosis, excluding the 19 confirmed milk-allergic participants. CMA overdiagnosis was defined by parent-reported milk reaction (n=195), positive mention of reaction to milk in the primary care records (n=124) and prescription of low-allergy formula in the records (n=77). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk whose prescription records were missing (n=5) were excluded from analysis. Remaining BEEP study participants who did not answer yes to any of the screening questions, and participants who did not have a mention of a milk reaction in the primary care records or prescription of low allergy formula were considered not to have CMA overdiagnosis. No data was available for 15 GP practices. Odds ratio (OR) >1 shows a positive association between each variable and each outcome. Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Adjusted values consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates. ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD.

Table 18.3: Combined participant and practice-level variables comparing participants with and without parent-reported cow's milk hypersensitivity

	Adjusted (n=529)†		**Adjusted** (n=529)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1209)	0.96 (0.91-1.01)	0.12	-	-
White maternal ethnicity (white, n=1037; non-white, n=172)	0.56 (0.23-1.35)	0.20	-	-
Antibiotics used in pregnancy (yes, n=345; no, n=854)	1.95 (1.17-3.27)	0.01	1.97 (1.19-3.26)	0.008
More than one first degree relative with atopic disease (two or more, n=767; one, n=442)	1.11 (0.64-1.92)	0.72	-	-
No other children in household (only child, n=506; other children, n=703)	1.00 (0.58-1.71)	0.99	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=188; no anxiety, n=709)	0.64 (0.32-1.29)	0.21	-	-
Maternal EQ-5D health state at baseline (n=891)	0.98 (0.96-1.00)	0.03	0.98 (0.96-1.00)	0.06
Exclusive formula feeding from birth to 6 months old (formula only, n=157; all other feeding, n=837)	1.80 (0.96-3.37)	0.07	1.73 (0.94-3.18)	0.08
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1149)	1.03 (0.96-1.05)	0.11	1.03 (1.00-1.05)	0.05
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1149)	1.00 (0.99-1.00)	0.78	-	-

Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1149)	1.04 (0.95-1.15)	0.41	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1149)	1.00 (0.95-1.05)	0.99	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1149)	1.00 (0.99-1.01)	0.81	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1149)	1.00 (0.99-1.01)	0.94	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1152)	1.91 (1.01-3.63)	0.05	1.86 (0.99-3.46)	0.05

Logistic regression comparing combined participant and practice-level variables of those participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort who answered the screening questions (n=1014). BEEP participants who did not answer the screening questions were excluded from analysis (n=166). Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1193) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD.

Table 18.4: Combined participant and practice-level variables comparing participants with and without a primary care record of cow's milk hypersensitivity

	Adjusted (n=515)†		**Adjusted** (n=515)†	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1209)	0.97 (0.91-1.03)	0.31	-	-
White maternal ethnicity (white, n=1037; non-white, n=172)	0.36 (0.14-0.95)	0.04	0.43 (0.17-1.06)	0.07
Antibiotics used in pregnancy (yes, n=345; no, n=854)	2.09 (1.12-3.88)	0.02	2.17 (1.19-3.97)	0.01
More than one first degree relative with atopic disease (two or more, n=767; one, n=442)	1.33 (0.67-2.64)	0.42	-	-
No other children in household (only child, n=506; other children, n=703)	0.92 (0.48-1.78)	0.80	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=188; no anxiety, n=709)	0.91 (0.41-2.02)	0.81	-	-
Maternal EQ-5D health state at baseline (n=891)	0.98 (0.96-1.01)	0.10	0.98 (0.96-1.00)	0.07
Exclusive formula feeding from birth to 6 months old (formula only, n=157; all other feeding, n=837)	2.52 (1.23-5.19)	0.01	2.39 (1.19-4.78)	0.01
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1154)	1.03 (1.00-1.06)	0.08	1.04 (1.01-1.07)	0.007
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1154)	0.99 (0.99-1.00)	0.59	-	-

Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1154)	1.06 (0.94-1.19)	0.38	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1154)	1.00 (0.94-1.07)	0.94	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1154)	1.00 (0.99-1.02)	0.63	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1154)	1.01 (1.00-1.01)	0.32	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1157)	1.60 (0.73-3.53)	0.24	-	-

Logistic regression comparing combined participant and practice-level variables associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have a reaction to milk (n=1045). Participants who did not answer any of the screening questions (n=166) and the primary care records that were not received (n=40) were excluded from analysis. Odds ratio (OR) >1 shows a positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1153) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD.

Table 18.5: Combined participant and practice-level variables comparing participants with and without a primary care record of low-allergy formula prescription

	Adjusted (n=514)†		**Adjusted** (n=514)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1209)	0.95 (0.88-1.02)	0.15	-	-
White maternal ethnicity (white, n=1037; non-white, n=172)	0.41 (0.13-1.22)	0.11	-	-
Antibiotics used in pregnancy (yes, n=345; no, n=854)	2.10 (1.02-4.29)	0.04	2.42 (1.22-4.82)	0.01
More than one first degree relative with atopic disease (two or more, n=767; one, n=442)	1.50 (0.67-3.34)	0.32	-	-
No other children in household (only child, n=506; other children, n=703)	1.15 (0.54-2.45)	0.71	-	-
Maternal anxiety/depression on EQ-5D (at baseline) (any anxiety, n=188; no anxiety, n=709)	0.74 (0.28-1.96)	0.54	-	-
Maternal EQ-5D health state at baseline (n=891)	0.98 (0.95-1.01)	0.12	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=157; all other feeding, n=837)	3.16 (1.42-7.02)	0.005	2.87 (1.35-6.10)	0.006
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1149)	1.04 (1.02-1.07)	0.001	1.04 (1.02-1.07)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1149)	0.998 (0.996-1.00)	0.02	-	-

Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1149)	0.96 (0.88-1.05)	0.36	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1149)	1.02 (0.99-1.06)	0.23	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1149)	1.00 (0.99-1.01)	0.98	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1149)	1.00 (0.99-1.01)	0.69	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1152)	1.64 (0.81-3.32)	0.17	-	-

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription (n=1086). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk whose prescription records were missing (n=5) were excluded from analysis. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1148) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD

18.4 Discussion

We identified higher practice-based prescribing of low-allergy formula as a risk factor for CMA overdiagnosis. Our findings suggest that the prescribing habits of primary care practitioners for low-allergy formula may be important for CMA overdiagnosis.

Higher GP practice-based prescribing of low-allergy formula was consistently associated with all three measures of CMA overdiagnosis – parent-reported, primary care record of CMA and primary care record of low-allergy formula prescription. This means that for each litre per infant increase in GP practice low-allergy formula prescribing in the previous year, there was a 2-7% increase in the odds that an infant registered with the practice would acquire a false label of CMA (adjusted OR ranging 1.03 to 1.04, 95% CI ranging 1.02 to 1.07). This suggests that receiving a false label of CMA may depend on the GP one sees when attending for primary healthcare which is an important finding when considering potential interventions.

Practice prescribing of antibiotics is a marker of over-prescribing but in this study, there was only a weak and inconsistent inverse relationship between high rates of antibiotic prescribing and CMA overdiagnosis, even when adjusted for age and gender (STAR-PU). (236-239) This suggests that primary care practices where CMA overdiagnosis is common are not the same practices which have poor prescribing practices in other areas. So the practice of CMA overdiagnosis and unnecessary specialised formula prescription is relatively specific, and not associated with other markers of poor prescribing. No association was found between CMA overdiagnosis and practice-based prescribing of AAI or anti-reflux treatments, including Gaviscon which is licensed specifically for infants. However, an association has been reported elsewhere between CCG-level prescribing of anti-reflux medications and thickeners and CCG-level prescribing of low-allergy formula. (131) The lack of association seen in this

small BEEP study dataset may be due to reduced statistical power; or it is possible that associations at CCG level differ from those at individual primary care practice level. It is conceivable that variations between practices or CCGs might be explained by CMA guidelines influencing primary care practitioner prescribing habits. However, we did not find any association between CMA overdiagnosis within a GP practice and local CMA guidelines that included 'specificity and reproducibility of symptoms on ingestion of cow's milk' in their diagnostic criteria for CMA. This is consistent with findings from a national study, where CCG guideline recommendations were not associated with prescribing practice. (131) However, many of the guidelines analysed lacked variability in their recommendations as they were commonly based on iMAP (277) which contains broad recommendations for diagnosing CMA and this may have attenuated any potential association.

No association was found between CMA overdiagnosis and deprivation suggesting that infants from lower income, less well-educated families are not at increased risk of CMA overdiagnosis, which is an interesting finding when considering potential interventions. National data from a recent study separate to this thesis further characterised prescribing habits of low-allergy formula in England and identified an association with prescribing rates of anti-reflux medications and milk feed thickeners (Gaviscon and Carobel Instant) as well as significant regional variation in low-allergy formula prescribing up to 60-fold. (131) In that study, a weak and inconsistent association was identified between low-allergy formula prescriptions and antibiotic prescribing but no association was found between deprivation, local paediatric allergy service provision or regional CMA guidelines although the lack of variability amongst guideline recommendations may have impacted analysis. (131)

These national, CCG-level associations support the findings of our study. Together, the work suggests that healthcare practitioner prescribing behaviours are an important factor in CMA overdiagnosis.

Limitations

The data analysed in this study was from 2014, the year before the BEEP study which may be different from more recent prescribing patterns of low-allergy formula. This study may not be generalisable to a non-clinical trial population. The cohort also differed from the general English population as inclusion criteria required a family history of atopic disease, and the study cohort had a higher distribution of white ethnicity and higher socioeconomic status (Table 14.4 Section 14.4). Our analysis of potential risk factors was constrained by the datapoints available in the BEEP dataset, which was not collated specifically with this analysis in mind. Therefore, our ability to evaluate healthcare-seeking behaviour, socioeconomic factors and other potential determinants of CMA overdiagnosis was limited. The power of the study was limited by the relatively small number of GP practices and participants included in the study.

Conclusion

Our study found that high rates of practice-based prescribing of low-allergy formula was associated with CMA overdiagnosis in the BEEP cohort. Prescribing habits of primary healthcare practitioners are likely to be an important determinant of CMA overdiagnosis which may be relevant for developing interventions to prevent CMA overdiagnosis.

19 Detection and management of milk allergy: Delphi consensus study

19.1 Introduction

Cow's milk allergy affects up to 1% of European children in their first 2 years, and clinical presentations can vary from typical acute allergic reactions to chronic, non-specific symptoms. (1,278) Prescriptions for specialised formula used by bottle-fed infants with cow's milk allergy have increased in Australia, England and Norway and currently exceed expected volumes by up to 10-fold. (3,279)

Milk allergy diagnosis can be difficult, making the condition vulnerable to overdiagnosis – and formula milk company sponsorship of milk allergy guidelines, their authors and healthcare professional education is thought to contribute to milk allergy overdiagnosis. (2,3)

Current milk allergy guidelines appear to promote overdiagnosis by labelling common symptoms of infancy as allergy indicators, and there is concern that guideline recommendations also undermine breastfeeding. (2,3,50) We undertook a Delphi consensus study to develop practical guidance for healthcare practitioners working in community and hospital settings on the safe detection and management of milk allergy in children under 2 years old. We specifically addressed the prevention of overdiagnosis or underdiagnosis, supporting breastfeeding women and the role of specialised formula products. We used the Delphi consensus method due to the lack of high-certainty research evidence to guide clinical practice in this field. (280)

19.2 Methods

This was a Delphi consensus study which following a standardised approach of 2 rounds of anonymous consensus building and a final face-to-face online meeting to discuss areas of uncertainty. Participants included a wide range of experts in allergy and infant nutrition, none

of whom had a recent conflict of interest with the nutrition industry. The panel of experts also sought views from a panel of parents affected by milk allergy or milk allergy overdiagnosis in their infant, and sought the views of authors of leading, conflicted milk allergy guidelines. A detailed description of methods is outlined in Section 12.6.

19.3 Results

The study commenced on 1st January 2021 and concluded with a consensus meeting on 9th July 2021. Twenty-eight experts from 11 countries were invited, of whom 17 were eligible and agreed to participate (Table 19.1). All 17 participants completed both Delphi survey rounds, 12 attended the consensus meeting. Five authors of milk allergy guidelines or awareness tools participated in both stages of the external consultation and seven PPI panel members provided feedback on at least one stage of the project - four mothers with experience of milk allergy mislabelling and three mothers with experience of delayed milk allergy diagnosis in their child. Figure 19.1 summarises the outcomes at each stage of the Delphi consensus process. An initial 38 statements were included in the first round, which expanded to 72 statements in the second round, mainly through splitting and adaptation of the original statements. Consensus was reached for 38 ‘essential’ statements, shown in Tables 19.2-19.4 with detailed explanatory notes, and summarised in Figures 19.2-19.4. There were no ‘recommended’ statements and the remaining statements were removed because consensus could not be reached after the two survey rounds and consensus meeting. Four key areas were discussed at the consensus meeting: symptoms suggestive of milk allergy in an exclusively breastfed infant, maternal dietary elimination, infants presenting with blood in the stool and agreed terminology.

Table 19.1. Characteristics of Delphi study participants

	No (%) invited (n = 28)	**No (%) enrolled (n=17)**
Female gender	15 (54)	9 (53)
Expertise		
General Practice (primary care)	4 (14)	3 (18)
General Paediatrics	3 (11)	1 (6)
Nutrition and Dietetics	5 (18)	2 (12)
Midwifery, infant feeding and lactation	4 (14)	4 (24)
Paediatric Allergy and Paediatric Allergy Nursing	6 (21)	3 (18)
Paediatric Gastroenterology	3 (11)	2 (12)
Paediatric Dermatology	1 (4)	1 (6)
Public Health and Epidemiology	2 (7)	1 (6)
Region		
Asia (India, Taiwan, Pakistan, Russia)	4 (14)	3 (18)

Australasia	6 (21)	1 (6)
Africa and Middle East (Kenya, Israel)	2 (7)	2 (12)
Europe (Netherlands, Sweden, United Kingdom)	12 (43)	8 (47)
Americas (United States)	4 (14)	3 (18)

Figure 19.1. Summary of each step of the Delphi consensus process.

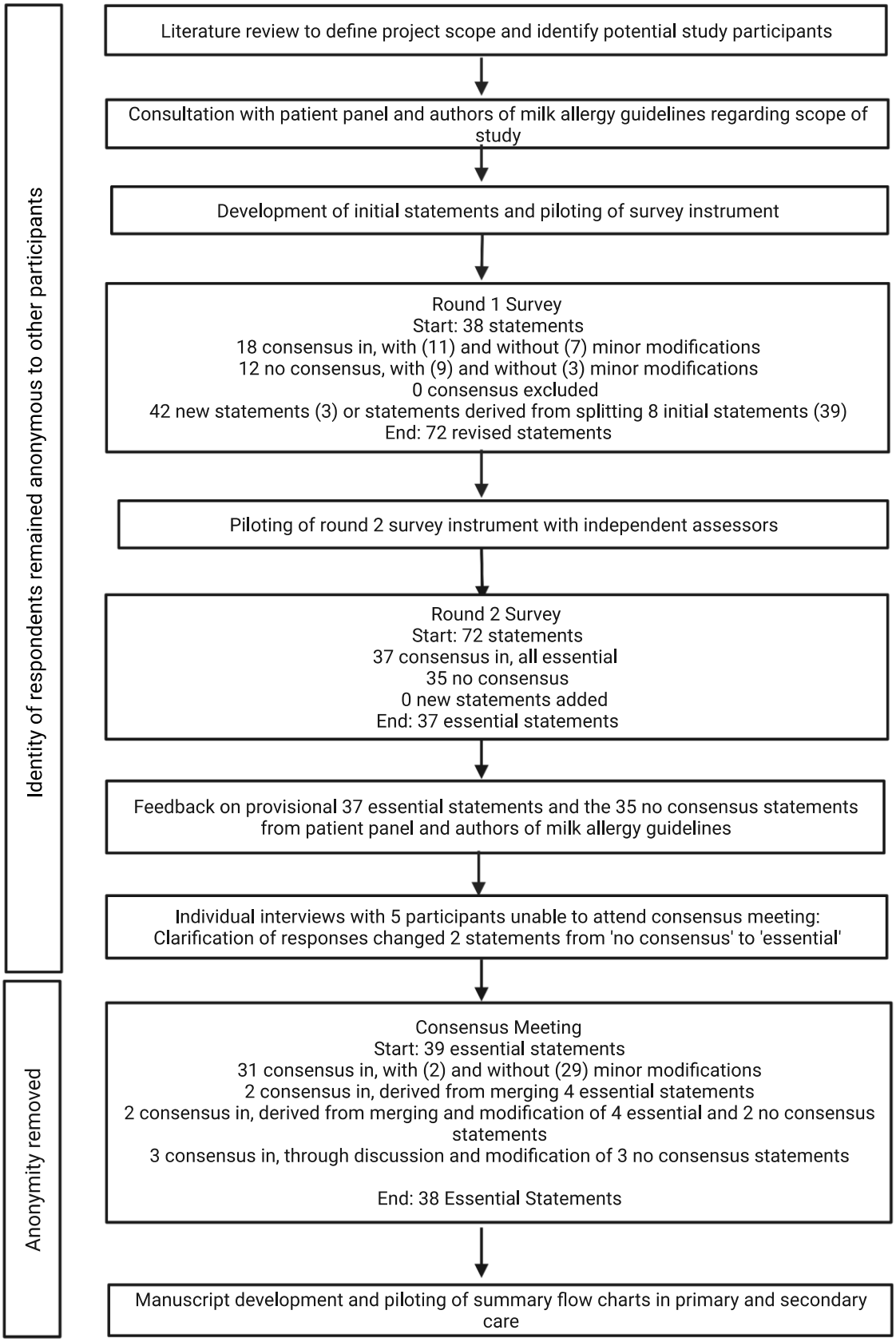


Table 19.2. What aspects of milk allergy detection are important to ensure that the condition is not overdiagnosed or underdiagnosed?

In an exclusively breastfed infant, symptoms such as crying, vomiting or eczema do not usually indicate milk allergy. However, milk allergy, or other food allergies, may be considered as part of the differential diagnosis for crying, vomiting or eczema in an exclusively breastfed infant in the following rare circumstances:
• Exclusively breastfed infant with faltering growth[a] AND protein-losing enteropathy[b] • Biopsy[c] findings of eosinophilic gastrointestinal disorders[d] associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in an exclusively breastfed infant
In a child who is not exclusively breastfed, symptoms such as crying, vomiting or eczema do not usually indicate milk allergy. However, milk allergy may be considered as part of the differential diagnosis in the following circumstances:
• Child consuming non-human milk products or formula with faltering growth[a] despite adequate nutritional intake • Recurrent passage of visible blood in stool at least once daily for at least 3 consecutive days, with or without mucus, in a child consuming non-human milk products or formula • Biopsy[c] findings of eosinophilic gastrointestinal disorders[d] associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in a child consuming milk products or formula
Acute symptoms such as erythema of the skin, urticaria, angioedema or vomiting which occur within 2 hours of ingesting a food or drink containing milk protein may indicate milk allergy. However, milk allergy is not likely if:
• Similar symptoms occurred on other occasions without ingestion of milk protein • An alternative, more common explanation for the symptoms such as a viral infection, gastroesophageal reflux seems more likely than milk allergy[e] • Symptoms are not reproducible on subsequent ingestion of milk protein
In children with delayed gastrointestinal or skin symptoms between 2- and 48-hours following ingestion of a food or drink containing milk protein, milk allergy is less likely but should be considered in the following circumstances:
• Skin symptoms such as eczema are severe or reproducible and the child is not tolerating milk protein in similar forms • Gastrointestinal symptoms such as repeated vomiting are severe or reproducible and the child is not tolerating milk protein in similar forms

- Behavioural symptoms such as crying are reproducible, and the child is not tolerating milk protein in similar forms

In breastfed or formula fed children without the acute or chronic symptoms described above, milk allergy does not need to be considered as a diagnosis for the following symptoms, either alone or in combination:

- Occasional spots of blood in the stool, without any daily, visible blood in the stool
- Other colour changes in stool, unrelated to blood in the stool
- Consistency changes in stool
- Frequency changes in stool
- Nasal or respiratory symptoms
- Aversive feeding

For the following symptoms, where milk allergy is sometimes included in the differential diagnosis, diagnosis and management need to consider the following:

- Bile-stained vomiting can be caused by intestinal malrotation so requires urgent assessment
- Faltering growth has a wide range of potential causes, including insufficient protein/calorie intake
- Blood in the stool can be caused by infection, clotting disorders or intestinal abnormalities
- Eczema management involves avoiding physical triggers, using moisturisers and topical anti-inflammatories
- Colic and crying are common in healthy children, but if severe these can also be related to a wide range of health issues in the child or their carer

Faltering growth and protein losing enteropathy in an exclusively breastfed infant is a rare presentation of food allergy, including milk allergy. [a]Faltering growth is slower weight gain than expected for age, gender, and current weight of the child.[3] The following provide reference measurements that are concerning for faltering growth on WHO growth charts: a fall ≥1 weight centile if birth weight was below 9th centile; a fall ≥2 weight centiles, if birth weight was between the 9th and 91st centiles; a fall ≥3 weight centiles, if birth weight was above the 91st centile.[3] The most common cause of faltering growth is inadequate nutritional intake, which can be related to feeding and eating behaviours such as ineffective suckling in breastfed infants. The differential diagnosis of faltering growth includes anaemia, malignancy, renal failure, liver failure, endocrine disorders, gastrointestinal conditions such as pyloric stenosis, malabsorption syndromes, coeliac disease in children consuming gluten, congenital cardiac disease, pulmonary disease such as cystic fibrosis, chronic infection, chronic inflammatory conditions, immunodeficiency conditions, autoimmune disease, metabolic disorders, neurodevelopmental disorders, chromosomal disorders and environmental factors including psychosocial deprivation.[4] [b]Protein losing enteropathy is characterised by low serum albumin, with or without oedema, secondary to

intestinal protein loss. A full differential diagnosis should be considered, and appropriate investigations undertaken in all cases. Differential diagnoses include: very early onset inflammatory bowel disease (VEO-IBD), congenital diarrhoeas and enteropathies (CODEs), coeliac disease, intestinal infections, primary intestinal lymphangiectasia and congenital heart disease.[5,6] [c]Endoscopic biopsy is not usually appropriate for food allergy diagnosis in children, because of the need for general anaesthetic and the frequency of non-specific histological findings and should only be undertaken in specialist paediatric gastroenterology centres. [d]Eosinophilic gastrointestinal disorders are rare conditions which result from local infiltration of the gastrointestinal tract by eosinophils.[7] When eosinophils are found on gastrointestinal biopsy, other differential diagnoses include: gastroesophageal reflux disease, Crohn's disease, chronic infection, and connective tissue disorders. [e]Age, previous dairy exposure/tolerance and duration of symptoms after an exposure to milk protein are all relevant to considering whether an alternative cause is more likely.

Table 19.3. In a child with milk allergy who is receiving breastmilk, what aspects of management are important to ensure that continuation of breastmilk feeding is fully supported?

Maternal dietary restriction is not usually necessary to manage milk allergy, however:

- maternal dietary restriction may be **advised** in an exclusively or partially breastfed infant with faltering growth AND protein-losing enteropathy
- maternal dietary restriction may be **supported** when a mother has noticed a clear relationship between her own dietary intake and symptoms of eczema in her child, and wishes to restrict her diet

For lactating mothers who restrict their own intake of milk protein:

- Ensure adequate maternal dietary intake of calcium and vitamin D
- Address the need for an exclusion diet, taking into consideration the physical and psychological burden of elimination diets on the family
- Advise that for mothers avoiding cow's milk, goat and sheep milk protein should be avoided as well, due to cross-reactivity
- Advise re-introduction of milk into the maternal diet if a trial of exclusion for 2 weeks has not resulted in resolution of symptoms
- Advise a trial of re-introduction of milk into the maternal diet if symptoms of concern have subsided for at least 2 weeks
- Advise that avoidance of baked products[a] containing milk is unlikely to be necessary, due to the very small quantity of milk protein transferred to breastmilk.

Protect, promote, and support exclusive breastfeeding to around 6 months and continued breastfeeding up to 2 years of age or beyond as recommended by the World Health Organization, or local recommendations, by:

- Signposting to local breastfeeding support services, including referring to a Lactation Specialist[b] for breastfeeding support where available
- Reassuring mothers and other family members that breastmilk is the most appropriate milk for all children, with and without milk allergy

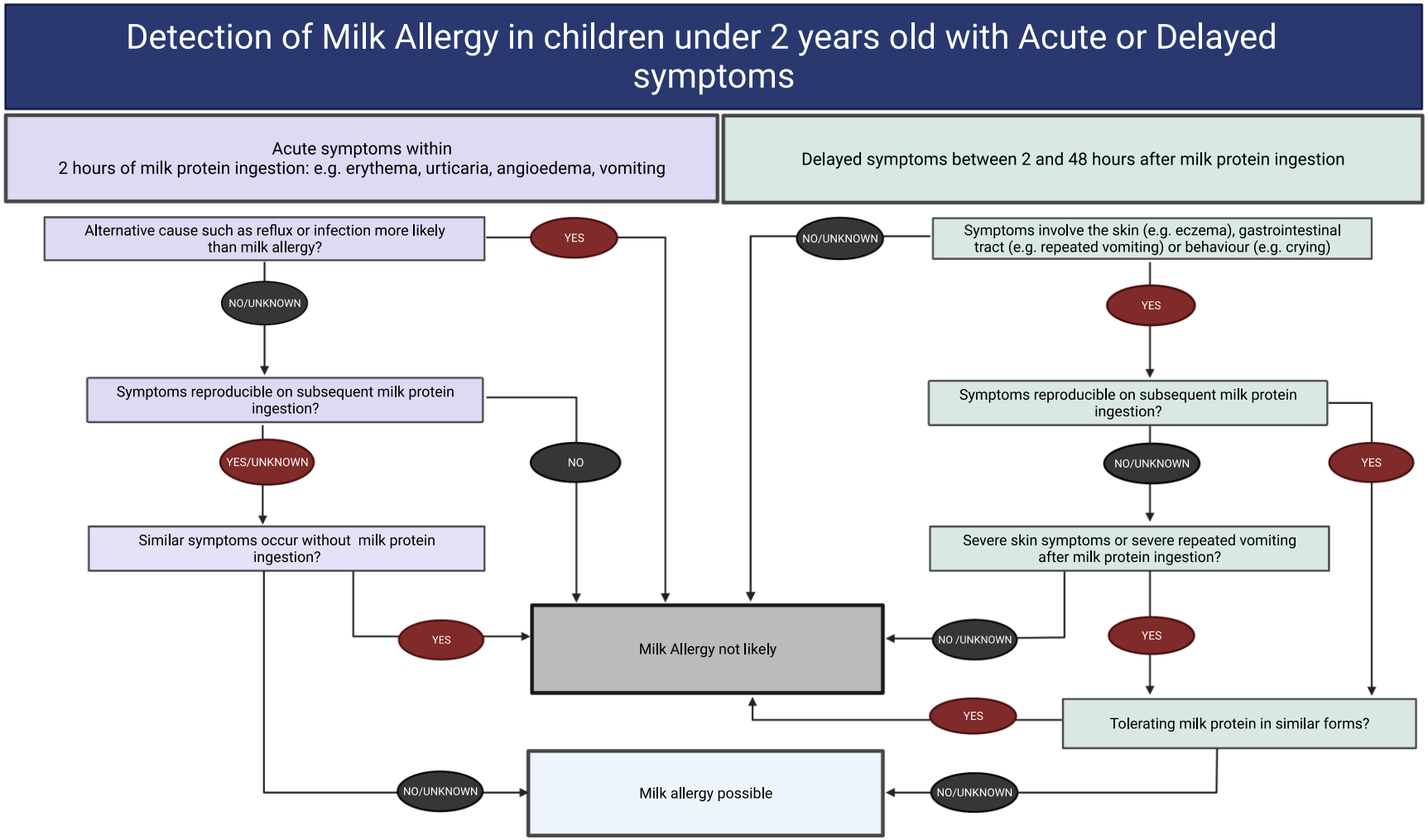
[a]Baked products refers to foods containing milk as a minor ingredient that are baked in an oven, for example bread, cakes, muffins, scones, biscuits. This statement may also be relevant for other foods containing only minor quantities of milk protein. [b]Lactation specialists may be International Board-Certified Lactation Consultants, La Leche league Leaders or other local suitably qualified breastfeeding support workers.

The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosemia.[8] However, carers who make a fully informed decision to use a breastmilk substitute in place of breastmilk should be supported, and advice about safe formula feeding should be given where needed.

Table 19.4. What aspects of milk allergy management are important to prevent unnecessary and potentially harmful use of specialised formulas such as amino acid formula, extensively hydrolysed formula or soya or rice-based formulas?

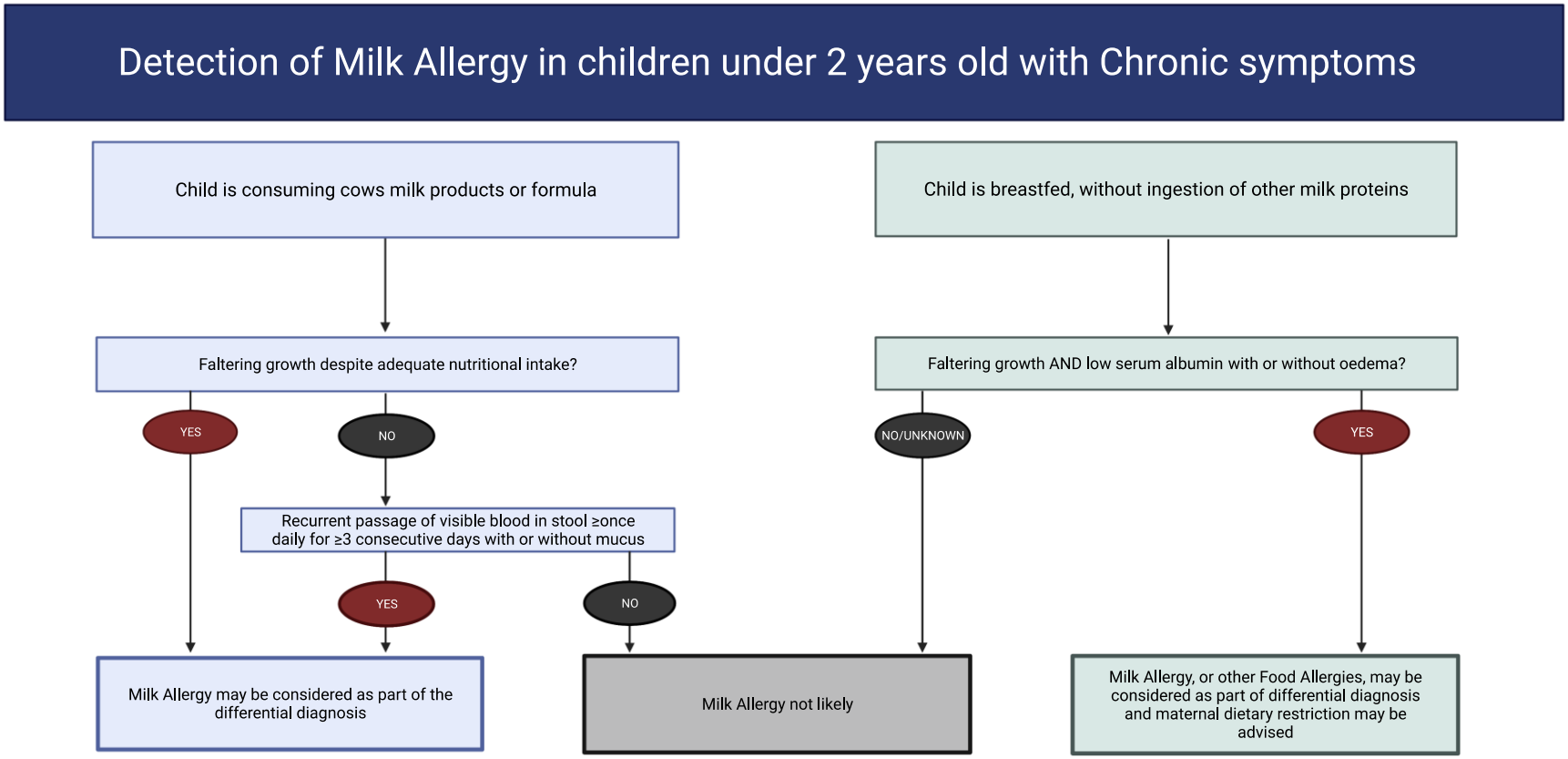
Initiation or continuation of specialised formula should not be advised for the following groups of patients with milk allergy:
• Children who are currently breastfed without use of any breastmilk substitute • Children aged over 12 months with a good, mixed diet[a] and normal growth pattern • Children who have received infrequent or small volumes of formula but can return to full breastfeeding without use of a breastmilk substitute, with appropriate support for caregivers.
Initiation of specialised formula should not be advised for preventing the development of milk allergy or other atopic conditions, even in children with a family history of allergy
Initiation of specialised formula should be advised for the following groups of patients with milk allergy:
• Formula-fed children aged under 12 months, with IgE-mediated milk allergy confirmed using clinical history and either skin prick test, serum IgE testing or food challenge • Formula-fed children aged under 12 months with non-IgE-mediated milk allergy confirmed via trial elimination diet and oral food challenge[b] with milk protein
For milk allergic children over age 12 months who require a breastmilk substitute, calcium-fortified plant-based milk alternatives or milk from animals with low cross-reactivity with cow's milk such as donkey or mare milk may also be considered, guided by a paediatric dietician, where available. [a]A good mixed diet was defined by the panel as at least two-thirds of energy intake being provided by a varied solid food diet (which may be vegetarian or vegan) and consuming a nutritionally appropriate milk or milk alternative at an age-appropriate volume. [b]Oral food challenge may not be required for the diagnosis of Food Protein Induced Enterocolitis Syndrome (FPIES) if the diagnosis is clear or the initial reaction(s) was severe.

Figure 19.2. Diagnosis of milk allergy in children under 2 years old with acute or delayed symptoms



Tolerating milk protein in similar forms means consuming milk protein in similar forms to that which triggered a reaction(s) on other occasions, but without any symptoms or signs of an allergic reaction. Age, previous milk protein exposure/tolerance and duration of symptoms after an exposure to milk protein are all relevant to considering whether an alternative cause is more likely. Bile-stained vomiting can indicate intestinal malrotation, so requires urgent assessment. Eczema management includes avoiding physical triggers, using moisturisers and topical anti-inflammatories. Colic and crying are common in healthy infants, but if severe, these can be related to a wide range of health issues in the infant or their carer. (281) Created in BioRender. Allen, H. (2025) https://BioRender.com/g87v600

Figure 19.3. Diagnosis of milk allergy in children under 2 years old with chronic symptoms

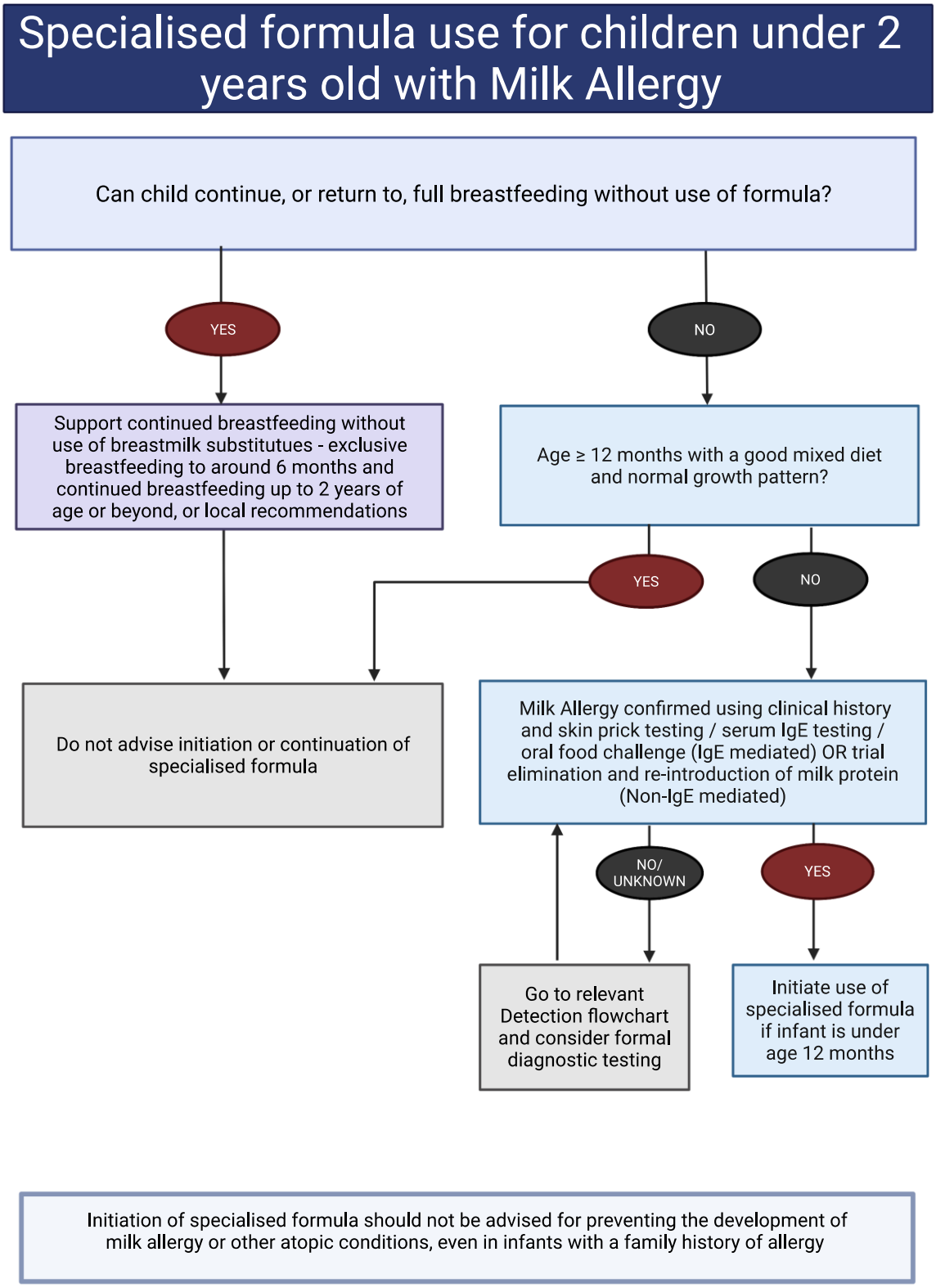


In breastfed or formula-fed children without acute or delayed symptoms or the chronic symptoms described here, milk allergy does not need to be considered as a diagnosis for the following symptoms, either alone or combined:

- Frequency changes in stool
- Consistency changes in stool
- Aversive feeding
- Nasal or respiratory symptoms
- Occasional spots of blood in the stool, without any daily, visible blood
- Other colour changes in stool

Chronic symptoms means symptoms without obvious temporal relationship to milk protein ingestion e.g. crying, vomiting, eczema. Cow's milk products include cheese, yoghurt and cream - products made with sheep or goat milk are also relevant due to cross-reactivity with cow's milk. Faltering growth is slower weight gain than expected for age, gender, and current weight of child and has a wide range of causes including insufficient protein/calorie intake. (282,283) Protein-losing enteropathy is a rare condition characterised by low serum albumin with or without oedema due to intestinal protein loss and has a wide differential diagnosis. (284,285) Blood in the stool can also be caused by infection, clotting disorders or intestinal abnormalities. Endoscopic biopsy is not usually appropriate for food allergy diagnosis in children due to need for general anaesthetic and frequency of non-specific histological findings, and should only be undertaken in specialist paediatric gastroenterology centres. Milk allergy may be considered as part of the differential diagnosis in an exclusively breastfed child, or child consuming cow's milk products, in those rare circumstances that biopsy is performed and confirms findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis. (286) Created in BioRender. Allen, H. (2025) https://BioRender.com/s13m355

Figure 19.4. Specialised formula use for children under 2 years old with milk allergy



Reassure families that breastmilk is the most appropriate milk for all children, with and without milk allergy, and if necessary signpost to local breastfeeding support services, including referral to a lactation specialist, where available. The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia (287) – however, carers who make a fully informed decision to use a breastmilk substitute should be supported and given advice about safe formula feeding, where needed. For milk allergic children over age 12 months who require a breastmilk substitute, calcium-fortified plant-based milk alternatives or milk from animals with low cross-reactivity with cow's milk such as donkey or mare milk may also be considered, guided by a paediatric dietician, where available. A good mixed diet was defined by participants as at least two-thirds of energy intake being provided by a varied solid food diet (which may be vegetarian or vegan), consuming a nutritionally appropriate milk or milk alternative at an age-appropriate volume and able to consume adequate macro and micronutrients from this diet. Oral food challenge may not be required for the diagnosis of Food Protein Induced Enterocolitis Syndrome if the diagnosis is clear or the initial reaction(s) was severe. Created in BioRender. Allen, H. (2025) https://BioRender.com/f55f535.

Recommendations regarding milk allergy diagnosis

Recommendations for milk allergy diagnosis highlight the distinction between acute, delayed or chronic symptoms in relation to milk protein ingestion. For children with acute or delayed symptoms, panel recommendations highlighted the importance of reproducibility and specificity of symptoms in relation to milk protein ingestion (Table 19.2; Figure 19.2). For children with chronic symptoms without any obvious temporal relationship to milk protein ingestion, consensus recommendations highlighted the distinction between children directly ingesting milk protein and those who were exclusively breastfed (Table 19.2; Figure 19.3). Consensus was reached that milk allergy does not need to be considered for changes to colour, frequency or consistency of stool, aversive feeding, occasional spots of blood in stool, nasal or respiratory symptoms, in the absence of a temporal relationship with milk protein ingestion. Exceptions to this were symptoms associated with biopsy-proven eosinophilic gastrointestinal disorders or protein-losing enteropathy or, in a child ingesting milk protein, with failure to thrive or daily visible blood in stools.

Participants reached consensus on recommendations for diagnosing food protein-induced allergic proctocolitis (FPIAP) in a child with chronic symptoms who is consuming milk protein (Table 19.2; Figure 19.3). Consensus could not be reached on diagnosing FPIAP in an exclusively breastfed infant with recurrent visible blood in the stool, with or without mucus. It was acknowledged that many food allergy guidelines consider milk allergy as part of the differential diagnosis for exclusively breastfed infants with visible blood in the stool. However, participants noted that visible blood in the stool in an exclusively breastfed infant is usually self-limiting and has many possible causes including infection and fissures. A PPI panel member highlighted the potential harms of making a milk allergy diagnosis in an exclusively breastfed infant with blood in the stools, such as unnecessary or unsupervised maternal dietary elimination. Participants did not reach consensus that severity of crying should trigger consideration of a milk allergy diagnosis. They did reach consensus that milk allergy diagnosis should be considered in a child with reproducible crying after milk protein ingestion. There was consensus that differential diagnoses need to be considered for bile-stained vomiting, faltering growth, blood in the stool, colic and crying.

Recommendations regarding milk allergy management

Consensus was reached that breastfeeding continuation should be supported in line with World Health Organization (109) or local recommendations - to exclusively breastfeed to around 6 months and continue breastfeeding up to 2 years and beyond – by signposting to local breastfeeding support and reassuring families that breastmilk is the most appropriate milk for children with or without milk allergy. The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia. (287,288) However, the panel commented that carers who make a fully informed decision to use a breastmilk

substitute in place of breastmilk should be supported, and advice about safe formula feeding should be given where needed (Table 19.4).

Consensus was reached that maternal dietary restriction is not usually necessary to manage milk allergy but may be supported if mother has noticed a clear relationship between her own dietary intake and eczema symptoms in her child, but consensus was not reached for other symptoms (Table 19.3). The panel reached consensus that maternal dietary restriction may be advised by healthcare professionals in the unusual circumstance of a breastfed infant with faltering growth and protein-losing enteropathy. The panel did not reach consensus that healthcare professionals should advise maternal dietary restriction in any other circumstances. The panel reached consensus on a number of important considerations for supporting families who are practicing maternal dietary restriction (Table 19.3).

Consensus was reached that specialised formula should not be advised or continued in children who are breastfed or can return to full breastfeeding; for preventing the development of atopic conditions; or for children aged over 12 months with a good, mixed diet and normal growth pattern (Table 19.4; Figure 19.4). The panel reached consensus that specialised formula should be used in infants aged under 12 months who require formula milk and have confirmed milk allergy, usually confirmed using history, allergy tests or a trial of elimination and re-introduction. The panel advised that the suitability and safety of using plant-based milk alternatives in a child's diet should be assessed by a paediatric dietician. (258)

Comparison with previous milk allergy guidelines

Tables 19.5-19.8 show a comparison between the characteristics and recommendations of this Delphi consensus study and nine leading guidelines including the National Institute for Health and Care Excellence (NICE) guideline, which all address milk allergy diagnosis and

management. (85,116,161,277,289-296) In contrast to our guidance, only three guidelines (277,289,290) included both primary care and patient representation and only one guideline (161) declared no financial conflicts of interest in relation to the formula industry (Table 19.5). Two guidelines were funded by the formula industry (Table 19.5). (85,292) Consistent with our guidance, five of nine guidelines emphasised the importance of reproducibility in making a diagnosis of milk allergy (Table 19.6). (85,161,289,290,294) However, only one guideline distinguished between formula fed and breastfed infants in making a diagnosis, and only one guideline provided differential diagnoses for vomiting, blood in stools or faltering growth (Table 19.6). (290) In contrast to our guidance, most guidelines recommended considering milk allergy diagnosis for stool changes, respiratory symptoms or aversive feeding in the absence of a temporal relationship with milk ingestion or a history of faltering growth (Table 19.6). (85,116,161,277,289-296)

Table 19.5. Comparison of study characteristics with published milk allergy guidelines

	Delphi study 2021	Global DRACMA 2010	Global iMAP 2019	North America AAAAI 2014	Japanese Guidelines for Food Allergy JSPACI, JSA 2020	Europe EAACI 2019	Europe ESPGHAN 2012	Middle East Consensus Statement on Prevention, Diagnosis and Management of Cow's Milk Allergy 2014	Latin American Guide for Diagnosis and Treatment of allergy to cow's milk proteins 2014	United Kingdom NICE 2011
Primary care representation	Yes	No	Yes	No	No	Yes	No	No	No	Yes
Patient representation	Yes	Organisational	Organisational	No	No	Organisational	No	No	No	Yes
Funded by formula industry	No	Yes	No	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	No
Author COI	0 / 17 (0%)	8 / 22 (36%)	9 / 12 (75%)	2 / 15 (13%)	0 / 3 (0%)	10 / 13 (77%)	9 / 12 (75%)	7 / 7 (100%)	Not stated	4 / 11 (36%)

AAAAI, American Academy of Asthma, Allergy and Immunology; COI, declared financial conflict of interest with respect to the formula industry; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines; EAACI, European Academy of Allergy and Clinical Immunology; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; iMAP, an international interpretation of the Milk Allergy in Primary Care guideline; JSA, Japanese Society of Allergology; JSPACI, Japanese Society of Paediatric Allergy and Clinical Immunology; MAP, Milk allergy in primary care; NICE, National Institute for Health and Clinical Excellence

Table 19.6. Comparison of study recommendations for milk allergy detection with published guidelines

	Delphi study 2021	Global DRACMA 2010	Global iMAP 2019	North America AAAAI 2014	Japanese Guidelines for Food Allergy JSPACI, JSA 2020	Europe EAACI 2019	Europe ESPGHAN 2012	Middle East Consensus Statement on Prevention, Diagnosis and Management of Cow's Milk Allergy 2014	Latin American Guide for Diagnosis and Treatment of allergy to cow's milk proteins 2014	United Kingdom NICE 2011
Reproducibility of allergy symptoms highlighted	Yes – for both acute and delayed symptoms	'Reproducibility of the reaction' listed as part of 'aspects of history of particular importance'	No reference to reproducibility, although this was mentioned in previous 2013 and 2017 versions of the MAP/iMAP guideline	'consider foods that consistently elicit symptoms of food allergy to improve the accuracy of diagnosing IgE-mediated disease'	'Symptom reproducibility' listed in 'Key points in history taking'	'Reproducibility' listed as part of 'Detailed clinical history for diagnosis'	No reference to reproducibility.	No reference to reproducibility	No reference to reproducibility	'Reproducibility of symptoms on repeated exposure'
Differentiates between diagnosis in formula fed and exclusively breastfed infants	Yes	No	No	No	No	Yes	No	No	No	No
Differential diagnoses for vomiting or faltering growth or blood in stools mentioned.	Yes	No	No	No	No	Yes	No	No	No	No
Specific diagnostic criteria for proctocolitis in a milk-consuming baby	Crying, vomiting or eczema and visible blood in stool ≥once daily, for ≥ 3 consecutive days	Low grade rectal bleeding, usually flecks of blood, and occasionally mild diarrhoea in an otherwise healthy infant	Blood and/or mucus in stools in an otherwise well infant	Healthy infants… visible specks or streaks of blood mixed with mucus in stool	No specific criteria given	Mucus-laden, bloody stools.	'Rectal bleeding.' No further detail.	No specific criteria given	Healthy children with normal stools or mild diarrhoea and low rectal bleeding. Stools containing mucus and streaks of blood.	Blood and/or mucus in stools listed as sign of possible Non-IgE-mediated food allergy
Blood in stools of an exclusively breastfed baby is considered a sign of milk allergy	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

In the absence of symptoms temporarily related to milk ingestion, or faltering growth or recurrent blood in stools, changes in consistency or frequency of stool may indicate milk allergy	No	Chronic constipation included as a symptom of delayed allergy	Signs of Non-IgE CMA include loose/frequent stools, constipation, irregular or uncomfortable stools, soft stools with excessive straining	Constipation might be food allergy in a subset of patients	Not specified	'Consider CMA if constipation does not resolve with conventional treatment'	Persistent constipation is listed as a sign of CMA	Constipation is a sign of Non-IgE CMA	Chronic constipation may be considered	Loose or frequent stools and constipation listed as signs of possible Non-IgE food allergy. Diarrhoea listed as sign of IgE food allergy
In the absence of symptoms temporally related to milk ingestion, or faltering growth or recurrent blood in stools, chronic nasal or respiratory symptoms can be a sign of milk allergy	No	Not mentioned	'Catarrhal airway symptoms' listed as a sign of mild-moderate Non-IgE CMA in 2013 version, but not 2019	Food allergy is an uncommon cause of chronic respiratory symptoms	Not mentioned	Not mentioned	Chronic cough may be a sign of CMA	Chronic cough may be a sign of CMA	Consider CMA in asthma	Cough, chest tightness, wheezing or shortness of breath listed as signs of possible IgE and Non-IgE food allergy
In the absence of symptoms temporally related to milk ingestion, or faltering growth or recurrent blood in stools, aversive feeding can be a sign of milk allergy	No	Not mentioned	Aversive feeding is a sign of CMA	Not mentioned	Not mentioned	Feeding difficulties mentioned	Anorexia and refusal to feed are signs of CMA	Anorexia mentioned	Not mentioned	Food refusal or aversion listed as a possible sign of Non-IgE food allergy

AAAAI, American Academy of Asthma, Allergy and Immunology; CMA, cow's milk allergy; COI, declared financial conflict of interest with respect to the formula industry; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines; EAACI, European Academy of Allergy and Clinical Immunology; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; IgE, immunoglobulin E; iMAP, an international interpretation of the Milk Allergy in Primary Care guideline; JSA, Japanese Society of Allergology; JSPACI, Japanese Society of Paediatric Allergy and Clinical Immunology; MAP, Milk allergy in primary care; NICE, National Institute for Health and Clinical Excellence

Only two guidelines (277,292) specified the duration of exclusive and total breastfeeding recommended by WHO (109), with other guidelines either not explicitly stating the recommendations or stating shorter durations than those recommended by WHO (Table 19.7). Four guidelines did not explicitly state that breastfeeding or breastmilk is the best milk for infants with milk allergy (Table 19.7). (85,161,289,293) Guidelines also recommended broader indications for maternal dietary restriction than the new Delphi consensus guidance, and while five guidelines (85,277,292,293,295) recommended total or strict milk exclusion from mother's diet, only one limited the degree of maternal dietary restriction by suggesting that complete milk exclusion may not be required (Table 19.7). (277) One guideline (293) recommended using specialised formula in a fully breastfed infant if symptoms failed to respond to maternal dietary exclusion (Table 19.8), no guideline stated that formula is not necessary after age one year, and two guidelines (85,295) recommended specialised formula up to age two years. Three guidelines (292,294,295) recommended using hydrolysed formula to delay or prevent the onset of allergic conditions, and only one guideline (161) noted there was insufficient evidence for this practice (Table 19.8).

Table 19.7. Comparison of study recommendations for breastfeeding support with published guidelines

	Delphi study 2021	Global DRACMA 2010	Global iMAP 2019	North America AAAAI 2014	Japanese Guidelines for Food Allergy JSPACI, JSA 2020	Europe EAACI 2019	Europe ESPGHAN 2012	Middle East Consensus Statement on Prevention, Diagnosis and Management of Cow's Milk Allergy 2014	Latin American Guide for Diagnosis and Treatment of allergy to cow's milk proteins 2014	United Kingdom NICE 2011
Recommended breastfeeding durations stated	As per WHO: exclusive breastfeeding to around 6 months; total breastfeeding up to 2 years or beyond	Durations not stated	'WHO recommends breastfeeding until 2 years or beyond'	Encourage exclusive breastfeeding for first 4-6 months; no statement about total duration	Durations not stated	Durations not stated but reference made to WHO guidance.	Durations not stated	As per WHO: exclusive breastfeeding to 6 months; total breastfeeding up to 2 years or beyond	Exclusive breastfeeding for at least 4 months and continued until 6 months to prevent allergies	No reference to breastfeeding except food avoidance advice to breastfeeding mothers
Breastmilk is explicitly recommended as appropriate for feeding children with milk allergy	Yes	No	Yes	'exclusive breast-feeding for all infants regardless of allergy risks'	No	Yes	No	Yes	Yes	No
Advice to restrict mother's diet to manage suspected or proven milk allergy	Not usually necessary but may be advised in faltering growth and protein-losing enteropathy	'Mothers should continue breastfeeding while avoiding dairy products'	'Strict elimination of cow's milk containing foods from maternal diet '	Proctocolitis: 'might include maternal dietary restriction' Food protein induced enterocolitis syndrome: 'Strict maternal dietary avoidance' if symptoms observed during breastfeeding	'In infants receiving mother's milk, the potential causative foods are eliminated from the mother's diet (1-2 weeks)'	Maternal elimination diet advised for food protein-induced constipation, for colic with other atopic symptoms, for food protein induced enteropathy, eosinophilic oesophagitis and persistent reflux and irritability	'In breast-fed infants, the mother should start a strict CMP-free diet'	'Exclusive breastfeeding and maternal dietary allergy avoidance are the best treatment'	'Treatment of choice is to feed human milk, avoidance of mother's intake of all kinds of food that contains cow's milk protein'	'For babies and young children with suspected CMA, offer food avoidance advice to breastfeeding mothers'
Completeness of maternal exclusion diets'	'Avoidance of baked products containing milk is unlikely to be necessary, due to	'The stricter the degree of elimination, the more likely to be	'Strict elimination of cow's milk containing foods from maternal diet' to manage	Not mentioned	Not mentioned	'Food protein induced allergic proctocolitis – treatment if required is based	'Avoid all milk and milk products from their own diet'	'The diet of breastfeeding mothers with infants with CMA should be	'Mother should follow a diet of total exclusion of milk protein'	Not mentioned

the very small quantity of milk protein transferred to breastmilk'	useful in decision making' 'Nursing mothers should follow a milk-free diet'	mild-moderate Non-IgE CMA 'As likelihood of sufficient cow's milk protein passage into breastmilk to trigger reactions is low, in breastfed cases, complete milk exclusion may not be required'	on a strict maternal exclusion'	restricted to avoid all dairy products'

AAAAI, American Academy of Asthma, Allergy and Immunology; CMA, cow's milk allergy; CMP, cow's milk protein; COI, declared financial conflict of interest with respect to the formula industry; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines; EAACI, European Academy of Allergy and Clinical Immunology; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; IgE, immunoglobulin E; iMAP, an international interpretation of the Milk Allergy in Primary Care guideline; JSA, Japanese Society of Allergology; JSPACI, Japanese Society of Paediatric Allergy and Clinical Immunology; MAP, Milk allergy in primary care; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organisation

Table 19.8. Comparison of study recommendations for use of specialised formula with published guidelines

	Delphi study 2021	Global DRACMA 2010	Global iMAP 2019	North America AAAAI 2014	Japanese Guidelines for Food Allergy JSPACI, JSA 2020	Europe EAACI 2019	Europe ESPGHAN 2012	Middle East Consensus Statement on Prevention, Diagnosis and Management of Cow's Milk Allergy 2014	Latin American Guide for Diagnosis and Treatment of allergy to cow's milk proteins 2014	United Kingdom NICE 2011
Initiation of specialised formula feeding in a breastfed infant	Not advised	'During breastfeeding, a substitute formula may not be necessary'	If top-up formula is needed, use a specialised formula (eHF or AAF).	Not mentioned	Not mentioned	Not mentioned	'For symptoms which persist despite strict maternal dietary exclusions: , 'further elimination of other highly allergenic foods or weaning from breastmilk to a therapeutic formula is recommended'	Not mentioned	'For breastfed infants, may be unnecessary to provide a cow's milk substitute'	Not mentioned
Use of specialised formula beyond age 12 months	Not advised, if child has good mixed diet and normal growth pattern	'Substitute formula is mandatory in children under 2 years'	Not mentioned	Not mentioned	Not mentioned	'In infants and young children [with CMA], substitutes are especially necessary to ensure a diet that is adequate for growth and development'	'CMPA beyond 12 months need individualised nutritional advice' 'Many patients regardless of age with multiple food allergies, including CMP and soy, require a therapeutic formula to fulfil their nutritional needs'	Not mentioned	'In children under 2 years of age it is recommended to substitute milk for eHF/AAF'	Not mentioned

Use of specialised formula for preventing allergic conditions	Not advised	Not mentioned	Not mentioned	Advised 'For infants with a family history of atopy, consider pHF or eHF for possible prevention of atopic dermatitis and infant CMA if exclusive breastfeeding not possible'	Not advised 'There is insufficient evidence on the usefulness of hydrolysed milk in preventing the onset of food allergies'	Not mentioned*	Not mentioned	Advised Familial history of allergy (1 or more immediate family members), pHF until 4-6 months old where exclusive breastfeeding not possible	Advised Atopic dermatitis can be delayed in the first years of life with the use of formulas extensively or partially hydrolyzed	Not mentioned

AAAAI, American Academy of Asthma, Allergy and Immunology; AAF, amino-acid formula; COI, declared financial conflict of interest with respect to the formula industry; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy Guidelines; EAACI, European Academy of Allergy and Clinical Immunology; eHF, extensively hydrolysed formula; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; iMAP, an international interpretation of the Milk Allergy in Primary Care guideline; JSA, Japanese Society of Allergology; JSPACI, Japanese Society of Paediatric Allergy and Clinical Immunology; MAP, Milk allergy in primary care; NICE, National Institute for Health and Clinical Excellence; pHF, partially hydrolysed infant formula. *The 2014 EAACI Primary prevention of food allergy guideline recommended use of 'a documented hypoallergenic formula' for preventing food allergy in some circumstances, but the 2020 update of the same guideline made no recommendation for or against use of hydrolysed formula for food allergy prevention (162,291)

Parental panel contribution

The PPI panel commented on the importance of breastfeeding support, dietetic support for mother and child, and healthcare professional follow-up for those who choose to restrict their diet during lactation due to concerns about milk allergy. PPI members cited physical harms such as maternal weight loss, and psychological harms such as maternal anxiety and depression which may be associated with maternal dietary restrictions, especially if dietary restrictions are severe or unsupervised. A member of the PPI panel commented that exclusive breastfeeding until 6 months is highlighted more often by healthcare practitioners than breastfeeding to 2 years and beyond and emphasised the importance of communicating both aspects of the WHO recommendation.

19.4 Discussion

Principal Findings

In this Delphi consensus study, we generated guidance to support the detection and management of milk allergy. Our new guidance aims to safely reduce milk allergy overdiagnosis and unnecessary use of specialised formula products, and to support breastfeeding women in the context of suspected milk allergy. To our knowledge, this is the first guidance for milk allergy diagnosis and management which has been generated by experts with a wide range of relevant topic expertise, without financial conflicts of interest in relation to the formula industry. The guidance differs from previous milk allergy guidelines by stating when symptoms and signs are not likely to be due to milk allergy, so that criteria for milk allergy diagnosis are more restrictive. This is likely to reduce the risk that normal infant symptoms are labelled as milk allergy. Our consensus guidance also places limits around the settings where healthcare practitioners should advise breastfeeding women to

restrict their diet, and aligns closer to international infant feeding recommendations than published milk allergy guidelines. (109,264,287,297)

Milk allergy guidelines have generated controversy due to their potential to promote overdiagnosis and undermine breastfeeding. Analysis of one guideline suggested that 74% of infants could be assigned a diagnosis of mild-moderate, and 9% severe non-IgE mediated milk allergy in the first year. (50) Guidelines typically have broad diagnostic criteria covering many common symptoms of infancy, and recommend strict maternal dietary exclusion of cow's milk protein. (85,116,161,277,289-296)

Milk elimination diets can be burdensome, and maternal dietary exclusion advice may cause harm through maternal anxiety or depression, weight loss, reduced breastfeeding confidence and early breastfeeding cessation. (137,298-300) In some high-income countries, there is up to 10-fold excess prescription of specialised formula for managing milk allergy in formula fed infants. (279) This is likely to place a significant financial burden on public health systems, and may have adverse health effects for infants unnecessarily fed specialised formula. Such products can affect taste perception and impact growth trajectory, and have been associated with micronutrient deficiencies. (115,170,171,173,301) Many specialised formula products contain free sugars such as glucose in place of milk lactose, and may thereby increase risk of dental decay and childhood obesity. (115)

Our new consensus guidance provides narrower criteria for identifying milk allergy in young children, by emphasising reproducibility and specificity of reactions, and setting very limited circumstances in which chronic symptoms without temporal relationship to cow's milk ingestion might be considered to indicate milk allergy. Milk allergy guidelines usually consider blood in the stool to be a sign of milk allergy (85,116,161,277,289-296), without reference to the mode of infant feeding, and two current guidelines specify specks, streaks or

flecks of blood to be indicators of allergic proctocolitis. (85,294) However, most infants presenting with blood in the stools do not have milk allergy, and the condition is generally of short duration without serious health consequences. (302-305) There is particular uncertainty about management of rectal bleeding as cow's milk protein induced allergic proctocolitis in an exclusively breastfed infant, where the infant is not directly exposed to cow's milk. (2,165) In contrast to existing guidelines (85,116,161,277,289-296), our consensus recommendations clearly distinguish between diagnosis of FPIAP in an exclusively breastfed infant, where PPI contributions highlighted the potential for harmful consequences when maternal dietary exclusions are advised; and FPIAP diagnosis in children directly consuming cow's milk protein, where our participants reached consensus on diagnostic criteria.

A recent survey of 70 primary care milk allergy guidelines in England found that all guidelines recommended consideration of non-IgE milk allergy in constipated infants, and this is consistent with some published milk allergy guidelines. (141) Constipation was not highlighted as a sign of milk allergy in this Delphi consensus study. Participants reached consensus that reproducible and specific gastrointestinal symptoms related to milk protein ingestion are a sign of possible milk allergy, and these could potentially include constipation, but in the absence of temporally related symptoms, there was consensus that changes in stool consistency or frequency were not a sign of milk allergy. While some studies have suggested responses to milk exclusion diets in a subset of children with treatment-resistant constipation, most participants in this study felt that the evidence for allergy is limited in patients with these responses, and that standard treatments such as laxatives are more appropriate for managing constipation than milk exclusion diets. (306,307) Trial of an exclusion diet may however be considered for children with treatment-resistant constipation who are referred for specialist paediatric gastroenterology assessment. This advice is consistent with NICE recommendations for managing constipation in children, where management focuses on

laxatives and behavioural interventions, and use of a cow's milk exclusion diet is not suggested without specialist advice. (307,308)

WHO breastfeeding recommendations are only referred to by a minority of milk allergy guidelines (277,290,292), but our recommendations align closely with international infant and young child feeding guidance. (109,264,309) Maternal decisions on breastfeeding are influenced by maternal confidence, healthcare practitioner advice and ability to resolve feeding difficulties. (97,310) Our consensus recommendation that breastfeeding is the most appropriate nutrition for children with milk allergy may help to support breastfeeding women in the context of suspected cow's milk allergy. Our consensus recommendations advise against the initiation or continuation of specialised formula in a child beyond 12 months old with normal growth pattern and nutritionally adequate diet. This contrasts with some published milk allergy guidelines (85,295), but is consistent with European Food Standards Agency recommendations, which advise against use of infant formula over 12 months old. (264) Our participants also reached consensus that specialised formula should not be advised for preventing the development of allergic conditions, a practice which was recommended for several decades but has now largely been withdrawn from guidelines. (158)

Limitations

Some milk allergy experts could not be invited to participate due to conflicts of interest with the formula industry. We tried to address this by including anonymous comments from authors of guidelines with author conflicts of interest during the consensus process. PPI participation was limited to commentary rather than voting on recommendations, because the objective of the study was to develop clinical guidance for healthcare practitioners. Our study is not a formal milk allergy guideline, so we did not address several relevant areas in milk allergy diagnosis and management – for example we did not address detailed guidance for

interpreting allergy tests or food challenges, detailed dietary management of children and mothers on exclusion diets, and treatments such as oral immunotherapy or biologics. In clinical practice, some parents may report improvements in infant symptoms with specialised formula in the absence of an allergic mechanism. For example, specialised formula can have physiological effects such as early satiation that may change infant symptoms. (173,311) So for some of the clinical settings where milk allergy is not likely, some practitioners and carers may still wish to try a specialised formula in case there are physiological effects which relieve infant symptoms.

Conclusions

We have produced new consensus recommendations on the safe detection and management of milk allergy in children under 2 years which aim to reduce harms associated with milk allergy overdiagnosis. Implementation of this new guidance is likely to better protect young children and their carers from receiving an inappropriate diagnosis of milk allergy or specialised formula prescription, and from advice which may undermine breastfeeding. However, further work is needed in order to formally evaluate the safety and effectiveness of using this guidance to prevent milk allergy overdiagnosis in practice.

20 Discussion

20.1 Summary of principal findings

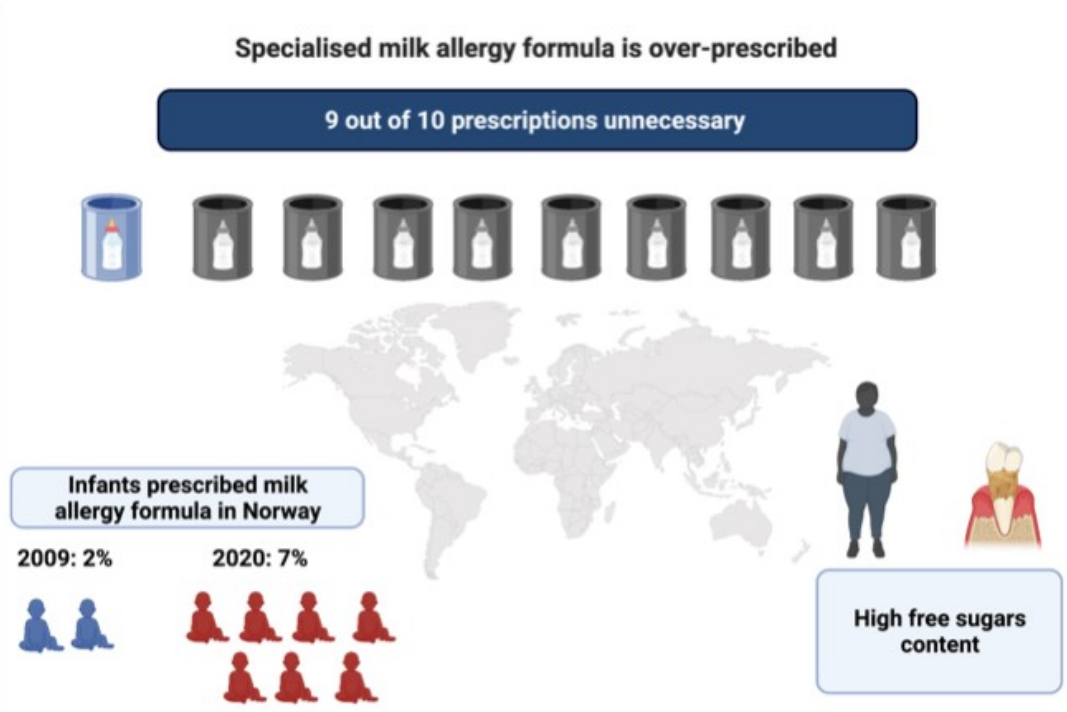
This thesis identified significant over-prescribing of low-allergy formula, which is likely to be unnecessary, or at least outside of the recognised indications for using low-allergy formula. Low-allergy formula is developed and marketed for managing cow's milk allergy, but most children labelled as milk-allergic or prescribed a low-allergy formula do not have CMA. This problem was documented in the small number of countries with publicly available, national prescribing data. CMA overdiagnosis occurred early in childhood (median age 49 days), mainly for gastrointestinal symptoms and exclusively formula-fed infants were more likely to receive unnecessary low-allergy formula compared to partially or exclusively breastfed infants. Primary care practice prescribing habits appear to be a relevant risk factor for CMA overdiagnosis, and maternal healthcare seeking behaviour may also be relevant. Independent guidance for diagnosing and managing CMA, developed as part of this thesis, may better protect mothers and infants from false labels of milk allergy than guidance funded by the formula industry.

National and international trends in low-allergy formula prescribing

In a cross-sectional analysis of national prescription databases evaluating specialised formula prescribing trends (Figure 20.1), we found the volumes of specialised formula for infants rose 2.8-fold in England from 2007-2018, with similar trends in other regions of the United Kingdom. Volumes rose 2.2-fold in Norway from 2009-2020 and 3.2-fold in Australia from 2001-2012. In 2020, total volumes were 9.7 to 12.6-fold greater than expected in England, 8.3 to 15.6-fold greater than expected in Norway and 3.3 to 4.5-fold greater than expected in Australia, where prescribing restrictions were introduced in 2012. In Norway the proportion of infants prescribed specialised formula increased from 2.2% in 2009 to 6.9% in 2020, or

11.2 to 13.3-fold greater than expected. In 2020, specialised formula for infants cost US$117 (103 euro) per birth in England, US$93 (82 euro) in Norway and US$27 (23 euro) in Australia. Soya formula prescriptions exceeded expected volumes 5.5 to 6.4-fold in England in 1994 and subsequently declined, co-incident with public health concerns regarding soya formula safety. A high proportion of specialised formula prescribed was amino-acid formula - in 2020, 30-50% across the three countries..

Figure 20.1: Summary of findings for National and International trends in low-allergy formula prescribing



Summary of findings from our survey of national and international prescribing trends for specialised low-allergy formula. We found increasing and excessive prescribing of these products, which contain higher free sugars content than standard infant formula, due to replacement of lactose with alternative carbohydrate sources. These include glucose syrups, maltodextrins, and less commonly fructose or other carbohydrates. Created in BioRender. Allen, H. (2025) https://BioRender.com/g87i985. (115)

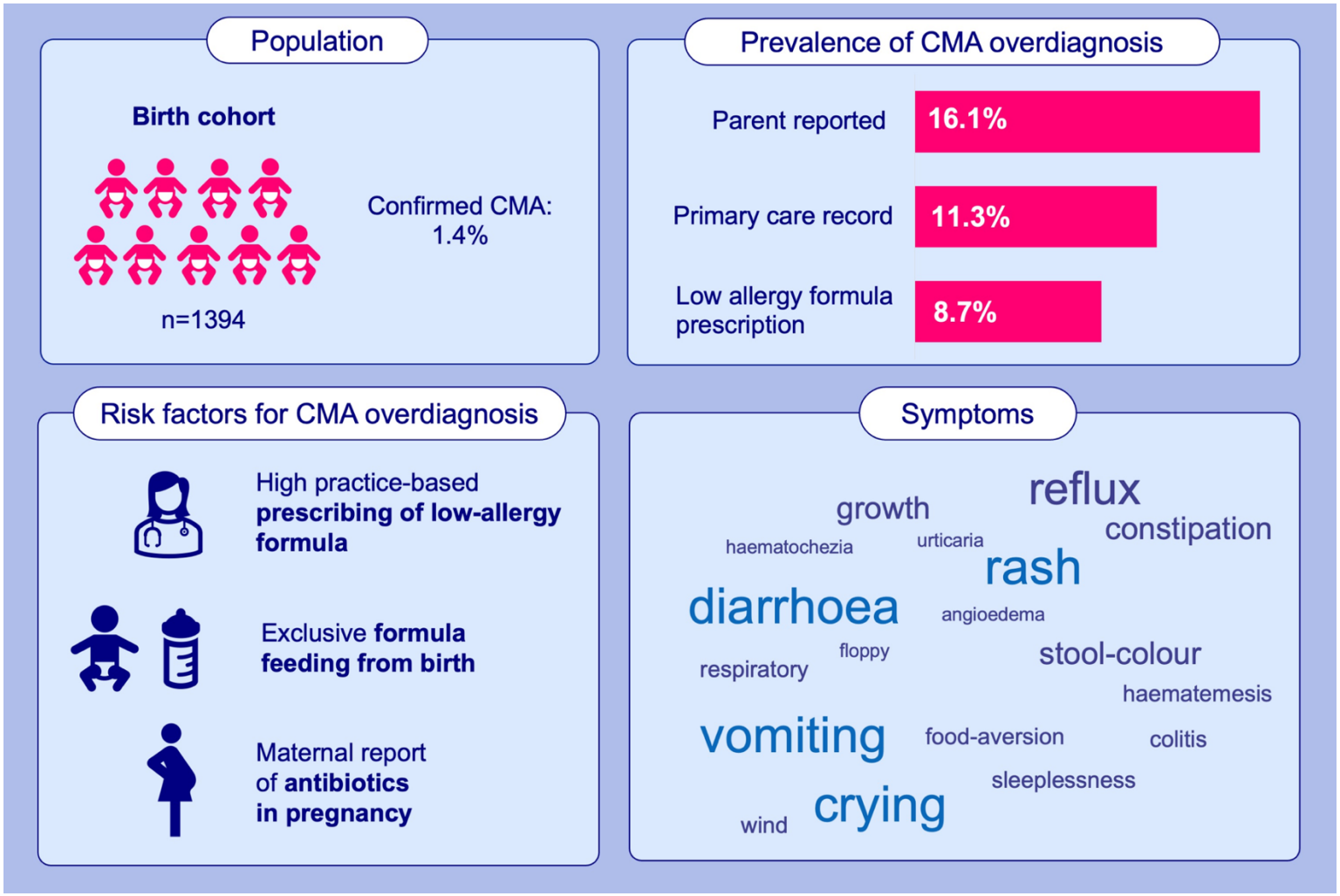
Prevalence, consultation features and risk factors for CMA overdiagnosis

In a clinical trial birth cohort which included prospective assessment of CMA diagnosis (Figure 20.2), we found that in the group who were not confirmed as milk-allergic, about 16% of parents reported a reaction to cow's milk in their child by age 2 years old, 11% had primary care records documenting a milk hypersensitivity and 9% of children were prescribed a low-allergy formula during the first two years of life. This means that approximately half of children with parent-reported CMA received an unnecessary prescription of low-allergy formula. Gastrointestinal symptoms were the most common indication for CMA overdiagnosis and unnecessary prescription, particularly diarrhoea, vomiting and reflux. Primary care practitioners were most commonly responsible for initiating CMA overdiagnosis and low-allergy formula prescription, although multiple healthcare practitioners and parents contributed to the process. Maternal dietary restrictions were commonly undertaken by mothers and advised by healthcare practitioners.

CMA overdiagnosis occurred at median 49 days old and was diagnosed median 37 days from symptom onset. Low allergy formula was usually initiated by GPs in CMA overdiagnosis, for duration of median 10 months, and median estimated volume consumed was 272 litres. Estimated daily low-allergy formula consumption was greater for AAF (median 1 litre per day) than EHF (median 0.64 litres per day).

We identified maternal report of antibiotic prescription during pregnancy and higher practice-based prescribing of low-allergy formula as risk factors for CMA overdiagnosis. Exclusive formula feeding from birth was associated with an increased risk of receiving a low-allergy formula prescription but was not associated with other markers of CMA overdiagnosis – for example, parent-reported CMA overdiagnosis frequently occurred in breastfed infants.

Figure 20.2: Summary of findings for prevalence, consultation features and risk factors for CMA overdiagnosis

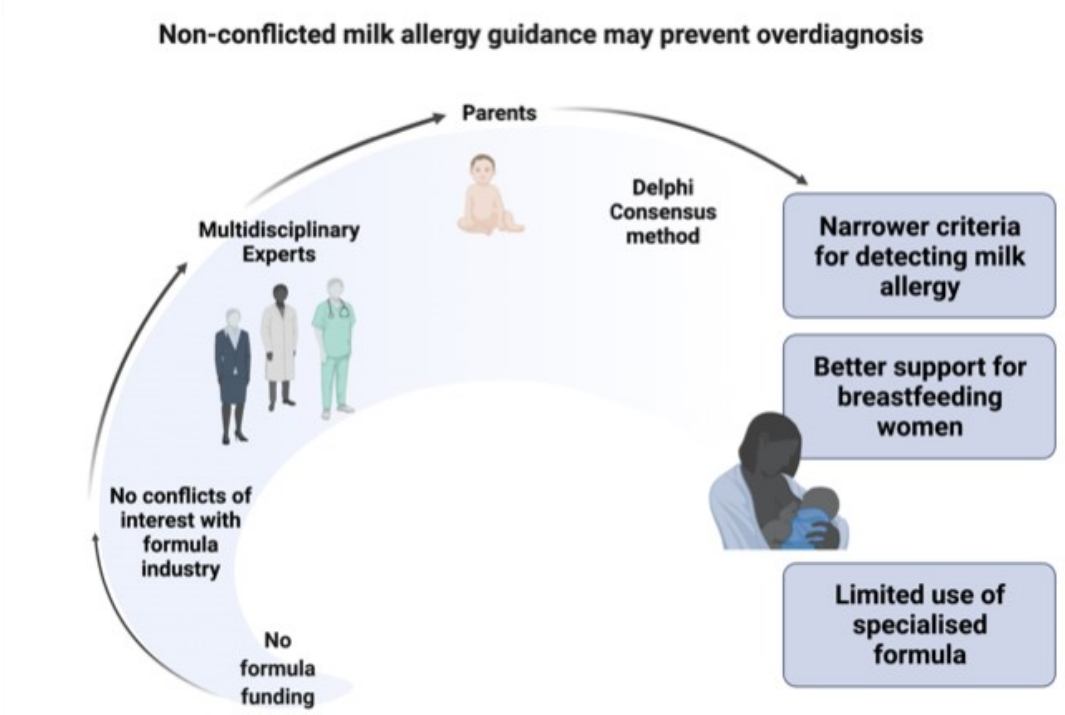


Summary of findings from our analysis of a prospective clinical trial birth cohort in England, enrolled between 2014 and 2016. CMA was carefully characterised in the cohort. In young children without confirmed CMA, CMA overdiagnosis was identified in a significant minority of participants.

Impact of conflicts of interest on CMA guideline development

We found that independent guidance, without formula industry funding produced recommendations that had narrower criteria for considering CMA as a possible diagnosis; better support for breastfeeding women; and a more limited role for use of specialised formula compared with previous mainly conflicted guidelines (Figure 20.3). The independent guidance was developed by multidisciplinary experts without conflicts of interest with formula industry, and involved parents. These independent recommendations highlighted the importance of reproducibility and specificity for diagnosing milk allergy in children with acute or delayed symptoms temporally related to milk protein ingestion; and distinguished between children directly consuming milk protein, and exclusively breastfed infants. Consensus was reached that maternal dietary restriction is not usually necessary to manage milk allergy, and that for exclusively breastfed infants with chronic symptoms, milk allergy diagnosis should only be considered in specific, rare circumstances. Consensus was reached that milk allergy diagnosis does not need to be considered for stool changes, aversive feeding, or occasional spots of blood in stool, if there is no temporal relationship with milk protein ingestion.

Figure 20.3: Summary of findings for impact of conflicts of interest on CMA guideline development



Summary of findings from development of CMA guidance without formula company sponsorship of the project or contributors. Compared with industry-sponsored guidance, independent CMA guidance identified narrower criteria for considering CMA diagnosis, more explicit support for continuation of breastfeeding and a more limited role for low-allergy formula in patient management. Created in BioRender. Allen, H. (2025) https://BioRender.com/j46d807

20.2 Consistency with other research studies

Excessive use of specialised formula for cow's milk allergy was previously reported in England between 2009 and 2018, with a 10-fold rise in amino acid formula prescriptions. (2) We updated the data for England, and completed the analysis for the whole United Kingdom. Our results were in agreement with this earlier study that low-allergy formula use in England is excessive and continuing to rise, and that this pattern is repeated in the other countries of the United Kingdom. Australian data previously also showed increased prescribing of amino acid formula over a decade from 2000. Our study confirmed a 5-fold increase in amino acid formula from 2001-2012 in Australia, prior to introduction of prescribing restrictions for amino acid formula which are likely to have impacted the data for the following years.

We found a high rate of CMA overdiagnosis in the BEEP cohort which was consistent with other studies suggesting excessive parent-reported CMA and low allergy formula prescriptions. (2,79) Our findings are consistent with recent evidence that 4.9% of store purchases of formula in the US were low-allergy products for CMA in 2017, rising to 7.6% in 2019. (196) Our findings add to the literature by identifying practice-based risk factors for prescribing low allergy formula.

CMA guidelines have been shown to promote CMA overdiagnosis and impact healthcare practitioner prescribing behaviours in primary care. (2,50,141) Our Delphi study showed that guidance recommendations generated without industry influence are less likely to promote CMA overdiagnosis and unnecessary use of low-allergy formula. This is consistent with wider literature on the impact of commercial conflicts of interest on prescribing practice and clinical care (312,313)

Key limitations

This thesis has several limitations. The international trends in specialised formula prescriptions is limited to 3 high income countries and only reimbursable items. Specialised formula prescriptions in the United Kingdom were only analysed in primary care, excluding prescriptions from secondary care. Specialised formula can also be obtained through online and direct sales sources and so data are incomplete and likely to underestimate prescribing/purchasing of low-allergy formula. Prevalence of true CMA was obtained from the Europrevall study which assessed CMA in children between 2005 and 2010. (1) It is possible, albeit unlikely, that CMA prevalence has changed since that time or that CMA prevalence in Australia differs from a European population.

CMA was formally evaluated within the BEEP study, meaning that confirmed CMA and over-reporting of CMA by parents was well-characterised within this cohort. This presented a unique dataset allowing us to identify the prevalence, features and risk factors for CMA overdiagnosis in this cohort. However, clinical trial populations differ from the general population and this specific trial population was restricted to children with a family history of atopic disease. Parental concern about allergy and healthcare practitioner awareness of potential allergy may be higher when there is a family history of atopic disease and so the findings in this clinical trial population may differ from the general population. This possibility is supported by the finding that amino-acid formula prescribing rates were relatively increased in BEEP study children with CMA overdiagnosis, compared with contemporaneous national prescribing rates for England.

We undertook an independent Delphi consensus study based on our hypothesis that existing conflicted guidelines contributed to CMA overdiagnosis. We interpreted our independent

Delphi recommendations as producing narrower diagnostic criteria for CMA, more supportive of breastfeeding women and more limited recommendations for specialised formula use. However, these recommendations have not been validated through clinical use and so it remains unknown if they would actually reduce CMA overdiagnosis in clinical practice; or indeed, support breastfeeding better or reduce low-allergy formula prescribing. We also interpreted the recommendations as different from current conflicted guidelines and attributed that difference to the lack of commercial interests amongst the Delphi panel. However, there were other differences between the Delphi guidance process and other CMA guidance/guidelines - for example, other guidance groups did not use a formal Delphi process, tended to have a narrower panel of experts and more limited parent involvement. All of these factors may also have contributed to differences in recommendations between our Delphi study and other published CMA guidance. However, the interpretation that a lack of commercial sponsorship may explain the differing CMA guidance recommendations is supported by evidence from other areas of medicine/healthcare, where commercial sponsorship is associated with increased prescribing and lower quality medical care. (312)

It is also worth noting that guidelines are only one contributor to overdiagnosis and in this thesis, we did not consider other contributors. Our BEEP study analysis identified parents as most frequently initiating the diagnosis of CMA after general practitioners. This thesis did not include qualitative work to explore parental or healthcare practitioners' concerns about infants that leads to a false label of CMA, unnecessary maternal dietary restriction or unnecessary low-allergy formula use. In this thesis, we considered financial conflicts of interest h the formula industry as contributing to CMA overdiagnosis. However, other conflicts of interest exist and may contribute to CMA overdiagnosis such as healthcare practitioners who have personal experience of allergy in their child and are motivated to

avoid “missing” a diagnosis of allergy, or academic bias from groups with strong views on the topic for other reasons.

20.3 Implications for theory and practice

CMA overdiagnosis presents early in life, mainly triggered by concern about gastrointestinal symptoms in infants, and it appears that low-allergy formula is being commonly used as a solution. We interpreted maternal report of antenatal antibiotics as a marker of healthcare-seeking behaviour, (274-276) and this may suggest an individual vulnerability for CMA overdiagnosis that is difficult to change. Gastrointestinal symptoms in babies are common and can be difficult for families to manage. Most current prescribed treatments lack good evidence of efficacy. (2,132) Uncertainty about the cause of troublesome infant symptoms may impede self-management, leading parents and carers to seek reassurance or a medical solution from their healthcare practitioner or through their own internet research. This information need is exploited by the formula industry, which leverages common parental concerns to drive earlier formula introduction and use of higher-cost formula products. (309,314) The formula industry actively creates awareness about CMA through website resources and targets parents and healthcare practitioners including sponsorship of milk allergy guidelines. (2,3,144,314,315) In many instances, the solution for benign but troublesome infant gastrointestinal symptoms is reassurance, parental support and time. However, in these cases, where an evidence-based medical solution is lacking, commercial influences can undermine messages aimed at reassuring parents and carers. Therefore, better support and education of parents in managing infant symptoms is needed as part of the solution for CMA overdiagnosis and this may involve more shared decision-making in consultations between healthcare practitioners and parents. It also requires consistency in the advice parents receive from healthcare practitioners and better consensus amongst the

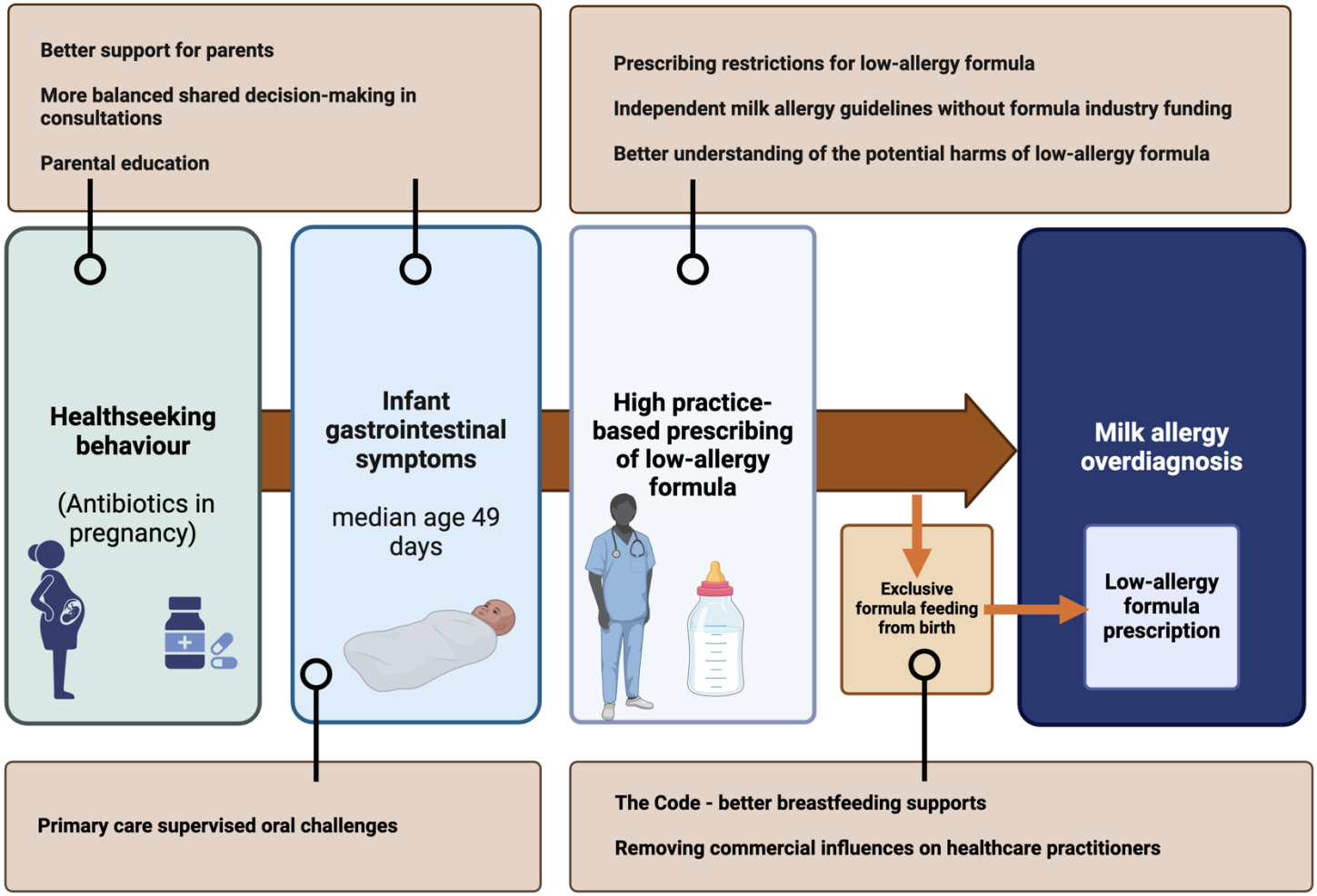
medical community on how to manage infants presenting with gastrointestinal symptoms. Formula industry influence on healthcare practitioner education and milk allergy guidelines should be banned as is best practice in guideline development and measures to protect breastfeeding recommended in the International Code of Marketing of Breastmilk Substitutes and subsequent World Health Assembly Resolutions. (2,3,144,314-316)

Our research identified an association between healthcare practitioner prescribing behaviours and CMA overdiagnosis. Therefore, an important potential intervention to manage CMA overdiagnosis may be to target prescribing healthcare practitioners. In Australia in 2012, low-allergy formula prescribing was restricted to specialists-only, resulting in a significant reduction in prescribed volumes of low-allergy formula. Prescribing restrictions may be an important potential intervention to reduce community prescribing of low-allergy formula, particularly as diagnosis of Non-IgE CMA usually relies on elimination and re-introduction of cow's milk. For exclusively formula-fed infants, the only option is trial of low-allergy formula during the elimination phase and it has been shown that home oral challenges in this context tend to over-estimate CMA. (124) Another option is to train community healthcare practitioners (such as dieticians, practice nurses or general practitioners) to perform supervised oral challenges as was undertaken in one Dutch study but this is time-consuming, requires additional expertise and given the current workload demands on primary care, is unlikely to be practical or cost-effective in all settings. (124) In primary care, it may be that healthcare practitioners see little consequence in prescribing low-allergy formula, particularly when an infant is already exclusively formula-fed. Therefore, educating healthcare practitioners on the harms of unnecessary dietary restrictions, false diagnostic labels and the potential harms of low-allergy formula in terms of carbohydrate content or other compositional features is another important potential intervention. More research is needed to

understand what these potential harms are, particularly in children who do not have milk allergy.

Finally, society as a whole would benefit from better investment in breastfeeding support (317), and this would likely also have positive effects for managing the problem of CMA overdiagnosis and excessive prescribing of low-allergy formula. The benefits of breastfeeding for the maternal infant dyad are well-recognised and there are few scenarios in which breastfeeding is contraindicated. (287,317) Low allergy formula is necessary for confirmed milk-allergic infants when breastfeeding is not possible. We have shown that low-allergy formula prescription is increased in infants who are exclusively formula-fed from birth. Therefore, better support of women to encourage higher rates of breastfeeding would likely reduce prescribing of low-allergy formula. Current evidence for maternal dietary restrictions to manage infant symptoms is inadequate, and strict maternal dietary restrictions have been associated with adverse maternal physical and psychological health outcomes, as well as contributing to early cessation of breastfeeding. (2,3,137,143,265) Food allergic reactions in exclusively breastfed babies are rare, confined to case reports and therefore, better education of breastfeeding women could potentially reduce unnecessary maternal dietary eliminations and potentially avoid early breastfeeding cessation which has been reported by mothers of children diagnosed milk-allergic. (137,165)

Figure 20.4. Concept of how CMA overdiagnosis arises and potential intervention points to prevent CMA overdiagnosis



Overview of risk factors for CMA overdiagnosis which have been identified in this thesis; and potential areas where interventions may be effective for preventing CMA overdiagnosis and associated low-allergy formula prescribing. Created in BioRender. Allen, H. (2025) https://BioRender.com/c64c555

20.4 Future research needed

In this thesis, we used reimbursement data for low-allergy formula prescriptions, mainly in primary care. However, specialised formula can be obtained from other sources, such as online sales. Secondary care prescriptions are also another source. Furthermore, prescriptions are not always used or product consumed by infants. Therefore, further research is needed to provide a more comprehensive and precise estimate of specialised formula consumption in infants. The 2023-24 England Infant Feeding Survey is likely to yield some representative and relevant information in this regard, which can be compared with national prescribing information to yield updated consumption estimates. (318) We also relied on an estimate of CMA incidence from the Europrevall study which is over 10 years old, although this remains the most reliable estimate of CMA incidence to date. Updated information about IgE and non-IgE mediated CMA incidence in infants would be helpful.

Within the BEEP study, we identified maternal use of antibiotics in pregnancy as a risk factor for CMA overdiagnosis. We interpreted this self-reported, single datapoint as a marker of healthseeking behaviour. Indeed, it was included in the analysis as the best potential measure of healthcare seeking behaviour in the BEEP dataset. However, further work is needed to understand whether maternal healthcare seeking behaviour is associated with CMA overdiagnosis. Qualitative research is required to understand parental concerns about symptoms in their child, their expectations and their experience of healthcare practitioner management of such concerns. Conversely, further research is also needed to understand healthcare practitioners' experiences of consultations with parents presenting with concerns about infant symptoms. In particular, research is required as to what factors influence healthcare practitioners to prescribe low-allergy formula, whether further allergy education is

required or if practitioners are influenced by educational events funded by formula industry. The impact of conflicts of interest with the formula industry on healthcare practitioner prescribing of low allergy formula also requires further evaluation.

Low allergy formula contains alternative carbohydrate sources to milk lactose, such as glucose syrups and maltodextrins. Evidence to date suggests an association between reduced lactose infant formula and risk of early childhood obesity. (192) Health warnings already exist regarding the intake of glucose syrups and dental caries from public health bodies, however these are poorly communicated to prescribers and purchasers, with no mandatory front of pack labelling or prescription warnings. (179,264) Further research is needed to assess if the excessive volumes of specialised formula consumed over the last few decades has impacted child health and if, in particular, specialised formula is associated with childhood obesity and/or dental caries. If potential associations can be clarified, then it will be possible to develop improved prescriber education and consumer information regarding any health effects of low-allergy formula consumption.

20.5 Conclusions

In this thesis, we found that milk allergy overdiagnosis was common, affecting 16.1% of infants compared with 1.4% of infants who had confirmed milk allergy. Half of those with parent-reported milk allergy overdiagnosis (16.1%) received an unnecessary low allergy formula (8.7%). Children acquired a false label of milk allergy mainly for gastrointestinal symptoms, at median age 49 days and most frequently from general practitioners.

The particular patient vulnerabilities that increased the risk of acquiring a false label of milk allergy included maternal report of antibiotic use in pregnancy (a potential marker of healthcare-seeking behaviour) and exclusive formula feeding from birth.

Healthcare practitioner behaviours that were associated with an increased risk of mis-diagnosing a child milk-allergic included high primary care practice prescribing of low-allergy formula.

Guidance on milk allergy diagnosis and management developed by multidisciplinary healthcare practitioners without conflicts of interest to the formula industry and with parental involvement was more supportive of breastfeeding women, included narrower diagnostic criteria for CMA and more limited recommendations for specialised formula use compared to current conflicted guidelines. Milk allergy overdiagnosis is a global problem at least in high income countries, where specialised formula prescriptions increased in the early 21st century and exceeded expected levels. Unnecessary specialised formula use may significantly contribute to free sugars consumption in young children. Potential harms to child health include risk of childhood obesity and dental caries through alternative carbohydrate sources that are present in specialised formula.

Potential interventions for addressing the problem of milk allergy overdiagnosis include prescribing restrictions for low-allergy formula, independent milk allergy guidelines without formula industry funding, better understanding of the potential harms of low-allergy formula, better support for parents with shared decision-making between parents and healthcare practitioners, primary care supervised oral challenges and better breastfeeding supports with removal of commercial influences on healthcare research and clinical practice (Figure 20.4).

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22 Appendices

22.1 Literature review search strategy

I performed an electronic literature search of MEDLINE and EMBASE from 2000 to 2024 using the keywords outlined below. I also undertook a hand search of additional references from relevant identified manuscripts and references which I read throughout my PhD including those shared with me by my supervisor,

Keywords: aaf; amino acid formula; breastfeeding; burden; children; commercial influence; commercial interests; conflicts of interest; consequences; cost; cow's milk allergy; CMA; cow's milk hypersensitivity; ehf; extensively hydrolysed formula; financial conflicts; financial implications; harm; hydrolysed formula; impact; infant; infant feeding; infant formula; lactation; low allergy formula; milk allergy; mood; overdefinition; overdetection; overdiagnosis; overmedicalisation; paediatric; pathologising; psychology; resources; soya formula; specialised formula; stress;

Ovid MEDLINE and Embase.

1 (Overdiagnosis or Over?diagnos$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
2 limit 1 to (english language and humans and yr="2000 -Current")
3 (Overmedicalisation or over?medicalis$ or pathologising).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
4 limit 3 to (english language and humans and yr="2000 -Current")
5 (Overdetection or over?detect$ or overdefinition or over?definition or over?defin$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
6 limit 5 to (english language and humans and yr="2000 -Current")
7 (Milk allergy or Cow's milk allergy or CMA or Cow's milk hypersensitivity or Cow's milk allerg$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
8 limit 7 to (english language and humans and yr="2000 -Current")
9 (Child$ or Paediat$ or P?diatri$ or infant).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word,

rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
10 limit 9 to (english language and humans and yr="2000 -Current")
11 8 and 10
12 2 or 4 or 6
13 11 and 12
14 8 and 12
15 (Breastfeeding or infant feeding or lactat$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
16 limit 15 to (english language and humans and yr="2000 -Current")
17 8 and 16
18 (Speciali?ed formula or low?allergy formula or infant formula or amino-acid formula or hydroly?ed formula or extensively hydroly?ed formula or soya formula or ehf or aaf).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
19 limit 18 to (english language and humans and yr="2000 -Current")
20 8 and 19
21 (psychol$ or mood or stress$ or burden or impact or consequence$ or harm$ or cost or resource$ or financ$ implication$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
22 limit 21 to (english language and humans and yr="2000 -Current")
23 8 and 22
24 (Conflicts of interest or conflict$ or financial conflict$ or commercial interests or commercial influence).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
25 limit 24 to (english language and humans and yr="2000 -Current")
26 8 and 25
27 8 and 16 and 22

22.2 Countries assessed for eligibility

Country	Data availability
Asia-Pacific	
Australia	Data available for EHF and AAF 1992-2020
China	No national dataset available
India	No national dataset available
Israel	No national dataset available
Japan	No national dataset available
Malaysia	No national dataset available
Pakistan	No national dataset available
Singapore	No national dataset available
Taiwan	No national dataset available
Europe	
Belgium	No national dataset available
United Kingdom	Data available for EHF, AAF and Soya 1991-2020
Germany	No national dataset available
Ireland	No national dataset available
Netherlands	No national dataset available
Norway	Data available for EHF, AAF and Soya 2009-2020
Poland	No national dataset available
Portugal	No national dataset available
Russia	No national dataset available
Switzerland	No national dataset available
Americas	
United States of America	No national dataset available
Canada	No national dataset available
Brazil	No national dataset available

AAF, amino acid formula; EHF, extensively hydrolysed formula; Soya, soya-based formula

22.3 Specialised formula products analysed in Chapter 13 and 15

Table S1. Products included in analysis

	Australia	England	Norway
Soya Formula			
Farley's OsterSoy Formula	-	1991 – 1993	-
Farley's Soya	-	1998 – 2015	-
Infasoy	-	1998 – 2019	-
ProSobee	-	1998 – 2008	2009 – 2010
ProSobee Concentrated Liquid	-	1991 – 1999	-
SMA Wysoy	-	1998 - 2019	-
Extensively Hydrolysed Formula			
Alfaré	1992 – 2020	2001	2009 – 2020
Althéra	-	2013	2009 – 2020
Alimentum	-	2013 – 2019	-
Aptamil Gold+ Pepti-Junior	1998 – 2020	-	-
Aptamil Pepti/ Cow and Gate Pepti	-	2010	-
Aptamil Pepti 1	-	2011 – 2019	-
Aptamil Pepti 2	-	2011 – 2019	-
Milupa Prejomin	-	1991 - 2010	-
Nutramigen[a]	1992 – 2001	1998 – 2016	2009 – 2018
Nutramigen 1 Lipil	-	2004 – 2019	2009 – 2020
Nutramigen 1 with LGG	-	2015 – 2019	-
Nutramigen 2 Lipil[a]	-	2003 – 2019	2009 – 2020
Nutramigen 2 with LGG	-	2015 – 2019	2009 – 2010
Nutramigen 3[b]	-	2018 – 2020	-
Pepticate	-	-	2013 – 2020
Pepticate Plus[b]	-	-	2016 – 2020
Profylac	-	-	2009 – 2017
Amino Acid Formula			
Alfamino	2014 – 2020	2014 – 2019	2014 – 2020
Elecare	2002 – 2020	-	-
Elecare LCP	2010 – 2020	-	-
Neocate	1994 – 2012	1998 – 2019	-
Neocate Active[b]	-	2007 – 2020	2009 – 2020
Neocate Advance[b]	2004 – 2020	1999 – 2020	2009 – 2020
Neocate Advance Tropical Flavour[b]	2007 – 2015	-	-
Neocate Gold	2011 – 2020	-	-
Neocate Junior[b]	2017 – 2020	2017 – 2020	2019 – 2020
Neocate Junior Vanilla[b]	2012 – 2020	2017 – 2020	-
Neocate LCP	2007 – 2020	2008 – 2019	2009 – 2020
Neocate Nøytral Pulv[b]	-	-	2009 – 2011
Neocate Syneo	2018 – 2020	2018 – 2019	-
Nutramigen AA Lipil	-	2008 – 2014	2009 – 2016
Nutramigen PurAmino	-	2014 – 2020	2015 – 2020

[a]In Norway, these include Nutramigen Farmag Nøytral Pulv, Nutramigen Pulv, Nutramigen Pulver Nøytral ('Nutramigen'); and Nutramigen 2 Farmag Pulv, Nutramigen 2 DHA Pulv, Nutramigen 2 Lipil Farmag, Nutramigen 2 Pulv ('Nutramigen 2 Lipil') [b]Marketed for children age over one year.

Table S2. Products excluded from analysis

Product	Reason for Exclusion	Countries
Pregestimil	Used mainly for managing malabsorption	Australia, England, Norway
Nutrison Soya/ Fortison Soya		England, Norway
Cow&Gate Pepti-Junior		England
Aptamil Pepti-Junior		England
Novalac Allergy rice formula	Not reimbursed	Australia
Karicare Soy		Australia
S-26 Gold Soy		Australia
Elecare	Only reimbursed for eosinophilic esophagitis	Australia (Item Code 2250K)
Neocate Gold		Australia (Item Code 1545H)
Neocate Syneo		Australia (Item Code 11343B)
Neocate Spoon	Solid food or semi-solid food	England and Norway
Neocate Nutra		

Products were excluded if volumes of reimbursed formula were not recorded on a publicly available national database, if their primary use was not cow's milk allergy and if not consumed as a liquid breastmilk substitute.

22.4 Estimated proportion of infants using formula within the first year of life

Table S3. Estimated proportion of infants using formula within first year in the United Kingdom

Age (months)	England		Wales		Scotland		Northern Ireland	
	2005	2010	2005	2010	2005	2010	2005	2010
<1	38[a]– 52	32[a]– 51	52[a] -60	49[a]-62	46[a]-56	42[a]-58	56[a]-63	56[a]-66
1	53 – 68	46 – 65	53-75	46-75	53-71	46-68	53-77	46-78
2-3	53 – 78	46 – 74	53-86	46-82	53-79	46-76	53-85	46-86
4-5	68 – 87	60 – 82	68-92	60-88	68-89	60-83	68-92	60-90
6-7	68 – 91	60 – 88	68-95	60-92	68-92	60-88	68-95	60-93
8	83 – 91	73 – 88	83-95	73-92	83-92	73-88	83-95	73-93
9-12	83 – 96	73 – 95	83-97	73-96	83-98	73-97	83-97	73-97

Data shown are estimated % receiving formula, taken from 2005 and 2010 UK Infant Feeding Surveys.[1,2] Data for the lower bound are the 'Formula only' row of Table 5.1'Type of milk given to babies in the last 7 days at each stage of the survey'. Data for the upper bound are from Table 5.4 'Age at which formula milk first introduced by country' for 2005 survey and from Table 5.4 'Age at which milk other than breastmilk was first introduced by country' for 2010 survey. Values from the 2005 survey were used for estimating the expected formula consumption for the years 1991-2009 and from the 2010 survey for the years 2010-2020. [a]No data point is available for < 1 month, so this was estimated as the converse of data from the 2 weeks row for each country in the Table 'Prevalence of breastfeeding at ages up to 9 months by country'. The range of expected volumes was calculated by multiplying 1% of the lower or upper bound for the number of live births receiving formula at a given age, by typical daily volumes consumed during the relevant time period.

Table S4. Estimated proportion of infants using formula within first year in Norway

Age (months)	Estimated % receiving formula		
	2007	2013	2019
<1	2 – 22	5 – 14	4 – 25
1	5 – 22	7 – 20	7 – 25
2	9 – 22	11 – 25	11 – 25
3	12 – 28	14 – 31	15 – 30
4	15 – 36	19 – 37	18 – 35
5	18 – 41	22 – 42	21 – 40
6	20 – 62	29 – 53	22 – 55
7	25 – 62	33 – 53	28 – 55
8	31 – 62	40 – 62	32 – 55
9	37 – 62	45 – 62	37 – 55
10	44 – 70	53 – 73	42 – 62
11	52 – 70	61 – 73	49 – 62
12	54 – 70	65 – 73	52 – 62

Data taken from the Norwegian National Dietary Surveys of infants.[3-7] Data for the lower bound are the converse of the reported proportion of infants who were fully or partially breastfed at different ages and the presented values represent the proportion who were not receiving any breast milk at each age. Data for the upper bound were taken from the tables for 'time of introduction for other food and drink – breastmilk substitute or other milk', converted to a cumulative proportion. The infant dietary surveys for 2007 and 2019,[3,4,6,7] presented data across two reports each. For 0-6 months from Tables 10 and 14 (2007) and Tables 14 and 17 (2019); for 6-12 months from Tables 9 and 12 (2007) and Tables 12 and 15 (2019). In the 2013 survey,[5] data for 0–12-month-olds were from Tables 7 and 8. Values from the 2007 survey were used to estimate the expected formula consumption for years 2009-2012, the 2013 survey for years 2013-2018, and 2019 survey for 2019-2020. The range of expected volumes was calculated by multiplying 1% of the lower or upper bound for the number of live births receiving formula at a given age, by typical daily volumes consumed during the relevant time period.

Table S5. Estimated proportion of infants using formula within first year in Australia

Age (months)	Estimated % receiving formula
<1	10 – 27
1	25 – 40
2	27 – 43
3	30 – 46
4	31 – 48
5	37 – 53
6	40 – 55
7	58 – 62
8	58 – 68
9	58 – 68
10	58 – 75
11	58 – 78
12	58 – 80

Data taken from 2010 Australian National Infant Feeding Survey.[8] The data for the lower bound are the converse of data from Table 10 'Proportion of children currently breastfed', and data for the upper bound are from Table 5 'Proportion of children who had received formula or non-human milk in the last 24 hours'. Values from the 2010 survey were applied to all years analysed, 1998-2020, to estimate expected formula consumption for the 1% of infants with milk allergy. The range of expected volumes was calculated by multiplying 1% of the lower or upper bound for the number of live births receiving formula at a given age, by typical daily volumes consumed during the relevant time period.

22.5 Copy of letter emailed to the parents of the BEEP participants

BEEP Trial – Barrier Enhancement for Eczema Prevention

BEEP Team
Nottingham Clinical Trials Unit
University of Nottingham
Building 42, University Park
Nottingham
NG7 2RD
Tel: 0115 8231603
E mail: beep@nottingham.ac.uk

NAME OF MOTHER
Address of Mother

Date letter sent.

Dear *NAME OF MOTHER,*

Firstly thank you again for your continued support with the BEEP Eczema Study, we really do appreciate it.

As you are aware, we are continuing to collect long term data about eczema and food allergy from the families participating in the trial via the questionnaires we have been sending out up until your child is 5. When you first signed up to the BEEP Study you also kindly agreed for us to review medical notes where relevant to taking part in BEEP. We are writing to you now to let you know that we would like to access your child's medical notes held by their GP.

The purpose of requesting your child's GP records now is to better understand the reliability of the different measures of food allergy diagnosis that we have used in the BEEP trial as food allergy can be difficult to diagnose. By looking at the GP notes of children from their first years we are hoping to better understand the patterns we have seen so far in the BEEP trial data shared with us by parents at the 2-year visit and the questionnaires. We will be reviewing these medical notes to find information related to allergy only. Your child's data will, as always, be kept confidential and secure, and will not be used to personally identify them in any way.

As it may have been several years since you first gave us permission to look at your child's medical notes, we wanted to let you know before we request these from the GP. If you **do not** now want us to contact your GP to ask for a copy of your child's medical notes, then please tell us within 2 weeks of receiving this letter. If you let us know you do not want us to contact your GP, we will have no communication with your GP about this matter.

If you are happy for us to contact your GP, you do not need to respond to this mail. As always, if you have any questions about this letter or any other aspect of the study, do not hesitate to get in touch – the easiest way is to email us at: beep@nottingham.ac.uk

With very best wishes,

Professor Hywel Williams DSc FMedSci
Consultant Paediatric Dermatologist on behalf of the BEEP team

22.6 Copy of letter emailed to the BEEP primary care practices

BEEP Trial – Barrier Enhancement for Eczema Prevention

BEEP Team
Nottingham Clinical Trials Unit
University of Nottingham
Building 42, University Park
Nottingham
NG7 2RD
Tel: 0115 8231603
E mail: beep@nottingham.ac.uk

Name of GP Practice
Address of GP Practice

For Attention Of: Practice Manager/ Administrator, GP Practice

Re: ***PATIENT FULL NAME, DATE OF BIRTH***

Around the time of the above child's birth, their mother or father consented for the child to take part in the BEEP study (funded by the NIHR HTA 12/67/12), which is looking at use of emollients in the prevention of eczema and allergy. As a part of this process, consent was given for the study team to review medical notes, where relevant to their taking part in the BEEP Study

We would like to request a copy of the primary care medical records for the above child, who is registered at your surgery.

With approval from Research Ethics Committee (West Midlands- Solihull, reference 14/WM/0162) the child's parent(s) was sent the attached letter on *22-Sep-2021* detailing our wish to consult their child's medical records in order to better understand the BEEP trial data. This letter gave them an option to opt out of this if they have changed their mind about allowing access to their records since they consented to participate in the BEEP trial some years ago. We have not received an opt-out request from the family in this time and would therefore like to proceed with requesting this child's medical records from you. We will review the medical notes for any information related to report, diagnosis or management of allergy, including history of prescriptions related to allergy. We would be happy to provide you with a copy of the original study consent form, ethics approval letter or the recent letter sent to the child's parents if that would be helpful.

Thank you very much for the time you are taking to contribute to this important national trial.

Sincerely,

Professor Hywel Williams DSc FMedSci
Consultant Paediatric Dermatologist

Dr Robert Boyle, Dr Hilary Allen
on behalf of the BEEP team

Study Number

22.7 BEEP study datasheet dictionary

Explanation of main datapoints extracted from the primary care records

Variable Name	Description	Explanatory notes
com_record	Complete or partial primary care records	Records were considered complete if there was sufficient information to answer the primary outcomes of primary care record of milk reaction and primary care record of specialised formula prescription
milk_issue	Reaction or possible reaction to milk	Any mention in the primary care records of a reaction or possible reaction to milk
def_dx_name	Definitive diagnostic name	Most definitive diagnostic name recorded at any time in the primary care records
class_milk_dx	Classification of diagnosis	Classification of milk reaction diagnosis according to World Allergy Organisation (5)
age_child_sx_days	Age of child at symptoms occurring	Age of child in days when symptoms relevant for diagnosis of milk reaction first started
child_age_dx_days	Age of child at diagnosis	Age of child in days when most definitive diagnosis was given
delay_age_dx_sx	Delay between symptoms and diagnosis	Time delay in days between symptoms relevant for diagnosis of milk reaction first started and age of child in days when most definitive diagnosis was given
class_sx_milkissue	Classification of symptoms of milk reaction	Classification of symptoms relevant for diagnosis of milk reaction. (Gastrointestinal, cutaneous, mixed)
who_concern_milk		Role of person (parent or healthcare professional) who first raised a concern that symptoms may be related to milk
who_dx_milk		Role of person (parent or healthcare professional) who made the most definitive diagnosis of a milk reaction
feed_milkissue		Infant feeding status at time of first concern that symptoms relevant for diagnosis may be related to milk
mat_diet_res	Maternal dietary restriction	Any mention in the records that maternal dietary restriction was undertaken by parent or was advised by a healthcare professional
who_mat_diet		Role of person (parent or healthcare professional) who undertook or advised maternal dietary restriction

agechild_mat_diet		Age of child in days at time maternal dietary restriction was undertaken by parent or first mentioned in the primary care records that a parent had undertaken maternal dietary restriction or first advised by a healthcare professional. The earliest age was recorded in cases where maternal dietary restriction was both undertaken and advised.
dietician	Dietician review of child	Any mention in the primary care records that child had been reviewed by a dietician at any stage regarding milk issue
agechild_dietician	Age of child in days at dietician review	Age of child in days at time of review by dietician regarding milk issue
soya_child_diet	Dietary restriction of soya in child's diet	Any mention of restriction of soya in the child's diet undertaken by parents or advised by a healthcare professional
first_soya_ehf_aaf	Type specialised formula first prescribed to child	Any first mention of a child consuming or having been prescribed specialised formula or a prescription record of specialised formula in the primary care records. In some cases, primary care records documented that child had been prescribed specialised formula elsewhere. Specialised formula refers to extensively hydrolysed, amino acid and soya formula.
who_first_form		Role of healthcare professional who first prescribed specialised formula documented in the primary care records
dx_first_form		Indication for prescription of specialised formula as recorded at time of prescription of specialised formula and not at time of diagnosis of milk reaction
class_dx_first_form		Classification of indication for first prescription of specialised formula according to World Allergy Organisation of hypersensitivity (5)
class_sx_first_form		Classification of symptoms mentioned as reason for first prescription of specialised formula and
type_sec_form / type_third_form		Extensively hydrolysed, amino acid or soya formula prescribed as a second or third formula
why_sec_form / why_third_form		Reason given for changing from initial specialised formula to a second formula, and from a second to a third formula
tot_form (ehf, aaf, soya)		Quantity of specialised formula prescribed in the primary care records in grams
vol_form (ehf, aaf, soya)		Volume of specialised formula prescribed in the primary care records in litres. Converted from total formula in grams using British National Formulary weight-to-volume conversions for individual brands of specialised formula. Volume of aaf separated into products suitable for age <1 year and age >1 year. No ehf products prescribed designed only for age >1 year.
cost_form (ehf, aaf, soya)		Cost of specialised formula prescribed in the primary care records in sterling. Calculated using quantity prescribed in grams and British National Formulary NHS indicative price.
child_age_days_first_form		Age of child in days at time of initial prescription or mention of use of any ehf, aaf, or soya formula if incomplete prescription records. All specialised formula assessed together and separately as first ehf, aaf suitable for age <1 year, aaf suitable for age >1 year, soya.
child_age_days_last_form		Age of child in days at time of final prescription of specialised formula. All specialised formula assessed together and separately as first ehf, aaf suitable for age <1 year, aaf suitable for age > 1 year, soya.

delay_first_last_form		Time delay in days between initial prescription (or mention of use of specialised formula) and final prescription (or mention of use of specialised formula). All specialised formula assessed together and separately as first ehf, aaf suitable for age <1 year, aaf suitable for age > 1 year, soya.
estimated_duration_days_first_soya_ehf_aaf		For participants who had a once off prescription or for whom the age at final prescription of specialised formula was not known, duration was estimated according to volume of formula prescribed and expected daily infant formula consumption of 780ml for infants aged <180 days old and 600ml for >/=180 days old. ((218)
duration_complete_and_estimated_days		Duration in days of prescribed specialised formula from initial prescription to final prescription and including estimated duration for once-off prescriptions or participants for whom age at final prescription was unknown.
vol_ehf_day (vol_aaf_day; vol_aaf_over12mths_day)		Volume of ehf or aaf or aaf designed for over 1 year old prescribed from initial prescription to final prescription excluding once-off prescriptions and excluding the volume prescribed at the final prescription. The reason for these exclusions is to remove any estimated duration calculated according to daily volumes consumed, in order to increase accuracy of actual daily volume consumed.

22.8 BEEP study ethical approval

NHS
Health Research Authority

West Midlands - Solihull Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

01 April 2021

Ms Angela Shone
Research and Innovation
East Atrium, Jubilee Conference Centre
Triumph road
Nottingham NG8 1DH

Dear Ms Shone

Study title: **A randomised controlled trial to determine whether application of emollient from birth for a year, can prevent eczema in high risk children.**
REC reference: **14/WM/0162**
Protocol number: **14044**
Amendment number: **SA11**
Amendment date: **26 February 2021**
IRAS project ID: **149888**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [149888_Substantial Amendment 11 (SA11)_]	1.0	01 March 2021
GP/consultant information sheets or letters [BEEP_Letter_GPrecords_Final V1.0_26Feb2021]	1.0	26 February 2021
Other [BEEP_PaperOnlineQuestionnaire_60 months email reminders_FinalV1.0_26Feb2021]	1.0	26 February 2021
Other [BEEP_PaperOnlineQuestionnaire_60months covering letter_FinalV1.0__26 Feb 2021]	1.0	26 February 2021
Other [BEEP_ParticipantNewsletter_SalivaStorageUpdate_Final1.0_26Feb2021]	1.0	26 February 2021
Other [BEEP_Letter_ParentGPrecords_Final V1.0_26 Feb 2021]	1.0	26 February 2021
Participant consent form [BEEP Allergy Test Consent Form_FINAL V1.0_20May2016.pdf]	1.0	20 May 2016
Participant consent form [BEEP Consent Form_FINAL_V1.2_13Nov14_PIS v1.4.pdf]	1.4	13 November 2014
Participant information sheet (PIS) [PIS BEEP FINAL_V1.5_24 May 2018.pdf]	1.5	24 May 2018
Participant information sheet (PIS) [BEEP Allergy Test PIS_FINAL V3.1 24May2018.pdf]	1.3	24 May 2018
Research protocol or project proposal [BEEP Protocol_FINAL_V7.0_26Feb2021]	7.0	26 February 2021
Research protocol or project proposal [BEEP Protocol_FINAL_V7.0__26Feb2021_tracked]	7.0	26 February 2021

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 149888:	**Please quote this number on all correspondence**

Yours sincerely

PP - Dr Rex J Polson
Chair

22.9 Method for calculating estimated data in the BEEP study cohort

Table S6: Estimations for incidence of cow's milk hypersensitivity and low-allergy formula prescription in BEEP study cohort

	Total BEEP cohort (n=1394)		**BEEP excluding participants with confirmed CMA (n=1375)**	
	Documented proportion	Estimated n	Documented proportion n	Estimated n
Parent report of milk reaction	214/(1394-166)=0.17	(0.17x166)=29+214=243	195/1209=0.16	(0.16x166)=27+195=222
Primary care record of milk hypersensitivity	140/171=0.82	(0.82x43)=35+140=175	124/155=0.8	(0.8x40)=32+124=156
Low-allergy formula prescription	91/(171-5)=0.55	(0.55x(43+5)) + (0.55x (0.17x166))=27+15+91=133	81/(155-5)=0.54	(0.54x(40+5)) + (0.54x (0.16x166)) =24+14+81=119

BEEP participants: 19/1394 with confirmed CMA, 195/1394 with CMA overdiagnosis, 1014/1394 assumed not to have CMA as parents answered no to screening questions.
Screening Questions for milk allergy: 214/1394 (yes), 1014/1394 (no), 166/ 1394 (never answered the questions)
Primary care records: 171/214 analysed, 43/214 unavailable records
Analysed primary care records: 5/171 prescription records missing (all CMA overdiagnosis), 16/171 confirmed CMA, 155/171 CMA overdiagnosis.
Unavailable primary care records: 40/43 CMA overdiagnosis, 3/43 confirmed CMA.

Table S7: Method for calculating estimated volume and cost of low-allergy formula per infant born

	Proportion of analysed cohort with a parent reported milk reaction	Proportion of analysed parent reported CMA with a primary care prescription of low-allergy formula	Number of parent-reported CMA with known formula prescription information	Number of parent-reported CMA with missing formula prescription information	Number of formula prescribed with missing volume information	Estimated number of participants without information on CMA or prescription or volume who had a low-allergy formula prescription
Total BEEP cohort	0.17	0.55	76	48	15	56.9†
BEEP cohort excluding confirmed CMA	0.16	0.54	68	45	13	51.6‡

BEEP participants who did not answer the screening questions = 166/1394
Number of parent-reported CMA with missing primary care records = 43 (40 CMA overdiagnosis, 3 confirmed CMA)
Number of parent-reported CMA with missing formula prescription information = 48 (43 missing primary care records and 5 missing prescription records)
†(166 no response to screening questions x 0.17 x 0.55) + (48 x 0.55) +15 = 56.9
‡ (166 no response to screening questions x 0.16 x 0.54) + (45 x 0.54) + 13 = 51.64
Documented volume and cost refer to the total sum observed in the primary care records.

22.10 Prescriptions of extensively hydrolysed and amino acid formula in BEEP

Table S8: Prescription of extensively hydrolysed formula and amino acid formula in BEEP cohort

	Participants included in analysis	Median (Q1, Q3)
Age at first prescription (Days)	ehf (n=64)	141 (70, 236)
	aaf (n=39)	115 (60, 155)
	aaf suitable >1year (n=6)	404 (368, 510)
Age at final prescription (Days)	ehf (n=56)	288 (106, 573)
	aaf (n=37)	390 (279, 539)
	aaf suitable >1year (n=6)	455 (368, 543)
Duration of low-allergy formula (Days)†	ehf (n=59)	64 (15, 373)
	aaf (n=37)	275 (115, 437)
	aaf suitable >1year (n=6)	32 (14, 61)
Duration of low-allergy formula prescribed excluding once-off prescriptions (Days)	ehf (n=36)	308 (94, 486)
	aaf (n=29)	335 (272, 483)
	aaf suitable >1year (n=2)	73 (42, -)
Volume / Day (Litres)‡	ehf (n=36)	0.61 (0.31, 1.04)
	aaf (n=29)	1.01 (0.77, 1.20)
	aaf suitable >1year (n=2)	0.37 (0.09, -)

ehf, extensively hydrolysed formula; aaf, amino acid formula (aaf). Q1, 25th centile. Q3, 75th centile. †For those participants with once-off prescriptions and with missing data for age at final prescription, duration (days) of low-allergy formula use was estimated according to volume of low-allergy formula prescribed and expected daily infant formula consumption of 780ml for infants aged <180 days old, 600ml for >/=180 days old and 400ml for infants aged =/> 365 days old at time of prescription of formula. (8,10) ‡Volume / Day refers to volume prescribed from initial prescription to final prescription excluding once-off prescriptions and excluding the volume prescribed at the final prescription.

Table S9: Repeat prescriptions of extensively hydrolysed formula and amino acid formula in BEEP cohort categorising participants according to the main formula prescribed

	Participants included in analysis (mainly ehf, n=21; mainly aaf, n=27)	Median (Q1, Q3)
Age at first prescription (Days)	ehf	168 (86, 227)
	aaf	84 (56, 119)
Age at final prescription (Days)	ehf	568 (403, 879)
	aaf	437 (345, 579)
Duration of low-allergy formula prescribed excluding once-off prescriptions and breastfeeding participants using top-up formula (Days)	ehf	429 (308, 684)
	aaf	358 (272, 496)
Volume / Day excluding once-off prescriptions and breastfeeding participants using top-up formula (Litres)	ehf	0.64 (0.42, 0.89)
	aaf	1.01 (0.86, 1.20)
Exclusively formula fed from birth	ehf 6/25 (24%)	
	aaf 6/29 (20.7%)	

ehf, extensively hydrolysed formula; aaf, amino acid formula (aaf). Q1, 25th centile. Q3, 75th centile. Participants were categorised into mainly ehf (n=25) or aaf (n=29) determined by longest duration of use of each formula. Once-off prescriptions, volume of final prescription and low volumes used for top-up formula with breastfeeding (mainly ehf, n=4; mainly aaf, n=2) were excluded from analysis. This ensured that only participants receiving repeat prescriptions of known volume and for known duration were analysed. A Mann-Whitney U test (n=48) was undertaken to determine differences between BEEP participants prescribed mainly extensively hydrolysed and mainly amino acid formula suitable for <1 year old. A statistically significant difference was found between participants prescribed mainly ehf or mainly aaf for age at first prescription (p=0.004, U=423) and volume consumed per day (p=0.001, U=126). No statistically significant difference was found for age at final prescription (p=0.07, U= 371) or duration of use (p=0.143, U=354).

22.11 Sensitivity Analysis in the BEEP study cohort

Table S10. Missingness of participant-level predictors and CMA outcome variables in the BEEP trial dataset

Predictor and outcome variables	Missing data
EQ5D health state at baseline (answered antenatally or shortly after birth)	445/1394 (31.9%)
EQ5D anxiety at baseline (answered antenatally or shortly after birth)	439/1394 (31.5%)
Infant feeding status from birth to 6 months	366/1394 (26.3%)
Decile of English Index of Multiple Deprivation 2015	26/1394 (1.9%)
Maternal use of antibiotics in pregnancy	12/1394 (0.9%)
Parent reported reaction to milk	166/1394 (11.9%)
Primary care record of milk reaction	209/1394 (15%)
Primary care record of low-allergy formula prescription	214/1394 (15.4%)

Table S11. Characteristics of BEEP study participants without confirmed CMA, comparing complete versus missing data for predictor variables with high levels of missingness.

		EQ-5D Any maternal anxiety at baseline		EQ-5D maternal Health state at baseline		Exclusive formula feeding from birth-6months	
		Complete (n=897)	**Missing (n=312)**	**Complete (n=891)**	**Missing (n=318)**	**Complete (n=994)**	**Missing (n=215)**
Maternal Age (n=1209)	Mean	32.37	30.91	32.34	31.03	32.27	30.70
	Std Dev	4.832	5.469	4.826	5.499	4.79	5.919
	Median	33	32	32	32	32.50	31
	(Q1, Q3)	(29, 36)	(27, 35)	(29, 36)	(27, 35)	(29, 36)	(26, 35)
White maternal ethnicity (n=1209)	White	804 (89.6%)	233 (74.7%)	799 (89.7%)	238 (74.8%)	876 (88.1%)	161 (74.9%)
	Non-White	93 (10.4%)	79 (25.3%)	92 (10.3%)	80 (25.2%)	118 (11.9%)	54 (25.1%)
Antibiotics used in pregnancy (n=1199, missing =10)	Yes	254 (28.3%)	91 (29.2%)	251 (28.2%)	94 (29.6%)	273 (27.5%)	72 (33.5%)
	No	636 (70.9%)	218 (69.9%)	633 (71%)	221 (69.5%)	711 (71.5%)	143 (66.5%)
	Unknown	7 (0.8%)	3 (1%)	7 (0.8%)	3 (0.9%)	10 (1%)	
More than one first degree relative with atopic disease (n=1209)	Two or more	554 (61.8%)	213 (68.3%)	551 (61.8%)	216 (67.9%)	623 (62.7%)	144 (67%)
	One	343 (38.2%)	99 (31.7%)	340 (38.2%)	102 (32.1%)	371 (37.3%)	71 (33%)
No other children in household (n=1209)	Other children	507 (56.5%)	196 (62.8%)	503 (56.5%)	200 (62.9%)	550 (55.3%)	153 (71.2%)
	Only Child	390 (43.5%)	116 (37.2%)	388 (43.5%)	118 (37.1%)	444 (44.7%)	62 (28.8%)
Maternal anxiety/depression on EQ-5D (at baseline) (n=897, missing=312)	No anxiety	709 (79%)	-	702 (78.8%)	7 (2.2%)	164 (16.5%)	66 (30.7%)
	Any anxiety	188 (21%)	-	187 (21%)	1 (0.3%)	643 (64.7%)	24 (11.2%)
	Unknown	-	312 (100%)	2 (0.2%)	310 (97.5%)	187 (18.8%)	125 (58.1%)
Maternal EQ-5D health state at baseline (n=891, missing=318)	Mean	79.85	60	79.81	-	79.92	78.79
	Std Dev	12.87	28.284	12.94	-	12.851	13.74
	Median	80	60	80	-	80	80
	(Q1, Q3)	(70, 90)	(40, -)	(70, 90)	-	(70, 90)	(70, 90)

Exclusive formula feeding from birth to 6 months old (n=994, missing =215)	Yes	118 (13.2%)	39 (12.5%)	117 (13.1%)	40 (12.6%)	157 (15.8%)	-
	No	689 (76.8%)	148 (47.4%)	684 (76.8%)	153 (48.1%)	837 (84.2%)	-
	Unknown	90 (10%)	125 (40.1%)	90 (10.1%)	125 (39.3%)	-	215 (100%)
Family decile of English Index of Multiple Deprivation 2015 (n=1185, missing=24)	Mean	6.33	5.17	6.33	5.19	6.28	4.89
	Std Dev	2.70	2.883	2.698	2.895	2.717	2.868
	Median	6	5	6	5	6	5
	(Q1, Q3)	(4, 9)	(3, 8)	(4, 9)	(3, 8)	(4, 9)	(2, 7)
Parent-reported CMA (Positive response to any of screening questions) (n=1209)	Yes	145 (16.2%)	50 (16%)	146 (16.4%)	49 (15.4%)	157 (15.8%)	38 (17.7%)
	No	752 (83.8%)	262 (84%)	745 (83.6%)	269 (84.6%)	837 (84.2%)	177 (82.3%)
Primary care record of reaction to milk (yes=124, no=31, records not analysed =1054)	Yes	96 (10.7%)	28 (9%)	96 (10.8%)	28 (8.8%)	102 (10.3%)	22 (10.2%)
	No	22 (2.5%)	9 (2.9%)	22 (2.5%)	9 (2.8%)	26 (2.6%)	5 (2.3%)
	No primary care records available	27 (3%)	13 (4%)	28 (3%)	12 (4%)	29 (3%)	11 (5%)
	No parental reported milk reaction	752 (84%)	262 (84%)	745 (84%)	269 (85%)	837 (84%)	177 (82%)
Primary care record of low-allergy formula prescription (yes=81, no=69, unknown as records not analysed=1054	Yes	66 (7.4%)	15 (4.8%)	66 (7.4%)	15 (4.7%)	63 (6.35)	18 (8.4%)
	No	50 (5.6%)	19 (6.1%)	50 (5.6%)	19 (6%)	61 (6.1%)	8 (3.7%)
	No primary care records available	29 (3%)	16 (5%)	30 (3%)	15 (5%)	33 (3%)	12 (6%)
	No parental reported milk reaction	752 (84%)	262/312 (84%)	745 (84%)	269 (85%)	837 (84%)	177 (82%)

EQ-5D, standardised measure of health related quality of life. Questionnaire was completed during the BEEP trial when the mother was enrolled
Participants included in analysis = 1209/1394. BEEP participants who did not answer the screening questions were excluded from analysis (n=166) and the 19 confirmed milk allergic participants. Low-allergy formula prescription includes extensively hydrolysed, amino acid and soya formula.

Table S12. Characteristics of BEEP participants with confirmed CMA, comparing complete versus missing data for predictor variables with high levels of missingness.

		EQD5 Any anxiety0		EDQ5 Health0		Formula fed only at first mention milk related symptoms		Parent only raised the initial concern about reaction to milk	
		Complete (n=94)	Missing (n=25)	Complete (n=94)	Missing (n=25)	Complete (n=104)	Missing (n=15)	Complete (n=108)	Missing (n=11)
Maternal Age (n=119)	Mean	32.05	29.48	32.05	29.48	31.53	31.40	31.68	29.91
	Std Dev	5.387	4.762	5.387	4.762	5.386	5.248	5.099	7.489
	Median	33	31	33	31	32	33	32	30
	(Q1, Q3)	(29, 36)	(27.50, 33)	(29, 36)	(27.50, 33)	(29, 35)	(30, 35)	(29, 35)	(24, 36)
White maternal ethnicity (n=119)	White	81 (86.2%)	22 (88%)	81 (86.2%)	22 (88%)	91 (87.5%)	12 (80%)	95 (88%)	8 (72.7%)
	Non-White	13 (13.8%)	3 (12%)	13 (13.8%)	3 (12%)	13 (12.5%)	3 (20%)	13 (12%)	3 (27.3%)
Antibiotics used in pregnancy (n=118, missing =1)	Yes	38 (40.4%)	12 (48%)	38 (40.4%)	12 (48%)	45 (43.3%)	5 (33.3%)	46 (42.6%)	4 (36.4%)
	No	55 (58.5%)	13 (52%)	55 (58.5%)	13 (52%)	58 (55.8%)	10 (66.7%)	61 (56.5%)	7 (63.6%)
	Unknown	1 (1.1%)	0	1 (1.1%)	0	1 (1%)	0	1 (0.9%)	0
No other children in household (n=119)	Other children	56 (59.6%)	16 (64%)	56 (59.6%)	16 (64%)	62 (59.6%)	10 (66.7%)	65 (60.2%)	7 (63.6%)
	Only Child	38 (40.4%)	9 (36%)	38 (40.4%)	9 (36%)	42 (59.6%)	5 (33.3%)	43 (39.8%)	4 (36.4%)
Maternal anxiety/depression on EQ-5D (at baseline) (n=94, missing=25)	No anxiety	74 (78.7%)	-	74 (78.7%)	-	65 (62.5%)	9 (60%)	67 (62%)	7 (63.6%)
	Any anxiety	20 (21.3%)	-	20 (21.3%)	-	16 (15.4%)	4 (26.7%)	19 (17.6%)	1 (9.1%)
	Unknown	-	25 (100%)	0	25 (100%)	23 (22.1%)	2 (13.3%)	22 (20.4%)	3 (27.3%)

Maternal EQ-5D health state at baseline (n=94, missing=25)	Mean	78.31	-	78.31	-	78.41	77.69	78.33	78.13
	Std Dev	12.44	-	12.44	-	12.75	10.727	12.58	11.63
	Median	80	-	80	-	80	80	80	30
	(Q1, Q3)	(70, 90)	-	(70, 90)	-	(70, 90)	(67.50, 85)	(70, 90)	(70, 91.25)
Family decile of English Index of Multiple Deprivation 2015 (n=115, missing=4)	Mean	6.13	4.76	6.13	4.76	5.86	5.64	5.98	4.3
	Std Dev	5.387	2.773	2.687	2.773	2.72	3.079	2.75	2.452
	Median	33	4	6	4	5	6	6	3
	(Q1, Q3)	(29, 36)	(2.50, 7)	(4, 9)	(2.50, 7)	(4, 9)	(2.75, 8.25)	(4, 9)	(2.75, 5.75)
Age of child when symptoms were first considered related to milk (weeks) (n=113, missing=6)	Mean	217.93	196.22	217.93	196.22	178.56	537.64	216.30	163.83
	Std Dev	196.75	211.64	196.75	211.64	159.98	239.63	203.23	95.56
	Median	169	142	169	142	137	462	168	169.50
	(Q1, Q3)	(76, 300)	(54, 256)	(76, 300)	(54, 256)	(57, 231)	(311, 712)	(62, 300)	(60, 244.50)
Formula fed only at first mention of milk related symptoms (n=104, missing=15)	Yes	34 (36.2%)	15 (60%)	34 (36.2%)	15 (60%)	55 (52.9%)	-	46 (42.6%)	3 (37.2%)
	No	47 (50%)	8 (32%)	47 (50%)	8 (32%)	49 (47.1%)	-	52 (48.1%)	3 (27.3%)
	Unknown	13 (13.8%)	2 (8%)	13 (13.8%)	2 (8%)	-	15 (100%)	10 (9.3%)	5 (45.5%)
Parent only raised the initial concern about reaction to milk (n=108, missing n=11)	Yes	28 (29.8%)	8 (32%)	28 (29.8%)	8 (32%)	30 (28.8%)	6 (40%)	36 (33.3%)	-
	No	58 (61.7%)	14 (56%)	58 (61.7%)	14 (56%)	68 (65.4%)	4 (26.7%)	72 (66.7%)	-
	Unknown	8 (8.5%)	3 (12%)	8 (8.5%)	3 (12%)	6 (5.8%)	5 (33.3%)	-	11 (100%)
Primary care record of reaction to milk (n=119)	Yes	94 (100%)	25 (100%)	94 (100%)	25 (100%)	104 (100%)	15 (100%)	108 (100%)	11 (100%)
	No	0	0	0	0	0	0	0	0
	Unknown	0	0	0	0	0	0	0	0
Primary care record of low-allergy formula prescription (n=119)	Yes	65 (69.1%)	15 (60%)	65 (69.1%)	15 (60%)	77 (74%)	3 (20%)	71 (65.7%)	9 (81.8%)
	No	29 (30.9%)	10 (40%)	29 (30.9%)	10 (40%)	27 (26%)	12 (80%)	37 (34.3%)	2 (18.2%)
	Unknown	0	0	0	0	0	0	0	0

Participants included in analysis = 119. BEEP participants with confirmed milk allergy (n=19) and participants with a milk reaction in primary care records but missing prescription records (n=5) were excluded. Low-allergy formula prescription includes extensively hydrolysed, amino acid and soya formula.

Table S13: Participant characteristics and parent-reported cow's milk reaction (excluding EQ5D)

	Unadjusted		**Adjusted** (n=963)†		**Adjusted** (n=963)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1209)	0.99 (0.96-1.02)	0.35	0.99 (0.96-1.04)	0.96	-	-
White maternal ethnicity (white, n=1037; non-white, n=172)	1.04 (0.67-1.62)	0.87	1.06 (0.60-1.85)	0.85	-	-
Antibiotics used in pregnancy (yes, n=345; no, n=854)	1.58 (1.15-2.19)	0.005	1.72 (1.19-2.48)	0.004	1.72 (1.19-2.48)	0.004
More than one first degree relative with atopic disease (two or more, n=767; one, n=442)	1.04 (0.75-1.42)	0.83	0.97 (0.66-1.42)	0.86	-	-
No other children in household (only child, n=506; other children, n=703)	0.96 (0.70-1.31)	0.80	0.97 (0.66-1.42)	0.87	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=157; all other feeding, n=837)	1.53 (1.00-2.35)	0.05	1.49 (0.96-2.32)	0.08	1.51 (0.97-2.34)	0.07
Family decile of English Index of Multiple Deprivation 2015 (n=1185)	0.97 (0.92-1.03)	0.34	0.99 (0.93-1.06)	0.75	-	-

Logistic regression comparing participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort who answered the screening questions (n=1014). BEEP participants who did not answer the screening questions were excluded from analysis (n=166). Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=963) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

Table S14. Participant characteristics and primary care record of cow's milk hypersensitivity (excluding EQ5D)

	Unadjusted		**Adjusted** (n=935)†		**Adjusted** (n=935)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age (n=1169)	0.99 (0.95-1.02)	0.45	0.99 (0.95-1.04)	0.72	-	-
White maternal ethnicity (white, n=1002; non-white, n=167)	0.98 (0.58-1.67)	0.94	0.85 (0.45-1.62)	0.63	-	-
Antibiotics used in pregnancy (yes, n=331; no, n=828)	1.91 (1.30-2.80)	<0.001	2.06 (1.33-3.19)	0.001	2.09 (1.36-3.23)	<0.001
More than one first degree relative with atopic disease (two or more, n=742; one, n=427)	1.14 (0.77-1.69)	0.52	0.93 (0.58-1.49)	0.76	-	-
No other children in household (only child, n=486; other children, n=683)	0.84 (0.57-1.24)	0.38	0.80 (0.50-1.28)	0.34	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=151; all other feeding, n=814)	1.78 (1.09-2.93)	0.02	1.74 (1.03-2.92)	0.04	1.77 (1.06-2.95)	0.03
Family decile of English Index of Multiple Deprivation 2015 (n=1146)	0.97 (0.90-1.04)	0.35	1.00 (0.92-1.08)	0.95	-	-

Logistic regression comparing potential risk factors associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have a reaction to milk (n=1045). Participants who did not answer any of the screening questions (n=166) and the primary care records that were not received (n=40) were excluded from analysis. Odds ratio (OR) >1 shows a positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=935) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

Table S15. Participant characteristics and primary care record of low-allergy formula prescription (excluding EQ5D)

	Unadjusted		Adjusted (n=932)†		Adjusted (n=932)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	
Maternal Age (n=1164)	0.97 (0.92-1.01)	0.10	0.97 (0.92-1.03)	0.33	-	-
White maternal ethnicity (white, n=999; non-white, n=165)	1.19 (0.60-2.35)	0.63	1.21 (0.50-2.96)	0.67	-	-
Antibiotics used in pregnancy (yes, n=330; no, n=824)	2.05 (1.30-3.26)	0.002	2.35 (1.38-4.02)	0.002	2.40 (1.41-4.08)	0.001
More than one first degree relative with atopic disease (two or more, n=738; one, n=426)	1.24 (0.77-2.01)	0.38	0.91 (0.51-1.62)	0.74	-	-
No other children in household (only child, n=486; other children, n=678)	0.96 (0.60-1.51)	0.85	0.85 (0.48-1.53)	0.59	-	-
Exclusive formula feeding from birth to 6 months old (formula only, n=150; all other feeding, n=811)	2.32 (1.31-4.13)	0.004	2.08 (1.13-3.82)	0.02	2.21 (1.22-4.01)	0.009
Family decile of English Index of Multiple Deprivation 2015 (n=1142)	0.97 (0.89-1.05)	0.39	1.01 (0.91-1.11)	0.94	-	-

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription (n=1086). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk whose prescription records were missing (n=5) were excluded from analysis. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=932) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression

Table S16: Participant characteristics and parent-reported cow's milk reaction (multiple imputation, 100 imputations).

	Unadjusted (n=1375)		**Adjusted** (n=1375)	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age	0.98 (0.96-1.02)	0.34	0.99 (0.96-1.02)	0.54
White maternal ethnicity	1.03 (0.65-1.62)	0.90	1.02 (0.63-1.65)	0.93
Antibiotics used in pregnancy	1.58 (1.15-2.19)	0.005	1.52 (1.10-2.11)	0.01
More than one first degree relative with atopic disease	1.03 (0.75-1.43)	0.85	1.02 (0.72-1.44)	0.93
No other children in household	0.96 (0.70-1.31)	0.78	0.95 (0.68-1.33)	0.75
Maternal anxiety/depression on EQ-5D (at baseline)	0.96 (0.64-1.43)	0.84	0.85 (0.55-1.30)	0.46
Maternal EQ-5D health state at baseline	0.99 (0.98-1.00)	0.18	0.99 (0.98-1.01)	0.19
Exclusive formula feeding from birth to 6 months old	1.38 (0.93-2.06)	0.11	1.34 (0.89-2.01)	0.16
Family decile of English Index of Multiple Deprivation 2015	0.97 (0.92-1.03)	0.32	0.98 (0.93-1.04)	0.56

Logistic regression comparing participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort (n=1180). Multiple imputation (100 imputations) was used for missing data within the exposure and outcome variables. Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values consider the association of all variables together on the outcome.

Table S17: Participant characteristics and primary care record of cow's milk hypersensitivity (multiple imputation, 100 imputations).

	Unadjusted (n=1375)		**Adjusted** (n=1375)	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age	0.99 (0.95-1.02)	0.43	0.99 (0.95-1.03)	0.62
White maternal ethnicity	0.96 (0.57-1.61)	0.87	0.95 (0.55-1.62)	0.84
Antibiotics used in pregnancy	1.90 (1.31-2.77)	<0.001	1.83 (1.25-2.68)	<0.002
More than one first degree relative with atopic disease	1.14 (0.77-1.69)	0.52	1.10 (0.72-1.69)	0.66
No other children in household	0.84 (0.58-1.23)	0.38	0.86 (0.57-1.30)	0.48
Maternal anxiety/depression on EQ-5D (at baseline)	1.03 (0.63-1.67)	0.91	0.92 (0.55-1.53)	0.74
Maternal EQ-5D health state at baseline	0.99 (0.98-1.00)	0.26	0.99 (0.98-1.01)	0.34
Exclusive formula feeding from birth to 6 months old	1.52 (0.95-2.44)	0.08	1.47 (0.91-2.38)	0.12
Family decile of English Index of Multiple Deprivation 2015	0.97 (0.90-1.04)	0.33	0.98 (0.91-1.06)	0.63

Logistic regression comparing potential risk factors associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Multiple imputation (100 imputations) was used for missing data within the exposure and outcome variables. Odds ratio (OR) >1 shows a positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values consider the association of all variables together on the out

Table S18: Participant characteristics and primary care record of low-allergy formula prescription (multiple imputation, 100 imputations).

	Unadjusted (n=1375)		**Adjusted** (n=1375)	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Maternal Age	0.96 (0.92-1.01)	0.11	0.97 (0.93-1.02)	0.27
White maternal ethnicity	1.14 (0.59-2.20)	0.71	1.06 (0.53-2.11)	0.88
Antibiotics used in pregnancy	2.00 (1.27-3.16)	0.003	1.91 (1.20-3.05)	0.007
More than one first degree relative with atopic disease	1.21 (0.74-1.99)	0.45	1.22 (0.72-2.07)	0.46
No other children in household	0.94 (0.60-1.49)	0.80	0.97 (0.59-1.60)	0.90
Maternal anxiety/depression on EQ-5D (at baseline)	1.00 (0.57-1.78)	0.99	0.91 (0.50-1.64)	0.75
Maternal EQ-5D health state at baseline	0.99 (0.98-1.01)	0.53	1.00 (0.98-1.02)	0.64
Exclusive formula feeding from birth to 6 months old	1.84 (1.07-3.15)	0.03	1.73 (0.98-3.02)	0.06
Family decile of English Index of Multiple Deprivation 2015	0.96 (0.89-1.05)	0.38	0.99 (0.90-1.08)	0.75

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription. Multiple imputation (100 imputations) was used for missing data within the exposure and outcome variables. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy

formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values consder the association of all variables together on the outcome

22.12 Open data API R code used to extract primary care practice prescribing data

Data source: NHS Business Service Authorities publicly available database

nhs_loop_formula_230323

```
# 1. Script details ----------------------------------------------------------

# Name of script: OpenDataAPIQuery
# Description:  Using R to query the NHSBSA open data portal API.
# Created by: Matthew Wilson (NHSBSA)
# Created on: 26-03-2020
# Latest update by: Adam Ivison (NHSBSA)
# Latest update on: 24-06-2021
# Update notes: Updated endpoint in the script, refactored code and added async

# R version: created in 3.5.3

# 2. Load packages -----------------------------------------------------------
extract_data_p <- function(year, bnf, prac_code) {
  # List packages we will use
  packages <- c(
    "jsonlite", # 1.6
    "dplyr",    # 0.8.3
    "crul"      # 1.1.0
  )

  # Install packages if they aren't already
  if (length(setdiff(packages, rownames(installed.packages()))) > 0) {
    install.packages(setdiff(packages, rownames(installed.packages())))
  }

  # 3. Define variables --------------------------------------------------------

  # Define the url for the API call
  base_endpoint <- "https://opendata.nhsbsa.net/api/3/action/"
  package_list_method <- "package_list"     # List of data-sets in the portal
  package_show_method <- "package_show?id=" # List all resources of a data-set
  action_method <- "datastore_search_sql?"  # SQL action method

  # Send API call to get list of data-sets
  datasets_response <- jsonlite::fromJSON(paste0(
    base_endpoint,
    package_list_method
  ))

  # Now lets have a look at the data-sets currently available
  datasets_response$result

  # For this example we're interested in the English Prescribing Dataset (EPD).
  # We know the name of this data-set so can set this manually, or access it
  # from datasets_response.
  dataset_id <- "english-prescribing-data-epd"
```

```
# Define the parameters for the SQL query
#regional_office_code <- roc # Can be Y54 Y55 Y56 Y57
bnf_chemical_substance <- bnf # Paracetamol

# You can use any of the fields listed in the data-set within the SQL query as
# part of the select or in the where clause in order to filter.

# Information on the fields present in a data-set and an accompanying data
# dictionary can be found on the page for the relevant data-set on the Open Data
# Portal.

# 5. API calls for data for multiple months ----------------------------------

# Now that you have extracted data for a single month, you may want to get the
# data for several months, or a whole year.

# Firstly we need to get a list of all of the names and resource IDs for every
# EPD file. We therefore extract the metadata for the EPD dataset.
metadata_repsonse <- jsonlite::fromJSON(paste0(
  base_endpoint,
  package_show_method,
  dataset_id
))

# Resource names and IDs are kept within the resources table returned from the
# package_show_method call.
resources_table <- metadata_repsonse$result$resources

# We only want data for one calendar year, to do this we need to look at the
# name of the data-set to identify the year. For this example we're looking at
# 2020.


resource_name_list <- resources_table$name[grepl(year, resources_table$name)]



# 5.2. Async -- ----------------------------------------------------------------

# We can call the API asynchronously and this will result in an approx 10x speed
# increase over a for loop for large resource_names by vectorising our approach.

# Construct the SQL query as a function
async_query <- function(resource_name) {
  paste0(
    "
  SELECT
     *
  FROM `",
    resource_name, "`
  WHERE
     1=1
  AND regional_office_code like '", prac_code, "'
  AND bnf_code = '", bnf_chemical_substance, "'
  "
```

```
  )
 }

 # Create the API calls
 async_api_calls <- lapply(
  X = resource_name_list,
  FUN = function(x)
   paste0(
    base_endpoint,
    action_method,
    "resource_id=",
    x,
    "&",
    "sql=",
    URLencode(async_query(x)) # Encode spaces in the url
   )
 )

 # Use crul::Async to get the results
 dd <- crul::Async$new(urls = async_api_calls)
 res <- dd$get()

 # Check that everything is a success
 all(vapply(res, function(z) z$success(), logical(1)))

 # Parse the output into a list of dataframes
 async_dfs <- lapply(
  X = res,
  FUN = function(x) {

   # Parse the response
   tmp_response <- x$parse("UTF-8")

   # Extract the records
   tmp_df <- jsonlite::fromJSON(tmp_response)$result$result$records
  }
 )

 # Concatenate the results
 async_dfs <- lapply(async_dfs, function(x) x[!(names(x) %in% c("POSTCODE",
"UNIDENTIFIED", "PRACTICE_NAME", "BNF_DESCRIPTION",
"BNF_CHAPTER_PLUS_CODE", "ADDRESS_1", "ADDRESS_2", "ADDRESS_3",
"ADDRESS_4", "AREA_TEAM_CODE", "REGIONAL_OFFICE_NAME",
"CHEMICAL_SUBSTANCE_BNF_DESCR", "AREA_TEAM_NAME", "STP_CODE",
"STP_NAME"))])
 async_df <- do.call(dplyr::bind_rows, async_dfs)


 # 6. Export the data ---------------------------------------------------------

 # Use write.csv for ease
 #write.csv(single_month_df, "single_month.csv")
 #write.csv(for_loop_df, "for_loop.csv")
 write.csv(async_df, paste("async_new" ,year,bnf,prac_code,".csv"))
}
```

```
# Can include specific months, or can list a whole year, if same regions apply
for (year_n in c("2020", "2021")){
  for (bnf_n in c("090401000BBTGA0", "090401000BBTHA0", "090401000BBUXA0")){
    for (prac_code in c("Y%")){
      extract_data_p(paste(year_n),paste(bnf_n),paste(prac_code))
    }
  }
}
getwd()
```

22.13 Primary care practice analysis

Table S19. Primary care practice prescription data analysis

Name	Type / strength	BNF Code
Aptamil pepti 1	ehf	090402000BBNZA0
Aptamil pepti 2	ehf	090402000BBTQA0
Farleys soya	soya	090401000BBFJA1
Infasoy	soya	090401000BBFLA6
Neocate LCP	aaf	090401000BBNQA0
Neocate	aaf	090401000BBBSA0
Nutramigen	ehf	090401000BBDIAZ
Nutramigen Puramino	aaf	090401000BBNMA0
Nutramigen 1 Lipil	ehf	090401000BBLUA0
Nutramigen 2 Lipil	ehf	090401000BBLPA0
Similac Alimentum	ehf	090900000BBKRA0
SMA Alfamino	aaf	090900000BBKWA0
SMA Althera	ehf	090900000BBKQA0
SMA Wysoy	soya	090401000BBGZBD
Epipen Jr Auto-injector	0.15mg	0304030C0BEAAA2
Adrenaline	150 mcg 0.3ml	0304030C0AAA2A2
Anapen Junior	150 mcg 0.3ml	0304030C0BGABA2
Jext	150 mcg 0.15ml	0304030C0BHAABF
Emerade	150 mcg 0.15ml	0304030C0BIAABF
Domperidone	1.9mg/5ml oral suspension	0406000J0AAALAL
Domperidone 1mg/ml oral suspension sugar free	1mg/ml oral suspension sugar free	0406000J0AAACAC
Gaviscon® infant oral powder sachets		0101021B0BEADAJ
Instant Carobel powder		0913161B0BBAAAF
Lansoprazole	15mg orodispersible tablets	0103050L0AAAGAG
Losec MUPS	10mg gastro-resistant tablets	0103050P0BBADAM
Omeprazole	10mg dispersible gastro-resistant tablets	0103050P0AAAMAM
Omeprazole	10mg gastro-resistant capsules	0103050P0AAAFAF

Omeprazole	2.5mg/5ml oral suspension	0103050P0AAALAL
Omeprazole	2mg/5ml oral liquid	0103050P0AABABA
Omeprazole	3.5mg/5ml oral liquid	0103050P0AABRBR
Omeprazole	3mg/5ml oral liquid	0103050P0AABFBF
Omeprazole	4mg/5ml oral liquid	0103050P0AAASAS
Omeprazole	5mg/5ml oral solution	0103050P0AABSBS
Omeprazole	5mg/5ml oral suspension	0103050P0AABNBN
Ranitidine	1.5mg/5ml oral liquid	0103010T0AAAZAZ
Ranitidine	3mg/5ml oral liquid	0103010T0AABHBH
Ranitidine	4mg/5ml oral liquid	0103010T0AAARAR
Ranitidine	5mg/5ml oral liquid	0103010T0AABQBQ
Ranitidine	5mg/5ml oral suspension	0103010T0AABRBR
Ranitidine	75mg/5ml oral solution sugar free	0103010T0AAAEAE

BNF, British National Formulary. The list includes all prescription items evaluated in analysis of practice-level risk factors for CMA overdiagnosis

Table S20. Primary Care Practice CMA guideline analysis

Criteria	Number of CCGs
No Guidelines	20
Partial guidelines	10
Complete guidelines	50
Differentiated between IgE and non-IgE mediated symptoms	40
Highlighted the need for reproducibility of symptoms	9
Advice on excluding differential diagnoses	3
Not tolerating other forms of cow's milk mentioned	10
Faltering growth mentioned as key symptom	39
States that generally breast milk is the optimal milk for infants with or without CMA	39
Recommends giving limited supply of low-allergy formula, until full diagnosis	23
Recommends re-introduction of cow's milk after low-allergy formula feeding trial	33
Recommends re-introduction of cow's milk after maternal dietary exclusion trial	30
Includes recommendations on review and discontinuation of formula	34
Recommends formula to be stopped when over 12 months with a good, mixed diet and normal growth OR rechallenge	21

Data summarise local Clinical Commissioning Group CMA guidelines for primary care practices which were evaluated for potential practice-level risk factors for CMA overdiagnosis. Criteria evaluated are based on a previous Delphi Consensus on detection and management of CMA in children under age 2 years (7) Data was categorised 'yes' if the CCG guideline referred to the criteria identified from the Delphi consensus study, 'no' if the criteria were not mentioned in the CCG guideline and 'missing' if there was no guideline. If the CCG CMA guideline referred to either reproducibility or specificity as being relevant to CMA diagnosis, this was coded as 'yes' and if neither were referred to this was coded as 'no' for the purposes of further analyses (See Tables S29-S37).

22.14 GP Practice level risk factors in the BEEP study

Table S21. Clustering of BEEP participants in primary care practices

	All BEEP participants† Practices, n=640	BEEP participants excluding confirmed CMA† Practices, n=636
Practices with 1 participant	352 (55%)	350 (55%)
Practices with >1 participant	288 (45%)	286 (45%)

†No practice code was available for 14 participants in the total cohort and 13 participants without confirmed CMA. Variance between practices or within practices could not be assessed due to the presence of singleton clusters.

Table S22: Practice-level variables comparing participants with and without parent-reported cow's milk hypersensitivity

	Unadjusted		**Adjusted** (n=1193)†		**Adjusted** (n=1193)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1194)	1.03 (1.01-1.05)	<0.001	1.03 (1.01-1.05)	0.002	1.03 (1.02-1.05)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1194)	0.999 (0.998-1.00)	0.17	0.995 (0.99-1.00)	0.05	0.996 (0.992-1.00)	0.09
Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1194)	1.00 (0.94-1.05)	0.88	0.97 (0.91-1.03)	0.33	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1194)	1.02 (1.00-1.05)	0.11	1.03 (1.00-1.05)	0.06	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1194)	1.00 (1.00-1.01)	0.46	1.00 (0.99-1.01)	0.85	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1194)	1.00 (1.00-1.01)	0.27	1.00 (1.00-1.01)	0.67	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1197)	1.06 (0.90-1.26)	0.50	1.59 (0.96-2.63)	0.07	-	-
Antibiotic Items/STARPU (Average of 4 quarters for 2014)§ (n=1195)	0.12 (0.01-1.46	0.10	0.97 (0.01-1.58)	0.10	0.10 (0.01-1.30)	0.08

Logistic regression comparing practice-level variables of those participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort who answered the screening questions (n=1014). BEEP participants who did not answer the screening

questions were excluded from analysis (n=166). No data was available for 15 GP practices. Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1193) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. §Antibiotic Items/STARPU was substituted for practice antibiotic prescription items as a predictor variable to adjust for gender and sex effect on antibiotic prescribing in the practice.

Table S23: Practice-level variables comparing participants with and without a primary care record of cow's milk hypersensitivity

	Unadjusted		**Adjusted** (n=1153)†		**Adjusted** (n=1153)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1154)	1.04 (1.02-1.06)	<0.001	1.04 (1,02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1154)	0.999 (0.998-1.00)	0.07	0.998 (0.997-1.00)	0.02	0.999 (0.997-1.00)	0.03
Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1154)	0.99 (0.93-1.06)	0.79	0.96 (0.89-1.04)	0.3	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1154)	1.02 (0.99-1.05)	0.19	1.03 (1.00-1.06)	0.09	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1154)	1.00 (1.00-1.01)	0.37	1.00 (0.99-.01)	0.60	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1154)	1.00 (1.00-1.01)	0.18	1.00 (1.00-1.01	0.64	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1157)	1.87 (1.05-3.34)	0.33	1.57 (0.86-2.86)	0.14	-	-
Antibiotic Items/STAR-PU (Average of 4 quarters for 2014)§ (n=1155)	0.04 (0.002-0.91)	0.04	0.16 (0.00-0.52)	0.02	0.03 (0.00-0.72)	0.03

Logistic regression comparing potential risk factors associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have a reaction to milk (n=1045). Participants who did not answer any of the screening questions (n=166) and the primary care records that were not received (n=40) were excluded from analysis. No data was available for 15 GP

practices. Odds ratio (OR) >1 shows a positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1153) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. §Antibiotic Items/STARPU was substituted for practice antibiotic prescription items as a predictor variable to adjust for gender and sex effect on antibiotic prescribing in the practice.

Table S24: Practice-level variables comparing participants with and without a primary care record of low-allergy formula prescription

	Unadjusted		**Adjusted** (n=1148)†		**Adjusted** (n=1148)‡	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Practice volume of low-allergy formula prescription (litres per infant aged 0–1-year practice population) (n=1149)	1.04 (1.02-1.07)	<0.001	1.04 (1.02-1.07)	0.001	1.04 (1.02-1.07)	<0.001
Practice antibiotic prescriptions (Items per 1000 total practice population) (n=1149)	0.999 (0.997-1.00)	0.07	0.998 (0.996-1.00)	0.02	0.998 (0.997-1.00)	0.03
Practice Decile of English Index of Multiple Deprivation (IMD) 2019 (n=1149)	0.98 (0.90-1.06)	0.60	0.96 (0.88-1.05)	0.36	-	-
Practice anti-reflux prescriptions (Items per infant aged 0–1-year practice population) (n=1149)	1.01 (0.98-1.05)	0.47	1.02 (0.99-1.06)	0.23	-	-
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0–1-year practice population) (n=1149)	1.00 (0.99-1.01)	0.65	1.00 (0.99-1.01)	0.98	-	-
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population) (n=1149)	1.00 (1.00-1.01)	0.68	1.00 (0.99-1.01)	0.69	-	-
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis (n=1152)	1.97 (1.00-3.87)	0.05	1.64 (0.81-3.32)	0.17	-	-
Antibiotic Items/STAR-PU (Average of 4 quarters for 2014)§ (n=1150)	0.02 (0.00-0.94)	0.05	0.01 (0.00-0.49)	0.02	0.02 (0.00-0.73)	0.03

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription (n=1086). Participants who did not answer any of the screening questions (n=166), the primary care records that were not received (n=40), and the participants with a positive mention of a reaction to milk

whose prescription records were missing (n=5) were excluded from analysis. No data was available for 15 GP practices. Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Unadjusted values indicate an association alone and adjusted values (n=1148) consider the association of all variables together on the outcome. †Step 1 of backward stepwise regression including all co-variates ‡Final step of backward stepwise regression. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. §Antibiotic Items/STARPU was substituted for practice antibiotic prescription items as a predictor variable to adjust for gender and sex effect on antibiotic prescribing in the practice.

Table S25: Combined participant and practice-level variables comparing participants with and without parent-reported cow's milk reaction (multiple imputation, 100 imputations)

	Adjusted (n=1356)	
	OR (95% CI)	**P-value**
Maternal Age	0.98 (0.95-1.01)	0.26
White maternal ethnicity	0.97 (0.59-1.58)	0.90
Antibiotics used in pregnancy	1.53 (1.10-2.14)	0.01
More than one first degree relative with atopic disease	1.02 (0.72-1.47)	0.90
No other children in household	0.89 (0.63-1.27)	0.53
Maternal anxiety/depression on EQ-5D (at baseline)	0.77 (0.49-1.20)	0.24
Maternal EQ-5D health state at baseline	0.99 (0.98-1.00)	0.15
Exclusive formula feeding from birth to 6 months old	1.40 (0.93-2.11)	0.11
Practice volume of low-allergy formula prescription (litres per infant aged 0-1 year practice population	1.03 (1.01-1.04)	0.006

Practice antibiotic prescriptions (Items per 1000 total practice population)	1.00 (0.99-1.00)	0.08
Practice Decile of English Index of Multiple Deprivation (IMD) 2019	0.97 (0.92-1.04)	0.41
Practice anti-reflux prescriptions (Items per infant aged 0-1 year practice population)	1.03 (1.00-1.05)	0.08
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0-1 year practice population)	1.00 (0.99-1.01)	0.95
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population)	1.00 (1.00-1.01)	0.58
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis	1.45 (0.87-2.41)	0.15

Logistic regression comparing combined participant and practice-level variables of those participants with a positive response to one of the 3 screening questions excluding the 19 confirmed milk allergic participants (n=195) with the remaining BEEP study cohort who answered the screening questions (n=1014). Odds ratio (OR) >1 shows a positive association between each variable and parental reported reaction to milk or low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Adjusted values (n=1356) consider the association of all variables together on the outcome. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. Multiple imputation (100 imputations) was used for missing participants data only within the exposure and outcome variables. Practice determinants were missing for 19 participants.

Table S26: Combined participant and practice-level variables comparing participants with and without a primary care record of cow's milk hypersensitivity (multiple imputation, 100 imputations)

	Adjusted (n=1356)	
	OR (95% CI)	**P-value**
Maternal Age	0.98 (0.94-1.02)	0.31
White maternal ethnicity	0.90 (0.51-1.59)	0.72
Antibiotics used in pregnancy	1.82 (1.23-2.69)	0.003
More than one first degree relative with atopic disease	1.10 (0.70-1.72)	0.68
No other children in household	0.78 (0.50-1.20)	0.25
Maternal anxiety/depression on EQ-5D (at baseline)	0.79 (0.46-1.38)	0.41
Maternal EQ-5D health state at baseline	0.99 (0.98-1.00)	0.30
Exclusive formula feeding from birth to 6 months old	1.56 (0.95-2.58)	0.08
Practice volume of low-allergy formula prescription (litres per infant aged 0-1 year practice population)	1.03 (1.00-1.05)	0.007

Practice antibiotic prescriptions (Items per 1000 total practice population)	0.99 (0.99-1.00)	0.06
Practice Decile of English Index of Multiple Deprivation (IMD) 2019	0.97 (0.90-1.04)	0.37
Practice anti-reflux prescriptions (Items per infant aged 0-1 year practice population)	1.02 (0.99-1.05)	0.14
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0-1 year practice population)	1.00 (0.99-1.01)	0.65
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population)	1.00 (1.00-1.01)	0.63
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis	1.42 (0.77-2.60)	0.26

Logistic regression comparing combined participant and practice-level variables associated with a positive mention of reaction to milk in the primary care records (n=124) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have a reaction to milk (n=1045). Odds ratio (OR) >1 shows a positive association between each variable and a reaction to milk in the records (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Adjusted values (n=1356) consider the association of all variables together on the outcome. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. Multiple imputation (100 imputations) was used for missing participants data only within the exposure and outcome variables. Practice determinants were missing for 19 participants.

Table S27: Combined participant and practice-level variables comparing participants with and without a primary care record of low-allergy formula prescription (multiple imputation, 100 imputations)

	Adjusted (n=1356)	
	OR (95% CI)	**P-value**
Maternal Age	0.96 (0.92-1.01)	0.13
White maternal ethnicity	1.04 (0.50-2.15)	0.92
Antibiotics used in pregnancy	1.85 (1.15-3.00)	0.01
More than one first degree relative with atopic disease	1.23 (0.71-2.13)	0.46
No other children in household	0.88 (0.52-1.48)	0.63
Maternal anxiety/depression on EQ-5D (at baseline)	0.81 (0.43-1.51)	0.50
Maternal EQ-5D health state at baseline	1.00 (0.98-1.01)	0.59
Exclusive formula feeding from birth to 6 months old	1.86 (1.04-3.31)	0.04
Practice volume of low-allergy formula prescription (litres per infant aged 0-1 year practice population)	1.03 (1.01-1.06)	0.01
Practice antibiotic prescriptions (Items per 1000 total practice population)	0.99 (0.99-1.00)	0.06

Practice Decile of English Index of Multiple Deprivation (IMD) 2019	0.97 (0.88-1.06)	0.46
Practice anti-reflux prescriptions (Items per infant aged 0-1 year practice population)	1.02 (0.98-1.05)	0.37
Practice Gaviscon® Infant prescriptions (Quantity per infant aged 0-1 year practice population)	1.00 (0.99-1.01)	0.95
Practice AAI prescriptions (Items per 1000 aged 0-5 years practice population)	1.00 (0.99-1.01)	0.92
CCG CMA guidelines highlights reproducibility or specificity as criteria for CMA diagnosis	1.45 (0.72-2.93)	0.30

Logistic regression comparing potential risk factors associated with a prescription of low-allergy formula in the primary care records (n=77) excluding the 19 confirmed milk allergic participants. Participants who did not answer yes to any of the screening questions were assumed not to have received a prescription (n=1086). Odds ratio (OR) >1 shows a positive association between each variable and a low-allergy formula prescription (outcome). Confidence intervals are 95% and p-value <0.05 indicates statistical significance. Adjusted values (n=1356) consider the association of all variables together on the outcome. Practice-level variables were assessed for the year prior to the BEEP study (2014) except IMD which was recorded for 2019 as this was the year used in the BEEP clinical trial for participant IMD. Multiple imputation (100 imputations) was used for missing participants data only within the exposure and outcome variables. Practice determinants were missing for 19 participants

22.15 Delphi Study Protocol

A Delphi consensus project to guide the detection and management of cow's milk protein allergy (CMPA) in infants and children

Study Management Group

Principal Investigator: Dr Robert Boyle

Co-investigators: Dr. Hilary Allen

ICREC Reference number: 21IC6572

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity.

This protocol describes the **"A Delphi consensus project to guide the detection and management of cow's milk allergy in children"** study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Principal Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research It will be conducted in compliance with the protocol, Data Protection Act 2018 and General Data Protection Regulations (Europe) and other regulatory requirements as appropriate.

INTRODUCTION

Background

Overdiagnosis of Cow's milk protein allergy (CMPA):

The reported incidence of CMPA is less than 1% of 2 year olds in Europe (1). Despite no observed increase in disease prevalence, prescriptions for specialised formula to treat CMPA have increased 7-fold in the UK from 2006 to 2016 (2,3). Controversy exists regarding the evidence to support dietary manipulation to treat suspected non-IgE CMPA (3). There are potential financial and health burdens associated with allergy mis-labelling, such as: cost of specialised infant formula to families and the healthcare system, which in the UK exceeded £60 million in 2016 (2-4); over-medicalisation of normal childhood behaviour with consequent increased health anxiety (5-7); unnecessary maternal / child dietary restriction, with consequent negative psychological impact of elimination diets on children and their families (8-11); nutritional deficiencies of elimination diets (12,13) and undermining maternal confidence in breastfeeding (3,14,15).

Current CMPA guidelines:

Several international guidelines exist for the management of CMPA. In all 11 guidelines recently reviewed, several guideline authors reported conflicts of interest or funding relationships with formula industry (16-26).

Why is conflict of interest important?

It is acknowledged that relationships between industry and healthcare professionals influence clinical decision-making (27,28) but that this bias is often unintentional (28,29). A 2013 study of guidelines for diagnosis of common diseases identified that the majority of panel members had benefited financially from pharmaceutical industry and that these guidelines commonly promoted disease diagnosis, which in-turn benefits the pharmaceutical industry (30). Authors highlighted that this was at odds with recommendations from the United States Institute of Medicine that guideline panel members should be non-conflicted (28,30).

Considering many of the current CMPA guidelines combine available evidence with expert consensus opinion (16-26,31), the need for non-conflicted expert panel members is particularly important in this context, as subconscious bias may be even more relevant.

Study Rationale

Why do we need an alternative approach to management of suspected CMPA?

The observed increased prescription rates of specialised formula for CMPA without increased disease prevalence point to a likelihood of medical excess in this area, with a paucity of evidence guiding these prescribing trends and at considerable expense to the NHS. Currently, there is an approximate 10-fold over-reporting of milk allergy amongst parents of young children in England, and a 10-fold excess of specialised formula prescription in the community in England (32). It is clear that an alternative approach to management of CMPA is required with a focus on preventing allergy mis-labelling within the healthcare system, informed by an international multi-disciplinary panel of non-conflicted experts, as is best practice for guideline development.

Aim:

The aim of this study is to develop guidance for primary healthcare providers managing concerns about CMPA, involving a multidisciplinary non-conflicted expert panel from primary, secondary and tertiary care, using Delphi consensus methods.

Research Question:

What is the safest way to detect and manage cow's milk allergy in infants and children?

Hypothesis:

Mis-labelling of milk allergy in children is preventable through a protocol / simple decision aid that addresses primary healthcare practitioner concerns at the point where most mis-labelling occurs.

STUDY OBJECTIVES

The **primary, overall objective** is to develop consensus guidance on the detection and management of cow's milk allergy in infants and young children.

Specific objectives to achieve this are:

1. review existing cow's milk allergy guidelines and areas of controversy or discrepancy
2. develop proposed new guidance based on the review of existing work
3. invite an expert group from a range of relevant disciplines to participate in the Delphi consensus project
4. run a Delphi consensus project to develop and modify the suggested new guidance for the detection and management of cow's milk allergy

STUDY DESIGN

Study Design and Purpose:

The study will undertake a Delphi consensus approach to develop a consensus statement around specific uncertainties in the detection and management of for managing suspected CMPA (33-35). The Delphi process facilitates amalgamation of anonymous expert opinion independently in order to reach a consensus on the management of a difficult problem where there is insufficient evidence to provide scientific certainty (33-35). Although Delphi consensus methods does not dictate a specific number of participants (34), it is recommended that the panel size has at least 6 members in order to improve reliability and that the process is limited to 2 rounds in order to prevent participation fatigue (34,36). A maximum of 40 participants will be recruited. The duration of the study will be approximately 1 year from the date of the study invitation. Experts will be given 3-4 weeks to complete each round, with weekly reminder emails sent to optimise participation. An electronic Delphi (e-Delphi) will be undertaken to enable international participation using Qualtrics e-survey software used for capturing data, to administer anonymous online questionnaires for the initial 2 rounds of

consensus building (34,35,37). A final consensus meeting (duration 2-3 hours) with all key experts, via online video consultation using Microsoft Teams (combined with a face to face meeting if feasible at the time), will be arranged to further discuss the areas of disagreement and reach consensus on a new protocol for management of CMPA (34,35,37).

The purpose of this Delphi consensus study is to develop new guidance for detecting and managing paediatric CMPA for community healthcare practitioners from a multidisciplinary expert panel, without conflicts of interest related to the breastmilk substitute (formula) industry. The rationale for this project is that most current CMPA guidance is written by experts with significant industry-related conflicts of interest, and concerns have been raised in the literature that current guidance a). promotes overdiagnosis of milk allergy, and b). may undermine breastfeeding through the advice given to breastfeeding women whose child has suspected or proven milk allergy.

Methods:

Design of initial draft statements for Delphi panel to consider:

We will undertake a review of guidance from the literature on CMPA management in order to inform the initial questionnaire that the Delphi expert panel will vote on in first 2 rounds of consensus building. We will include areas where there already appears to be broad consensus but will take care to include any areas which have aroused controversy in the literature or are discrepant between guidelines. We will review recent CMPA guidelines and discuss with experts in the field to identify a preliminary list of uncertainties for the panel to comment on and amend in the first round of consensus building.

Delphi Method:

Delphi Round 1:

The initial survey will use statements derived from the initial literature search. Participants will be asked to rank the importance of each statement using a ranking scale 1-9 as outlined

in Table 1 (38). Participants will also be invited to express additional criteria which they feel are important regarding detection and management of CMPA and to also rank these new criteria using the same scale 1-9. New criteria will be reviewed, any duplication removed, and added to the second round survey of the Delphi process. Areas of uncertainty relating to participant responses or duplication will be discussed by the study team. Maximum 40 participants.

Critical for clinical decision making	9
	8
	7
Important, but not critical for clinical decision making	6
	5
	4
Low importance for clinical decision making	3
	2
	1

Table 1: Importance of outcomes using a scale 1-9 used in Delphi consensus methods. Guyatt et al. (38)

Delphi Round 2

In the second survey, the same questionnaire from Round 1 with the additional criteria will be presented to the participants, along with all participant's anonymous responses. If criteria are excluded after round 1, they will not be included in round 2, but if criteria are 'no consensus' in round 1 they will be included in round 2, together with a summary of previous comments/ratings. The individual participant's score and the average score for each criterion

will also be presented. The participants will be requested to re-rank the revised responses using the same nine-point scale (35,38,39). No new criteria may be added at the second stage. Maximum 40 participants.

Classification for Consensus

The responses from Round 2 will be reviewed by the study team and the classification of consensus applied, as outlined in Table 2 (39). This will result in a list of "essential" and "recommended" criteria to be included in a CMPA protocol (39). Any 'no consensus' criteria will be removed after the relevant Delphi round, and any 'consensus not reached' criteria in both Delphi 1 and Delphi 2 will be taken forward for discussion at the meeting (39).

Consensus Classification	**Description**	**Definition**
Consensus essential	Consensus that criterion is essential to CMPA protocol	70% or more participants scoring as 7-9 AND <15% participants scoring 1-3
Consensus recommended	Consensus that criterion is essential to CMPA protocol	70% or more participants scoring as 4-6 AND <15% participants scoring 1-3
Consensus not reached	Consensus that criterion should not be included in CMPA protocol	70% or more participants scoring as 1-3 AND <15% participants scoring 7-9
No consensus	Uncertainty about importance of outcome	Anything else

Table 2: Definition of consensus. (39)

External Consultation

Following completing of round 2, action of ratings and incorporation of comments, a 3rd draft of the recommendations will be produced by the study team. This will then be sent for external consultation – to the guideline authors of the 2021 updated DRACMA milk allergy guideline (16) and, as appropriate, other major international CMPA guidelines and a cohort of parents who have had a child with a diagnosis of suspected CMPA. Both groups will be invited to submit individual or pooled comments, and if necessary, a workshop will be convened to assist the patient representatives with understanding the task and providing meaningful commentary on the proposed recommendations.

Consensus Meeting

An online meeting using Microsoft Teams (combined with a face to face meeting if feasible at the time), for the study participants will be organised to further discuss areas of disagreement and to reach a consensus on a protocol for management of suspected CMPA. This meeting will be chaired by Dr. Hilary Allen (study team member). A fourth version of the recommendations will be presented prior to the meeting, with proposed changes following DRACMA and patient feedback and a summary of the feedback received. The list of "essential" and "recommended" criteria will be presented and any 'consensus not reached' criteria will be discussed by the panel in an attempt to reach consensus. Those participants wishing to make comments anonymously will be facilitated in submitting questions prior or during the meeting which will then be raised by the meeting Chair on their behalf. The meeting will be recorded, and minutes circulated to all attendees. Any amendments to the meeting minutes will be facilitated via email following the meeting and a final, 5th draft will be produced by the study team, reviewed and revised by the participants and submitted for publication following the meeting. Maximum 40 participants.

What to do if don't reach a consensus?

For any criterion where there is a persistent status of 'consensus not reached' following the final meeting, will be removed from the recommendations and the resulting publication.

Data Analysis:

Simple descriptive statistics will be used. Statistical comparisons will not be required as we will be using the guidance in the protocol for deciding consensus reached or not and will just report percentages.

PARTICIPANT RECRUITMENT

Pre-recruitment evaluations

We will identify non-conflicted, international experts with good publication records as potential study participants through literature review using databases MEDLINE, EMBASE and/or the Cochrane library and on discussion with experts.

We will aim to enrol at least 2 participants within each area of expertise in general paediatrics, paediatric allergy, paediatric gastroenterology, paediatric dermatology, general practice and community healthcare, dietetics, infant nutrition, breastfeeding support, public health and clinical care pathways. We will aim to include experts from diverse geographic and cultural settings and will ask each enrolled expert to nominate other relevant experts (maximum 40 participants).

Identified experts will be invited to participate in the Delphi consensus project via an invitation email. The reason for this is that the main burden of participation in the study is filling in questionnaires. In order to facilitate participation, reducing any additional burden, and acknowledging current more efficient electronic methods of working, the study team propose an email invitation. The email invitation will include information about the study and an online link to a study participant information leaflet (PIL). Participants will be advised to study the PIL and email a member of the study team should they have any further queries.

The email invitation will include the following information:

1. information about the study and what is expected of participants
2. Participation is voluntary. Non-participation does not require aa reason and will not affect their relationship with the study team
3. Withdrawal information
4. Time for consideration and that a follow-up email will be sent 1 week after invitation
5. Data protection
6. Email consent accepted

Email response will be accepted to confirm consent to participate in the study, Participants will be required to return email confirming their consent worded as follows:

Please study the participant information leaflet [online link] and email a member of the study team if you have any further queries [hilary.allen16@ic.ac.uk]

*If you agree to participate, please **copy and paste** the following and respond via this email:*

1. *I confirm that I have read and understand the participant information sheet version 2.0 dated 21.01.21 for the above study and have had the opportunity to ask questions which have been answered fully.*
2. *I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason, without my legal rights being affected and this will not affect my relationship with the study team*
3. *I give permission for Imperial College London to access my research records that are relevant to this research.*
4. *I consent to take part in the above study*
5. *I consent to storage of my name, email address, expertise and survey responses on a database at Imperial College London as part of this project*

6. *I give permission for the recording of the consensus meeting to take place. I understand that this recording will be deleted once it has been transcribed.*

Please note a follow-up email will be sent 1 week from the date of this invitation to allow time for consideration and as a gentle reminder.

The right of the participant to refuse to participate without giving reasons will be respected. Participants will be allowed to withdraw from the study at any time. If they decide to withdraw then we will use any information gathered up until that point for the study, unless they request that we discard their previous responses or information at the time of withdrawal. This information regarding withdrawal will be included in the email invitation and the participant information leaflet.

The initial online questionnaire will include an opening statement advising that completing and submitting the questionnaire as further evidence of consent to participate.

Inclusion Criteria

- No relevant conflict of interest to declare, using the BMJ definition of a relevant conflict of interest i.e., activities anticipated to occur in the near future, or which have occurred in the 3 calendar years prior to enrolment in the survey
- A working knowledge of English

Exclusion Criteria

- Experts who declare a conflict of interest
- Vulnerable persons

Withdrawal Criteria

Participants will be invited by email to partake. This will include information about withdrawal. Participants will be allowed to withdraw from the study at any time. If they decide to withdraw then we will use any information gathered up until that point for the

study, unless they request that we discard their previous responses or information at the time of withdrawal.

ASSESSMENT AND FOLLOW UP

The final, 5th draft of the recommendations for management of CMPA will be produced by the study team after the consensus meeting, reviewed and revised by the study participants and submitted for publication following the meeting. No follow up will be required once the study is submitted for publication.

REGULATORY ISSUES

Ethics approval

The Principal Investigator has obtained approval from the Head of Department and Research Governance and Integrity Team (RGIT). The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent

Identified experts will be invited to participate in the Delphi consensus project via an invitation email. The reason for this is that the main burden of participation in the study is filling in questionnaires. In order to facilitate participation, reducing any additional burden, and acknowledging current more efficient electronic methods of working, the study team propose an email invitation. The email invitation will include information about the study and an online link to a study participant information leaflet (PIL). Participants will be advised to study the PIL and email a member of the study team should they have any further queries. The email invitation will include the following information:

1. information about the study and what is expected of participants
2. Participation is voluntary. Non-participation does not require aa reason and will not affect their relationship with the study team

3. Withdrawal information
4. Time for consideration and that a follow-up email will be sent 1 week after invitation
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6. Email consent accepted

Email response will be accepted to confirm consent to participate in the study, Participants will be required to return email confirming their consent worded as follows:

Please study the participant information leaflet [online link] and email a member of the study team if you have any further queries [hilary.allen16@ic.ac.uk]

*If you agree to participate, please **copy and paste** the following and respond via this email:*

1. I confirm that I have read and understand the participant information sheet version 2.0 dated 21.01.21 for the above study and have had the opportunity to ask questions which have been answered fully.

2. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason, without my legal rights being affected and this will not affect my relationship with the study team

3. I give permission for Imperial College London to access my research records that are relevant to this research.

4. I consent to take part in the above study

5. I consent to storage of my name, email address, expertise and survey responses on a database at Imperial College London as part of this project

6. I give permission for the recording of the consensus meeting to take place. I understand that this recording will be deleted once it has been transcribed.

Please note a follow-up email will be sent 1 week from the date of this invitation to allow time for consideration and as a gentle reminder.

The right of the participant to refuse to participate without giving reasons will be respected. Participants will be allowed to withdraw from the study at any time. If they decide to withdraw then we will use any information gathered up until that point for the study, unless they request that we discard their previous responses or information at the time of withdrawal. This information regarding withdrawal will be included in the email invitation and the participant information leaflet.

The initial online questionnaire will include an opening statement advising that completing and submitting the questionnaire as further evidence of consent to participate.

Confidentiality

The Principal Investigator will preserve the confidentiality of participants taking part in the study and fulfil transparency requirements under the General Data Protection Regulation for health and care research. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. Anonymity is an important ethical consideration in the Delphi method as this prevents any dominance of expert opinion between panel members and thus, prevents bias of peer pressure within the group. This will be addressed by ensuring the initial 2 stages of the Delphi will be anonymised and online. Individual responses to Delphi rounds will only be made available to other Delphi panel members in anonymous form and will not be made publicly available except as summarised, anonymised responses included in the peer-reviewed journal publication(s) that arise(s) from the project.

Participants could be assigned a unique reference number or code during consent and this number used during data analysis to keep the participants identifiable information pseudonymised.

Data protection

All data collected during this study, including personal information (participant name, clinical role, contact details and responses to questionnaires) and a recording of the consensus meeting, will be stored in a secure database at Imperial College London. No sensitive data will be collected and the data will only be used for this research study and not for other projects. Consent for storage of this data will be sought at initial invitation email to participate in the study. Participants' data will only be used for this study and will not be used for other studies. Storage of participants' data will comply with General Data Protection Regulation. All data will be stored on Imperial College London computers or servers. If participants withdraw from the study, information gathered up until that point for the study ill be used, unless specifically requested to be discarded.

Indemnity

Imperial College London holds negligent harm insurance policies which apply to this study.

Sponsor

Imperial College London will act as the main sponsor for this study.

Funding

This study is funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen.

Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor.

PUBLICATION POLICY

Summarised, anonymised responses that arise from the Delphi project will be included in a peer-reviewed journal publication(s). All participants will be co-authors on the publication, unless they indicate that they would prefer not to be a co-author.

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22.16 Recommendations for the Conducting and REporting of DElphi Studies (CREDES) Checklist

Section / Topic	No.	Checklist Item	Reported on Page No.
		Rationale for the choice of the Delphi technique	
Justification	1	The choice of the Delphi technique as a method of systematically collating expert consultation and building consensus needs to be well justified.	Protocol p.3
		Planning and Design	
Planning and Process	2	The Delphi is a flexible method. Any modifications should be justified by a rationale and be applied systematically and rigorously.	Protocol p.3-4
Definition of consensus	3	Includes a clear and transparent guide for action on how to proceed to the next survey round, the required threshold to terminate the Delphi process and procedures to be followed when consensus is (not) reached.	Supplementary material Table S1 and Protocol p. 4-8
		Study Conduct	
Informational input	4	All material provided to the expert panel at the outset of the project and throughout the Delphi process should be carefully reviewed and piloted in advance.	Delphi responses document and Protocol
Prevention of Bias	5	Researchers need to take measures to avoid influencing the experts judgements. If a research team member has a conflict of interest, entrusting an independent research with the main study co-ordination is advised.	Main manuscript Methods
Interpretation and processing of results	6	Consensus and non-consensus provide informative insights and highlight differences in perspectives.	Main manuscript Results and Delphi responses document

External validation	7	Recommended to have final draft of resulting guidance reviewed by an external board before publication	Delphi responses 'External consultation' section
		Reporting	
Purpose and rationale	8	Purpose of study clearly defined. Rationale for choice of Delphi technique as most suitable method should be provided.	Protocol p.2-3
Expert panel	9	Criteria for selection of experts, transparent information on recruitment, sociodemographic details including information on expertise regarding the topic, response and non-response rates over ongoing iterations should be reported.	Main manuscript methods and Figure 1. Supplement Table S2 Protocol p.5-7
Description of the methods	10	Information on preparatory steps, piloting of material and survey instruments, survey design, number and design of survey rounds, methods of data analysis, processing and synthesis of experts responses to inform each survey round and methodological decisions taken by the research team throughout.	Main manuscript Methods section, Figure 1, Protocol.
Procedure	11	Flowchart to illustrate the stages of the Delphi process.	Figure 1
Definition and attainment of consensus	12	Information on how consensus was achieved throughout and strategies to deal with non-consensus	Supplementary material Table S1 and Protocol p.3-5
Results	13	Reporting of results for each round separately to make the evolving of consensus over the rounds transparent. This includes average group responses, changes between rounds, and modifications to survey instruments.	Figure 1. Supplementary material Tables S3-S5 and Delphi responses document
Discussion of limitations	14	Critical reflection of potential limitations and their impact on the resulting guidance	Main manuscript Discussion section

Adequacy of conclusions	15	Conclusions should adequately reflect the Delphi outcomes with a view to scope and applicability of resulting practice guidance.	Main manuscript Discussion section
Publication and dissemination	16	The resulting guidance should be clearly identifiable from the publication, including recommendations for transfer into practice and implementation. A dissemination plan should include endorsement of the guidance by professional associations and healthcare authorities to facilitate implementation.	Figures 2-4. Supplementary material Tables S3-S5

Junger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med.* 2017;31(8):684-706.

22.17 Delphi Study Participant invitation email and consent

Imperial College London

Study title: A Delphi consensus project to guide the detection and management of cow's milk allergy in children

ICREC Reference number: 21IC6572

Dear (name of invited participant),

We would like to invite you to participate in a Delphi consensus study to develop new guidance for detecting and managing milk allergy in infants and young children.

The aim of this study is to develop guidance for community healthcare practitioners from a multidisciplinary expert panel, without conflicts of interest related to the breastmilk substitute (formula) industry. The rationale for this project is that most current milk allergy guidance is written by experts with significant industry-related conflicts of interest, and concerns have been raised in the literature that current guidance a). promotes overdiagnosis of milk allergy, and b). may undermine breastfeeding through the advice given to breastfeeding women whose child has suspected or proven milk allergy. This new guidance will be developed using the Delphi consensus method, including a panel of participants with expertise in general paediatrics, paediatric allergy, paediatric gastroenterology, paediatric dermatology, paediatric allergy nursing, general practice, dietetics/nutrition, health visitors, lactation support, infant feeding networks and midwifery. Eligibility for participation

depends on not having any recent conflict of interest in relation to the breastmilk substitute industry, which includes companies manufacturing or marketing specialised formulas for use in children with milk allergy. For the purpose of this project, we define recent conflict of interest as follows:

Personal financial support for speaking, travel, consultancy or other activities including research grants, employment or institutional support from a company that develops or markets breastmilk substitutes, within the 3 years prior to commencement of the project or during the course of the project (which is expected to be a maximum of 1 year from the date of this invitation).

Data protection

All data collected during this study, including personal information (participant name, clinical role, contact details and responses to questionnaires) and a recording of the consensus meeting, will be stored in a secure database at Imperial College London. No sensitive data will be collected and the data will only be used for this research study and not for other projects. Storage of participant data will comply with General Data Protection Regulation and will only be stored on Imperial College London computers or servers. If you withdraw from the study, information gathered up until that point for the study will be used, unless you request it to be discarded.

If you are happy to participate in this project, we will expect you to:

- Respond to 2 separate electronic surveys with proposed statements about best practice in the detection and management of milk allergy. These statements will be drawn from the literature by the study team and you will have the opportunity to rank the importance of the statements and to add comments. During the first survey, you will have the opportunity to add your own statements if you think that important issues have not been adequately covered. Both surveys will be completed anonymously and responses from the first survey will be summarised

anonymously for participants when completing the second survey. We expect each survey to take a maximum of 1 hour to complete.

- Attend an online consensus meeting to discuss any statements where consensus was not reached during the electronic surveys. To inform the discussion at the consensus meeting, the proposed statements will also be sent to existing milk allergy guideline groups and to patients with relevant experience for their comments and a summary of feedback received will be sent to participants prior to the meeting. We expect the online consensus meeting to take approximately 2 hours and to require approximately 1 hour of reading time.
- Review, edit and approve the final recommendations for detection and management of milk allergy in the form of a journal manuscript, in advance of submission for publication. All participants will be co-authors on the publication, unless they indicate that they would prefer not to be a co-author.

Please study the participant information leaflet [*attached*] and email a member of the study team if you have any further queries [hilary.allen16@ic.ac.uk]

If you agree to participate, please **copy and paste** the following and respond via this email:

1. I confirm that I have read and understand the participant information sheet version 2.0 dated 21.01.21 for the above study and have had the opportunity to ask questions which have been answered fully.
2. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason, without my legal rights being affected and this will not affect my relationship with the study team
3. I give permission for Imperial College London to access my research records that are relevant to this research.
4. I consent to take part in the above study

5. I consent to storage of my name, email address, expertise and survey responses on a database at Imperial College London as part of this project
6. I give permission for the recording of the consensus meeting to take place. I understand that this recording will be deleted once it has been transcribed.

   Please note a follow-up email will be sent 1 week

   from the date of this invitation to allow time for consideration and as a gentle reminder.

   Kind regards,

   Dr. Hilary Allen (PhD student NHLI, Imperial College London. UK)

   Ursula Pendower (iBSc student. NHLI, Imperial College London. UK)

   Dr. Robert Boyle (Principal Investigator. Clinical Reader Paediatric Allergy. NHLI. Imperial College London, UK.)

   This study was given ethical approval by the Imperial College London Research Governance and Integrity Team. Imperial College London is the main research sponsor for this study. This study is funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen.

   Consent Form, version 3.1 July 2020 Version 3.0

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Date 24.01.2021

22.18 Delphi Study Participant information leaflet

Imperial College London

Study title: A Delphi consensus project to guide the detection and management of cow's milk allergy in children

ICREC Reference number: 21IC6572

Principal Investigator: Dr Robert Boyle

Co-investigators: Dr. Hilary Allen

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for your interest in our study and for reading this document.

What is the purpose of the study?

The aim of this study is to develop guidance for community healthcare practitioners from a multidisciplinary expert panel, without conflicts of interest related to the breastmilk substitute (formula) industry. The rationale for this project is that most current milk allergy guidance is written by experts with significant industry-related conflicts of interest, and concerns have been raised in the literature that current guidance a). promotes overdiagnosis of

milk allergy, and b). may undermine breastfeeding through the advice given to breastfeeding women whose child has suspected or proven milk allergy. This new guidance will be developed using the Delphi consensus method, including a panel of participants with expertise in general paediatrics, paediatric allergy, paediatric gastroenterology, paediatric dermatology, general practice and community healthcare, dietetics, infant nutrition, breastfeeding support, public health and clinical care pathways.

This study forms part of a PhD thesis undertaken by Dr Hilary Allen at the NHLI, Imperial College London.

Why have I been invited?

Eligibility for participation depends on not having any conflict of interest in relation to the breastmilk substitute industry, which includes companies manufacturing or marketing specialised formulas for use in children with milk allergy. For the purpose of this project, we define conflict of interest as follows:

Personal financial support for speaking, travel, consultancy or other activities including research grants, employment or institutional support from a company that develops or markets breastmilk substitutes, within the 3 years prior to commencement of the project or during the course of the project (which is expected to be a maximum of 1 year from the date of this invitation).

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you decide to withdraw, we will use any information gathered up until that point for the study, unless you request that we discard your previous responses or information at the time of withdrawal. You

do not need to give a reason if you decide not to participate and this will not affect your relationship with the study team.

What do I have to do if I decide to take part?

If you are happy to participate in this project, we will expect you to:

- Respond to 2 separate electronic surveys with proposed statements about best practice in the detection and management of milk allergy. These statements will be drawn from the literature by the study team and you will have the opportunity to rank the importance of the statements and to add comments. During the first survey, you will have the opportunity to add your own statements if you think that important issues have not been adequately covered. Both surveys will be completed anonymously and responses from the first survey will be summarised anonymously for participants when completing the second survey. We expect each survey to take approximately 1 hour to complete.
- Attend an online consensus meeting to discuss any statements where consensus was not reached during the electronic surveys. To inform the discussion at the consensus meeting, the proposed criteria will also be sent to existing milk allergy guideline groups and to patients with relevant experience for their comments and a summary of feedback received will be sent to participants prior to the meeting. We expect the online consensus meeting to take approximately 2 hours and to require approximately 1 hour of reading time.
- Review, edit and approve the final recommendations for detection and management of milk allergy in the form of a journal manuscript, in advance of submission for publication. All participants will be co-authors on the publication, unless they indicate that they would prefer not to be a co-author.

The duration of this study is expected to be a maximum of 1 year from the date of this invitation. You will be given 4 weeks to complete each of the initial 2 survey rounds and weekly reminder emails will be sent. The duration of the final consensus meeting is expected

to be 2-3 hours and will be hosted online via Microsoft Teams or face-to-face, if feasible at the time.

Data protection

All data collected during this study, including personal information (participant name, clinical role, contact details and responses to questionnaires) and a recording of the consensus meeting, will be stored in a secure database at Imperial College London. No sensitive data will be collected and the data will only be used for this research study and not for other projects. Storage of participant data will comply with General Data Protection Regulation and will only be stored on Imperial College London computers or servers. If you withdraw from the study, information gathered up until that point for the study will be used, unless you request it to be discarded.

What are the possible disadvantages and risks of taking part?

The main disadvantage to partaking in the study is the personal time required to complete the online surveys and partake in the consensus meeting.

What are the possible benefits of taking part?

This study will not be of personal benefit to you as a participant. However, the information gained from the study may help guide healthcare practitioners in the detection and management of CMPA, which in-turn, may help patients with suspected CMPA.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator Dr. Robert Boyle, Imperial College London

(r.boyle@imperial.ac.uk). If you are still not satisfied with the response, you may contact the Imperial College Research Governance and Integrity Team.

What will happen to the results of the research study?

A summary of anonymised information resulting from this project will be submitted for publication in a peer reviewed journal.

Who is organising and funding the research?

Imperial College London is the main research sponsor for this study. This study is being performed by Dr. Hilary Allen as part of a PhD thesis at the NHLI, Imperial College London under the supervision of Dr. Robert Boyle and co-supervision of Prof. Andrew Murphy, National University of Ireland, Galway, Ireland.

Dr. Allen has received a research fellowship from the Irish College of General Practitioners. No other funding has been received for this research.

Who has reviewed the study?

This study was given ethical approval by the Head of Department, Faculty of Medicine, Imperial College London and the Imperial College Research Governance and Integrity Team (RGIT)

Contact for Further Information

Dr. Hilary Allen (hilary.allen16@ic.ac.uk) Mobile: +353866036569

Dr. Robert Boyle (r.boyle@imperial.ac.uk)

Thank you for participating in this study.

A copy of the written information is available via online link from the study invitation email.

Transparency Notice

Summary Information sheet

In this research study we will use information from you. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study, we will save some of the data in case we need to check it.

We will make sure no-one can work out who you are from the reports we write.

The information pack tells you more about this.

How will we use this information about you?

Research Study Title: <u>A Delphi consensus project to guide the detection and management of cow's milk allergy in children</u>

Imperial College London is the sponsor for this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

We will need to use information from you for this research project.

This information will include your:

- Name
- Contact details
- Clinical Role

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results.

We will write our reports in a way that no-one can work out that you took part in the study.

Legal Basis

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

International Transfers

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (**EC**) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

Sharing your information with others

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties:

Other College employees, agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above).

Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- by asking one of the research team
- by sending an email to Dr. Hilary Allen (hilary.allen16@ic.ac.uk) / Dr. Robert Boyle (r.boyle@imperial.ac.uk)
- or by ringing us on Dr. Hilary Allen Mobile: +353866036569

Complaint

If you wish to raise a complaint on how we have handled your personal data, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

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22.19 Detailed Delphi responses

22.19.1 Delphi Round 1 Invitation Email

Dear [Study Participant],

Thank you for participating in our Delphi consensus study to develop new guidance for detecting and managing milk allergy in infants and young children.

Please find below a Qualtrics link to our Round 1 questionnaire. We would appreciate if you could complete the survey by 2nd April 2021.

There is an option to leave comments after each set of questions and at the end of the survey. We invite you to give your opinion if you feel the study questions require modification or if there are other aspects of milk allergy detection and management that you feel are important to be considered in this consensus process.
You may complete this questionnaire multiple times; your most recent response will be used for this study.
Responses will be anonymised and distributed with the Round 2 questionnaire.

[Qualtrics E-survey Link]

A reminder email will be sent in one week.
If you have any queries or technical difficulties with the survey link, please contact the study team via return of this email.

Kind regards,

Ursula Pendower (iBSc student. NHLI, Imperial College London. UK)
Dr. Hilary Allen (PhD student NHLI, Imperial College London. UK)
Dr. Robert Boyle (Principal Investigator. Clinical Reader Paediatric Allergy. NHLI. Imperial College London, UK.)

This study was given ethical approval by the Imperial College London Research Governance and Integrity Team. Imperial College London is the main research sponsor for this study. This study is funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen.

22.19.2 Round 1 Qualtrics Electronic Delphi Survey

Cow's Milk Allergy Delphi Consensus Round 1 Questionnaire

Please give your full name and expertise below
N.B. This information is for the study team only; your responses to this questionnaire will not be identified as yours to other participants at any stage of this project

_____

I hereby consent to continue to partake in this study and to answer the following questionnaire

- ○ Yes
- ○ No

I hereby confirm that I have no recent conflicts of interest related to the breast milk substitute ('formula') industry as defined below:

Personal financial support for speaking, travel, consultancy, employment or shares in a company that develops or markets breast milk substitutes ('formula'), within the 3 years prior to commencement of this project or during the course of 2021.

- ○ I have no conflict of interest as defined above
- ○ I have or may have a conflict of interest as defined above

If you have or may have a conflict of interest as defined above, please summarise the details below:

Please contact a member of the study team (hilary.allen16@imperial.ac.uk) if you have any queries about your conflict of interest declaration.

Please complete all survey questions, using the ranking scale 1-9 as shown within each statement.
You may change your answers at any time during the survey by using the arrow button at the bottom left of the page.

You will be unable to amend your answers once you have submitted them using the arrow button at the bottom right of the final page.

You may take the survey multiple times if you wish. All responses will be recorded, but your most recent response will be used for the purpose of the study.

If you do not submit your responses, partially completed responses will automatically be recorded 1 week after your last activity.

References relied on for developing the initial set of statements may be found on the final page.

Please contact us (hilary.allen16@imperial.ac.uk) if you require any clarification before finalising your responses.

What aspects of CMA detection are important to ensure that the condition is not over diagnosed or underdiagnosed?
If you wish, please comment on the scope and wording of this question below:_____

Statement 1: In an exclusively breastfed infant, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, CMA or other food allergies should be considered in the following circumstances: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Infant is failing to thrive with severe eczema and protein-losing enteropathy									
Recurrent passage of visible blood ('hematochezia'), with or without mucus, in stool, or endoscopic biopsy finding of proctocolitis									

Please leave any comments or suggested edits to Statement 1 or the examples:_____

Statement 2: In an infant consuming cow's milk products or cow's milk formula as a regular part of their diet, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, CMA should be considered in the following circumstances:
1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Symptoms started within 3 days of initiating formula feeding or during the first 6 weeks of life									
Infant is failing to thrive despite adequate nutritional intake									
Recurrent passage of visible blood ('hematochezia') with or without mucus, in stool, or endoscopic biopsy finding of proctocolitis									
Biopsy findings of eosinophilic gastrointestinal disorders such as eosinophilic oesophagitis									

Please leave any comments or suggested edits to Statement 2 or the examples:_____

Statement 3: Acute symptoms such as rash or vomiting which occur within 2 hours of ingesting a food or drink containing cow's milk protein may indicate CMA. However, CMA is not likely if: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Infant has been consuming cow's milk protein in similar forms at least once per day for at least 3 days, with no previous acute symptoms									
Symptoms persist for longer than 4 hours									
An alternative, more common explanation for the symptoms seems more plausible, bearing in mind that rashes and vomiting are common during infancy and CMA only affects about 1% of infants									
Symptoms have occurred on other occasions without ingestion of cow's milk protein									
Symptoms are not reproducible on subsequent ingestion of cow's milk protein									

Please leave any comments or suggested edits to Statement 3 or the examples:_____

Statement 4: In infants with delayed symptoms between 2 and 48 hours following ingestion of a food or drink containing cow's milk protein, CMA is less likely but should be considered in the following circumstance:
1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Symptoms are severe or reproducible and the infant is not tolerating cow's milk protein in similar forms									

Please leave any comments or suggested edits to Statement 4 or the example

Statement 5: If the acute or chronic symptoms described above are not present, then CMA does not need to be considered as a diagnosis for infants with:
[Note - a score of 1 means that you think these features should always be thought of as signs of possible CMA, even if they are the only sign; and a score of 9 means that you think these features are not, on their own, signs of CMA]

	1	2	3	4	5	6	7	8	9
Occasional spots of blood in the stool									
Colour changes in stool									
Consistency changes in stool									
Frequency changes in stool									
Aversive feeding									
Nasal or respiratory symptoms									

Please leave any comments or suggested edits to Statement 5 or the examples

Statement 6: For the following symptoms, where CMA is sometimes included in the differential diagnosis, diagnosis and management need to consider some other important issues: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Bile-stained vomiting can be caused by intestinal malrotation so requires urgent assessment									
Failure to thrive has a wide range of potential causes, including insufficient protein/calorie intake									
Hematochezia can be caused by infection, clotting disorders or intestinal abnormalities									
Eczema management involves avoiding physical triggers, using moisturisers and topical anti-inflammatories when needed									

Colic and crying are common in healthy infants, but if severe these can also be related to a wide range of health issues in the infant or their carer

Please leave any comments or suggested edits to Statement 6 or the examples

---

In a fully or partially breastfed child who has CMA, what aspects of management are important to ensure breastfeeding is not undermined?
If you wish, please comment on the scope and wording of this question below:_____

Statement 7: Maternal dietary restriction is not usually necessary, unless: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
The child has erythrodermic eczema, protein-losing enteropathy, failure to thrive and multiple IgE-mediated food allergies, and is exclusively breastfed									
Mother has noticed a clear relationship between her own dietary intake and symptoms in her child, and wishes to restrict her diet									
Mother wishes to avoid consuming cow's milk products herself as part of household cow's milk avoidance, in order to prevent accidental exposure of her child									

Please leave any comments or suggested edits to Statement 7 or the examples:

Statement 8: For mothers who restrict their own intake of cow's milk protein: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Ensure dietetic assessment to support adequate maternal nutrient intake including calcium and vitamin D									
Address the need for an exclusion diet, taking into consideration the physical and psychological burden of elimination diets on the family									

Advise the exclusion of cow's milk in small, processed quantities such as baked products is not usually necessary

Do not advise maternal consumption of other mammalian milks as cow's milk substitutes, due to cross-reactivity

Please leave any comments or suggested to Statement 8 or the examples:_____

Statement 9: Protect, promote and support exclusive breastfeeding to around 6 months and continued breastfeeding to at least 2 years, by: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

1 2 3 4 5 6 7 8 9

Signposting to local breastfeeding support services

Reassuring mothers and other carers that breastmilk is the most appropriate milk to feed children with CMA

Please leave any comments or suggested edits to Statement 9 or the examples:

What aspects of CMA management are important to prevent unnecessary use of specialised formulas such as amino acid formula, extensively hydrolysed formula or soya or rice based infant formulas?
If you wish, please comment on the scope and wording of this question below:_____

Statement 10: Initiation of specialised formula should not be advised for the following groups of patients with CMA:
1-3 = Not important, 4-6 = Important, 7-9 = Critical

1 2 3 4 5 6 7 8 9

Children aged over 12 months

Fully breastfed infants

Infants who have received formula but can return to full breastfeeding with appropriate support for caregivers

Please leave any comments or suggested edits to Statement 10 or the examples:_____

Statement 11. Please consider the statement below, assessing importance using the ranking scale 1-9. 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Initiation of specialised formula should not be advised for preventing the development of CMA or other atopic conditions									

Please leave any comments or suggested edits to Statement 11 or the example:_____

Statement 12: Initiation of specialised formula should be advised for the following groups of patients with CMA: 1-3 = Not important, 4-6 = Important, 7-9 = Critical

	1	2	3	4	5	6	7	8	9
Formula-fed infants aged under 12 months, with IgE-mediated CMA confirmed using clinical history and either skin prick test, serum IgE testing or food challenge									
Formula-fed infants with non-IgE-mediated CMA confirmed via trial elimination diet and oral food challenge with cow's milk protein									

Please leave any comments or suggested edits to Statement 12 or the examples:_____

Please leave any further comments or suggested statements below:

You may change your answers at any time during the survey by using the arrow button at the bottom left of the page.

You will be unable to amend your answers once you have submitted them on this page, using the arrow button at the bottom right of this page.

You may take the survey multiple times if you wish. All responses will be recorded, but your most recent response will be used for the purpose of the study.
If you do not submit your responses, partially completed responses will automatically be recorded 1 week after your last activity.

Please contact us (hilary.allen16@imperial.ac.uk) if you require any clarification before finalising your responses. Thank you very much for taking part in this survey.

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22.19.3 Delphi Round 2 Invitation Email

Dear [Study Participant],

Thank you for participating in our Delphi consensus study to develop new guidance for detecting and managing milk allergy in infants and young children.

Please find below a Qualtrics link to our Round 2 questionnaire.
[Qualtrics E-survey Link]

We would appreciate if you could complete the survey by 12th May 2021.

We invite you to give your opinion in the comments section after each statement and at the end of the survey, if you feel the study statements require modification or if there are other important aspects of milk allergy that you feel should be considered in this study.

A reminder email will be sent in one week.
If you have any queries or technical difficulties with the survey link, please contact the study team via email [hilary.allen16@ic.ac.uk].

Kind regards,

Ursula Pendower (iBSc student. NHLI, Imperial College London. UK)
Dr. Hilary Allen (PhD student NHLI, Imperial College London. UK)
Dr. Robert Boyle (Principal Investigator. Clinical Reader Paediatric Allergy. NHLI. Imperial College London, UK.)

This study was given ethical approval by the Imperial College London Research Governance and Integrity Team. Imperial College London is the main research sponsor for this study. This study is funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen.

22.19.4 Round 2 Qualtrics Electronic Delphi Survey

A Delphi consensus project to develop guidance for the safe detection and management of cow's milk allergy (CMA) in children

Thank you very much for your continued participation in this study.

The aim of this study is to develop guidance for primary healthcare practitioners for the safe detection and management of CMA without undermining breastfeeding, from a multidisciplinary expert panel, without conflicts of interest related to the breastmilk substitute (formula) industry.

The study seeks to address 3 main questions:

1. What aspects of cow's milk allergy (CMA) detection are important to ensure that the condition is not overdiagnosed or underdiagnosed?
2. In a child with CMA who is receiving breastmilk, what aspects of management are important to ensure that continuation of breastmilk feeding is fully supported?
3. What aspects of CMA management are important to prevent unnecessary and potentially harmful use of specialised formulas such as amino acid formula, extensively hydrolysed formula or soya or rice based infant formulas?

Instructions
In this Round 2 survey we present the Round 1 revised statements and new suggested statements, according to participant comments. No statements have been excluded from Round 1.

We include your previous score, the mean and range of scores for each statement from Round 1. Anonymised participant comments are included along with their area of expertise to give context to the comments.

Please re-rate each statement using the following scale:

1-3: This is **not important** for the safe detection and management of CMA
4-6: This is **important** for the safe detection and management of CMA
7-9: This is **critical** for the safe detection and management of CMA

If you feel the question is outside your area of expertise, you may select 'Not sure'.

No completely novel statements may be added at this stage. Please add comments and suggest modifications to the current statements, including suggestions to split or merge statements where necessary.

Please use the arrows at the bottom of the screen to move forwards or backwards through the questionnaire. If you close the survey, it is not possible to save your responses midway and come back to finish the questionnaire at a later time.

On the final page, please submit your answers by clicking the arrow button in the bottom right of the screen. If you do not submit your answers, your response will be automatically collected 1 week after your last activity. You may resubmit a new questionnaire at any time;

all responses will be recorded, but your most recent response will be used for the study.

We expect that this questionnaire will take approximately 30 minutes to complete.

Please contact us (hilary.allen16@imperial.ac.uk) if you have any queries or concerns about the questionnaire.

Please give your name below:

_____

General Round 1 comments:	
Paediatric Allergist	1) Cow's milk allergy should be rephrased as milk allergy 2) Milk allergy and milk intolerance needs to be differentiated as milk intolerance usually requires milk abstinence for only short duration 3) Transdermal route of milk exposure should be mentioned along with ingestion of milk
Public Health Nutritionalist	Suggest that duration of use for specialised formula needs to be covered given that CMA resolves, especially if non IgE mediated. Suggest a 'don't know' option for all examples as well as scores 1-10.
Expert in Breastfeeding	Some of the questions require quite advanced medical knowledge about symptoms and treatment of CMA and should be targeted to practitioners with this expertise.

The following set of statements (1-6) will seek to answer this question:
What aspects of cow's milk allergy (CMA) detection are important to ensure that the condition is not overdiagnosed or underdiagnosed?
(Note: This section covers both IgE and non-IgE mediated CMA)

If you wish, please comment on the scope and wording of this question below:

---

1. In an exclusively breastfed infant, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, IgE or non-IgE mediated CMA, or other food allergies should be considered in the following circumstances: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think it is not important to consider CMA in this circumstance; a score of 9 indicates you think it is critically important to consider CMA in this circumstance)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Exclusively breastfed infant with severe eczema, accompanied by faltering growth and protein-losing enteropathy										
b) Exclusively breastfed infant with severe eczema, without faltering growth or protein-losing enteropathy										
c) Exclusively breastfed infant with severe vomiting after feeding, accompanied by faltering growth and protein-losing enteropathy										
d) Exclusively breastfed infant with severe vomiting after feeding, without faltering growth or protein-losing enteropathy										
e) Exclusively breastfed infant with severe crying after feeding, accompanied by faltering growth and protein-losing enteropathy										
f) Exclusively breastfed infant with severe crying after feeding, without faltering growth or protein-losing enteropathy										

g) Endoscopic biopsy finding of proctocolitis in an exclusively breastfed infant

h) Recurrent passage of visible blood in stool at least once daily for at least 3 consecutive days, with or without mucus in an exclusively breastfed infant

i) Recurrent, intermittent passage of visible blood in stool, less frequently than once daily, with or without mucus in an exclusively breastfed infant

j) Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in an exclusively breastfed infant

Please provide comments or modifications to the statements here

---

1(a) to (f) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 6 stems, (a) to (f)

1(g) to (j) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 2-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 4 stems, (g) to (j)

Statement 1 Round 1 comments:

Paediatric Allergist	The degree of vomiting or eczema (i.e., severe vomit/eczema) would make me worry about food allergy even if no PLE (protein-losing enteropathy). And so the first choice statement links FTT (failure to thrive) with PLE but either one would make me worry.
Paediatric Dermatologist	Severe CMA with failure to thrive and blood in stools in a breastfed child would be most unusual

Dietician	I might think of isolated vomiting as a symptom of CMA depending on when it occurs after feedings.
Public Health Nutritionalist	The term 'failure to thrive' has been replaced with 'faltering growth' see NICE QS 197
Lactation Consultant	I notice the exclusion of the word "Colic" in this statement. In practice, I see that this term is used by parents and clinicians very often to diagnose CMA. If it is intentional given the lack of consensus on the definition of Colic, I understand. Otherwise, I would suggest adding "colic" to the Statement 1
Paediatric Allergist	The second statement forces me to answer both for visible blood without mucous and for proven proctocolitis (biopsy would be rarely done. So if you had asked: visible blood on a few occasions I would have not been too interested in CMA. You may have seen recent publication that in a Massachusetts pediatrics practice they diagnoses FPIAP in 17% of babies. A follow up study found high rates of CMA in the group later maybe from too much unproven milk elimination.
General Paediatrician	Proctocolitis in a controversial issue. For sure this is "allergy" - as we define an immunology mediated response, no risk of anaphylaxis. The condition is benign ant transient. However there are reports that suggest improvement with avoiding CMP.
Paediatric Allergist	The question regarding 'hematochezia' is not very specific as it really depends on the recurrency and severity of this sign. However, maybe the question was formulated this way on purpose

2. In an infant consuming cow's milk products or cow's milk formula or other mammalian milk products or formula as a regular part of their diet, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, IgE or non-IgE mediated CMA should be considered in the following circumstances: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think it is not important to consider CMA in this circumstance; a score of 9 indicates you think it is critically important to consider CMA in this circumstance)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Symptoms (crying, vomiting or eczema) of any degree start within 3 days of initiating mammalian milk formula feeding										
b) Symptoms of eczema are severe and start within 3 days of initiating mammalian milk formula feeding										

c) Symptoms of vomiting are severe and start within 3 days of initiating mammalian milk formula feeding

d) Symptoms of crying are severe and start within 3 days of initiating mammalian milk formula feeding

e) Symptoms (crying, vomiting or eczema) of any degree start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from soon after birth

f) Symptoms of eczema are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth

g) Symptoms of vomiting are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth

h) Symptoms of crying are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth

i) Infant consuming mammalian milk products or formula with faltering growth, despite adequate nutritional intake

j) Endoscopic biopsy finding of proctocolitis in an infant consuming mammalian milk products or formula

k) Recurrent passage of visible blood in stool at least once daily for at least 3 consecutive days, with or without mucus, in an infant consuming mammalian milk products or formula

l) Recurrent, intermittent passage of visible blood in stool, less frequently than once daily, with or without mucus, in an infant consuming mammalian milk products or formula

m) Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in an infant consuming mammalian milk products or formula

Please provide comments or modifications to the statements here:

2(a) to (h) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 5 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 8 stems, (a) to (h)

2(i) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 3-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

2(j), (k), (l) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 4-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 3 stems, (j), (k) and (l)

2(m) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 5-9

Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified to clarify it relates to non-IgE mediated milk allergy

Statement 2 Round 1 comments:

Paediatric Allergist	'Cow's milk' should be changed to 'other mammal milk' or 'formula milk' or 'top milk'
Paediatric Allergist	Again, some questions include multiple aspects like the first one within 3 days (higher suspicion) or any in first 6 weeks (less suspicion) and then I am not sure if we are talking lots of vomit/eczema or all mild. Also, am I judging colic (only crying) in Q about 3 days or first 6 weeks (highly unlikely CMA) or more significant symptoms?
Public Health Nutritionalist	The first example needs to be split in two as there is a big difference between three days of initiating formula and first 6 weeks of life. For the second example see comment on 'failure to thrive' above.
General Paediatrician	These conditions are not IgE mediated.

3. Acute symptoms such as erythema, urticaria, angioedema or vomiting which occur within 2 hours of ingesting a food or drink containing cow's milk protein or another mammalian milk protein may indicate CMA. However, CMA is not likely in this setting, if:
1-3 Not Important. 4-6 Important. 7-9 Critical.
(Note: A score of 1 indicates you think CMA is likely in this circumstance; a score of 9 indicates you think CMA is not likely in this circumstance)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Infant aged over 6 months has previously consumed mammalian milk protein in similar forms at least once per day for at least 3 consecutive days, without any previous acute symptoms										
b) Infant aged under 6 months has previously consumed mammalian milk protein in similar forms at least once per day for at least 7 consecutive days, without any previous acute symptoms										
c) Erythema, urticaria or vomiting persist for longer than 4 hours, or angioedema persists for longer than 6 hours, without further exposure to mammalian milk protein										

d) An alternative, more common explanation for the symptoms such as a viral infection or gastroesophageal reflux seems more likely than CMA

e) Similar symptoms occurred on other occasions without ingestion of mammalian milk protein

f) Symptoms are not reproducible on subsequent ingestion of mammalian milk protein

Please provide comments or modifications to the statements here:_____

3(a) and (b) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 5 Range: 1-8
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 2 stems, (a) and (b)

3(c) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 4 Range: 1-8
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

3 (d) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 2-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

3(e) Round 1 outcomes:

Your previous score

Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

3(f) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions in view of comments	Statement has been modified

Statement 3 Round 1 comments:

General Paediatrician	There are 2 separate issues. One, if the infant has consumed the CMP in 3 separate occasion – in that case he is likely to have CMPA, the other example is when the infant has been consuming the cmp in 3 consecutive days - in that case, then IgE CMA cannot be ruled out. But most infants with IgE-CMA develop symptoms earlier. We cannot ignore the possibility that the infant had very mild symptoms that were ignored.
Health Visitor	(a+b) It (the fact that the infant hasn't reacted in the previous 3 days) is important as part of my clinical decision making. Unless the infant is 4 days old and this is the first sign of an immediate reaction. Otherwise I would feel that this is unlikely to be an 'acute' reaction to cows milk. Unlikely CMPA. (c) Important symptom. Vomiting and rashes can easily last for longer than 4 hours. (d) If there is a more common explanation for symptoms, then it is unlikely to be CMPA. Needs to be reproducible. Unlikely, but need to exclude other causes. (e) I feel this is a clear way of excluding allergy as there isn't the reaction to milk.
Paediatric Allergist	As I mentioned in the comments, the question is not very clear. Do you mean that "Infant has been consuming cow's milk protein in similar forms at least once per day for at least 3 days, with no previous acute symptoms prior to the described event or since the described event. " If you meant that after the described event infant has been consuming the cow's milk protein, this means that CMA is highly unlikely. I think that it doesn't make any difference as they could have subsequently developed CMA, although it is less likely if the baby is older, have been consuming milk products for

	months and have never experienced any problems. The safest approach, however, would be investigation of CMA if infant is within the first months of life and have recently started having infant formula.
Paediatric Allergist	For the 4 hour question I would wonder if the baby is continuing on milk. I assumed not.
Dietician	Also for persistent symptoms vomiting would be rare but significant eczema that occurs following ingestion of a bottle of CM formula in an infant who did not have this kind of eczema before would be likely to last 4 hours. It is hard for me to answer with these two grouped together.
General Paediatrician	Usually symptoms especially respiratory symptoms are treated and subside within 4 hours. Cutaneous symptoms can persist for longer period.
Paediatric Allergist	Again, information is lacking, but here I would be more on a safer side to be honest.
General Paediatrician	I need the whole situation in order to comment.
General Practitioner	I'm not sure why 3rd stem includes info about infrequency of CMA, feels 'leading'
General Paediatrican	(e) This depends on the specific condition. If rash appears immediately upon exposure – it is very suspicious for IgE CMA.

4. In infants with delayed gastrointestinal or skin symptoms between 2 and 48 hours following ingestion of a food or drink containing cow's milk protein or another mammalian milk protein, CMA is less likely but should be considered in the following circumstance:
1-3 Not Important. 4-6 Important. 7-9 Critical.
(Note: A score of 1 indicates you think it is not important to consider CMA in this circumstance; a score of 9 indicates you think it is critically important to consider CMA in this circumstance)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Skin symptoms such as eczema are severe and the infant is not tolerating mammalian milk protein in similar forms										

b) Skin symptoms such as eczema are reproducible and the infant is not tolerating mammalian milk protein in similar forms

c) Gastrointestinal symptoms such as repeated vomiting are severe and the infant is not tolerating mammalian milk protein in similar forms

d) Gastrointestinal symptoms such as repeated vomiting are reproducible and the infant is not tolerating mammalian milk protein in similar forms

e) Behavioural symptoms such as crying are severe and the infant is not tolerating mammalian milk protein in similar forms

f) Behavioural symptoms such as crying are reproducible and the infant is not tolerating mammalian milk protein in similar forms

Please provide comments or modifications to the statements here: __

Statement 4 Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been split into 6 stems, (a) to (f)

Statement 4 Round 1 comments:

Paediatric Dermatologist	Maybe you should have separated severe symptoms from reproducible here as I would have liked to have suggested different responses for each element
General Paediatrician	Vomiting and lethargy (FPIES)

---

5. In breastfed or formula fed infants without the acute or chronic symptoms described above, CMA does not need to be considered as a diagnosis for the following symptoms, either alone or in combination: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think that these symptoms (alone or in combination) do indicate CMA; a score of 9 indicates you think that these symptoms (alone or in combination) do not indicate CMA)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Occasional spots of blood in the stool, without any daily, visible blood in the stool										
b) Other colour changes in stool, unrelated to blood in the stool										
c) Consistency changes in stool										
d) Frequency changes in stool										
e) Aversive feeding										
f) Nasal or respiratory symptoms										

Please provide comments or modifications to the statements here:

5(a) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 6 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

5(b) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

5(c) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

5(d) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

5(e) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 3-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement unchanged

5(f) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 3-9

Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement unchanged

Statement 5 Round 1 comments:

Dietician	Occasional spot of blood not concerning, but if lots of mucus and blood then would consider CMA as diagnosis, especially if formula fed. Daily blood with mucus - would be more worried, consider trying different formula. I see lot of breastfed infants with allergic proctocolitis and would consider CMP elimination diet for mother, if she is amenable If symptoms not terrible would encourage mother to live with it if possible. None of these symptoms are concerning on their own
General Paediatrician	Well, I really don't think that proctocolitis is an allergy. I know that this is a very controversial issue.
Paediatric Allergist	I meant that I agree with the statement that CMA does not need to be considered as a diagnosis for infants with the symptoms listed below in the absence of acute or chronic symptoms described above.
Health Visitor	(a) Always consider: but still unlikely (b) (c) (d) Not a symptom of CMA (e) Need to consider this having ruled out other causes such as behavioural and force feeding (f) Need to consider, but unlikely if only symptom
Lactation Consultant	"Colour changes in stool" needs to be clarified and differentiated from red colour (visible blood)
General Paediatrician	(f) (You scored this as 1, indicating that you think these symptoms often do indicate CMA). True, but only if there is a clear linkage between the the symptoms and the consumption of milk protein.

6. For the following symptoms, where CMA is sometimes included in the differential diagnosis, diagnosis and management need to consider some other important issues:
1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think it is not important to consider these other issues in the differential diagnosis; a score of 9 indicates you think it is critically important to consider these other issues in the differential diagnosis)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Bile-stained vomiting can be caused by intestinal malrotation so requires urgent assessment										
b) Faltering growth has a wide range of potential causes, including insufficient protein/calorie intake										
c) Hematochezia can be caused by infection, clotting disorders or intestinal abnormalities										
d) Eczema management involves avoiding physical triggers, using moisturisers and topical anti-inflammatories when needed										
e) Colic and crying are common in healthy infants, but if severe these can also be related to a wide range of health issues in the infant or their carer										

Please provide comments or modifications to the statements here:

Please add other important differential diagnoses here that you feel may need to be considered:

6(a) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

6(b) Round 1 outcomes:
Your previous score

Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

6(c) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

6(d) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

6(e) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement unchanged

Statement 6 Round 1 comments:

Public Health Nutritionalist	See comment about 'failure to thrive' above. The fifth example could be clarified - it is not clear what health issues of the carer might include, is it meant to imply mental health issues?

The following set of statements (7-9) will seek to answer this question:

In a child with CMA who is receiving breastmilk, what aspects of management are important to ensure that continuation of breastmilk feeding is fully supported?

If you wish, please comment on the scope and wording of this question below:

Round 1 comments:

General Practitioner	I would consider changing the word undermined to compromised or another synonym.
Public Health Nutritionalist	This is worded in a passive way. Suggest it is made active by replacing 'undermined' with 'supported'
Expert in Breastfeeding	The scope is fine. I wonder if it would be better to turn it to a positive statement e.g. to ensure breastfeeding is supported
Lactation Consultant	I am wondering why you use the word 'fully' instead of 'exclusively' breastfed.

7. Maternal dietary restriction is not usually necessary to manage CMA. However, maternal dietary restriction may be advised or supported in the following circumstances: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think it is not important to advise or support maternal dietary restriction in this circumstance; a score of 9 indicates you think it is critically important to advise or support maternal dietary restriction in this circumstance)
Please note that these statements are similar to the statements under Section 1 (Diagnosis, p.4); you may wish to refer to your Section 1 responses when answering this question.

	1	2	3	4	5	6	7	8	9	Not Sure
a) Exclusively or partially breastfed infant with severe eczema, accompanied by faltering growth and protein-losing enteropathy and multiple IgE-mediated food allergies										

b) Exclusively or partially breastfed infant with severe eczema, without faltering growth or protein-losing enteropathy

c) Exclusively or partially breastfed infant with severe vomiting after feeding, accompanied by faltering growth and protein-losing enteropathy

d) Exclusively or partially breastfed infant with severe vomiting after feeding, without faltering growth or protein-losing enteropathy

e) Exclusively or partially breastfed infant with severe crying after feeding, accompanied by faltering growth and protein-losing enteropathy

f) Exclusively or partially breastfed infant with severe crying after feeding, without faltering growth or protein-losing enteropathy

g) Endoscopic biopsy finding of proctocolitis in an exclusively or partially breastfed infant

h) Mother has noticed a clear relationship between her own dietary intake and symptoms of eczema in her child, and wishes to restrict her diet

i) Mother has noticed a clear relationship between her own dietary intake and symptoms of vomiting in her child, and wishes to restrict her diet

j) Mother has noticed a clear relationship between her own dietary intake and symptoms of crying in her child, and wishes to restrict her diet

k) Mother wishes to avoid consuming cow's milk products herself as part of household cow's milk avoidance, either because she dislikes cow’s milk herself or in order to prevent accidental exposure of her milk allergic child

Please provide comments or modifications to the statements here:

7(a) to (g) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 7 stems, (a) to (g)

7 (h), (i), (j) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 5 Range: 1-7
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been split into 3 stems, (h) (i) and (j)

7(k) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 5 Range: 2-8
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

Statement 7 Round 1 comments:

Paediatric Allergist	Nuances here that I cannot account for are how long the trial off for the mother would be discussed (#2) or what we are talking about with this other child and household dynamics (#3) for example a very busy 3 year old is only child and

	mother does not "need" milk around and the child has extremely severe CMA, why not agree she does not need to be leaving milk in the house if she prefers that?
Public Health Nutritionalist	(h)This statement is not inline with current NICE guidelines which do suggest dietary exclusion. With that in mind suggest it states 'Evidence suggests that'
Lactation Consultant	Breastfeeding is undermined when dietary restriction is difficult for the mother. Many times, the mother hates drinking cow's milk and is being forced (by family/providers) to drink so she 'can make healthy milk'. If the mother is comfortable with dietary restriction, breastfeeding will not be undermined.

8. For mothers who restrict their own intake of cow's milk protein and other mammalian milk proteins: 1-3 Not Important. 4-6 Important. 7-9 Critical.
(Note: A score of 1 indicates you think the following statements are not important to consider for mothers restricting their own diet; a score of 9 indicates you think the following statements are critically important to consider for mothers who restrict their own diet)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Ensure adequate maternal dietary intake of calcium and vitamin D										
b) Address the need for an exclusion diet, taking into consideration the physical and psychological burden of elimination diets on the family										
c) Advise that avoidance of baked products containing milk is unlikely to be necessary, due to the very small quantity of milk protein transferred to breastmilk										
d) Advise that goat and sheep milk protein should be avoided as well as cow's milk protein, due to cross-reactivity										
e) Advise that soya protein should be avoided as well as cow's milk protein, due to cross-reactivity										
f) Advise re-introduction of mammalian milk into the maternal diet if a trial of exclusion for 2 weeks has not resulted in resolution of symptoms										

g) Advise a trial of re-introduction of mammalian milk into the maternal diet if symptoms of concern have subsided for at least 2 weeks

Please provide comments or modifications to the statements here: _____

8(a) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

8(b) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement unchanged

8(c) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 6 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

8(d) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 7 Range: 3-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

Parts(e), (f) and (g) are new statements added from Round 1 in response to participant comments.

Statement 8 Round 1 comments:

General Practitioner	(a) It depends, for instance mothers who are already following a plant-based diet may have good understanding of dietary requirements
Public Health Nutritionalist	I would like to remove my score for the first example and suggest it is reworded: mothers should be advised to take calcium and vitamin D to ensure adequate intake. Assessment by a dietitian is likely impractical.
Paediatric Allergist	I am reading these as counseling issues so why not discuss them even if not critical to do so? Seems like we decided that you wanted to avoid milk, OK, well we need to make sure you have a good diet. By the way, this may not really be necessary and let's discuss this may impact you more than you think if we are not so sure it is necessary in the first place. And by the way, such a trace amount of milk from your diet is in your breastmilk you can likely have baked products with milk or small amounts of milk in your coffee...and by the way if we think cow's milk is truly an issue, don't have sheep or goat milk, it is similar to cow, but you can have donkey milk with less likely an issue...
Paediatric Dermatologist	Responses here will depend on the severity of the CMA
Lactation Consultant	I like the term that you used 'physical and psychological burden of elimination diets on the family'. Well articulated!
Infant Feeding / Health Visitor	Part 3 - depends where the assessment is up to. Milk ladder via breastmilk.
Public Health Nutritionalist	It seems inconsistent to talk about assessing the need for an exclusion diet at the same time as saying that evidence suggests this is not needed. In addition the way this example is worded suggests breastfeeding might be undermined, and increasing/maintaining/continuing breastfeeding should be a key objective for the majority of infants suspected of having CMA.
Paediatric Gastroenterologist	Other milks are not all equal. Likely to have more cross reactivity with soy

Public Health Nutritionalist	For clarity vis a vis the fourth example, I think it is critical that mothers who restrict their own intake of CM protein should be advised to avoid other mammalian milks
Dietician	For breastfed child, mums have usually eliminated cow's milk and soya by the time you see them. Most important thing is to reintroduce to see if symptoms recur. Important to manage the CMA but also, the thought of the CMA rather than eliminating and sending them on their way.

9. Protect, promote and support exclusive breastfeeding to around 6 months and continued breastfeeding to at least 2 years as recommended by the World Health Organization, or local recommendations, by:
1-3 Not Important. 4-6 Important. 7-9 Critical.
(Note: A score of 1 indicates you think the following statements are not important to consider to support breastfeeding in the context of CMA; a score of 9 indicates you think the following statements are critically important to consider to support breastfeeding in the context of CMA)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Signposting to local breastfeeding support services, including referring to an IBCLC for breastfeeding support where available										
b) Reassuring mothers and other family members that breastmilk is the most appropriate milk for all infants and young children, with and without CMA										

Please provide comments or modifications to the statements here:__

9(a) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

9(b) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential

Actions taken in view of comments	Statement has been modified

Statement 9 Round 1 comments:

Public Health Nutritionalist	The first example should be strengthened e.g. 'refer to an IBCLC for breastfeeding support'.
Paediatric Gastroenterologist	The AAP recommends introduction of solid food between 4 -6 months
Paediatric Allergist	Is this asking how helpful you think the sub-statements are in your community? And I guess this is in context of diagnosed CMA?
Dietician	Until 4-6 months when developmentally ready as some infants may need complementary foods early for nutritional reasons and for food allergy prevention. Also, I would not say until at least 2 years of age but in the US we say to at least 1 year of age or longer as long as mutually desired by parent and child. If international survey, consider country specific guidance.
Public Health Nutritionalist	The second example should be clarified: 'Reassure mothers and other family members that breastmilk is the most appropriate milk for all infants and young children, with and without CMA'. Suggest adding a third example in relation to the protection of breastfeeding: 'Clinicians should avoid conflict of interest with breastmilk substitute companies, including by avoiding the display branded materials in their practice'

The following set of statements (10-12) will seek to answer this question:

What aspects of CMA management are important to prevent unnecessary and potentially harmful use of specialised formulas such as amino acid formula, extensively hydrolysed formula or soya or rice based infant formulas?

Round 1 comments:

General Paediatrician	I think that soya formula is safe and well tolerated in CMPA

Public Health Nutritionalist	Suggest after unnecessary add 'and potentially harmful'. I don't understand why rice-based infant formulas are mentioned here as I thought the first line formula is usually hydrolysed, then amino acid is second line, and soya protein an option but discouraged for under 6 month olds (and those with CMA may also have soya allergy)?

10. Initiation or continuation of specialised formula should not be advised for the following groups of patients with CMA: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think initiation of specialised formula should be advised for this group of patients; a score of 9 indicates you think initiation of specialised formula should not be advised for this group of patients)

1	2	3	4	5	6	7	8	9	Not Sure

a) Children aged over 12 months with a good, mixed diet and normal growth pattern

b) Infants who are currently breastfed without use of any breastmilk substitute

c) Infants who have received infrequent or small volumes of formula, but can return to full breastfeeding without use of a breastmilk substitute, with appropriate support for caregivers

Please provide comments or modifications to the statements here:_____

10(a) Round 1 outcomes:

Your previous score	
Other participant scores	Mean score: 6 Range: 1-9
Status of consensus	No consensus to include or exclude yet
Actions taken in view of comments	Statement has been modified

10(b) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential

Actions taken in view of comments	Statement has been modified

10(c) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

Statement 10 Round 1 comments:

Paediatric Allergist	There are many nuances that would alter my thoughts of each circumstance. I feel like I was answering as "this could be the case, depends on total picture of diet, maternal preferences, access to dietitian, how child is doing, etc
Dietician	I am also not sure what you mean by fully breastfed (this is inappropriate at 12 months and the infant would have iron deficiency anemia at least!). Do you mean breast milk along with complementary foods?
Lactation Consultant	The second option is confusing when we don't know of the health status of the fully (exclusively) breastfed infant.
Dietician	If the child is already on specialised formula, keep them on it until their nutritional status can be assessed. If the child is still getting the majority of their calories from a drink then need to continue formula beyond 12 months. Sort wording of 'fully breastfed'- in this context means breast milk is the only milk being received. Change current wording to something like: return to full breastfeeding if they want to and can with full support.
Public Health Nutritionalist	I have scored the third example 5 because it may take some time to reestablish full breastfeeding and in this time it might be appropriate for the infant to be given a specialised formula instead of a non-specialised formula (assuming that available expressed milk is insufficient) depending on the severity the baby's symptoms

11. Initiation of specialised formula should not be advised in the following circumstance: 1-3 Not Important. 4-6 Important. 7-9 Critical.
(Note: A score of 1 indicates you think initiation of specialised formula should be advised for this group of patients; a score of 9 indicates you think initiation of specialised formula should not be advised for this group of patients)

	1	2	3	4	5	6	7	8	9	Not Sure
For preventing the development of CMA or other atopic conditions, even in infants with a family history of allergy										

Please provide comments or modifications to the statement here:_____

Statement 11 Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached: Essential
Actions taken in view of comments	Statement has been modified

Statement 11 Round 1 comments:

Public Health Nutritionalist	Considering adding, even in babies with a family history of allergy

12. Initiation of specialised formula should be advised for the following groups of patients: 1-3 Not Important. 4-6 Important. 7-9 Critical. (Note: A score of 1 indicates you think it is not important to advise initiation of specialised formula in this circumstance; a score of 9 indicates you think it is critically important to advise initiation of specialised formula in this circumstance)

	1	2	3	4	5	6	7	8	9	Not Sure
a) Formula-fed infants aged under 12 months, with IgE-mediated CMA confirmed using clinical history and either skin prick test, serum IgE testing or food challenge										
b) Formula-fed infants aged under 12 months with non-IgE-mediated CMA confirmed via trial elimination diet and oral food challenge with cow's milk protein										

Please provide comments or modifications to the statements here:_____

12(a) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached; Essential
Actions taken in view of comments	Statement unchanged

12(b) Round 1 outcomes:

Your previous score	
Status of consensus	Consensus reached; Essential
Actions taken in view of comments	Statement has been modified to include the age specification

Statement 12 Round 1 comments:

Paediatric Dermatologist	Depends what their CMA allergy is doing to them. If mild, maybe press on, but if severe symptoms, then specialised formula
Public Health Nutritionalist	The second patient group does not specify age under 12 months and assume it should.

Thank you very much for taking the time to answer these questions, you have now reached the end of the questionnaire.

Please click the arrow button in the bottom right of the screen to submit your answers.

Before you do so, you may go back through the questionnaire to review or change your answers using the arrow button in the bottom left of the screen.

You may also resubmit a new questionnaire at any time, if you so wish. All responses will be recorded, but your most recent response will be used for the study.

We will be in touch to organise the consensus meeting soon. If you have any queries or concerns about the questionnaire in the meantime, please contact us. (hilary.allen16@imperial.ac.uk)

Please provide any final comments here:

_____

22.19.5Provisional recommendations following Delphi Round 2 Survey

This summary includes feedback from patient panel and guideline authors on the Round 2 Survey outcomes, and individual interviews with five study participants who were unable to attend the Consensus meeting

Summary of RECOMMENDATIONS following Round 2 of Delphi Consensus process: (This includes both Essential Recommendations; **Statements almost reaching consensus for Essential Recommendation* and ***Statements not reaching consensus*)	
SECTION 1: What aspects of Cow's Milk Allergy detection are important to ensure that the condition is not overdiagnosed or underdiagnosed? (Note that this section covers both IgE-mediated and non-IgE mediated Cow's Milk Allergy.)	
Paediatric Allergist	Cow's milk allergy should be re-phrased as Milk allergy
General Paediatrician	It might be difficult and confusing to cover IgE-CMA, which is a well-defined entity, and Non-IgE CMA together. Non IgE-CMA should be addressed separately, and to be well defined (FPIES, cFPIES, proctocolitis? and other conditions).
Parent 1	I feel giving parents a solution is important because there are many different opinions from different Healthcare Practitioners (HCP). No-one was fixing the problem for me. The blood was still in the nappies. I was constantly worried and checking nappies with a torch at night-time. Once you have a solution / plan,

	then you need support. I felt traumatised to not be able to have dairy in my own diet (was advised to eliminate from maternal diet during breastfeeding). I needed most support with not eating dairy and was worried that it would affect my breastmilk supply. Mum's job is to search for a document as to what she can eat – felt dietician wasn't able to give her this either and then dietician offered her a sample of Nutramigen. I felt I needed more guidance with my own diet.
Parent 3	I was looking for a solution but also support. I would rather have a plan and something to try, rather than to wait it out. I don't think it is fair to do that to a baby. I know it might be colic or immaturity but when a parent describes 8 hours of solid crying at night-time with all the other symptoms, I feel this has to be taken seriously and looked into. I would have liked something to have been tried sooner than 3 months.
Parent 4	I thought it was important that the document focussed on diagnosis. I found it difficult as a parent not having a defined answer – "does she have a milk allergy or not?" I got mixed messages from clinicians. "Try 2/52 of this, try 2/52 of that and if it doesn't work, we'll put her on the allergy formula". GPs seem very lost. I received advice from a paediatrician to go dairy free but this was never in the letter he sent to the GP. I also feel there needs to be more advice for when a child is over 12 months old – what does a parent do after that age? I'm worried that my child is small and that this might be because she didn't get dairy. As a mother, in the situation, you want a solution initially. And then support. Someone needs to tell you that it's a long path.
Pre-Consensus Phone call: Health Visitor/Infant Feeding Lead	• Perspective on Milk Allergy – reports that her main target as a health visitor is to get women breastfeeding and that breastfeeding journeys are often hampered by conversations on reflux, CMA, and mothers and infants on restricted diets. • Thinks the scope of the guidance should include all non-human milks.
Paediatric Gastroenterologist	• Feels that this guidance should state that it does not cover pre-term infants as there is a sub-group of infants with Necrotising Enterocolitis that are FPIES.
Statement 1: In an exclusively breastfed infant, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, IgE or non-IgE mediated CMA, or other food allergies, should be considered in the following circumstances:	
a) Exclusively breastfed infant with severe crying after feeding, accompanied by faltering growth and protein-losing enteropathy	

b) *Exclusively breastfed infant with severe eczema, accompanied by faltering growth and protein-losing enteropathy*
c) *Exclusively breastfed infant with severe vomiting after feeding, accompanied by faltering growth and protein-losing enteropathy*
d) *Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in an exclusively breastfed infant*
e) **Exclusively breastfed infant with severe eczema, without faltering growth or protein-losing enteropathy*
f) **Exclusively breastfed infant with severe vomiting after feeding, without faltering growth or protein-losing enteropathy*
g) **Exclusively breastfed infant with severe crying after feeding, without faltering growth or protein-losing enteropathy*
h) **Endoscopic biopsy finding of proctocolitis in an exclusively breastfed infant*
i) **Recurrent passage of visible blood in stool at least once daily for at least 3 consecutive days, with or without mucus in an exclusively breastfed infant*
j) **Recurrent, intermittent passage of visible blood in stool, less frequently than once daily, with or without mucus in an exclusively breastfed infant*

General Practitioner	I'm not entirely sure what protein-losing enteropathy means in primary care. Severe and persistent vomiting and/or diarrhoea? 'Severe' eczema, i.e. not responding to treatment?
Paediatric Gastroenterologist	Vomiting is different from regurgitation (effortless reflux). I interpreted the word vomiting to be different.
Dietician	Regarding the severe eczema questions- to me it is important to know if the infant is receiving adequate skin care as this is always in my mind the first step prior to evaluation for food allergy.
General Paediatrician	I'm not sure that proctocolitis should be diagnosed as "milk allergy"

Guideline Author	• I saw several infants with cow's milk-induced eczema without faltering growth – I suggest to modify into "*Exclusively breastfed infant with severe, accompanied or not by faltering growth and protein-losing enteropathy"* • EoE is absolutely exceptional in infants, while other GI disorders are possible. I suggest to change into " *Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy in an exclusively breastfed infant"* • I suggest to change into " *Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy in an exclusively breastfed infant"* • There is a fourth condition: "*Infant consuming mammalian milk products or formula with anaemia withouth other causes, despite adequate nutritional intake"* • Statement 1(e), 1(g)-(j): I would include this one • Statement 1(f): I would include this one, in particular FPIES
Guideline Author	Agree with statements. Question – how is 'protein-losing enteropathy' defined?
Guideline Author	Statement 1(a)-(c): Any infant falling into any of these 3 categories requires assessment by a paediatrician in secondary care and there is certainly no facility to diagnose PLE in the primary care setting. This essentially means milk allergy in the breastfed baby becomes a specialist-only diagnosis. This has potential benefits regarding minimising overdiagnosis but it also institutes potential delay in the pathway and may add a significant burden to paediatricians as well as cost. However, a greater risk is that parents, who we know have very early recourse to dietary exclusions (and always have done) for eczema, reflux etc if not adequately supported in primary care and waiting for referral onwards, will make their own unsupported decisions. This may be further exacerbated if you exclude those with severe and treatment unresponsive eczema or reflux, where there may be no faltering growth, from being considered as possibly at risk.
Parent 1	Fussiness and visible blood in stool were also symptoms in my child
Parent 2	My child had recurrent blood with mucus in every nappy from 6 weeks old until 6 months old without any other symptoms
Parent 3	My child also had severe bloating and discomfort associated with the bloating.

Parent 4	This covered all the symptoms in my child.
Pre-Consensus Phone call: General Paediatrician	Breastfed baby – sees no indication for diagnosing CMA or restricting maternal diet in an exclusively breastfed infant.
Pre-Consensus Phone call: Health Visitor / Infant Feeding Lead	• Rarely considers CMA as a diagnosis in an exclusively breastfed infant and only if symptoms (eczema, crying, vomiting, consistent blood/mucus in stools, faltering growth) are occurring in combination, are severe and are reproducible. • Would not consider CMA in an exclusively breastfed or formula fed infant if blood in the stool was the only symptom.
Pre-Consensus Phone call: General Practitioner	• Would consider CMA in a child with faltering growth but feels it is difficult to look for PLE in primary care as diagnostics limited. • Would consider CMA or other food allergy in biopsy proven eosinophilic GIT disorders.
Pre-Consensus Phone call: Paediatric Gastroenterologist	• Feels that clinical presentation of PLE is rare and suggests that "low albumin and / or oedema" covers PLE and is a more useful term to the generalist than PLE. • Would consider CMA in an infant with faltering growth, PLE and other symptoms and would only consider blood in the stool as a symptom if other severe symptoms, such as faltering growth, co-existed. • Feels that performing biopsies and biopsy-proven eosinophilic disease are uncommon in breastfed infants • Feels that any dietary protein can cause symptoms in breastfed babies and suggests the guidance includes explanatory text that this is food allergy, of which milk would be a common type, rather than just CMA. • Feels that many infants present with blood in the stool that is benign but would consider CMA if an association between blood and other symptoms.
Statement 2: In an infant consuming cow's milk products or cow's milk formula or other mammalian milk products or formula as a regular part of their diet, symptoms such as crying, vomiting or eczema do not usually indicate CMA. However, IgE or non-IgE mediated CMA should be considered in the following circumstances:	
a) Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis, in an infant consuming mammalian milk products or formula	

*b) *Infant consuming mammalian milk products or formula with faltering growth, despite adequate nutritional intake*
*c) *Recurrent passage of visible blood in stool at least once daily for at least 3 consecutive days, with or without mucus, in an infant consuming mammalian milk products or formula*
*d) **Symptoms (crying, vomiting or eczema) of any degree start within 3 days of initiating mammalian milk formula feeding*
*e) **Symptoms of eczema are severe and start within 3 days of initiating mammalian milk formula feeding*
*f) **Symptoms of vomiting are severe and start within 3 days of initiating mammalian milk formula feeding*
*g) **Symptoms of crying are severe and start within 3 days of initiating mammalian milk formula feeding*
*h) **Symptoms (crying, vomiting or eczema) of any degree start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from soon after birth*
*i) **Symptoms of eczema are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth*
*j) **Symptoms of vomiting are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth*
*k) **Symptoms of crying are severe and start within the first 4 weeks of life, in an infant fed with a mammalian milk formula from the first days after birth*
*l) **Endoscopic biopsy finding of proctocolitis in an infant consuming mammalian milk products or formula*
*m) **Recurrent, intermittent passage of visible blood in stool, less frequently than once daily, with or without mucus, in an infant consuming mammalian milk products or formula*

Paediatric Allergist	(d) and (h) As severity of the symptoms has not been specified, I am unable to respond. Obviously if child presents with mild eczema or a single episode of vomiting it is very different to the child presenting with severe eczema and recurrent vomiting. Crying is just too non-specific to make any definitive conclusions.
Public Health Nutritionalist	'symptoms of crying are severe' is perhaps a confusing phrase. Would something like 'crying is persistent' be clearer perhaps? why is the term colic not being used?
General Paediatrician	I might change my recommendation in case of late onset (>30 min) repetitive vomiting especially with lethargy.
Lactation Consultant	Mammalian milk product can technically also include human milk. How about the term “non-human milk products”.
Guideline Author	• Statement 2(a): I suggest to change into " *Biopsy findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy in an exclusively breastfed infant”* • Statement 2(c): There is a fourth condition: “*Infant consuming mammalian milk products or formula with anaemia without other causes, despite adequate nutritional intake* • Statement 2(d)-(m): To be sincere, I would include all these cases.
Guideline Author	• Statement 2(b): This is a quite a reductive statement – most faltering growth is due to inadequate intake but those cases that aren’t would be very much guided by the presence of other symptoms. To triage as possible CLPA in the absence of any other symptoms is unlikely to be helpful to a clinician. • By taking each symptom in isolation, you are simply drawing arbitrary (and non-evidence based) lines as to when CMA should be considered and losing the element of clinical judgement that also considers not just symptom severity but its persistence, multiple symptoms in different systems as well as treatment resistance. This is not going to be easy to manage as a series of statements in this format.
Pre-Consensus Phone Call: General Paediatrician	• Formula fed baby – Would consider trying a non-dairy milk such as soya if an infant has failure to thrive, repeated severe vomiting or diarrhoea while formula fed, despite adequate calorie/protein intake. • Formula fed baby with eczema – concerned about losing tolerance if CM is taken out of the diet, so he wouldn’t advise this even if there seems to be a relationship between CM intake and eczema flares.

Pre-Consensus Phone call: Health Visitor / Infant Feeding Lead	• Would consider CMA as a diagnosis in a formula fed infant over 5 weeks old if symptoms (eczema, crying, vomiting, ongoing blood/mucus in stools) occur in combination, are severe, and are not responding to initial conservative management of individual symptoms eg. standard eczema treatment, paced feeding for reflux, avoiding over-feeding. • Would not consider CMA in an exclusively breastfed or formula fed infant if blood in the stool was the only symptom.
Pre-Consensus Phonecall: Paediatric Gastroenterologist	• Feels that persistent screaming, often in association with eczema, can indicate CMA in a thriving formula-fed child with no temporal history of response to milk exposure. • Feels that CMA and a therapeutic trial of an extensively hydrolysed formula is to be considered as part of a comprehensive diagnostic work-up for faltering growth
Pre-Consensus Phonecall	• Feels that CMA would be considered in the differential diagnosis if there is faltering growth without other symptoms, if no other obvious cause
Statement 3: Acute symptoms such as erythema, urticaria, angioedema or vomiting which occur within 2 hours of ingesting a food or drink containing cow's milk protein or another mammalian milk protein may indicate CMA. However, CMA is not likely if:	
a) An alternative, more common explanation for the symptoms such as a viral infection or gastroesophageal reflux seems more likely than CMA	
b) Similar symptoms occurred on other occasions without ingestion of mammalian milk protein	
c) Symptoms are not reproducible on subsequent ingestion of mammalian milk protein	
*d) **Infant aged over 6 months has previously consumed mammalian milk protein in similar forms at least once per day for at least 3 consecutive days, without any previous acute symptoms*	
*e) **Infant aged under 6 months has previously consumed mammalian milk protein in similar forms at least once per day for at least 7 consecutive days, without any previous acute symptoms*	
*f) **Erythema, urticaria or vomiting persist for longer than 4 hours, or angioedema persists for longer than 6 hours, without further exposure to mammalian milk protein*	

Paediatric Allergist	(a) this question is still very non-specific and predisposes to a variety of clinical scenarios.
Guideline Author	Statement 3(d)-(f): I tend to agree with all these statements
Guideline Author	The no consensus statements section 1 statement 3 is good - earlier tolerating at least 7 days should be clear and is an important statement.
Guideline Author	• Is there a way of capturing here that the closer the temporal relationship, the more likely it is related ie urticaria immediately on exposure is more meaningful that 2 hours later. • But aren't formula top ups in early postnatal period a risk factor for CMA on later exposure???

Statement 4: In infants with delayed gastrointestinal or skin symptoms between 2 and 48 hours following ingestion of a food or drink containing cow's milk protein or another mammalian milk protein, CMA is less likely but should be considered in the following circumstance:

a) Skin symptoms such as eczema are severe and the infant is not tolerating mammalian milk protein in similar forms

b) Skin symptoms such as eczema are reproducible and the infant is not tolerating mammalian milk protein in similar forms

c) Gastrointestinal symptoms such as repeated vomiting are severe and the infant is not tolerating mammalian milk protein in similar forms

d) Gastrointestinal symptoms such as repeated vomiting are reproducible and the infant is not tolerating mammalian milk protein in similar forms

e) Behavioural symptoms such as crying are reproducible and the infant is not tolerating mammalian milk protein in similar forms

*f) *Behavioural symptoms such as crying are severe and the infant is not tolerating mammalian milk protein in similar forms*

Paediatric Allergist	I guess we are assuming no other unique allergenic protein is under diagnostic consideration.
Public Health Nutritionalist	'Behavioural symptoms such as crying' lacks clarity, as it is suggestive of other behavioural symptoms which are not described. There is also internal inconsistency with other sections where just 'crying' is used. Why not colic instead of crying?
Guideline Author	Throughout this section, I do not understand the locution "*and the infant is not tolerating mammalian milk protein in similar forms*"
Guideline Author	I'm a little worried that point d) can be confused with infantile benign GER. May be: "repeated severe reproducible" or repeated considerable reproducible"…I imagine c) refers to FPIES suspicion.
Guideline Author	• Statement 4: This is a relative term…less likely that what? Shouldn't it be 'unlikely' • Are these statements missing an opportunity to use treatment resistance and multiple symptoms in different systems as clues rather than an isolated focus on severity.
Pre-Consensus Phone call: Health Visitor / Infant Feeding Lead	• In an infant with severe crying, JB would advise first excluding other causes such as pacing feeds, parenting support, eczema management and conservative reflux management.
Statement 5: In breastfed or formula fed infants without the acute or chronic symptoms described above, CMA does not need to be considered as a diagnosis for the following symptoms, either alone or in combination:	
a) Occasional spots of blood in the stool, without any daily, visible blood in the stool	
b) Other colour changes in stool, unrelated to blood in the stool	
c) Consistency changes in stool	
d) Frequency changes in stool	
e) Nasal or respiratory symptoms	

*f) *Aversive feeding*	
Paediatric Allergist	(e) it would be useful to provide a better explanation of "respiratory symptoms" character and severity.
Guideline Author	Statement 5 is a very good statement list! What about poor sleeping at nights or waking up repeatedly. b) maybe add green stools with gall colouring in infants pooing several times/day, smell of stool?
Pre-Consensus Phone call: Health Visitor / Infant Feeding Lead	Advises that aversive feeding is often a late sign of missed problems early on and is unlikely to be CMA if occurring in isolation. Advises that behaviour management and observation of feeding behaviours is essential with aversive feeding.
Pre-Consensus Phone call: General Practitioner	Feels that it is not necessary to consider CMA if aversive feeding is only symptom or combined with other symptoms.
Pre-Consensus Phone call: Paediatric Gastroenterologist	Feels that CMA should be considered with aversive feeding and that there should be no change to the yellow grading of aversive feeding.
Statement 6: For the following symptoms, where CMA is sometimes included in the differential diagnosis, diagnosis and management need to consider some other important issues:	
a) Bile-stained vomiting can be caused by intestinal malrotation so requires urgent assessment	
b) Faltering growth has a wide range of potential causes, including insufficient protein/calorie intake	
c) Hematochezia can be caused by infection, clotting disorders or intestinal abnormalities	
d) Eczema management involves avoiding physical triggers, using moisturisers and topical anti-inflammatories when needed	
e) Colic and crying are common in healthy infants, but if severe these can also be related to a wide range of health issues in the infant or their carer	

General Practitioner	'Blood in stool' in previous questions but 'hematochezia' here - I'm unsure there is a difference?
Paediatric Gastroenterologist	Hematochezia is different from bloody diarrhea. infection usually causes bloody diarrhea;
Public Health Nutritionalist	Helpful to use the term 'colic and crying' and suggest this is used elsewhere where 'crying' is referred to for clarity
General Practitioner	'Colic' is used to mean many different things, both by health professionals and patients, so is a confusing term
Guideline Author	Statement 6(e): Is a similar statement amount reflux not needed here. Most is physiological but its routinely over medicalised

SECTION 2: In a child with CMA who is receiving breastmilk, what aspects of management are important to ensure that continuation of breastmilk feeding is fully supported?

Public Health Nutritionalist	The phrases 'receiving breastmilk' and 'breastmilk feeding' may be confusing/distracting to many health care professionals. I think they're meant to inclusive but given that it's more common for babies to be breastfed than to be given breastmilk in another way I think it would be more appropriate to keep the words 'breastfed' and 'breastfeeding' and these other terms could be included in brackets
Parent 2	I was told by my Consultant that the reason for my baby passing PR blood was not well understood . I didn't go for a second opinion but had a lot of HCP telling me to try the specialised formula and the only reason I didn't was because my Consultant kept encouraging me to continue breastfeeding. So in my case, a solution to the symptoms wasn't provided but the support I got from her Consultant was incredibly important to her to continue breastfeeding

Statement 7: Maternal dietary restriction is not usually necessary to manage CMA. However, maternal dietary restriction may be advised or supported in the following circumstances:

a) Exclusively or partially breastfed infant with severe eczema, accompanied by faltering growth and protein-losing enteropathy and multiple IgE-mediated food allergies	
b) Exclusively or partially breastfed infant with severe vomiting after feeding, accompanied by faltering growth and protein-losing enteropathy	
c) Exclusively or partially breastfed infant with severe crying after feeding, accompanied by faltering growth and protein-losing enteropathy	
d) Mother has noticed a clear relationship between her own dietary intake and symptoms of eczema in her child, and wishes to restrict her diet	
*e) *Mother has noticed a clear relationship between her own dietary intake and symptoms of vomiting in her child, and wishes to restrict her diet*	
*f) **Exclusively or partially breastfed infant with severe eczema, without faltering growth or protein-losing enteropathy*	
*g) **Exclusively or partially breastfed infant with severe vomiting after feeding, without faltering growth or protein-losing enteropathy*	
*h) **Exclusively or partially breastfed infant with severe crying after feeding, without faltering growth or protein-losing enteropathy*	
*i) **Endoscopic biopsy finding of proctocolitis in an exclusively or partially breastfed infant*	
*j) **Mother has noticed a clear relationship between her own dietary intake and symptoms of crying in her child, and wishes to restrict her diet*	
*k) **Mother wishes to avoid consuming cow's milk products herself as part of household cow's milk avoidance, either because she dislikes cow's milk herself or in order to prevent accidental exposure of her milk allergic child*	
Lactation Consultant	For statements (d),(e),(j) & (k), I would not 'advice' it, but if the mother wishes to try diet restriction, I can 'support' it.
Expert in breastfeeding	While maternal dietary restriction may not be necessary, a mother's choice should be supported and dietary information provided

General Practitioner	In (d),(e),(j) & (k), I wouldn't advise maternal dietary restriction but I would attempt to support a mother who wished to restrict her diet despite advice
Health Visitor	(d),(e),(j) & (k), - wouldn't want to dismiss a mother's concerns, but want to carefully review and see if re-producible as part of confirming or excluding. (k)- wouldn't want someone to exclude unnecessarily, would want to explore this, doesn't mean it isn't important so put - unsure here
Guideline Author	Statement 7(f)-(k): I would include each one
Guideline Author	• Statement 7(a): Not sure of the relevance of multiple – if the child has CMPA and faltering growth/PLE why would the presence of other allergies influence the decision to restrict CMPA • Statement 7(d): The above are pretty rare and extreme cases and the decision making is not difficult there. The challenge is greater when the symptoms are less clearly related and milder. There needs to be consideration given to shared decision making here with the mother, with discussion of the risks and benefits of dietary exclusion rather that setting a very high proscriptive bar here. Each mother will have an individual view on how difficult exclusion would be and this needs to be considered in the context of the symptoms and their impact and severity.
Parent 1	I feel maternal dietary advice should come from healthcare practitioners, particularly if a first time mother.
Parent 2	Advice regarding maternal dietary restriction should be from healthcare practitioners (HCP). If parents aren't getting advice from HCP, then you either go to the internet or a friend of a friend. I feels all dietary advice should come from HCP - whether women should exclude or if they decide to when there is no evidence, then how should it be done without causing harm.
Parent 3	A mother can tell when something isn't suiting her baby. Women are in a position to guide or discuss with the healthcare practitioner (HCP) if they need an intervention (eg. another formula). Women need help with this. Women can restrict a food themselves easily enough but maternal dietary restriction should be parent-led as well as HCP-led.

Pre-Consensus Phone call: Health Visitor/Infant Feeding Lead	• Rarely advises maternal elimination diets and commonly encourages mothers to re-introduce dairy into diet. JB feels parental concerns should not be dismissed but would want to explore what they mean by a "clear relationship" as it doesn't always mean it is CMA. • Would only consider cow's milk maternal elimination diet when breastfeeding in an infant over than 8/52 old if symptoms (eczema, with consistent blood/mucus in stools and faltering growth) occur in combination and are severe but would limit the trial elimination diet to 2/52, followed by re-introduction and thinks this may be helpful to exclude CMA prior to referral to a Paediatrician, when this is required.
Pre-Consensus Phone call: Paediatric Gastroenterologist	• Feels that although CMA diagnosis is not advised for isolated blood in the stool in a well-infant, a 2 week trial of elimination is sometimes tried
Pre-Consensus Phone call: General Practitioner	• Feels that a child with severe crying/vomiting/eczema without faltering growth should be referred to Paediatrics for diagnostic clarity even though CMA is unlikely but to give parents confidence that they are being heard and their worries taken seriously and to prevent unnecessary dietary restriction
Statement 8: For mothers who restrict their own intake of cow's milk protein and other mammalian milk proteins:	
a) Ensure adequate maternal dietary intake of calcium and vitamin D	
b) Address the need for an exclusion diet, taking into consideration the physical and psychological burden of elimination diets on the family	
c) Advise that goat and sheep milk protein should be avoided as well as cow's milk protein, due to cross-reactivity	
d) Advise re-introduction of mammalian milk into the maternal diet if a trial of exclusion for 2 weeks has not resulted in resolution of symptoms	
e) Advise a trial of re-introduction of mammalian milk into the maternal diet if symptoms of concern have subsided for at least 2 weeks	
*f) *Advise that avoidance of baked products containing milk is unlikely to be necessary, due to the very small quantity of milk protein transferred to breastmilk.*	

*g) **Advise that soya protein should be avoided as well as cow's milk protein, due to cross-reactivity*	
General Practitioner	I don't quite understand the scenario. Most women I see who are restricting their own intake of CMP are doing so because they choose to be vegan, so (b)-(g) don't apply
Health Visitor	(d) - we would recommend another 2 weeks to ensure it is completely out of their system and there hasn't been accidental exposure. (e) - yes we would advise a re-introduction hope i have scored this correctly (f) - it can sometimes make a massive difference, but not always. (g) - controversial. Our policy says not to exclude soya unless they react after exposure rather than exclude without review.
Paediatric Dermatologist	2 weeks too short to judge effect on things like eczema that fluctuates of its own accord - we suggest 6 weeks
Dietician	I like the addition of the re-introduction questions. I still find some of these questions difficult -baked milk for instance can be a small amount in a commercial product which would be an unlikely problem in most.
Guideline Author	• Statement 8(c): I would include here also donkey and mare milk, as they may also cross-react in particular in the most severe forms of IgE mediated CMA • Statement 8(f): Absolutely agree! I would add also beef here; many paediatricians restrict unnecessarily it in case of CMA • Statement 8(g): I disagree here, at least in IgE-mediated.
Guideline Author	• Statement 8(a) add protein and calories. Some mothers risk losing weight too fast. • Statement 8(d) is an important statement.
Guideline Author	Exclusion period of 2 weeks seems short to me. Happy is you are sure this is what is recommended
Parent 1	I feels that the 2 weeks elimination is too short. I feel that with elimination diets, it's important to support the mother and advise her that symptoms will get better and that she is doing the right thing breastfeeding.

Parent 2	I thought the "2 week timeline" was very good. I had a HCP tell me that if I was already excluding, then to just keep going with it. What I wanted was to be told, "if you've tried it and it's not working, you can stop now".
Parent 4	Only comment is that the guideline mentions Vitamin D for the mother. However, what is the advice for Vitamin D for the child who either has or is being treated as a suspected Milk allergy? And again, what do you do when they are over 12 months.
Pre-Consensus Phone call: Health Visitor/Infant Feeding Lead	Advises that it is important to exclude breastfeeding difficulties such as position and attachment prior to advising elimination of baked products from maternal diet as it is unlikely to be CMA.
Pre-Consensus Phone call Paediatric Gastroenterologist:	Feels that baked goods unlikely to cause symptoms
Pre-Consensus Phone call	Feels that parents should be advised eating baked milk products is very unlikely to cause symptoms
Statement 9: Protect, promote and support exclusive breastfeeding to around 6 months and continued breastfeeding to at least 2 years as recommended by the World Health Organization, or local recommendations, by:	
a) Signposting to local breastfeeding support services, including referring to an IBCLC for breastfeeding support where available	
b) Reassuring mothers and other family members that breastmilk is the most appropriate milk for all infants and young children, with and without CMA	
Public Health Nutritionalist	I would like to reiterate my suggestion to add a third example in relation to the protection of breastfeeding: 'Clinicians should avoid conflict of interest with breastmilk substitute companies, including by avoiding the display branded materials in their practice'
Parent 1	I feel there needs to be online support for parents from a professional body. Giving parents a leaflet and signposting to breastfeeding services isn't enough. Mothers can feel very isolated at home and then just turn to Google. As a member of online parent groups about CMA, I feel the online groups are all about formula

	feeding.Also, I feel family support is critical – if you don't have family support for breastfeeding for the first few weeks, then it's very hard to maintain it. The partner needs to be on board.
Parent 2	I think breastfeeding to 2 years is a good message because I feel that message doesn't get through – I feel the message "breastfeed until 6 months" is the message that gets through.
Parent 3	I realise as time goes on as a mother that formula is very medicated. What is difficult is that the supports for breastfeeding aren't there. There was no lactation consultant in the postnatal ward. I didn't breastfeed on my second child as it was such a difficult time with my first child that I didn't feel I was going to be able to breastfeed my second child and look after a toddler and as my husband works nights. If I had known how difficult it was going to be with my 2nd child (8 hours of solid crying at night), I wouldn't have had them so close together. If I had a 3rd child, I would make sure and have made contact with a lactation consultant and have supports in place before the birth because they are not available in the hospital or with the public health nurse.
Parent 4	I felt this section was all very informative

SECTION 3: What aspects of CMA management are important to prevent unnecessary and potentially harmful use of specialised formulas such as amino acid formula, extensively hydrolysed formula or soya or rice based infant formulas?

General Paediatrician	I think that soya formula is safe and well tolerated in CMPA

Statement 10: Initiation or continuation of specialised formula should not be advised for the following groups of patients with CMA:

a) Children aged over 12 months with a good, mixed diet and normal growth pattern

b) Infants who are currently breastfed without use of any breastmilk substitute

c) Infants who have received infrequent or small volumes of formula, but can return to full breastfeeding without use of a breastmilk substitute, with appropriate support for caregivers.	
Dietician	From a nutrition perspective, "a good mixed diet" is too vague. Generally I like to see other criteria prior to transitioning off breast milk or hypoallergenic formula (a nutritionally appropriate substitute available, getting a good volume- at least 2/3 of energy intake- from a varied solid food diet, being able to eat age appropriate textures (may lose foods once transitioning to textures), etc. But it by "good mixed diet" you mean all of these things, then it is okay.
Public Health Nutritionalist	For statement (c) - suggest change 'but can return to full breastfeeding' to 'but can be breastfed/be given breastmilk without use' .. because I don't think the term 'full breastfeeding' is a formal term (and exclusive breastfeeding would only be applicable to <6 month olds)
Parent 1	I feel women need to be informed that introducing bottles could result in the end of breastfeeding. It is often a family member that will say “just give a bottle at night so they can sleep”. This habit then tends to take over the breastfeeding.
Parent 2	I didn’t understand this as have no experience of using formula. I was told to stop breastfeeding and change to specialised formula. I started pumping in preparation for possibly having to go to a bottle. I had one doctor tell me that the symptoms could continue even if I went to a specialised formula and that not to expect that changing to a formula would solve everything and then I may not be able to return to breastfeeding, which could be very distressing for me.
Parent 3	Why would they not return to breastfeeding? Apart from breastfeeding being better, there is also the cost of formula. The cost for specialised formula for my 2nd child for last year amounted to €2500 for 1 year alone.
Statement 11. Initiation of specialised formula should not be advised for preventing the development of CMA or other atopic conditions, even in infants with a family history of allergy	
Paediatric Allergist	New studies have muddied this a bit as I can imagine some parents with another child with severe persistent milk allergy asking if their next baby might benefit from small, consistent CM formula feeding alongside breast milk right from the start. We are not there yet but the plot thickens...

Guideline Author	Good to have included this here.
Statement 12: Initiation of specialised formula should be advised for the following groups of patients with CMA:	
a) Formula-fed infants aged under 12 months, with IgE-mediated CMA confirmed using clinical history and either skin prick test, serum IgE testing or food challenge	
b) Formula-fed infants aged under 12 months with non-IgE-mediated CMA confirmed via trial elimination diet and oral food challenge with cow's milk protein	
General Practitioner	For (a) I'm not sure whether clinical history plus skin prick test is sufficient. For (b) it may depend on severity of symptoms
Paediatric Dermatologist	Considered rather than advised maybe
Guideline Author	In our country a challenge test is needed since only test positive we consider clinical history + IgE+ not to be enough. Many studies with positive test and a resolution of symptoms after avoidance do nor reappear after re-introduction. I realize this in not doable with a large population. We are only 5 milj.
Guideline Author	Only concern is recommendation in non-IGE CMPA for OFC following exclusion to confirm diagnosis.

Table S1: Summary of Essential Recommendations and **Statements almost reaching consensus for Essential Recommendation*, (defined as statements within 1-2 votes of consensus), and ***Statements not reaching consensus*, following Round 2 of Delphi study.

22.19.6 Consensus meeting minutes

A Delphi consensus project to develop guidance for the safe detection and management of cow's milk allergy (CMA) in children

Online Consensus Meeting – 9th July 2021. 12pm midday – 2pm UK time

Chair: Dr. Michael Perkin
(Reader in Clinical Epidemiology and Consultant Paediatric Allergist, St. George's Hospital, London UK)

Attendees:
Professor Hywel Williams. *Professor of Dermato-Epidemiology and Co-Director, Centre of Evidence-Based Dermatology Centre of Evidence-Based Dermatology. Nottingham University Hospitals.*
Dr Neeraj Gupta. *Paediatric Intensivist & Allergy Specialist. Institute of Child Health & Sir Ganga Ram Hospital, Delhi, India*
Professor Scott Sicherer. *Paediatric Allergy and Immunology. Icahn School of Medicine at Mount Sinai, New York, USA*
Professor Mitchell Cohen, *Paediatric Gastroenterology. University of Alabama & Childrens of Alabama.*
Dr Sabeen Adil. *President of International Lactation Consultant Association*
Ms. Josephine Munene. *Certified Lactation Educator. Nairobi, Kenya.*
Professor Alison McFadden. *Professor of Mother and Infant Public Health. University of Dundee, Scotland.*
Professor Miriam Santer. *Professor of Primary Care, University of Southampton, United Kingdom.*
Dr Matthew Ridd. *General Practitioner and Reader in Primary Healthcare, University of Bristol, United Kingdom.*
Dr Daniel Munblit. *Paediatric Allergist*. *Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child's Health, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia.*
Dr Jennifer Koplin. *Epidemiologist with expertise in food allergy. Murdoch Childrens Research Institute, Melbourne, Australia.*
Assistant Professor Marion Groetch, *Dietician, Department of Paediatrics, Icahn School of Medicine at Mount Sinai, New York, USA*

Ms. Kate Heneghan-Sykes (Parent Observer)
Ms. Beth Jones (Parent Observer)

Dr. Robert Boyle. *Paediatric Allergist. National Heart and Lung Institute, Imperial College London, United Kingdom*
Dr. Hilary Allen. *General Practitioner and PhD student, National Heart and Lung Institute, Imperial College London, United Kingdom*

Apologies:
Professor Yitzhak Katz, *General Paediatrician. School of Medicine, Tel Aviv, Israel.*

Dr. Vicky Sibson, *Public Health Nutritionalist. Director, First Steps Nutrition. United Kingdom*
Ms. Justine Baines, *Infant feeding lead/Health Visitor, Manchester, United Kingdom*
Dr. Eefje de Bont, *General Practitioner – Assistant Professor, Maastricht University, The Netherlands.*
Professor Simon Murch, *Paediatric Gastroenterologist, University of Warwick, United Kingdom*

Note that individual 1 to 1 meetings were held with all those who could not attend on 9th July 2021 by Dr Boyle and Dr Allen, and their views were recorded and represented during the meeting as appropriate.

Consensus Meeting Panel Decisions:	
Statement 1	• Statement re-phrased as something like "may be considered as part of differential diagnosis" and list the other differential diagnoses in a footnote for both faltering growth/PLE and Eosinophilic disorders • Define faltering growth, or refer to other publications discussing the definition • Remove the symptoms with faltering growth and PLE – change this to 'consensus met', as Neeraj and Josephine are happy to support this statement, with the revised wording and explanatory notes • No change to statement "CMA or other food allergies" • Describe the conversation textually in the document regarding blood in the stool and the concerns raised / discussion by the panel • Take care to avoid overemphasising biopsy diagnoses, for fear of triggering increased biopsies of breastfed young infants. • Change Biopsy findings of Eosinophilic disorders to 'consensus met', as Josephine happy to support this statement, with the revised wording and explanatory notes
Statement 7	• Remove the symptoms with faltering growth and PLE • No change to status of consensus/lack of consensus on statements relating to maternal observation of clear dietary relationship and symptoms • Change wording of Maternal observation / choice statements to "support" and use "advise" for other stems • Confirm with Kate Heneghan-Sykes regarding PPI views on maternal dietary exclusions for eczema, in case further explanatory notes would be helpful here • Phone call between Kate and Dr. Allen on 27th July 2021 as IT issue prevented Kate from contributing during the meeting: Kate advised explanatory text around the importance of follow-up for a mother who chooses to eliminate from her diet, to prevent

	multiple food elimination and to assess if the elimination diet is helping the eczema
Statement 2	• Statement to be re-phrased as something like "may be considered as part of differential diagnosis" and list the other differential diagnosis in a footnote. • Severe crying/vomiting/eczema without faltering growth or temporal relationship between symptoms and feeding to remain "red" – no recommendation • Change faltering growth despite adequate nutrition to 'consensus met' because Neeraj is happy to support this statement with the modified wording and explanatory text about differential diagnosis. • Change recurrent blood/mucus to 'consensus met' because Mitch, Marion and Alison are happy to support this statement with the modified wording and explanatory text about differential diagnosis. • Describe the conversation textually in the document regarding blood in the stool in the document and the concerns raised / discussion by the panel
Statement 4:	• No change to "no consensus" status of severe crying
Statement 6:	• Change hematochezia to blood in the stools
Statement 9	• Add "taking into account mother's wishes" to stem 2 of Statement 9 • Change IBCLC to lactation specialist and add a footnote that IBCLC, La Leche league and others would be suitable.
Statement 12	• Add a footnote that for FPIES oral food challenge may not be needed
Terminology	• Milk Allergy – with explanatory text that it is mammalian, non-human milk.
AOB	• Write a section on appropriate alternative plant based beverages that can be used in CMA and those nutritionally inadequate that should be avoided – Marion will help with this • Develop some explanatory text around the difference in recommendations for the infant with blood in their stools between the exclusively breastfed scenario and the 'receiving cow's milk as a regular part of the diet' scenario, together with the recommendations for less frequent blood in the stools.

22.19.7Public and Patient feedback on scope of project:

Parent 1 Feedback via Telephone interview:

- Thought the 3 main questions covered the important areas regarding milk allergy
- Felt it very important to advise mothers about the very low amount of allergen in breast milk
- Advised adding something along the lines of: 'should they choose to continue to eliminate dairy, tell them how to do it safely, but make sure they know it's not scientifically necessary'
- Advised separating the two points into the medical advice and then if the patient decides to eliminate anyway, here is how to support them as this will help to make it less confusing
- Would like some very definitive patient info/pathway chart to follow because her experience as s a mother was that there was a lot of misinformation/confusing information such as NICE guidelines
- Advised including advice about weaning and not needing to worry about it if doctors have said baby does not have CMA but symptoms are persisting
- Advised it may be helpful to make it clear to mothers that the mechanism of rectal bleeding isn't always allergy
- Advised emphasising the potential LOSS if breastfeeding stops and that even if symptoms improve, at what cost? Benefit of continued breastfeeding is far greater than any 'damage' caused by rectal bleeding. Felt it was important to prevent the overestimation of harm by specialists
- Advised highlighting that formula is not the solution, just an option and that it won't necessarily fix the symptoms

Parent 2 Feedback via Telephone interview:

- Thought the 3 main questions cover all of the important aspects
- Advised making maternal mental health statement more clear; maternal mental health care needs to be considered up to and after diagnosis and when adjusting to allergy management
- Advised that re-challenging at home is scary and mothers are unlikely to want to do it without hospital supervision
- Advised considering Calcium supplements for infant as concern expressed over impact on bone health later in life for child
- Advised important to emphasise that every child needs to see dietician if eliminating cow's milk

Parent 3 Feedback via Telephone interview:

- Thought the 3 main questions cover the scope of milk allergy
- Feels there needs to be clearer information for mothers – how long will it last? How long do they remove dairy?
- Feels there needs to be dietetic support with weaning – not just at initial stages. Expressed concern about ongoing nutritional deficiencies

Parent 4 Feedback via Email:

I feel the questions asked cover all aspects of the milk allergy. The responses to the second question posed, are of paramount importance for me personally, as this was the area where I struggled most.

The support of a specialised Paediatric Dietician in the early days in our case was not available. My child needed to be under the care of a Consultant before we were referred to a Paediatric Dietician and was almost 5 months before we saw a Consultant Paediatrician specialising in Allergic conditions & his symptoms had largely settled at this stage. I feel our journey would have been much smoother if we had been seen and gotten this support earlier.

Also, the continued support of a Dietician is imperative, especially during the weaning stages & beginning the milk ladder at 12 months. Reassurance and advice with this aided us greatly.

One other point made was a time frame of 4 weeks for trial of maternal elimination diet. In my case, it took 7 weeks for the stool to return to normal, blood free. I felt quite alone at this stage as most advice given was that symptoms should have stopped a lot earlier. Support with this would too have been welcomed.

22.19.8 Guideline Authors' feedback on scope of project and study protocol:

Guideline Author 1 Feedback via Email:
DELPHI CONSENSUS PROJECT
Background:

- Limited prevalence data – with variable reports over Europe particularly for non-IgE mediated CMPA). However agree that widely accepted that a prevalence of 1-2% is widely accepted.
- Undoubted discrepancy between prevalence and year-on-year increase in prescriptions.
- Clear, prompt and accurate diagnosis of CMPA is clearly desirable but is it achievable – particularly for non-IgE-mediated CMPA. There is almost no original data on symptom presentation for CMPA, particularly CMPA. ALL reviews and guidelines extrapolate symptoms from articles (many of which are reviews and therefore also without a proper evidence base) on food allergy in general.
- There is an emphasis that guideline bias arises from commercial pressure. There is no mention that guideline authors work in tertiary care referral settings and so their experience of CMPA is inherently biased as they possibly/probably see more severe/complicated cases where there is possibly greater use of AAF.

Aims:
Develop guidance to prevent mislabelling/supporting prompt detection.
This is a clinical conundrum that challenges me in every clinic. A number of issues make this particularly challenging:

- Very little research into how children with non-IgE CMPA present.
- Often very young children (<2-3months) so clinicians feel pressurised to do something.
- Parental pressure for diagnosis of CMPA – family history, read on internet.
- Children already on amino-acid formula as first choice in primary care, so difficult to reverse decision.

What do we mean by 'independent 'guidance?
No comments.

Study aim/research questions/hypothesis

- Developing new guidance must be based on evidence. Have you referenced any research into the presentation of CMPA?
- Not sure what the research question means – particularly without a diagnostic reference.
- Consensus – agreement may perpetuate prejudices.

Methods

Overall study design.

No comments

Recruitment of participants

Really important to include experts from diverse backgrounds – outside the traditional sources i.e. Europe and North America.

Agree with selection of participants – suggest ensuring inclusion of dietitians, particularly community dietitians. In my region this group deals with higher numbers of infants presenting with suspected CMPA; possibly more than we do in our allergy service.

Delphi consensus process

Return to concern that evidence on symptom presentation is limited; NO guideline used an original source/reference.

Appendix A: Study participants invitation email

I personally feel that the phrase 'written by experts with significant industry-related conflicts of interest' is potentially adversarial / controversial. Whilst I am not contradicting the sentiment, perhaps you might want to soften it (without losing the focus in your proposal) by say 'written by experts who might be biased by their experience'. This will cover the aspect of commercial bias as well as the bias of seeing patients in a tertiary setting.

Guideline Author 2 Feedback via Email:

Very important work, and very good protocol. Congratulations!
One of your questions focuses on specialized formula. I presume you mean extensively hydrolysed casein/whey formulas, amino-acid formulas, soya formulas and rice hydrolysates (the latter in some countries only). However, equally problematic is the (over)use of plant-based drinks which have grown in popularity over the last 5-10 years (mainly due to environmental concerns). Do you plan to address it?

With regard to conflict of interest, current discussions mainly focus on the industry. However, other factors, such as ideological biases, strong beliefs, and predetermined views also play a role. Managing non-financial interests may be even more challenging (and not always easy to identify). However, they should not be overlooked.

Guideline Author 3 Feedback via Email:

Thanks for the chance to comment on this - overall the methodology is v sound. We all know the challenges around areas where the evidence base is lacking and this is a sensible way to develop guidance.

Few issues though:
The key end point here is to establish the best possible guidance and hence whilst it makes sense to avoid involving people with a potential COI, it also doesn't make sense to present this to them as being the reason they were selected. As you point out, many factors influence behaviour and few are stronger than perceived peer pressure so this will also influence their responses - for example, even if they see children in their practice presenting with certain symptoms they consider to be related to milk allergy, or have experienced breast fed babies reacting to milk in their mother's diet, there is a risk they will deliberately minimise voicing these so as to go along with a certain proscribed narrative. You are introducing conscious bias.

Another key aim here is to explore whether including only people without COI has a meaningful impact of guidance. I would therefore have liked to have seen a series of key 'decision points' that can be compared between current guidelines and the ones generated here. This could help provide some evidence of an effect.
How do you define 'unconflicted' - will there be a check of undeclared interests especially in those who haven't published? how long will these extend back?
Minor points - i am not sure reference 5 or 6 evidence the rise in infant HA formula use. Primary sources are needed.

ref 21-31 are referenced as existing guidelines but both have been superceded by the 2019 MAP guidance, which does directly address the issues raised.

Guideline Author 4 Feedback via Email:

Your questions are wisely composed.
I think it is important to avoid overdiagnosis, which is a problem in many countries. At the same time, I realize that in UK, the time to spot the right infants is a challenge and good, simple guidelines are necessary to find infants with CMA early enough. Your question on breastfeeding is also important as at a busy doctor’s office it is easy not give this aspect enough consideration.

The third Q is important so that special formulas are not used for too long when the child already eats a broad variety of solid foods, grows and develops normally. In Finland reimbursement for special formulas can be granted until 2 years of age, but many children can skip them already at around 1.5 years, even earlier. According to results from our national Allergy program, we could decrease unnecessary avoidance diets considerably by information. We grade CMA according to severity of symptoms and children with mild IgE associated symptoms are early encouraged to introduce baked milk and processed milk at home gradually and unnecessary long avoidance diets have been diminished clearly and hospital-based food challenges avoided. Also, important that AA formulas are not used when more palatable and much cheaper hydrolyzed formulas should be encouraged. We have managed to decrease their use also by legislation that there must be food-challenge proven reactions against hydrolyzed before AA formulas are reimbursed and hydrolyzed are reimbursed only when challenge to regular formulas provokes reactions.

However, we sometimes meet infants that have not been prescribed special formulas after proven CMA and are not growing well due to energy and protein shortage. If this is a European phenomenon, it could be useful to be asked for to spot guideline driven harms? I'm happy to comment your statements after your rounds.

Guideline Author Feedback 5 via Online meeting:

Scope of study and study protocol is appropriate.

22.19.9 Feedback from piloted Flowcharts

Area of Expertise	Diagnosis Flowchart	Management Flowchart
Paediatric Allergist	'Alternative cause such as reflux or infection more likely than milk allergy' box - could add spontaneous urticaria as a possibility. Could also add a footnote (main manuscript, not chart) that the age, previous dairy exposure/tolerance and duration of symptoms after an exposure are all relevant to considering whether an alternative cause is more likely. A lot of these were tried in the Delphi and consensus couldn't be reached - but a general statement could be useful and signpost to e.g. NICE food allergy guideline. 'Chronic symptoms' flow chart worked well but need to be careful it doesn't encourage biopsy (also highlighted by a consultant in the St Mary's team); acute symptoms flowchart also worked well. Need to ensure faltering growth is well-described as this might be overcalled too - for eg a slip of one centile. Refer to the bmj article.	Footnote for the WHO bit on the management chart - for women who have chosen not to breastfeed or where a fully-informed decision to not breastfeed is firmly established, that decision should be respected and supportive advice about safe formula feeding should be given where needed. In general I found they worked well, including the link between diagnosis flow chart and management flowchart.
Paediatric Allergy department including Dietetics	Need health visitor input - the dietitians think a lot of the diagnosis is made by health visitors They asked for us to clarify 'tolerating milk protein in similar forms'	Suggest signpost to reliable websites in the footnotes Suggest footnote 5 includes 'and iodine'

	Suggested changing 'without temporal' but struggled to find an alternative - 'symptoms not obviously connected with milk protein ingestion'? Need good link for footnote a about faltering growth e.g. to NICE guidance Biopsy a bit too prominent - could encourage unnecessary and risky biopsies 'non-human milk' doesn't work - best to put 'cow's milk' and then have a footnote explaining that this also applies to other mammalian milks such as sheep and goat. Could clarify a bit what non-human/cow's milk products are, in the 'milk products or formula' phrase. Scope (age group) needs to be made clearer	In footnote 2 (on the right) they suggest that the milk alternatives should be calcium fortified/enriched(e.g. organic plant milks in the UK are not calcium enriched so make poor substitutes) They weren't sure that everyone will recognise the term 'protein losing enteropathy' and requested a simpler term.
General Practitioner		I was confused about the management flowchart. Seems surprising that it starts with the words ‘advising maternal dietary restriction’ when this is what we are trying to avoid. For instance, “Has mother noticed relationship between her dietary intake and symptoms of eczema?” If yes, then “support mother if she wishes to restrict diet”. Shouldn’t we also add that there is no evidence for this and first step is to check eczema management? And why no mention of GI symptoms and behaviour here? I appreciate that this is the ‘management’ flowchart and not the ‘diagnosis’ one. But I don’t really get it.

		I also wonder whether we are making it too confusing by including children over 12m as well as infants under 12m, especially in the 2nd column. It keeps saying 'child' and yet I think that most of the suspected allergy we see is in infants.
General Practitioner	I think it would be useful to include some guidance on referral e.g. for faltering growth It sort of looks like the boxes beneath the symptoms boxes only apply to that symptom box - I don't think that's 100% clear either way. The information at the bottom of the diagnosis page is very useful - perhaps it could appear on a separate page and make things less busy?	I think it may be better split over two pages again but has some really good information. The management flowchart for CMPA looks a bit simpler and is more relevant to GPs with referral information and other additional info.
General Practitioner	However, as I'm sure you know, anything that takes you several minutes to read is unlikely to be actually used in a consultation. I wonder if it might be easier if you focused on a few key messages in addition to (or instead of) the flowcharts? From a quick look at the diagnosis one it seems like some of the key messages might be: Milk allergy is unlikely unless: • Symptoms recur following each episode of milk protein ingestion, OR • There is faltering growth or recurrent passage of visible blood	For the management one key messages might be: • Promote ongoing breastfeeding (with maternal dietary restriction if necessary) • Maternal dietary restriction only necessary if there is a clear relationship between infant symptoms and maternal diet or there is faltering growth or protein-losing enteropathy • Advise use of specialised formulas only for children <12 months who are not exclusively breast fed

	In terms of the flowcharts, I think they are good and reasonably clear. A couple of minor points: You use numbers for endnotes but also within the endnotes, which may be confusing. Suggest using letters for the endnotes instead. The endnotes are also confusing on the diagnosis one as it looks like the boxes relate only to the column above, but I don't think that is the case. Maybe reformat the boxes? Try and think of ways of simplifying it – it can seem a bit overwhelming at first with so many boxes.	
General Practitioner	Good to see explanation of common conditions such as colic etc and other causes and not always milk allergy I like the suggestion and signposting of what to act on urgently for other symptoms. It's a complex diagram for a complex condition how much time do you think it would take in a consultation ? Would this be better done online partly by the patient before or taken by a dietician with experience which could be ARRS role one rather than GP Often mums and parents stressed and tired and had multiple consultations with mixed messages and poor continuity and GPs time pressured but one longer consultation with consistent review might help so perhaps framing that	Good to see encouragement of breastfeeding Some parents may not be aware babies given formulae milk on maternity unit by staff, How much do the breastfeeding organisations know about supporting and possible allergy ? In reality some women though just don't want to breastfeed no matter what the diagnosis is. I'm not sure the algorithm recognises this - how big a percentage do you think that might be ? How many in the UK are continuing breast feeding for 2 years ? Agree with not recommending formulas for preventing allergy What is the time frame for organising the allergy tests etc in the units. Hopefully not that many mums requiring dietary avoidance advice - is that clear from diagram what is the percentage? As I think this varies by clinicians in their approach. Agree important to reintroduce but often difficult to achieve

	Would it be helpful to have mode of possible reaction higher in the headings IgE Non IgE etc	My experience is that this is often an emotive consultation with mums tired and feeling like a failure or with different beliefs and I think emotional support to the mothers important with questioning of the understanding important with no judgements so whilst promoting breast feeding important a pragmatic supportive approach also helpful. I'm not sure that is captured but you may have that somewhere else.
Health Visitor	Overall • Could the language be a little more inclusive - 'parent' rather than 'mother'? 'Feeding parent' in the case of breast/chestfeeding? Diagnosis flowchart: • 'Symptoms reproducible'. With a formula fed baby this is often hard to determine at first presentation. Obviously you have plenty of cow's milk protein in their milk which they will be having very frequently. So if the symptoms take longer than a few hours to appear as with a non-IGE mediated allergy, then they are typically already ingesting it again before first exposure is over, and it's my understanding that there may be some impact of layering or build-up of high levels of protein? Normally there's a long history of regular ingestion over a period of days or weeks before presentation. So what I'm trying to say is that there is not normally a sufficient gap to determine whether symptoms are being	Management flowchart: • 'Lactation specialist' would perhaps be better to specify an IBCLC since lactation specialist isn't a protected term. • Love the emphasis on supporting breast/chestfeeding. • Would it be worth including something around the risks of using CMP free formula in the absence of true allergy (do we have evidence this increase risk of atopy in future)? Exclusion diets: In my experience in practice, elimination trials with CMP free formula tend to be used rather than skin prick/serum testing. There's a few problems with these which you will obviously be aware of; • Placebo effect from parent to child. Symptoms are often non-specific and sometimes can self-resolve just with the parent feeling like they've done something, feeling like they've been listened to, feeling like they're in control again. So it can appear that the elimination diet is working even in the absence of a real allergy. Parent is often very resistant to reintroduction/challenge with dairy and this can then impact the validity of this as a test of reproducible symptoms in the same way.

	reproduced by subsequent ingestion or whether they are still reacting to the last time they were exposed? (see my below comments on elimination diet). • 'Tolerating milk protein in similar forms?' - I'm not sure what this would look like pre introduction of solid foods. Perhaps more useful for older babies? Or have I missed something obvious? • The third column 'without temporal relationship' has the same issue as I mentioned in point 1 - babies are ingesting very frequently. So I would guess this applies to older children? Or have I misunderstood and columns 2 and 3 should be considered together as part of the diagnosis for the more vague symptoms like crying/growth? • I love the 'important considerations' subtext - great to have the differentials there as a reminder.	• How much do you challenge with following an exclusion diet? 1 bottle of formula containing CMP? More? If only one bottle then is there a danger of missing allergies that only emerge with the build-up of protein? If more bottles then how long do you observe symptoms for? Danger of overdiagnosis from misinterpretation/attribution of common infant symptoms unrelated to the CMP. • For families mix feeding/combination feeding with breastmilk and formula - do we advise an elimination diet for the feeding parent too? If so then it can be difficult afterwards to explain that this isn't usually necessary with an allergy diagnosis, if not then can we be sure any symptoms aren't attributable to tiny amounts of CMP in the mother's milk? If we CAN be sure; because we are confident it's extremely unlikely to transfer in breastmilk in sufficient quantities to cause problems for the infant; then why does the option exist on the management flowchart to restrict mother's diet?! Essentially, I think most of the confusion and issues around diagnosis comes from the exclusion diet itself. I am wondering if these flowcharts were designed for use AFTER an exclusion diet? In which case it would be REALLY useful to have some guidance on when to trial this milk, how to run the elimination trial and how to run the subsequent food challenge. If this already exists I would love to know where! My worry is that it is the exclusion diets and problems with them that may contribute to the misdiagnosis/overdiagnosis of allergy. But perhaps that is a different/extra piece of work.
General Practice	We discussed the flow charts in practice today and the following points we hope are helpful: · 5 GP's (3 male, 2 female; age range 34-59 years) and one female PN participated	Management a. Surprised that breast feeding promotion not first drop down b. For children already using specialised formulae return to breast feeding considered unlikely

	· This guidance is very much welcomed and perceived independence regarded as very important · Key point was how to access once flowcharts completed and disseminated; laminated colour charts helpful but good on-line access where updates possible preferred · Charts are very 'busy' especially as I had printed in black and white but agreement is a complex area with no easy answers and no helpful suggestions bar noting the importance of presentation Diagnosis a. Relevant Age should be highlighted plus relevant websites where charts available from b. Double negatives confusing e.g. 'without milk' … 'No'…. c. For primary care practitioners, having too often diagnose and manage in one consultation, reference to diagnoses requiring additional investigations such as 'protein-losing enteropathy' 'low serum albumin' is unhelpful	c. As per point c above, reference to hospital based tests such as skin prick testing, decreases relevance to primary care d. Bottom right corner, where specialised formulae are referred to, be good to at least clarify what type of constituents and when e. Some advice on duration of maternal dietary restrictions welcome Again, very positive about perceived need and approach.
Community Dietetics	Five of us had the opportunity to use the flowcharts and the feedback was really positive. The comments are: • Fantastic detail in these two documents. • The diagnosis page is full of information, can it be broken down into three separate pages or	Management flowchart- • You might want to consider adding- exclusion for children over 1 with a fortified alternative milk and check if symptoms resolve, if not re-introduce. If resolved then start milk ladder. • On the management page– can you include the amount of calcium and vitamin D needed for Moms.

	2 as the third section does not overlap with the first 2?	• It might be good to define what milks have low cross reactivity with cow's milk • It would be fantastic if we could turn the diagnosis chart into some sort of AFCH questionnaire to use with parents in clinic • Overall great information and very useful.
Paediatric Allergy	Unfortunately, I was unable to run the pilot on patients. But I have discussed in our team meeting (including Pediatric Intensivists, Pediatric Gastroenterologists and Pediatric Allergist) about the flow charts. They all have agreed with the described flow and information. I think we should go ahead with the current flowcharts. Kindly add a paragraph about the replacement milks and other products which will suffice for appropriate growth in children who are having suspected or proven milk allergy.	
Community Dietician	These look great! And so much clearer than the existing guidelines.	Just wondering about the piece on maternal exclusion. Are you planning on mentioning other restrictions? If symptoms don't resolve after 2 weeks on a milk-free maternal exclusion what about adding other exclusions as suggested by the iMAP guidelines?
Community Paediatric Dieticians / Infant feeding Health Visitors / Community Midwives	Regarding Box "Milk Allergy does not need to be considered for these symptoms in infants, alone or combined": • we do see babies with allergy with those symptoms in the UK – sometimes blood in stools is one of the first presenting symptoms	Regarding "Blood in the stool can be caused by infection, clotting disorders or intestinal abnormalities" – this can also be caused by allergy Regarding "advise re-introduction of milk into maternal diet if a trial of 2 weeks has not resulted in resolution of symptoms": • In the UK we would usually trial for longer than 2 weeks

	• I consider diarrhoea and constipation in this category. They are well recognised potential symptoms of CMPA once other causes have been ruled out and I would consider them as differential diagnosis for CMPA. • Aversive feeding is something that we see in infants with CMPA, usually alongside reflux symptoms. Regarding "Colic and crying are common in healthy infants, but if severe these can be related to a wide range of health issue in the infant or their carer": • this statement needs clarity • more information please. • I'd like to know what these are- in a list for better clarity. I agree – it is rarely CMPA – but this doesn't give you any indication of what else to look at here. - ?refer to Health Visitor for parenting support as an initial intervention? Would this need to be a specialist infant feeding Health Visitor as it is difficult to be confident in supporting parents when there is the possibility of a medical cause? Regarding "Biopsy is not usually indicated for food allergy diagnosis due to procedural risks" • Again, the "not usually" is a statement we may want to change • Agree	• EAACI 2019 position statement and NICE recommends longer than 2 weeks to see a resolution of symptoms. Please could you clarify the shorter 2 week period that you suggest is long enough to exclude milk for. Is it possible that the worse the baby's symptoms are when the milk exclusion is started, the longer it may take to see a resolution – especially in the gut. Regarding "Ensure adequate maternal dietary intake of Calcium and Vitamin D": • What if they can't meet requirements through diet? • SACN recommends vitamin D supplement for breastfeeding mothers. This statements reads that calcium and vitamin D should only come from the diet, i.e.. food sources. • I would like to see clarity, how is maternal diet being assessed. We know in areas of high deprivation that diet will be adequate so this needs to be properly assessed, or should we always offer supplements and then mother can make her decision? • Very few areas have access to dietetic support at this point – I would rather prescribe to ensure there are no issues as we move forward. Regarding "For milk allergic infants over age 12 months who require a breastmilk substitute, plant-based milk alternatives or milk from animals with low cross-reactivity with cow's milk may also be considered, guided by a paediatric dietitian, where available": - Could you clarify which mammalian milks with low cross- reactivity is being referred to?

	• Don't like the wording of this…needs to be clear as parents could be confused if reading this guidance. • Biopsy would not be indicated in primary or secondary care – tertiary maybe.	
General Practitioner	The Diagnosis chart doesn't include "with or without mucus" in the blood in stool for temporal relationship	After 'Do not advise initiation or continuation of specialised formula" – doesn't tell us how to manage milk allergy in the > 12 months age group. Do we need to signpost to a guideline then? For clear diagnosis with diet and eczema, first step is support mother if wishes to restrict – Need to be clearer that this wouldn't be advised but can be supported
Adult allergy dietician	As you know, adults can, albeit rarely, present with an IgE-mediated allergy to milk, usually with severe allergic reactions. However, a more common presentation is GI symptoms 30-60 minutes after consuming milk due to lactose intolerance. So I wondered whether lactose intolerance needs to be considered as a differential diagnosis in the section of the flow chart dealing with symptoms within 2 hours of eating.	
Paediatric Allergist	1. There is no mention of constipation - a. Infrequent stooling e.g. once every 6-7 days with subsequent passage of a soft stool or	

	b. infrequent passage of a hard stool requiring Movicol. Both can be a feature of non-IgE mediated milk allergy. 2. Milk allergy CAN present with marked feeding aversion usually in association with reflux. Babies can stop feeding altogether if the diagnosis is missed 3. Chronic respiratory symptoms i.e. productive cough (reflux chest), chronic nasal congestion, recurrent respiratory /ENT infection regrettably CAN be secondary to cow's milk protein allergy. 4. There is rarely an observed temporal relationship of milk allergy in widespread moderate to severe eczema of early onset. The relationship only becomes clear once a trial of elimination and challenge has been completed alongside clearance of the eczema using topical steroids/treatments Happy to discuss further and/or present cases which illustrate these points. The above symptoms are common and I hear your concern re overdiagnosis. I am however acutely aware of under diagnosis which can cause considerable morbidity too. There is an evidence base for constipation. Minimal evidence base for 2 and 3. The fall out of group 3 is often considerable.	

22.20 Publication Licences

All peer-reviewed journal publications related to this thesis were open access CC-BY licence.

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