Dietary intake and risk of asthma in children and adults– protocol for a systematic review and meta-analysis

Dr Vanessa Garcia-Larsen PhD*, Respiratory Epidemiology, Occupational Medicine, and Public Health Group, National Heart and Lung Institute, Imperial College London, United Kingdom; v.garcialarsen@imperial.ac.uk

Dr Stefano R Del Giacco MD, Department of Medical Sciences "M Aresu", University of Cagliari, Italy; stedg@medicina.unica.it

Dr André Moreira MD PhD, Faculty of Medicine, University of Porto and Hospital São João, Portugal; andremoreira.fmup@gmail.com

Dr Matteo Bonini MD PhD Department of Public Health and Infectious Diseases, Lung Function Unit, Sapienza University of Rome; National Heart and Lung Institute, Imperial College London matte.bonini@gmail.com

Professor Tari Haahtela MD, Skin and Allergy Hospital, Helsinki University Central Hospital, Helsinki, Finland; Tari.Haahtela@haahtela.fi

Professor Sergio Bonini MD, European Medicines Agency, London, UK; Second University of Naples and IFT-CNR, Rome, Italy; se.bonini@gmail.com

Professor Kai-Håkon Carlsen MD PhD Department of Medicine and Allergology, University of Oslo, Norway; k.h.carlsen@medisin.uio.no

Dr Ioana Agache MD, Faculty of Medicine, Transylvania University, Brasov, Romania; ibrumaru@unitbv.ro

Dr João Fonseca MD PhD CINTESIS, Faculdade Medicina da Universidade do Porto and Imunoaergologia, CUF-Porto, Portugal; fonseca.ja@gmail.com

Professor Nikolaos G Papadopoulos MD PhD, Institute of Human Development, University of Manchester; Allergy Department, 2nd Paediatric Clinic, University of Athens, Greece; nikolaos.papadopoulos@manchester.ac.uk

Professor Luís Delgado MD PhD, Laboratory of Immunology, and CINTESIS (Centre for Health Technology and Services Research), Faculty of Medicine, University of Porto and Hospital São João, Porto, Portugal; ldelgado@med.up.pt

Key words - Asthma, wheeze, diet, nutrients, systematic review

*Corresponding author: Vanessa Garcia-Larsen

Imperial College London, Emmanuel Kaye Building, Manresa Road, London SW3 6LR, UK

Abstract

Background

Diet has been proposed to modulate the risk of asthma in children and adults. An increasing body of epidemiological studies have been published in the last year investigating the association between dietary intake and asthma. As part of the Evidence-Based Clinical Practice Guideline Task Force on 'Lifestyle Interventions in Allergy and Asthma' funded by the European Academy of Allergy and Clinical Immunology (EAACI), we will use a systematic approach to review the evidence from published scientific literature on dietary intake and asthma in children and adults.

Methods

This systematic review will be carried out following the PRISMA-P guidelines. The protocol has been published in PROSPERO (CRD42016036078). We will review the evidence from epidemiological studies in children (from the age of 2 years) and adults and dietary intake of foods and nutrients.

Discussion

The findings from this review will be used as a reference for guidelines recommendations

Keywords

Asthma, wheeze, diet, nutrients, antioxidants, children, adults, systematic review

Introduction

Since the late 60s, a sharp increase in the incidence of asthma was observed, which seems to have reached a plateau in the last 10 years in some countries [1], but it continues to rise in others [2]. Asthma prevalence and poor asthma control [3] represent a major problem of public health and a socio-economic burden, particularly in developed countries as well as in nations with fast growing economies where the highest rates of disease have been reported [3]. This trend has been accompanied by noticeable changes in lifestyle. Improved access to technology and development have led to a more sedentary life. Easier access to food and a shift in the eating patterns from naturally sourced to processed food have been accompanied by a reduced intake of fresh fruits and vegetables, less fibre, and an increased intake foods rich in refined sugar.

It is known that oxidative stress and airway inflammation are central features in the manifestation of asthma [4], which might be exacerbated by the poorer quality of the diet [5]. The possible effect of diet on asthma, particularly in relation to the role of dietary antioxidants and polyunsaturated fatty acids has been investigated in numerous observational studies [6]. Current evidence suggests that antioxidant vitamins C and E and a higher intake of fresh vegetables and fruits might have a protective effect on asthma, but most of the findings are still considered weak due to the cross-sectional design of the studies and the heterogeneity in diet assessment between studies [7]. Intervention trials have so far added little to understand the role of nutrients on asthma, which opens the question of whether the sources of nutrients matter (e.g. diet vs supplements). We recently completed an overview of high quality systematic reviews on diet and asthma [8] and found some evidence to suggest that intake of fruits and vegetables as well as adherence to a Mediterranean diet during childhood might reduce the risk of asthma in children. The evidence from studies in adults was less clear.

In this systematic review we aim to comprehensively assess the existing scientific literature on the relationship between exposure to dietary intake and the risk of asthma in children and adults published in the last five years. The number of studies has considerably increased since then. There have been few high quality systematic reviews (AMSTAR score ≥32) published since 2011 and none included both children and adults as target populations. We will not include maternal or infant dietary intake (solids or breastfeeding) as three large systematic reviews have just been completed covering these age groups (International Prospective Register of Systematic Reviews [PROSPERO http://www.crd.york.ac.uk/PROSPERO/search.asp] references CRD42013003802 – REVIEW A; CRD42013004239 – REVIEW B; CRD42013004252 – REVIEW C).

The scope of our Task Force is to provide evidence on dietary intake and dietary habits in relation to risk of asthma, wheeze (recurrent or persistent), and bronchial hyper-responsiveness (BHR). Our findings will serve as a reference for practical guidelines on dietary habits in susceptible and general population to reduce the risk and/or severity of asthma in children and adults. This systematic review will be carried out in line with the new PRISMA-P recommendation guidelines for high quality systematic reviews [9].

Objectives

The aim of this systematic review is to evaluate the association between dietary intake and risk of asthma in children and adults. To this end, we will seek to answer the following questions:

1. Does exposure to diet (as a whole, as grouped or individual foods) during childhood influence the risk of asthma during childhood or later in life?

2. Does exposure to diet (as a whole, as grouped or individual foods) in adults influence their risk of asthma later in life?

Methods

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs

We will include randomised controlled trials (RCT), quasi RCT, as well as cohort (prospective or retrospective) studies, nested case-control studies, other case-control studies and cross-sectional studies (including those with retrospective data)

Participants

We will investigate the role of diet on asthma in children from the age of 2 years old to adulthood. Participants of any age group within this range, unrestricted by disease severity, previous or current treatment, will be included

Interventions

The objective of this systematic review is to collate the evidence on intake of foods and nutrients on asthma as a baseline for guidelines, a decision was made *a-priori* to examine the evidence from studies that included actual food or nutrients (i.e. not supplements). Observational studies that used a dietary questionnaire to capture dietary intake will be included. Intervention studies with actual food rather than supplementation will also be included. Foods and nutrients will be classified, whenever possible, according to their nutritional properties and/or similarities.

Comparator(s)/control

All comparators will be included in the description of eligible studies. We will include report of different doses of forms of an exposure (e.g. frequency/total daily grams intake). For the studies that only report frequency of intake of foods we will report differences as binary comparisons e.g. weekly vs. never, daily vs. never.

Outcomes

The primary outcomes are asthma or wheeze. Acceptable definitions of asthma will include 'doctor diagnosed asthma', 'self-reported asthma', 'ever had asthma', 'persistent asthma', 'allergic asthma', 'atopic asthma', 'wheeze in the last 12 months', 'current wheeze', 'recurrent wheeze' or any other definition of asthma clearly documented in the selected study. Outcomes will be collected as reported. Due to possible variations in disease definitions, we will extract definitions of outcomes as reported in individual studies. We will extract outcomes in all data forms (e.g. dichotomous, continuous,) as reported in the included studies.

Timing

Eligible studies will be selected for inclusion regardless of the time length between exposure and outcome. Prospective and retrospective exposure will be considered, as well as cross-sectional.

Setting

There will be no restrictions by type of setting

Language

We will include articles reported in the English language. A list of possibly relevant titles in other languages will be provided as an appendix.

Exclusion criteria

This systematic review is centred on the role that diet might have on asthma outcomes, therefore the exclusion criteria applies to those factors listed below:

1. Non-comparative studies
2. Reviews
3. Non-human study
4. In vitro/In vivo studies
5. Chronic obstructive pulmonary disease (COPD)
6. Chronic bronchitis
7. Allergy/Food allergy
8. Eczema/atopic dermatitis
9. Atopy
10. Exposure in pregnancy (in utero)
11. Breastfeeding
12. Use of nutritional supplements not naturally extracted from the diet (e.g. capsules of vitamin a, C, E, fish oils, fish capsules, mineral, pro- and pre-biotic, or herbal supplementation)
13. Food challenge (e.g. white or red wine given as a food challenge rather than studied as usual intake)
14. Food avoidance for allergy prevention (i.e. antigen protein cow milk)
15. Nutrients measured in blood (serum or plasma)
16. Work related exposure to foods (e.g. bakery, bakers)
17. Occupational asthma
18. Obesity/weight loss [low calorie diets] /exercise
19. Indoor pollution (e.g. cooking gas)

20. Medication alone as treatment for asthma (e.g. corticosteroids, Montelukast, etc.) but medication combined or in parallel to food intake will be accepted
21. Asthma grouped with other diseases such as COPD or bronchitis
22. Sodium chloride/sodium 0.9% (as saline solution e.g. intravenous) but dietary or supplemented sodium will be included
23. Ethanol as intravenous or oral supplementation – consumption of alcohol will be accepted
24. Exposure to rural-related environmental risk factors that do not include any specific dietary exposures
25. Inhalation of milk proteins or aerosol-related food particles in the air
26. Studies in which participants where defined by a disease state (other than the relevant outcomes studied here) e.g. children or adults with specific nutritional deficiencies

Information sources

Literature search strategies have been developed using medical subject headings (MeSH) and text words related to asthma or wheeze. We will search MEDLINE (OVID interface), EMBASE (OVID interface), Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL; Wiley interface). The electronic database search will be supplemented by searching for trial protocols of food intervention by searching through metaRegister (http://www.controlled-trials.com/mrct/).

Search strategies

We will search for eligible studies published in the last 5 years (1st January 2011-2nd March 2016). The specific search strategies have been designed by VGL in collaboration with a Librarian at Imperial College with expertise in systematic review searching. The strategies were developed with input from the co-authors to ensure that relevant outcome and exposure

terms were included. The search strategies were also reviewed by a second Librarian, not involved in the project. The search strategies for MEDLINE, Web of Science and Cochrane Library is included in Appendix 1. Per reviewed abstracts presented in scientific conferences will also be screened. We will check if these were followed by the corresponding peer reviewed publication. The International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov will be searched for ongoing or recently completed trials. We will also search for studies in progress or completed but unpublished using http://apps.who.int/trialsearch/ . The bibliography of all selected eligible papers will be examined for potential relevant additional publications.

We will also separately search for existing systematic reviews published in the same period as in our review (2011-2016) which cover relevant exposures and outcomes. These findings will be used in the Discussion section as part of the interpretation of our findings.

Data management

Relevant study characteristics and results will be recorded in a spreadsheet file (excel). We will pilot the file to ensure that the descriptors are clear. A template has been prepared by the research team and a calibration exercise will be undertaken to pilot and refine the screening questions.

Selection process

Two members of the research team (VGL and SDG) will independently review titles and abstracts of all identified studies. The search strategies will be piloted and checked for completeness to ensure that as far as possible, all potentially eligible titles are captured. The full text of the paper will also be independently assessed by VGL and SDG, and will be assessed for eligibility against the inclusion and exclusion criteria. Any discrepancies will be resolved

through discussions with the research team. Electronic records will be kept regarding included and excluded studies for audit purposes, specifying reasons for any exclusion. Full text articles will be reviewed in duplicate (by two research team members – VGL and SDG), and studies for inclusion will be selected – any discrepancies will be resolved through discussions with the research team. The reasons for the exclusion of any relevant studies will be recorded. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

Data collection process

A pilot of the data extraction form will be undertaken using a minimum of 5 papers, after which the extraction form will be amended/updated as necessary. The data extraction form will be used to extract the relevant data fields from each included study independently (by two research team members - VGL and SDG). Data abstracted will include demographic information, methodology, intervention details, and all reported relevant outcomes. Reviewers will resolve disagreements by discussion, and one of two arbitrators (AM or LD) will adjudicate unresolved disagreements. We will contact study authors to resolve any uncertainties. Where appropriate data will be entered into STATA statistical software for meta-analysis.

Data items (exposures)

We will extract all effect estimates available for any dietary exposure studied, as well as all the relevant study characteristics to compile the PICO tables. If effect sizes cannot be calculated, we will report the results as a narrative. We anticipate to find wide variations in the way dietary data is recorded, both with regards to frequency of consumption and to levels of intake compared. Once the data is entered, we will group exposures according to similarities in time and comparison levels (e.g. weekly vs never; highest quintile of intake vs lowest). Data will be extracted either using raw values, crude estimates of effect (including odds ratios, risk ratios,

incidence rate ratios, hazard ratios, mean differences) or as adjusted estimates of effect. Adjusted estimates of effect will be used in preference, where available.

Outcomes and prioritisation

The primary outcome will be asthma or wheeze. In the case of pre-school children 'wheezing illness' will also be accepted as proxy definition for asthma. As a secondary outcome, we will include bronchial hyper-responsiveness (BHR). Lung function measurements will be included as outcomes only if used as a direct measure of asthma status, asthma control, or severity in patients with asthma. In children and adults, any established definition of asthma or wheeze will be accepted.

Risk of bias (quality) assessment

Study level bias

We will only include RCTs if these are food interventions (e.g. Mediterranean diet, high fruit intake intervention). If we identify any such trials, the risk of bias will be assessed using the Cochrane Collaboration risk of bias tool, which includes sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting, and other bias [10]. RCTs will be considered at low risk of bias where the risk of bias is judged to be low for all key domains of the Cochrane Handbook for Systematic Reviews of Interventions [11].

The risk of bias in observational studies will be assessed using the National Institute for Clinical Excellence Methodological Checklist for cohort, and case-control and cross-sectional studies, which includes considerations of subject selection, assessment of exposure and outcome, and measures to assess confounding [12]. Studies will be considered at low risk of bias where most of the criteria in the checklist are addressed, and those that are not addressed or not reported are judged unlikely to change the study findings. For both RCTs and cohort studies, a level of

<20% loss to follow up will generally be accepted as representing low risk of bias from incomplete outcome data, if there are no other features to suggest increased risk of bias. For all studies, a summary Table of Study Characteristics according to the PICO guidelines from NICE [13] will be presented for each relevant exposure and outcome, which will include a summary of each study's risk of bias, in addition to the population characteristics, methods used for assessing exposure and for outcome assessment.

Strategy for data synthesis

Separate analyses will be undertaken for each group of similar outcome assessment methods and for each intervention/exposure. Results for randomised or quasi-randomised controlled trials, prospective cohort or longitudinal studies, or where appropriate retrospective cohort studies, nested case-control studies, case-control and cross-sectional studies will be reported separately for each comparison. If the studies are sufficiently homogeneous in terms of design and comparator, we will conduct meta-analyses using a random-effects model.

Measures of treatment/exposure effect

Data from individual studies will be pooled using the generic inverse variance method. Pooled results for binary outcomes will be presented as relative risks s with 95% confidence intervals and 2-sided p values, and also expressed as risk differences where possible. Relevant results will be presented in Summary of Findings tables similar to those used by the Cochrane Collaboration. For dichotomous outcomes, we will use odds ratio (OR) with 95% confidence interval (CI).Continuous outcomes (e.g. BHR slope) will be analysed using weighted mean differences (with 95% CI) or standardised mean differences (95% CI) if different measurement scales are used. All analyses will be performed using STATA. Non-quantitative data will be presented descriptively.

Assessment of heterogeneity

We will examine the heterogeneity between studies by considering variability in participant factors (e.g. age, setting, type of diet or dietary exposure studied). Statistical heterogeneity will be quantified using I-squared (I^2; 0-40% might not be important; 30 to 60% may represent heterogeneity; >60% may represent moderate heterogeneity; >75% considerable heterogeneity).

Analysis of subgroups or subsets

Increased disease risk - studies of populations at increased risk for asthma will be separately analysed - for example children with a family history of atopic disease.

Narrative synthesis

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination.

Meta-bias assessment

Publication bias will be assessed using funnel plots and Egger's test. Where asymmetry is evident on the funnel plot, a trim and fill analysis will be used. Possible causes for asymmetry other than publication bias (e.g. between study heterogeneity) will also be considered.

Contributions

VGL is the study guarantor. VGL drafted the protocol following agreement with all co-authors on the scope and objectives set out for the systematic review. VGL developed the search strategies. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. All authors approved the final manuscript.

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Registration of protocol

This systematic review has been planned following the **PRISMA-P** guidelines and the protocol was registered on PROSPERO on 3 March 2016 (registration number CRD42016036078).

Conflict of interest

All authors declare no conflict of interest

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Appendix 1 Search strategies

MEDLINE and EMBASE (through OVID)

1. asthma.ab,ti.
2. Asthma/
3. wheeze.ab,ti.
4. wheezing.ab,ti.
5. bronchial hyperresponsiveness.ab,ti.
6. bronchial hyperreactivity.ab,ti.
7. Bronchial Hyperreactivity/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Diet/
10. Diet Therapy/
11. Nutritional Sciences/
12. diet.ab,ti.
13. diets.ab,ti.
14. Diet, Mediterranean/
15. mediterranean diet$.ab,ti.
16. dietetic.ab,ti.
17. dietary.ab,ti.
18. eating.ab,ti.
19. intake.ab,ti.
20. nutrient$.ab,ti.
21. nutrition.ab,ti.
22. vegetarian$.ab,ti.
23. vegan$.ab,ti.
24. macrobiotic.ab,ti.
25. Food/
26. food$.ab,ti.
27. cereal$.ab,ti.
28. grain$.ab,ti.
29. granary.ab,ti.
30. wholegrain.ab,ti.
31. wholewheat.ab,ti.
32. whole wheat.ab,ti.
33. roots.ab,ti.
34. tuber.ab,ti.

35. tubers.ab,ti.
36. vegetable$.ab,ti.
37. onion$.ab,ti.
38. spinach.ab,ti.
39. chard.ab,ti.
40. tomato$.ab,ti.
41. pepper$.ab,ti.
42. carrot$.ab,ti.
43. beetroot.ab,ti.
44. asparagus.ab,ti.
45. garlic.ab,ti.
46. pumpkin.ab,ti.
47. sprouts.ab,ti.
48. broccoli.ab,ti.
49. cabbage$.ab,ti.
50. ginger.ab,ti.
51. potato$.ab,ti.
52. olive$.ab,ti.
53. fruit$.ab,ti.
54. apple$.ab,ti.
55. pear$.ab,ti.
56. banana$.ab,ti.
57. orange$.ab,ti.
58. grape$.ab,ti.
59. kiwi$.ab,ti.
60. citrus.ab,ti.
61. grapefruit$.ab,ti.
62. pulses.ab,ti.
63. beans.ab,ti.
64. lentils.ab,ti.
65. chickpeas.ab,ti.
66. legume$.ab,ti.
67. soy.ab,ti.
68. soya.ab,ti.
69. nut.ab,ti.
70. nuts.ab,ti.
71. almond$.ab,ti.
72. peanut$.ab,ti.

73. groundnut$.ab,ti.
74. seeds.ab,ti.
75. meat.ab,ti.
76. beef.ab,ti.
77. pork.ab,ti.
78. lamb.ab,ti.
79. poultry.ab,ti.
80. chicken.ab,ti.
81. turkey.ab,ti.
82. duck.ab,ti.
83. fish.ab,ti.
84. fat.ab,ti.
85. fats.ab,ti.
86. fatty.ab,ti.
87. egg.ab,ti.
88. eggs.ab,ti.
89. bread.ab,ti.
90. oils.ab,ti.
91. omega.ab,ti.
92. shellfish.ab,ti.
93. seafood.ab,ti.
94. sugar.ab,ti.
95. syrup.ab,ti.
96. dairy.ab,ti.
97. milk.ab,ti.
98. yoghurt.ab,ti.
99. probiotic.ab,ti.
100. prebiotic$.ab,ti.
101. butter.ab,ti.
102. herbs.ab,ti.
103. spices.ab,ti.
104. chilli.ab,ti.
105. chillis.ab,ti.
106. condiments.ab,ti.
107. Beverages/
108. fluid intake.ab,ti.
109. water.ab,ti.
110. drinks.ab,ti.

111. drinking.ab,ti.
112. tea.ab,ti.
113. coffee.ab,ti.
114. caffeine.ab,ti.
115. juice$.ab,ti.
116. beer.ab,ti.
117. spirits.ab,ti.
118. liquor.ab,ti.
119. wine.ab,ti.
120. alcohol intake.ab,ti.
121. alcohol consumption.ab,ti.
122. beverage$.ab,ti.
123. yerba mate.ab,ti.
124. Food Preservation/
125. pickled.ab,ti.
126. bottled.ab,ti.
127. canned.ab,ti.
128. canning.ab,ti.
129. smoked.ab,ti.
130. preserved.ab,ti.
131. preservatives.ab,ti.
132. nitrosamine.ab,ti.
133. hydrogenation.ab,ti.
134. fortified.ab,ti.
135. nitrates.ab,ti.
136. nitrites.ab,ti.
137. ferment$.ab,ti.
138. processed.ab,ti.
139. antioxidant$.ab,ti.
140. genetic modif$.ab,ti.
141. genetically modif$.ab,ti.
142. Cooking/
143. cooking.ab,ti.
144. cooked.ab,ti.
145. grill.ab,ti.
146. grilled.ab,ti.
147. fried.ab,ti.
148. fry.ab,ti.

149. roast.ab,ti.
150. bake.ab,ti.
151. baked.ab,ti.
152. stewing.ab,ti.
153. stewed.ab,ti.
154. casserol$.ab,ti.
155. broil.ab,ti.
156. broiled.ab,ti.
157. boiled.ab,ti.
158. poach.ab,ti.
159. poached.ab,ti.
160. steamed.ab,ti.
161. barbecue$.ab,ti.
162. chargrill$.ab,ti.
163. Dietary Carbohydrates/
164. Dietary Proteins/
165. salt.ab,ti.
166. salting.ab,ti.
167. salted.ab,ti.
168. fiber.ab,ti.
169. fibre.ab,ti.
170. polysaccharide$.ab,ti.
171. starch.ab,ti.
172. starchy.ab,ti.
173. carbohydrate$.ab,ti.
174. lipid$.ab,ti.
175. linoleic acid$.ab,ti.
176. sugar$.ab,ti.
177. sweetener$.ab,ti.
178. saccharin$.ab,ti.
179. aspartame.ab,ti.
180. sucrose.ab,ti.
181. xylitol.ab,ti.
182. cholesterol.ab,ti.
183. hydrogenated dietary oils.ab,ti.
184. hydrogenated lard.ab,ti.
185. hydrogenated oils.ab,ti.
186. dietary protein.ab,ti.

187. dietary proteins.ab,ti.
188. protein intake.ab,ti.
189. animal protein$.ab,ti.
190. total protein$.ab,ti.
191. vegetable protein$.ab,ti.
192. plant protein$.ab,ti.
193. Vitamins/
194. vitamin$.ab,ti.
195. retinol.ab,ti.
196. carotenoid$.ab,ti.
197. tocopherol.ab,ti.
198. folate$.ab,ti.
199. folic acid.ab,ti.
200. methionine.ab,ti.
201. riboflavin.ab,ti.
202. thiamine.ab,ti.
203. niacin.ab,ti.
204. pyridoxine.ab,ti.
205. cobalamin.ab,ti.
206. mineral$.ab,ti.
207. sodium.ab,ti.
208. iron.ab,ti.
209. calcium.ab,ti.
210. selenium.ab,ti.
211. iodine.ab,ti.
212. magnesium.ab,ti.
213. potassium.ab,ti.
214. zinc.ab,ti.
215. copper.ab,ti.
216. phosphorus.ab,ti.
217. manganese.ab,ti.
218. chromium.ab,ti.
219. phytochemical.ab,ti.
220. polyphenol$.ab,ti.
221. phytoestrogen$.ab,ti.
222. genistein.ab,ti.
223. saponin$.ab,ti.
224. coumarin$.ab,ti.

225. flavonoid$.ab,ti.

226. polyphenol$.ab,ti.

227. flavonol$.ab,ti.

228. flavone$.ab,ti.

229. isoflavone$.ab,ti.

230. catechin$.ab,ti.

231. ascorbic acid$.ab,ti.

232. hydroxy cholecalciferol$.ab,ti.

233. hydroxycholecalciferol$.ab,ti.

234. tocotrienol$.ab,ti.

235. carotene$.ab,ti.

236. cryptoxanthin$.ab,ti.

237. lycopene$.ab,ti.

238. lutein$.ab,ti.

239. zeaxanthin$.ab,ti.

240. selenium$.ab,ti.

241. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240

242. analytical stud$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

243. exp Epidemiologic Studies/

244. exp Intervention Studies/

245. exp comparative study/

246. exp Follow-Up Studies/

247. exp Prospective Studies/

248. prospectiv$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

249. exp Cohort Studies/

250. cohort stud$.mp.

251. exp cross-sectional studies/

252. cross-sectional stud$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

253. birth cohort.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

254. exp Case-Control Studies/

255. case-control stud$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

256. etiology.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

257. trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

256. exp Clinical Trial/

258. clinical trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

259. exp Controlled Clinical Trial/

260. controlled clinical trial$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

261. exp Randomized Controlled Trial/

262. exp Placebos/

263. exp Random Allocation/

264. exp Double-Blind Method/

265. double-blind design.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

266. exp Single-Blind Method/

267. single-blind design.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

268. randomi?ed controlled trial.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

269. random$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

270. 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269

270. 8 and 241 and 270

271. limit 270 to humans

Cochrane Library

1. asthma:ab,ti
2. MeSH descriptor [Asthma] this term only
3. wheeze:ab,ti
4. wheezing:ab,ti
5. “bronchial hyperresponsiveness”:ab,ti
6. “bronchial hyperreactivity”:ab,ti
7. MeSH descriptor [Bronchial Hyperreactivity] this term only
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. MeSH descriptor [Diet] this term only
10. MeSH descriptor [Diet Therapy] this term only
11. MeSH descriptor [Nutritional Sciences] this term only
12. diet:ab,ti
13. diets:ab,ti
14. MeSH descriptor [Diet, Mediterranean] this term only
15. “mediterranean diet*”:ab,ti
16. dietetic:ab,ti
17. dietary:ab,ti
18. eating:ab,ti
19. intake:ab,ti
20. nutrient*:ab,ti
21. nutrition:ab,ti
22. vegetarian*:ab,ti
23. vegan*:ab,ti
24. macrobiotic:ab,ti

25. MeSH descriptor [Food] this term only
26. food*:ab,ti
27. cereal*:ab,ti
28. grain*:ab,ti
29. granary:ab,ti
30. wholegrain:ab,ti
31. wholewheat:ab,ti
32. “whole wheat”:ab,ti
33. roots:ab,ti
34. tuber:ab,ti
35. tubers:ab,ti
36. vegetable*:ab,ti
37. onion*:ab,ti
38. spinach:ab,ti
39. chard:ab,ti
40. tomato*:ab,ti
41. pepper*:ab,ti
42. carrot*:ab,ti
43. beetroot:ab,ti
44. asparagus:ab,ti
45. garlic:ab,ti
46. pumpkin:ab,ti
47. sprouts:ab,ti
48. broccoli:ab,ti
49. cabbage*:ab,ti
50. ginger:ab,ti
51. potato*:ab,ti
52. olive*:ab,ti
53. fruit*:ab,ti
54. apple*:ab,ti
55. pear*:ab,ti
56. banana*:ab,ti
57. orange*:ab,ti
58. grape*:ab,ti
59. kiwi*:ab,ti
60. citrus:ab,ti
61. grapefruit*:ab,ti
62. pulses:ab,ti

63. beans:ab,ti
64. lentils:ab,ti
65. chickpeas:ab,ti
66. legume*:ab,ti
67. soy:ab,ti
68. soya:ab,ti
69. nut:ab,ti
70. nuts:ab,ti
71. almond*:ab,ti
72. peanut*:ab,ti
73. groundnut*:ab,ti
74. seeds:ab,ti
75. meat:ab,ti
76. beef:ab,ti
77. pork:ab,ti
78. lamb:ab,ti
79. poultry:ab,ti
80. chicken:ab,ti
81. turkey:ab,ti
82. duck:ab,ti
83. fish:ab,ti
84. fat:ab,ti
85. fats:ab,ti
86. fatty:ab,ti
87. egg:ab,ti
88. eggs:ab,ti
89. bread:ab,ti
90. oils:ab,ti
91. omega:ab,ti
92. shellfish:ab,ti
93. seafood:ab,ti
94. sugar:ab,ti
95. syrup:ab,ti
96. dairy:ab,ti
97. milk:ab,ti
98. yoghurt:ab,ti
99. probiotic:ab,ti
100. prebiotic*:ab,ti

101. butter:ab,ti
102. herbs:ab,ti
103. spices:ab,ti
104. chilli:ab,ti
105. chillis:ab,ti
106. condiments:ab,ti
107. MeSH descriptor [Beverages] this term only
108. “fluid intake”:ab,ti
109. water:ab,ti
110. drinks:ab,ti
111. drinking:ab,ti
112. tea:ab,ti
113. coffee:ab,ti
114. caffeine:ab,ti
115. juice*:ab,ti
116. beer:ab,ti
117. spirits:ab,ti
118. liquor:ab,ti
119. wine:ab,ti
120. “alcohol intake”:ab,ti
121. “alcohol consumption”:ab,ti
122. beverage*:ab,ti
123. “yerba mate”:ab,ti
124. MeSH descriptor [Food Preservation] this term only
125. pickled:ab,ti
126. bottled:ab,ti
127. canned:ab,ti
128. canning:ab,ti
129. smoked:ab,ti
130. preserved:ab,ti
131. preservatives:ab,ti
132. nitrosamine:ab,ti
133. hydrogenation:ab,ti
134. fortified:ab,ti
135. nitrates:ab,ti
136. nitrites:ab,ti
137. ferment*:ab,ti
138. processed:ab,ti

139. antioxidant*:ab,ti
140. “genetic modif*”:ab,ti
141. “genetically modif*”:ab,ti
142. MeSH descriptor [Cooking] this term only
143. cooking:ab,ti
144. cooked:ab,ti
145. grill:ab,ti
146. grilled:ab,ti
147. fried:ab,ti
148. fry:ab,ti
149. roast:ab,ti
150. bake:ab,ti
151. baked:ab,ti
152. stewing:ab,ti
153. stewed:ab,ti
154. casserol*:ab,ti
155. broil:ab,ti
156. broiled:ab,ti
157. boiled:ab,ti
158. poach:ab,ti
159. poached:ab,ti
160. steamed:ab,ti
161. barbecue*:ab,ti
162. chargrill*:ab,ti
163. MeSH descriptor [Dietary Carbohydrates] this term only
164. MeSH descriptor [Dietary Proteins] this term only
165. salt:ab,ti
166. salting:ab,ti
167. salted:ab,ti
168. fiber:ab,ti
169. fibre:ab,ti
170. polysaccharide*:ab,ti
171. starch:ab,ti
172. starchy:ab,ti
173. carbohydrate*:ab,ti
174. lipid*:ab,ti
175. “linoleic acid*”:ab,ti
176. sugar*:ab,ti

177. sweetener*:ab,ti
178. saccharin*:ab,ti
179. aspartame:ab,ti
180. sucrose:ab,ti
181. xylitol:ab,ti
182. cholesterol:ab,ti
183. “hydrogenated dietary oils”:ab,ti
184. “hydrogenated lard”:ab,ti
185. “hydrogenated oils”:ab,ti
186. “dietary protein”:ab,ti
187. “dietary proteins”:ab,ti
188. “protein intake”:ab,ti
189. “animal protein*”:ab,ti
190. “total protein*”:ab,ti
191. “vegetable protein*”:ab,ti
192. “plant protein*”:ab,ti
193. MeSH descriptor [Vitamins] this term only
194. vitamin*:ab,ti
195. retinol:ab,ti
196. carotenoid*:ab,ti
197. tocopherol:ab,ti
198. folate*:ab,ti
199. “folic acid”:ab,ti
200. methionine:ab,ti
201. riboflavin:ab,ti
202. thiamine:ab,ti
203. niacin:ab,ti
204. pyridoxine:ab,ti
205. cobalamin:ab,ti
206. mineral*:ab,ti
207. sodium:ab,ti
208. iron:ab,ti
209. calcium:ab,ti
210. selenium:ab,ti
211. iodine:ab,ti
212. magnesium:ab,ti
213. potassium:ab,ti
214. zinc:ab,ti

215. copper:ab,ti

216. phosphorus:ab,ti

217. manganese:ab,ti

218. chromium:ab,ti

219. phytochemical:ab,ti

220. polyphenol*:ab,ti

221. phytoestrogen*:ab,ti

222. genistein:ab,ti

223. saponin*:ab,ti

224. coumarin*:ab,ti

225. flavonoid*:ab,ti

226. polyphenol*:ab,ti

227. flavonol*:ab,ti

228. flavone*:ab,ti

229. isoflavone*:ab,ti

230. catechin*:ab,ti

231. “ascorbic acid*”:ab,ti

232. “hydroxy cholecalciferol*”:ab,ti

233. hydroxycholecalciferol*:ab,ti

234. tocotrienol*:ab,ti

235. carotene*:ab,ti

236. cryptoxanthin*:ab,ti

237. lycopene*:ab,ti

238. lutein*:ab,ti

239. zeaxanthin*:ab,ti

240. selenium*:ab,ti

241. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or

223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240

242. “analytical stud*”:ab,ti

243. MeSH descriptor [Epidemiologic Studies] explode all trees

244. MeSH descriptor [Intervention Studies] explode all trees

245. MeSH descriptor [comparative study] explode all trees

246. MeSH descriptor [Follow-Up Studies] explode all trees

247. MeSH descriptor [Prospective Studies] explode all trees

248. prospectiv*:ab,ti

249. MeSH descriptor [Cohort Studies] explode all trees

250. “cohort stud*”:ab,ti

251. “birth cohort”:ab,ti

252. MeSH descriptor [Case-Control Studies] explode all trees

253. “case-control stud*”:ab,ti

254. etiology:ab,ti

255. trial:ab,ti

256. MeSH descriptor [Clinical Trial] explode all trees

257. “clinical trial”:ab,ti

258. MeSH descriptor [Controlled Clinical Trial] explode all trees

259. “controlled clinical trial*”:ab,ti

260. MeSH descriptor [Randomized Controlled Trial] explode all trees

261. MeSH descriptor [Placebos] explode all trees

262. MeSH descriptor [Random Allocation] explode all trees

263. MeSH descriptor [Double-Blind Method] explode all trees

264. “double-blind design”:ab,ti

265. MeSH descriptor [Single-Blind Method] explode all trees

266. “single-blind design”:ab,ti

267. “randomi?ed controlled trial”:ab,ti

268. random*:ab,ti

269. 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268

270. 8 and 241 and 269

ISI Web of Science

1. Topic=(asthma or wheeze or wheezing or “bronchial hyperresponsiveness” or “bronchial hyperreactivity”)

2. Topic=(diet or diets or “mediterranean diet*” or dietetic or dietary or eating or intake or nutrient* or nutrition or vegetarian* or vegan* or macrobiotic or food* or cereal* or grain* or

granary or wholegrain or wholewheat or "whole wheat" or roots or tuber or tubers or vegetable* or onion* or spinach or chard or tomato* or pepper* or carrot* or beetroot or asparagus or garlic or pumpkin or sprouts or broccoli or cabbage* or ginger or potato* or olive* or fruit* or apple* or pear* or banana* or orange* or grape* or kiwi* or citrus or grapefruit* or pulses or beans or lentils or chickpeas or legume* or soy or soya or nut or nuts or almond* or peanut* or groundnut* or seeds or meat or beef or pork or lamb or poultry or chicken or turkey or duck or fish or fat or fats or fatty or egg or eggs or bread or oils or omega or shellfish or seafood or sugar or syrup or dairy or milk or yoghurt or probiotic or prebiotic* or butter or herbs or spices or chilli or chillis or condiments or "fluid intake" or water or drinks or drinking or tea or coffee or caffeine or juice* or beer or spirits or liquor or wine or "alcohol intake" or "alcohol consumption" or beverage* or "yerba mate" or pickled or bottled or canned or canning or smoked or preserved or preservatives or nitrosamine or hydrogenation or fortified or nitrates or nitrites or ferment* or processed or antioxidant* or "genetic modif*" or "genetically modif*" or cooking or cooked or grill or grilled or fried or fry or roast or bake or baked or stewing or stewed or casserol* or broil or broiled or boiled or poach or poached or steamed or barbecue* or chargrill* or salt or salting or salted or fiber or fibre or polysaccharide* or starch or starchy or carbohydrate* or lipid* or "linoleic acid*" or sugar* or sweetener* or saccharin* or aspartame or sucrose or xylitol or cholesterol or "hydrogenated dietary oil*" or "hydrogenated lard" or "hydrogenated oil*" or "dietary protein*" or "dietary protein*" or "protein intake" or "animal protein*" or "total protein*" or "vegetable protein*" or "plant protein*" or vitamin* or retinol or carotenoid* or tocopherol or folate* or "folic acid" or methionine or riboflavin or thiamine or niacin or pyridoxine or cobalamin or mineral* or sodium or iron or calcium or selenium or iodine or magnesium or potassium or zinc or copper or phosphorus or manganese or chromium or phytochemical or polyphenol* or phytoestrogen* or genistein or saponin* or coumarin* or flavonoid* or polyphenol* or flavonol* or flavone* or isoflavone* or catechin* or "ascorbic acid*" or "hydroxy cholecalciferol*" or hydroxycholecalciferol* or tocotrienol* or carotene* or cryptoxanthin* or lycopene* or lutein* or zeaxanthin* or selenium*)

3. Topic=("analytical stud*" or "Epidemiologic Stud*" or "Intervention Stud*" or "cross-sectional stud*" or "comparative stud*" or "Follow-Up Stud*" or "Prospective Stud*" or "cohort stud*" or "birth cohort" or "case-control stud*" or "clinical trial*" or "controlled clinical trial*" or Placebo$ or "double-blind design*" or "single-blind design*" or "randomi$ed controlled trial")