BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants

Dagfinn Aune,[1,2] Abhijit Sen,[1] Manya Prasad,[3] Teresa Norat,[2] Imre Janszky,[1] Serena Tonstad,[3] Pål Romundstad,[1] Lars J Vatten[1]

[1]Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Epidemiology and Biostatistics, Imperial College, London, UK

[3]Department of Community Medicine, Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India

[4]Section of Preventive Cardiology, Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital Ullevål, Oslo, Norway

Correspondence to: D Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London W2 1PG, UK d.aune@imperial.ac.uk

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ABSTRACT

OBJECTIVE

To conduct a systematic review and meta-analysis of cohort studies of body mass index (BMI) and the risk of all cause mortality, and to clarify the shape and the nadir of the dose-response curve, and the influence on the results of confounding from smoking, weight loss associated with disease, and preclinical disease.

DATA SOURCES

PubMed and Embase databases searched up to 23 September 2015.

STUDY SELECTION

Cohort studies that reported adjusted risk estimates for at least three categories of BMI in relation to all cause mortality.

DATA SYNTHESIS

Summary relative risks were calculated with random effects models. Non-linear associations were explored with fractional polynomial models.

RESULTS

230 cohort studies (207 publications) were included. The analysis of never smokers included 53 cohort studies (44 risk estimates) with >738 144 deaths and >9 976 077 participants. The analysis of all participants included 228 cohort studies (198 risk estimates) with >3 744 722 deaths among 30 233 329 participants. The summary relative risk for a 5 unit increment in BMI was 1.18 (95% confidence interval 1.15 to 1.21; I^2=95%, n=44) among never smokers, 1.21 (1.18 to 1.25; I^2=93%, n=25) among healthy never smokers, 1.27 (1.21 to 1.33; I^2=89%, n=11) among healthy never smokers with exclusion of early follow-up, and 1.05 (1.04 to 1.07; I^2=97%, n=198) among all participants. There was a J shaped dose-response relation in never smokers ($P_{non\text{-}linearity}$ <0.001), and the lowest risk was observed at BMI 23-24 in never smokers, 22-23 in healthy never smokers, and 20-22 in studies of never smokers with ≥20 years' follow-up. In contrast there was a U shaped association between BMI and mortality in analyses with a greater potential for bias including all participants, current, former, or ever smokers, and in studies with a short duration of follow-up (<5 years or <10 years), or with moderate study quality scores.

CONCLUSION

Overweight and obesity is associated with increased risk of all cause mortality and the nadir of the curve was observed at BMI 23-24 among never smokers, 22-23 among healthy never smokers, and 20-22 with longer durations of follow-up. The increased risk of mortality observed in underweight people could at least partly be caused by residual confounding from prediagnostic disease. Lack of exclusion of ever smokers, people with prevalent and preclinical disease, and early follow-up could bias the results towards a more U shaped association.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A high BMI is associated with increased risk of all cause mortality

A recent meta-analysis found a reduced risk with overweight and that only obesity grade 2 (BMI ≥35) increased risk, but the results could have been confounded by smoking and prevalent and prediagnostic disease and biased because of exclusion of many large cohort studies

WHAT THIS STUDY ADDS

In never smokers and healthy never smokers, there was a J shaped association between BMI and mortality, and the lowest risk was observed at BMI 23-24 and 22-23, respectively

When analysis was restricted to studies with a longer duration of follow-up (to reduce confounding by prediagnostic weight loss) the lowest risk was observed with BMI 20-22

Lack of exclusion of ever smokers, people with prevalent and prediagnostic disease, or early follow-up could bias the associations between BMI and mortality towards a more U shaped association

Introduction

The prevalence of overweight and obesity has increased rapidly over the past decades throughout the world.[1] This has raised serious public health concerns because of the association between overweight and obesity and increased risk of a wide range of chronic diseases, including cardiovascular diseases,[2] type 2 diabetes,[3] several types of cancer,[4-8] gallbladder disease,[9] gout,[10] osteoarthritis,[11] and several other conditions, [11-13] as well as all cause mortality.[2 14]

Though many studies have shown an increased risk of all cause mortality with greater adiposity as measured by body mass index (BMI),[15-24] questions remain about the shape of the dose-response relation. Several large scale prospective studies[15-24] and pooled analyses (each with 900 000 to 1.46 million participants)[2 14 25] have reported increased risk of all cause mortality with greater BMI, and most of these found the lowest risk among participants with BMI in the range of 20 or 22.5 to 24.9. A large meta-analysis of 97 cohort studies with 2.88 million participants and 270 000 deaths, which used the WHO cut-off points for overweight and obesity, however, found summary hazard ratios of 0.94 (95% confidence interval 0.90 to 0.97), 0.97 (0.90 to 1.04), and 1.34 (1.21 to 1.47) for a BMI of 25-<30, 30-<35, and ≥35, respectively, suggesting a protective effect of overweight

on mortality and that only severely obese people are at increased risk of mortality.[26] That review, however, had several limitations—for example, it excluded several large and some smaller studies including >5.4 million participants and >1.1 million deaths that used more refined categorisations of BMI than the WHO categorisations.[15 16 18-20 24 27-54] Thus more deaths and participants were excluded than included in the analysis, and questions have been raised with regard to the validity of the findings.[55] In addition, a large number of additional cohorts were either missed by the search or excluded from the analysis,[56-65] and at least 53 additional studies have since been published, including >2.3 million deaths and >21.6 million participants.[23 24 65-115] An updated analysis is therefore warranted.

It is well known that smoking strongly increases risk of mortality and many specific causes of death,[116 117] and there is therefore a great potential for residual confounding by smoking as it is typically also associated with lower weight.[118] Indeed, many studies have reported a different shape of the dose-response relation between BMI and mortality when the analysis is restricted to people who have never smoked or in comparisons between smokers and never smokers,[2 14-22 24 77] but this was not adequately dealt with in the previous meta-analysis.[26] Furthermore, confounding by prevalent or undiagnosed illness could also have biased the results. It is well known that many chronic diseases (which increase the risk of death) lead to weight loss.[119] Weight loss can precede a diagnosis of disease by many years and because of such preclinical weight loss the associations between low BMI and increased mortality might at least partly be caused by confounding by preclinical disease.[120] Such bias might be avoided by the exclusion of people with prevalent disease at baseline, by exclusion of the early follow-up period of the studies, and by stratifying studies by duration of follow-up, but the most recent meta-analysis did not conduct such subgroup or sensitivity analyses.[26]

For these reasons we conducted a systematic review and dose-response meta-analysis of published cohort studies to clarify the strength and the shape of the dose-response relation between BMI and all cause mortality, the potential confounding effects of smoking, and whether prevalent disease, exclusion of early follow-up, or stratification by duration of follow-up, or the quality of the studies influenced the association between BMI and all cause mortality. We used fractional polynomial models to assess the association between BMI and mortality, and this allowed for inclusion of all relevant studies reporting results for three or more categories of BMI and not only those reporting results using the WHO criteria for categorisation of BMI.

Methods

Search strategy and inclusion criteria

We searched PubMed and Embase up to 23 September 2015 for eligible studies (DA, AS), using wide search terms (appendix 1). We followed standard criteria for conducting and reporting meta-analyses.[121] In addition, we searched the reference lists of a previous meta-analysis[26] for further studies. Study quality was assessed with the Newcastle-Ottawa scale.[122]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Study selection

We included cohort studies of the association between BMI and risk of all cause mortality published in English language and excluded abstract only publications and grey literature. In each publication, adjusted relative risk estimates (hazard ratios or risk ratios) for three or more BMI categories had to be available, either with the 95% confidence intervals or with the information to calculate them. The dose-response analysis, a quantitative measure of the exposure (BMI), also had to be available. Studies from populations living in the community were included, while studies that included only patients (for example, those with diabetes, stroke, heart disease, and cancer), nursing home residents, and disabled people were excluded. When multiple publications were published from the same study, in general we used the publication with the largest number of deaths. Exceptions to this rule were made when publications with smaller number of deaths provided more detailed analyses with restriction to never smokers, healthy people, and/or exclusion of early follow-up than the publications with larger number of deaths. In the analysis of never smokers, the definition of never smokers was strict so we did not include data from studies that combined never smokers and former smokers who had quit for a long duration. When more detailed analyses (restricted to never smokers or other subgroups) were published in an overlapping publication but not in the publication used for the main analysis we used the information from the overlapping publication in the specific analysis, but each study was included only once in each analysis. Studies that reported only a continuous linear risk estimate were excluded as there is evidence that the association between BMI and mortality is non-linear. A list of the excluded studies and reasons for exclusion is provided in table A in appendix 2.

Data extraction

We extracted the following data from each study: the first author's last name, publication year, country or region where the study was conducted, study period, sample size, number of deaths/participants, whether exclusions were made for prevalent disease, whether exclusions were made for early follow-up, BMI and any subgroup, exposure level, relative risks and 95% confidence intervals for categories of BMI, and variables adjusted for in the analysis. One author (DA) extracted data, and another author (MP) checked them for accuracy. For one study[16] we contacted the authors for clarification of which studies were included in the analysis.

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Statistical methods

We used a random effects model to calculate summary relative risks and 95% confidence intervals for a 5 unit increment in BMI.[123] For the primary analysis we used the model from each study that had the greatest degree of control for potential confounding, with the exception of studies that also adjusted mutually between BMI and waist circumference and waist to hip ratio or that adjusted for potentially intermediate variables such as diabetes, hypertension, and serum cholesterol, for which we used the multivariate model without such adjustment if available. If the alternative model was adjusted only for age and the multivariate model included other confounders as well, we chose the multivariate model with intermediates. We estimated the average of the natural logarithm of the relative risks and weighted the relative risk from each study according to the method of DerSimonian and Laird.[123] A two tailed P<0.05 was considered significant. If studies reported results separately for men and women or other subgroups we combined the subgroup specific estimates using a fixed effects model to generate an estimate for both subgroups combined so that each study was represented only once in the analyses.

We used the method described by Greenland and Longnecker[124] for the linear dose-response analysis of BMI and mortality and calculated study specific slopes (linear trends) and 95% confidence intervals from the natural logs of the reported relative risks and confidence intervals across categories of BMI. When the reference category was not the lowest category (because, for example, of power issues) we excluded the categories below the reference category for the linear dose-response analysis to model the association between higher BMI and mortality. The mean or median BMI level in each category was assigned to the corresponding relative risk for each study, and for studies that reported the exposures in ranges we used the midpoint of the upper and the lower cut-off point. When upper and lower categories were open ended or had extreme upper or lower values, we used the width of the adjacent category to calculate an upper or lower bound. When studies reported analyses by the WHO categories of overweight and obesity we used a BMI of 15 as a lower bound for the underweight category (<18.5) and 18.5 as the lower bound for the normal weight category (<25). A potential non-linear dose-response relation between BMI in relation to mortality was examined by using fractional polynomial models.[125] We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test assessed the difference between the non-linear and linear models to test for non-linearity.[125] For the non-linear dose-response analysis we included all categories of BMI (even the underweight categories) to model the association between BMI and mortality across the full BMI range and used the method of Hamling and colleagues to convert risk estimates when the lowest category was not the reference category.[126] The analyses were re-scaled so the reference category was a BMI of 23, which seemed to be the nadir of the curve among never smokers, so there was no loss of statistical power from these re-calculations. The fractional polynomial method estimated a dose-response curve for each study across the BMI values observed in the whole dataset (which was extrapolated across the full BMI range for studies with a limited BMI range), so all studies contributed to the pooled risk estimates across the full BMI range. The dose-response curves for each of the individual studies were then pooled into an overall dose-response curve, which are the curves showed in the non-linear figures. The relative risk estimates in the tables were based on the non-linear figures but show risk estimates for selected BMI values.

We conducted subgroup and meta-regression analyses to investigate potential sources of heterogeneity and heterogeneity between studies quantitatively assessed by the Q test and I^2.[127] Small study effects, such as publication bias, were assessed by inspection of the funnel plots for asymmetry and with Egger's test[128] and Begg's test,[129] with the results considered to indicate small study effects when P<0.10. To avoid potential confounding by smoking we present results on BMI and mortality in never smokers as the primary analysis, and conducted further restrictions to healthy never smokers and healthy never smokers with exclusion of the early follow-up in supplementary analyses (here and throughout, healthy never smokers refers to never smokers who were healthy at baseline). We also report results among all participants (not excluding smokers) for comparison with the most recent meta-analysis[26] and in smokers in secondary analyses. Further subgroup analyses were conducted by sex, method of assessment of weight and height, duration of follow-up, geographical location, number of deaths, study quality and adjustment for confounders, adjustment for mediators, and restriction to studies with appropriate adjustment for age, smoking, alcohol, and physical activity, but without adjustment for prevalent disease or intermediate factors. Because we did not have access to the original data and because not every study excluded early follow-up we also conducted analyses stratified by duration of follow-up to investigate the influence of undiagnosed disease on the results. As the number of deaths increases with increasing duration of follow-up, the early follow-up (when participants with undiagnosed disease most likely would have died) will account for a smaller and smaller proportion of the total deaths the longer the duration of follow-up is. As preclinical weight loss can precede the diagnosis of disease by many years, stratification by duration of follow-up can allow for assessments of the longer term impact of confounding by undiagnosed disease. We used Stata, version 12.0 (Stata Corp, College Station, TX) for the statistical analyses.

Results

From a total of 112 173 records identified by the search we included 207 publications[16-24 27-54 56-115 130-239] with 230 cohort studies including >3 748 549 deaths among 30 361 918 participants in the meta-analysis of BMI and risk of all cause mortality (table B in appendix 2; fig 1). Table 1 summarises the main characteristics (number of

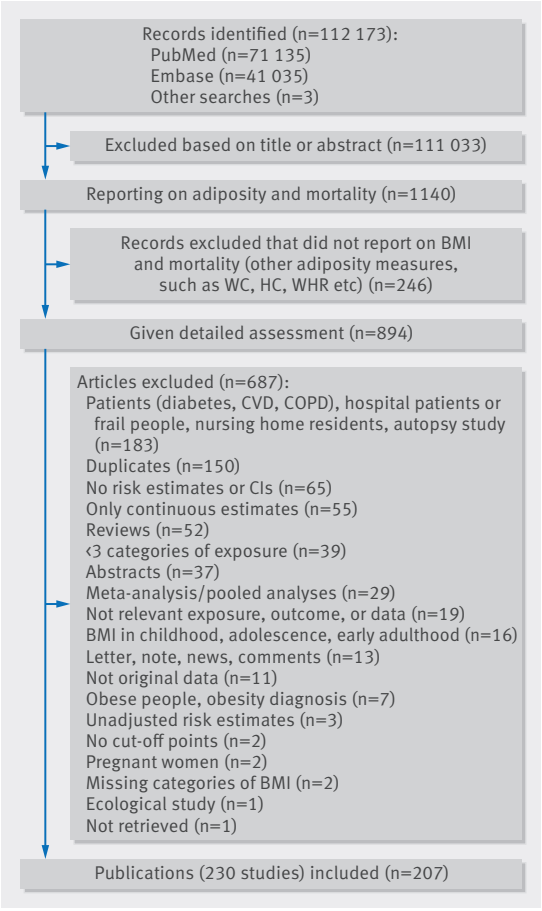

Fig 1 | Flow chart of study selection in systematic review and non-linear dose-response meta-analysis of BMI and all cause mortality

Table 1 | Key characteristics of studies included in review of BMI and all cause mortality in never smokers and all participants

	Never smokers	All participants
No of studies (risk estimates)	53 (44)	228 (198)
No of deaths	>738 144	>3 744 722
No of participants	>9 981 558	30 233 329
No of studies (risk estimates) by geographical location:		
North America	22 (20)	70 (67)
South America	0 (0)	3 (3)
Europe	18 (11)	96 (69)
Australia	2 (2)	9 (9)
Asia	11 (11)	49 (49)
Pacific	0 (0)	1 (1)
No of studies (risk estimates) by study size:		
<1000	2 (2)	15 (12)
1000-<10 000	13 (13)	92 (90)
10 000-<100 000	20 (18)	89 (71)
100 000-<1 000 000	14 (7)	20 (20)
≥1 000 000	1 (1)	12 (5)
Missing	3 (3)	0 (0)
Range of study size	441-7 436 748	162-12 832 637
Mean, median	243 453, 20 346	152 694, 8876
Duration of follow-up:		
Range of follow-up (years)	3.9-35	2-42
Mean, median (years)	14.2, 12	13.8, 12

studies, cases, and participants, geographical location, study size, and mean or median duration of follow-up) of the studies included in the analysis of never smokers and among all participants. Some publications reported on or included data from more than one study (which were analysed as one combined dataset); one publication included data from nine studies,[138] and another publication included eight cohort studies that were combined in one analysis,[16] one publication reported results from six studies that were combined,[95] five publications reported results from three studies that were combined,[74 140 142 150 178] four publications reported results from two studies,[163 170 189 191] which were included in the analysis. Four publications reported on men and women separately from the same two studies.[30 31 131 132] Two duplicate publications were included only in subgroup analyses by sex[229 235] as the main article provided only results for both sexes combined[140] or because the duplicate publication had a longer follow-up.[235] That publication was not used for the main analysis as it reported only on women, while the main publication reported on both men and women.[166] One publication was included only in the analysis of African Americans[237] as the main publication reported results from the full population.[17]

Ninety six studies were from Europe, 71 were from North America, three were from Latin or South America, 49 were from Asia, 10 were from Australia and New Zealand, and one was from the Pacific region (table B in appendix 2). Of the 198 risk estimates included in the non-linear dose-response analysis among all participants, 38 (19.2%) had three categories of BMI, 61 (30.8%) had four categories, 47 (23.7%) had five categories, 17 (8.6%) had six categories, 15 (7.6%) had seven categories, four (2%) had eight categories, 10 (5.1%) had nine categories, and six (3%) had 10 or more categories. Of the 44 risk estimates among never smokers, five (11.4%) had three categories of BMI, five had four categories (11.4%), 13 (29.6%) had five categories, four (9%) had six categories, three (6.8%) had seven categories, four (9%) had eight categories, five (11.4%) had nine categories, and five (11.4%) had 10 or more categories.

BMI and mortality among never smokers and healthy never smokers

We included 53 cohort studies (43 publications, 44 risk estimates)[16-22 24 27 30 31 33 36 38 48 49 51 62 77 94 96 107 131 132 140 159 166 178-180 183 185 187 188 201 221 228 230 231 234 236 238 239] with >738 144 deaths and >9 976 077 participants in the analysis of never smokers. The summary relative risk for a 5 unit increase in BMI was 1.18 (95% confidence interval 1.15 to 1.21; I^2=95%, $P_{heterogeneity}$<0.001; fig A in appendix 3). There was no evidence of publication bias with Egger's test (P=0.67) or Begg's test (P=0.66) (fig B in appendix 3). There was evidence of non-linearity (P<0.001), and there was a J shaped association between BMI and mortality in never smokers with the lowest mortality observed with a BMI of 23-24 (fig 2). Table 2 shows the relative risk estimates from the non-linear dose-response analysis for selected BMI values, and these are derived from the non-linear figures. The association was similar in men and in women

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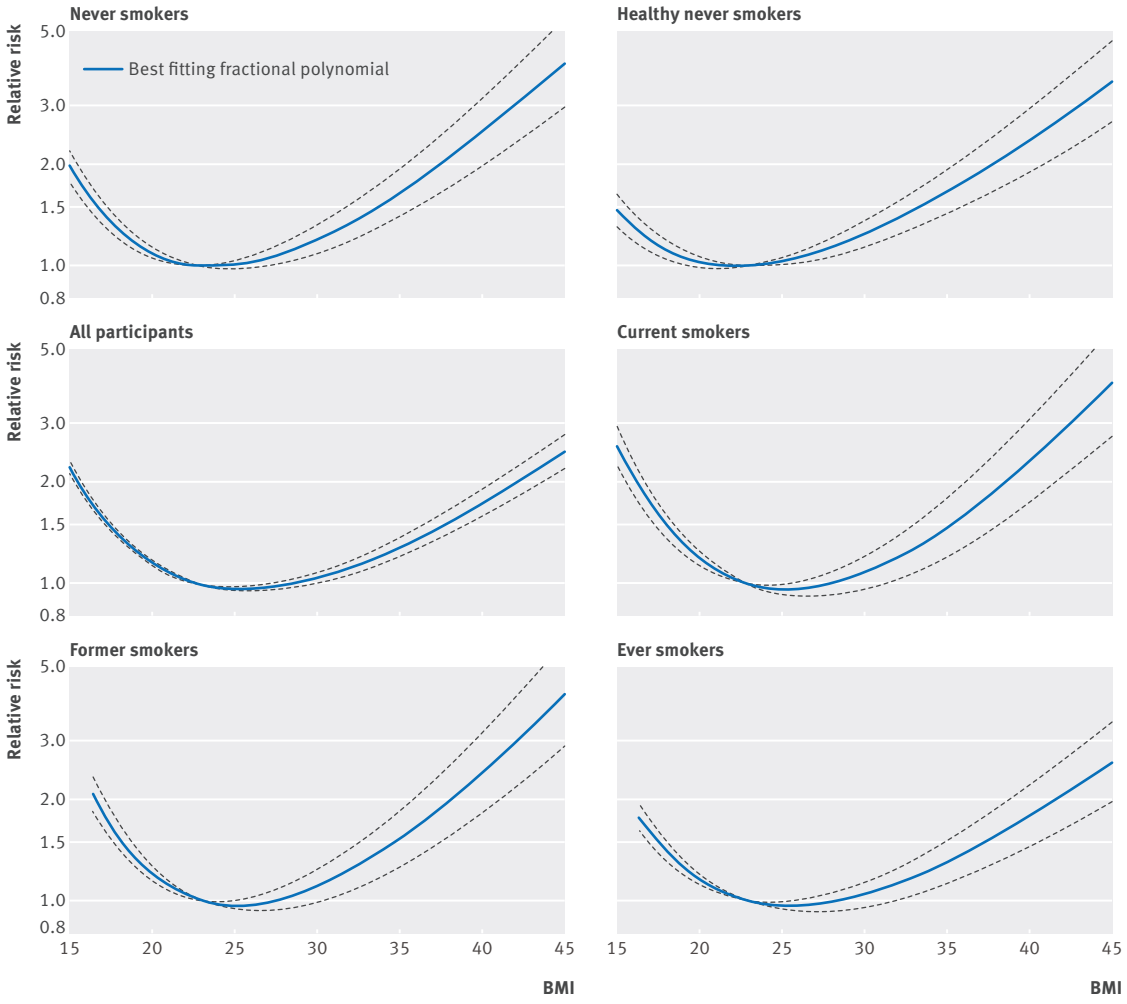

Fig 2 | **Non-linear dose-response analysis of BMI and all cause mortality among never smokers, healthy never smokers, all participants, current, former, and ever smokers**

(tables C and D in appendix 2). In an analysis of five studies of African American people who had never smoked,[22 24 94 96 237] the summary relative risk was 1.13 (1.10 to 1.17) for a 5 unit increase in BMI (fig C in appendix 3), and there was evidence of a J shaped association ($P_{non\text{-}linearity}<0.001$; fig D in appendix 3).

We included 26 cohort studies (25 publications, 25 risk estimates) [18 19 20 21 22 24 27 30 38 48 51 77 94 131 132 140 159 178 180 183 185 188 228 236 238] with >74 464 deaths among 727 687 participants in the analysis of healthy never smokers (which in general excluded people with prevalent cancer, cardiovascular disease, and in some cases diabetes, and/or people with recent weight loss). The summary relative risk for a 5 unit increment in BMI was 1.21 (95% confidence interval 1.18 to 1.25; I^2=93%, $P_{heterogeneity}<0.001$; fig E in appendix 3, table 2). There was evidence of non-linearity (P<0.001), and there was a J shaped association between BMI and mortality in healthy people who had never smoked with the lowest mortality observed with a BMI of 22-23 (fig 2). Further restriction of the analysis to 11 studies[18 19 21 24 27 30 51 185 228 229 238] among healthy people who had never smoked (88 860 deaths, 1 192 443 participants), which also excluded early follow-up (from first year up to six years of follow-up) gave a summary relative risk of 1.27 (1.21 to 1.33; I^2=89%, $P_{heterogeneity}<0.001$; fig F in appendix 3).

BMI and all cause mortality (all participants)

We included 228 cohort studies (191 publications, 198 risk estimates)[16-24 27-29 32-54 56-76 78-115 130-227] in the analysis of BMI and risk of all cause mortality and included a total of >3 744 722 deaths among 30 233 329 participants. The summary relative risk for a 5 unit increase in BMI was 1.05 (95% confidence interval 1.04 to 1.07; I^2=97%, $P_{heterogeneity}<0.001$; fig G in appendix 3). There was indication of publication bias with Egger's test (P=0.002) but not with Begg's test (P=0.82), though the funnel plot indicated missing studies with positive results (fig H in appendix 3).

There was strong evidence of non-linearity (P<0.001), with a U shaped dose-response curve. The lowest mortality was observed with a BMI of 25 (fig 2, table 2).

BMI and mortality in current, former, and ever smokers

We included 22 studies (21 publications)[17 20 22 27 33 38 49 51 77 107 131 132 149 159 166 180 183 188 230 231 233] (>270 620 deaths, 3 911 812 participants), 17 studies (18 publications)[17 20 22 27 38 49 51 77 107 131 132 149 159 180 183 230 231 233] (>126 786 deaths,

Table 2 | Association between BMI and all cause mortality in never smokers, healthy never smokers, all participants, and in smokers. Figures are relative risk estimates from non-linear dose-response analysis

BMI	Never smokers (n=44*)	Healthy never smokers (n=26*)	All participants (n=198*)	Current smokers (n=18*)	Former smokers (n=15*)	Ever smokers (n=24*)
15	2.01 (1.80 to 2.24)	1.48 (1.32 to 1.65)	2.24 (2.15 to 2.34)	2.61 (2.27 to 2.99)	—†	—†
16	1.66 (1.51 to 1.83)	1.31 (1.19 to 1.44)	1.83 (1.77 to 1.91)	2.08 (1.84 to 2.34)	2.15 (1.91 to 2.42)	1.81 (1.66 to 1.97)
17.5	1.35 (1.25 to 1.45)	1.15 (1.07 to 1.24)	1.47 (1.43 to 1.51)	1.61 (1.46 to 1.76)	1.68 (1.53 to 1.84)	1.50 (1.40 to 1.60)
20	1.10 (1.05 to 1.14)	1.03 (0.99 to 1.07)	1.15 (1.13 to 1.17)	1.19 (1.13 to 1.25)	1.20 (1.14 to 1.26)	1.16 (1.12 to 1.20)
22	1.01 (1.00 to 1.03)	1.00 (0.99 to 1.01)	1.03 (1.02 to 1.04)	1.04 (1.02 to 1.06)	1.04 (1.03 to 1.06)	1.04 (1.02 to 1.05)
23	1.00	1.00	1.00	1.00	1.00	1.00
24	1.00 (0.98 to 1.01)	1.01 (1.00 to 1.02)	0.98 (0.97 to 0.99)	0.97 (0.96 to 0.99)	0.98 (0.96 to 0.99)	0.98 (0.97 to 0.99)
25	1.01 (0.98 to 1.03)	1.03 (1.00 to 1.06)	0.97 (0.96 to 0.98)	0.96 (0.93 to 1.00)	0.97 (0.94 to 1.00)	0.97 (0.94 to 0.99)
27.5	1.07 (1.01 to 1.14)	1.11 (1.05 to 1.18)	0.98 (0.96 to 1.01)	0.99 (0.92 to 1.06)	1.00 (0.93 to 1.08)	0.98 (0.93 to 1.04)
30	1.20 (1.09 to 1.32)	1.24 (1.14 to 1.36)	1.04 (1.00 to 1.08)	1.08 (0.96 to 1.21)	1.11 (0.99 to 1.24)	1.05 (0.96 to 1.14)
32.5	1.39 (1.22 to 1.58)	1.42 (1.26 to 1.60)	1.14 (1.09 to 1.20)	1.24 (1.06 to 1.45)	1.28 (1.10 to 1.49)	1.15 (1.02 to 1.30)
35	1.65 (1.40 to 1.94)	1.66 (1.43 to 1.94)	1.29 (1.21 to 1.37)	1.48 (1.21 to 1.80)	1.54 (1.27 to 1.87)	1.31 (1.13 to 1.52)
37.5	2.02 (1.66 to 2.46)	1.98 (1.64 to 2.38)	1.49 (1.37 to 1.61)	1.82 (1.43 to 2.32)	1.91 (1.51 to 2.41)	1.51 (1.27 to 1.81)
40	2.50 (1.98 to 3.15)	2.37 (1.91 to 2.95)	1.74 (1.59 to 1.91)	2.32 (1.74 to 3.08)	2.44 (1.85 to 3.20)	1.79 (1.45 to 2.21)
42.5	3.16 (2.42 to 4.12)	2.88 (2.24 to 3.69)	2.07 (1.86 to 2.30)	3.03 (2.18 to 4.20)	3.15 (2.30 to 4.32)	2.14 (1.68 to 2.73)
45	4.02 (2.98 to 5.43)	3.54 (2.67 to 4.69)	2.49 (2.22 to 2.81)	4.01 (2.77 to 5.81)	4.18 (2.92 to 5.97)	2.61 (1.99 to 3.43)

*No of risk estimates.
†Lowest value was BMI 16.25.

>1 523 435 participants), and 24 studies (25 publications)[17-20 22 27 33 36 38 49 51 77 94 107 131 132 159 180 183 201 221 230 231 232 239] (>696 134 deaths, 6 616 140 participants) studies in the analyses of current, former, and ever smokers, respectively. There was strong evidence of non-linearity in all analyses (P<0.001 for all), and there was a U shaped curve for the association between BMI and mortality among current, former, and ever smokers (fig 2, table 2).

Subgroup and sensitivity analyses

In the analysis of never smokers there was indication of heterogeneity (P=0.02) when we stratified studies by median or mean duration of follow-up (table C in appendix 2), and the summary relative risks for a 5 unit increment in BMI were 1.21 (95% confidence interval 1.14 to 1.28; n=1), 1.11 (0.94 to 1.30; n=11), 1.18 (1.14 to 1.22; n=18), 1.24 (1.09 to 1.40; n=4), 1.30 (1.19 to 1.42; n=2), and 1.25 (1.20 to 1.30; n=7) for <5, 5-<10, 10-<15, 15-<20, 20-<25 and ≥25 years of follow-up, respectively. In the non-linear dose-response analysis restricted to studies with ≥20 or ≥25 years of follow-up, there was no increased risk at the low BMI range down to a BMI of 20, while risk increased slightly even within the high normal range (BMI of 24-<25) but was more pronounced in the overweight, obese, and severely obese BMI ranges (table E in appendix 2, fig 3). In the analysis of all participants there was also significant heterogeneity (P<0.001) when we stratified studies by median or mean duration of follow-up (table B in appendix 2), and the summary relative risks for a 5 unit increment in BMI were 0.90 (0.83 to 0.97; n=15), 1.00 (0.96 to 1.04; n=53), 1.07 (1.05 to 1.08; n=66), 1.09 (1.05 to 1.13; n=27), 1.12 (1.08 to 1.17; n=15), and 1.15 (1.11 to 1.19; n=22) for <5, 5-<10, 10-<15, 15-<20, 20-<25, and ≥25 years of follow-up, respectively. In the non-linear dose-response analysis, the shape of the dose-response curve changed gradually from a U shape to a J shape with increasing durations of follow-up (table G in appendix 2, fig 4).

There was no heterogeneity in the analyses among never smokers when we stratified by sex, and, although there was heterogeneity when we stratified analyses of all participants by sex, this seemed to be due to no association among the studies of men and women combined, and when analysis was restricted to studies in either men or women there was no heterogeneity (tables C, D, and F in appendix 2, fig I in appendix 3). Although there was evidence of heterogeneity by geographical location in the linear dose-response analysis of all participants (P=0.04), with a significant positive association observed only for Europe and North America (table F in appendix 2), there was no heterogeneity by geographical location in never smokers (P=0.91) and positive associations were observed in European, North American, Australian, and Asian studies (table C in appendix 2), although slight variations in the risk estimates from the non-linear dose-response analyses were observed (table H in appendix 2, fig J in appendix 3). There was evidence of heterogeneity between studies when we stratified by study quality scores in the analysis of all participants (P=0.03), with a significant association among studies with high study quality scores but not among the studies with medium study quality scores (table F in appendix 2). The non-linearity was also more pronounced among the studies with medium study quality compared with the studies of high study quality (table I in appendix 2, figs K and L in appendix 3). There was, however, no heterogeneity by study quality scores in the subgroup analyses of never smokers (table C in appendix 2, figs M and N in appendix 3). There was evidence of heterogeneity when we stratified studies by the number of deaths in the analysis of all participants (P<0.001), with a stronger association among studies with a larger number of deaths compared with studies with a smaller number of deaths (table F in appendix 2), but this was not observed in never smokers (table C in appendix 2).

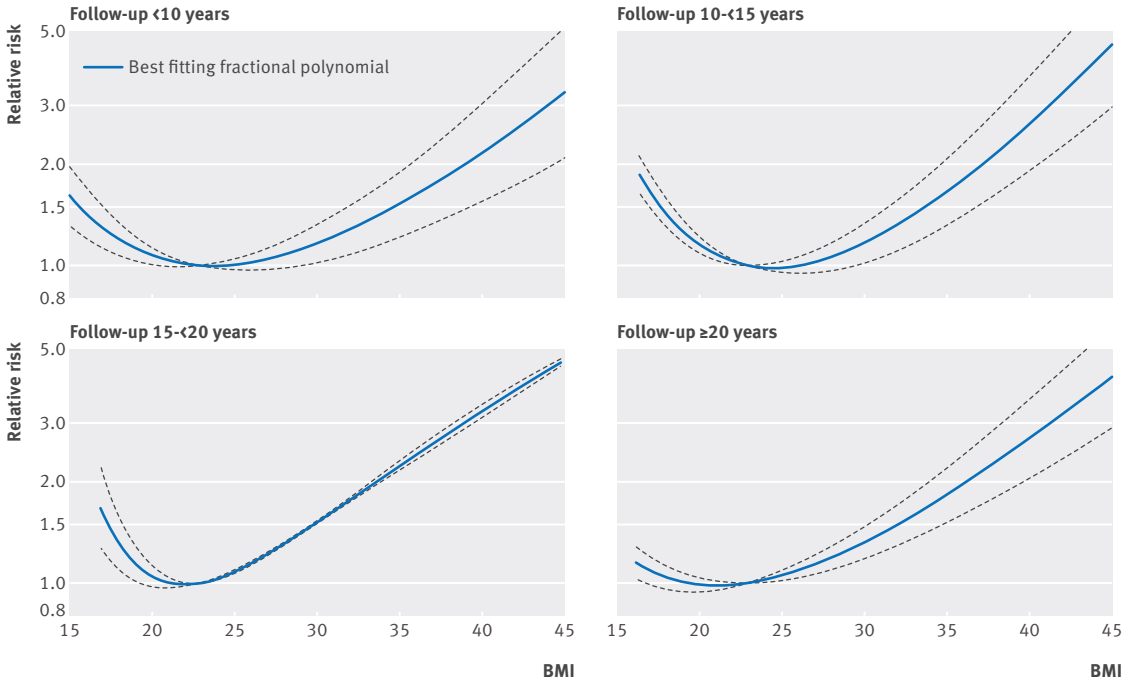

Fig 3 | Non-linear dose-response analysis of BMI and all cause mortality in never smokers stratified by duration of follow-up

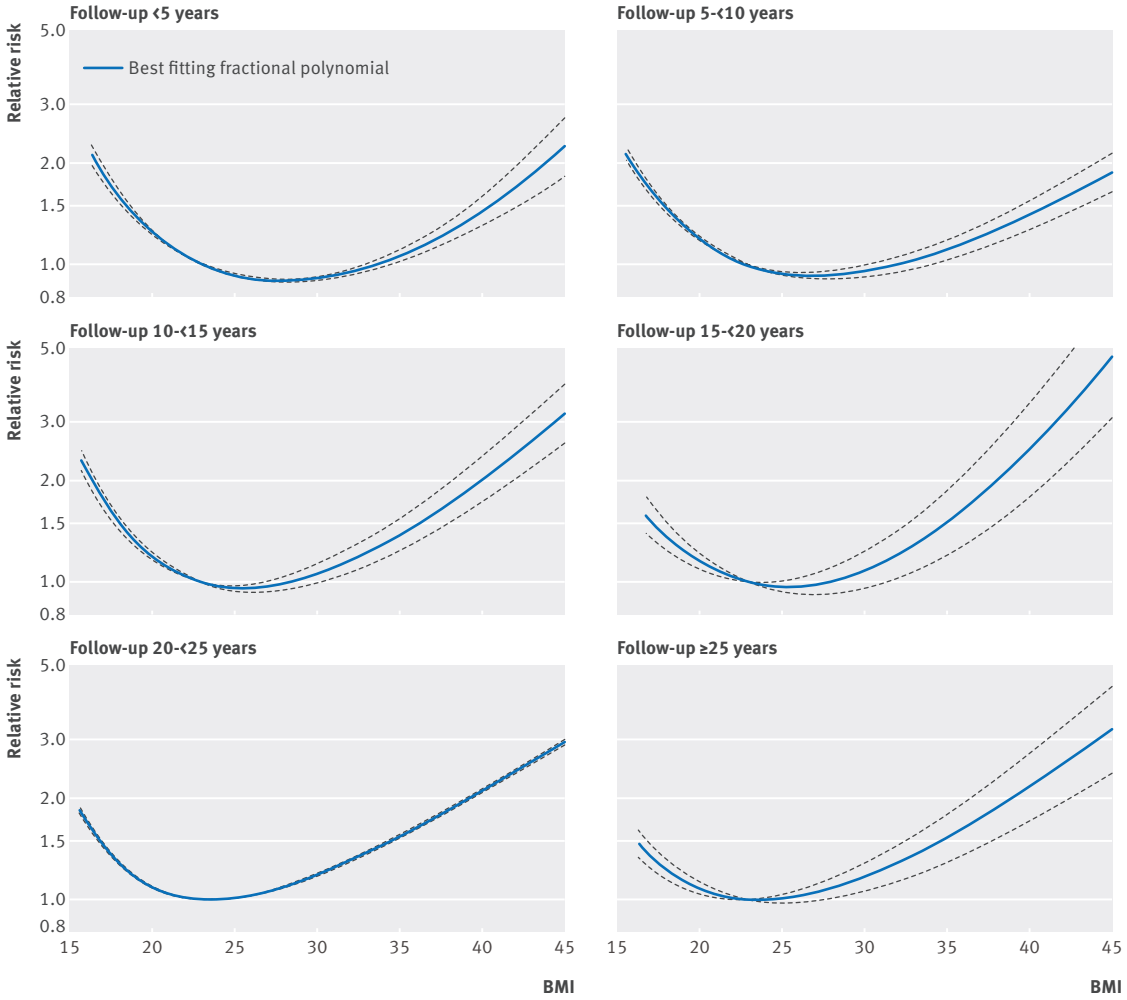

Fig 4 | Non-linear dose-response analysis of BMI and all cause mortality in all participants stratified by duration of follow-up

The positive association between BMI and all cause mortality among never smokers persisted in subgroup analyses defined by sex, assessment of anthropometric measures, geographical location, number of deaths, and adjustment for confounding factors including age, education, alcohol, physical activity, height, dietary pattern, and intake of fat, fruit, and vegetables. There was little evidence of heterogeneity between any of these subgroups with meta-regression analyses (table C in appendix 2). We observed no association among the few studies that adjusted for potential intermediate factors (diabetes, hypertension, cholesterol). In general, heterogeneity was high in most of the subgroup analyses.

In the analysis of all participants there was no evidence of heterogeneity when we stratified studies by adjustment for age, education, socioeconomic status, alcohol, smoking status, pack years, years since quitting, physical activity, height, dietary pattern, fat intake, or fruit and vegetable intake. There was heterogeneity among studies when we stratified by adjustment for number of cigarettes smoked a day (P<0.001), with a stronger association among studies with such adjustment compared with studies without such adjustment (table F in appendix 2). There was also indication of a stronger association among studies with adjustment for years since quitting compared with studies without such adjustment, though the test for heterogeneity between subgroups was not significant.

When we stratified studies by potential intermediates, there was heterogeneity by whether studies adjusted for diabetes, with no association among studies with such adjustment (table F in appendix 2). Although the test for heterogeneity was not significant, there was also no association among studies with adjustment for systolic blood pressure and hypertension. There was also heterogeneity by adjustment for prevalent coronary heart disease (P=0.003), stroke (P=0.07), and prevalent cancer (P=0.03), with no association among studies with such adjustment (table F in appendix 2). Although the test for heterogeneity between subgroups was not significant, the association between BMI and mortality was stronger among studies that had adjusted for the most important confounding factors (age, smoking, alcohol, physical activity) but that did not adjust for intermediate factors or prevalent disease. These associations were further strengthened among studies with longer duration of follow-up (table C and F in appendix 2).

In a further subgroup analysis among never smokers the association between BMI and all cause mortality was considerably stronger among people aged <65 (summary relative risk 1.27, 95% confidence interval 1.22 to 1.34; I^2=91%, $P_{heterogeneity}$<0.001, n=14) than among people aged ≥65 (1.04, 1.01 to 1.07; I^2=72%, $P_{heterogeneity}$=0.004, n=6), with significant heterogeneity between subgroups (P<0.001; fig O in appendix 3). The association was also considerably stronger among younger people in the non-linear dose-response analysis (figs P and Q in appendix 3, table J in appendix 2).

In sensitivity analyses that excluded one study at a time there was minimal variation in the summary relative risk for never smokers (table K in appendix 2) and all participants (table L in appendix 2). In a further sensitivity analysis that excluded studies in which the BMI in the reference category was <18.5 or <20.0, the summary relative risks were 1.19 (95% confidence interval 1.17 to 1.22; I^2=92%, $P_{heterogeneity}$<0.001, n=43) and 1.19 (1.16 to 1.22; I^2=92%, $P_{heterogeneity}$<0.001, n=41), respectively, per 5 BMI units among never smokers, and 1.07 (1.06 to 1.08; I^2=96%, $P_{heterogeneity}$<0.001, n=178) and 1.07 (1.06 to 1.08; I^2=96%, $P_{heterogeneity}$<0.001, n=172), respectively, among all participants.

Discussion

This meta-analysis of 230 cohort studies with >3.74 million deaths among >30.3 million participants provides further evidence that adiposity as measured by BMI increases the risk of premature mortality. There is also some increase in risk in underweight people, but this might at least partly be a non-causal association. In the analysis of all participants the lowest mortality was observed in those with a BMI of around 25. In subgroup analyses, however, the lowest mortality was observed in the BMI range of 23-24 among never smokers, 22-23 among healthy never smokers, and 20-22 among studies of never smokers with longer durations of follow-up (≥20 and ≥25 years).

The analysis of all participants needs to be interpreted carefully as there is a greater possibility of confounding by smoking and confounding from prediagnostic weight loss associated with disease. Some studies might have over-adjusted the analysis by including some intermediate factors such as diabetes, blood pressure, hypertension, and serum cholesterol in the multivariate models. In addition, there was heterogeneity by study quality scores, with more evidence of a U shaped association among moderate quality than among high quality studies. There was some evidence of small study bias, such as publication bias, in the analysis of all participants, although this was not observed in the analysis of never smokers. If anything, however, the funnel plot indicated the presence of missing studies with positive results, suggesting a possible underestimation of the association in the analysis of all participants.

The shape of the dose-response curve differed greatly when we included all people (no exclusions) and when we restricted the analysis to never smokers and healthy never smokers as there was more of a U shaped dose-response relation in the analysis of all participants and a J shaped dose-response relation among never smokers. This is consistent with a pooled analysis from the National Cancer Institute (NCI) Cohort Consortium[14] and partly consistent with the results of the Prospective Studies Collaboration,[2] in which the increased risk in participants with a BMI <20 was much more pronounced in current smokers than in never smokers. In this analysis of all people and former, current, and ever smokers there was a slight inverse association towards the overweight range compared with a BMI of 23 and weaker relative risks in the overweight and obese range than among never smokers. The relative risks were also more similar to that observed in the meta-analysis by Flegal and colleagues[26] in the

unrestricted analysis, in studies with a shorter duration of follow-up, and among smokers, subgroups that could be particularly prone to confounding by smoking and confounding from existing illness. When we restricted the analysis to never smokers there was evidence of increased mortality in the overweight range with more substantial increases in risk in the obese and morbidly obese range. Furthermore, when the analysis was restricted to studies with a longer duration of follow-up, which would be less influenced by confounding by pre-diagnostic weight loss, the increased risk among people with a BMI of 20 disappeared and was substantially attenuated in the underweight never smokers, while in all participants the inverse association in the overweight range was reversed and in the direction of increased risk. Thus, the increased risk observed with a BMI of 20 in the analysis of all participants and never smokers and the lower risk in overweight people in the analysis of all participants is likely to be caused by confounding by smoking and prediagnostic weight loss.

We also found significant heterogeneity when we stratified studies by study quality scores in the analysis of all participants, with no significant association among studies with moderate scores compared with a stronger association in studies with higher scores in the linear dose-response analysis. In the non-linear dose-response analysis, the lowest risk was observed in the overweight range at a BMI of 27.5 in the studies with medium quality scores, while the lowest risk was observed at a BMI of 24-25 in the studies with the highest quality scores. This finding provides further support that issues related to the study quality could have contributed to the slight inverse association at the high end of the normal weight category and in the overweight category in the analysis of all participants. Finally, we also found significant heterogeneity when we stratified studies in never smokers by baseline age, with a much stronger association among people aged <65 than among those aged ≥65, and this is at least partly consistent with the data from the NCI Cohort Consortium.[14]

Results in context

The results of our analysis of never smokers and healthy never smokers are in line with the results from the NCI Cohort Consortium, which reported hazard ratios of 1.09, 1.19, 1.44, 1.88, and 2.51 in the BMI ranges 25-27.4, 27.5-29.9, 30.0-34.9, 35.0-39.9, and 40-49.9 for women and 1.06, 1.21, 1.44, 2.06 and 2.93 for men in the respective BMI categories compared with 22.5-24.9,[14] while we found summary relative risks of 1.11, 1.24, 1.42, 1.98 and 3.54 for BMI values of 27.5, 30, 32.5, 37.5, and 45 compared with a BMI of 23. The somewhat weaker association in the linear dose-response analysis in the current analysis (summary relative risk 1.18 (95% confidence interval 1.15 to 1.22) per 5 BMI units increase for never smokers, 1.21 (1.18 to 1.25) for healthy never smokers, and 1.27 (1.21 to 1.34) for healthy never smokers with exclusion of early follow-up) compared with the NCI Cohort Consortium (hazard ratio 1.31 (95% confidence interval 1.29 to 1.33) for healthy never smokers with exclusion of the first year of follow-up in the BMI range 25-49.9)[14] and the Prospective Studies Collaboration (1.32 (1.28 to 1.36) for never smokers with exclusion of first five years of follow-up)[2] might be because of differences in the number of studies and participants included but might also be because these pooled analyses had access to the original data from each study and restricted the linear dose-response analysis in two ranges, 15-25 and 25-50. In our linear dose-response analysis we used the reference category as reported in each publication, which meant the BMI range would go lower as most of the studies had midpoints for the reference category between BMI 20 and 22, the part of the curve where the dose-response relation was less steep.

Limitations of study

Our meta-analysis has some limitations that need to be mentioned. As a meta-analysis of observational studies, confounding by unmeasured or imperfectly measured risk factors could have influenced the results. Smoking is a strong risk factor for premature mortality and several specific causes of death.[116 117] A recent comprehensive analysis in the Million Women's Study reported increased risk from 23 specific causes of death among current smokers compared with never smokers,[116] while a pooled analysis of five American cohort studies with more than a million participants reported increased risk of 35 and 41 specific causes of death in men and women, respectively.[117] At the same time smoking is associated with reduced body weight, leading to a lower BMI.[118 240] The adverse effects of smoking are so strong that conventional multivariate adjustment is not sufficient to remove the confounding effects of smoking on the relation between BMI and several cancers (mouth, oesophagus, larynx, lung, and possibly pancreas, gallbladder, and liver)[5 241-243] and several specific causes of death (most notably chronic obstructive pulmonary disease and pneumonia),[12 244] and this is also likely to be the case for all cause mortality. Further in support of this argument is the observation that the conditions most strongly associated with smoking (cancers of the lung and upper aerodigestive tract and other respiratory diseases[116 117]) are also the conditions for which the BMI-disease association shows the largest difference in risk estimates when analyses are restricted to never smokers.[8 241 243] Therefore it is necessary to restrict the analysis to never smokers to obtain valid results. The differences in the shape of the dose-response relation between BMI and mortality in smokers and never smokers as well as the stronger risk estimates among studies with adjustment for smoking (smoking status, cigarettes per day, time since quitting) we observed provide further support that smoking is a powerful confounder of the relation between adiposity and mortality.

Though other confounding factors could have influenced the results, in the analysis of never smokers the results persisted among studies that adjusted for age, education, alcohol, physical activity, height, dietary pattern, and intake of fat and fruit and vegetables, although few studies adjusted for dietary factors, suggesting that at least these confounders do not explain the association between BMI and mortality. In addition, it is possible that the increased risk observed in the underweight BMI range

could be attenuated by physical activity or a generally healthy lifestyle,[14 159] but we were not able to investigate potential interactions between BMI and physical activity or dietary factors in relation to all cause mortality as few studies reported such results. Although BMI is an imperfect measure of body fatness as it does not distinguish between lean mass and fat mass, in most people it is highly correlated with measures of body fat[245 246] and has been shown to be predictive of several chronic diseases.[8 12 247] BMI might be a less reliable marker of adiposity in the elderly as the prevalence of chronic disease (and associated weight loss) increases with age and because of loss of muscle mass from the ageing process.[248] This might explain the weaker association observed between BMI and mortality in older than in younger people. These findings are also consistent with the results of several previous studies,[14 17 94 107] though because of higher death rates absolute risks are much greater in older people.[249] A pooled analysis[250] and a meta-analysis[251] and the European Prospective Investigation into Cancer and Nutrition study[20] reported linear increases in risk of mortality with greater waist circumference and waist to hip ratio, even among older people[20] and within the normal BMI range,[20 250] thus incorporating waist measures might have additional clinical relevance for risk assessment.

The results were slightly stronger when we restricted the analysis to healthy never smokers (without prevalent disease at baseline), but the increased risk in the participants with a low BMI persisted in these analyses. Nevertheless, residual confounding is still possible as an explanation for the increased risk with a low BMI because most studies excluded only participants with prevalent cardiovascular disease and cancer, and only five of the 26 studies additionally excluded people with respiratory disease. In the NCI Cohort Consortium the effect of exclusion of participants with prevalent disease on the association between BMI and mortality was more pronounced in men and for heart disease rather than for cancer, stroke, or respiratory disease.[14] Confounding by undiagnosed disease, however, is still a possibility as weight loss can precede the diagnosis of some neurological and respiratory diseases by as much as 10-15 years[2 34 252 253] and because most of the studies excluded only the first one, two, or three years of follow-up. In a further subgroup analysis stratified by duration of follow-up we found that the increased risk among people with a BMI of 20 disappeared and in underweight people was substantially attenuated and the increased risk in overweight and obese people was strengthened among studies with ≥20 or ≥25 years of follow-up. This is in line with the results from the NCI Cohort Consortium, where the increased risk among people with a BMI between 18.5 and 19.9 disappeared and that of underweight people was greatly reduced in the subgroup with 15 or more years of follow-up,[14] while the positive association with higher BMI was strengthened with a longer duration of follow-up. This suggests that weight loss from prediagnostic disease could explain the increased risk we observed in the low-normal weight and underweight BMI ranges. However, another potential explanation might be if people gained weight over time, as some underweight people might become normal weight and obese people become even more obese over the follow-up period. It has been shown that weight loss associated with disease before baseline is associated with increased risk of mortality[254] and that in people with stable BMI there was a linear increase in risk of mortality with higher BMI, while in those who previously experienced weight loss (likely because of chronic illness) there was a more U shaped association between BMI and mortality.[255] Any further large scale cohort studies or pooled analyses should investigate these issues further by incorporating repeated anthropometric assessments during follow-up.

Another limitation is that the number of studies that conducted analyses stratified by smoking status was small compared with the total number of studies (53 out of 228 studies). However, many of the studies that provided results for never smokers were very large and accounted for 68% of the total participants and 63% of the total deaths in this meta-analysis (2 372 930 deaths and 20 542 502 participants out of a total of >3 744 722 deaths among 30 233 329 participants), thus most likely the results for never smokers would not have been dramatically different if all studies had reported such data. The analyses of healthy never smokers and healthy never smokers with exclusion of early follow-up had a more limited number of studies included (26 and 11, respectively) and might therefore be less representative of all the studies included but still included a larger number of deaths and participants among healthy never smokers than previous pooled analyses.[2 14]

Measurement errors in the assessment of height and weight could have influenced the results. Most validation studies have found high correlations between self reported and measured height and weight,[256-258] though some under-reporting of weight and over-reporting of height can occur. When studies were stratified by whether weight and height was measured or self reported the summary relative risk was slightly weaker among studies that used measured data compared with studies that used self reported data, though there was no significant heterogeneity between these subgroups. Height, weight, smoking status, and other covariates were measured only at baseline and changes in these factors could have occurred during follow-up, but we were not able to take such changes into account because most studies lacked such data.

One final limitation is that because of resource constraints we included only English language publications. We assumed that most of the large scale and well conducted cohort studies of importance will have been published in English language journals. Given the large number of studies included in the present analysis any additional studies published in non-English journals would have to be very large and/or have a substantially different result than the present cohort studies to change any of the results meaningfully, but we consider this possibility less likely.

Strengths of the study

Our meta-analysis has several strengths. As we used fractional polynomial models for the analyses we were able to

include a larger number of studies with a much larger number of deaths and participants than previously with more than 3.74 million deaths among 30.2 million participants in 228 studies in the analysis of all participants, which is almost 14 times the number of deaths and >10 times the number of participants and more than twice the number of studies compared with the meta-analysis by Flegal and colleagues.[26] In the analysis of never smokers, there were >738 000 deaths among >9.97 million participants, among healthy never smokers there were >74 464 deaths among 727 687 participants, and among healthy never smokers with exclusion of early follow-up there were 88 860 deaths among 1 192 443 participants, which compares favourably with the 35 369 deaths and 687 590 healthy never smokers (first year of follow-up excluded) in the NCI Cohort Consortium.[14] The fractional polynomial method has the advantage that studies are not required to use the exact same cut-off points when analysing BMI, thus we were able to include important studies that were previously excluded.[26] We conducted analyses stratified by smoking status, prevalent disease, and exclusion of early follow-up to investigate the potential impact of residual confounding from smoking and prevalent and undiagnosed disease. We observed important differences between studies among never smokers and those among former, current, and ever smokers with a more J shaped curve for never smokers, while there was a U shaped curve among smokers, suggesting that smoking might have influenced previous results that showed inverse associations in the overweight range. In addition, we stratified the analyses by duration of follow-up to clarify the potential influence of confounding by illness from prediagnostic weight loss. We found large differences in the shape of the dose-response relation with different durations of follow-up, with more U shaped associations with shorter follow-up and J shaped associations with longer follow-up. We conducted several subgroup analyses by study characteristics, study quality scores, and adjustment for confounding and mediating factors, and the findings persisted in sensitivity analyses excluding one study at a time, suggesting that no individual study explained the results.

Mechanisms

Several potential mechanisms could explain an association between BMI and risk of premature mortality. Adiposity is an established risk factor for cardiovascular disease (coronary heart disease, stroke) and increases risk through increased cholesterol and triglyceride concentrations, raised blood pressure, low grade inflammation, and insulin resistance.[2] Overweight and obesity is the strongest established risk factor for type 2 diabetes,[3] which is associated with a two-threefold increase in risk of mortality.[259] Adiposity is an established risk factor for at least 10 different cancers, including cancers of the oesophagus (adenocarcinoma), liver, gallbladder, colorectum, pancreas, kidney, prostate (advanced cancer only), breast (postmenopausal), endometrium, and ovaries,[4 6 7 8] and there is some evidence to suggest an association with several other cancers, including thyroid cancer, leukaemia, multiple myeloma, and lymphomas[8] as well as with worse survival after cancer diagnosis.[260 261] A wide range of mechanisms could explain the association with these cancers, including hormonal effects of adipose tissue, insulin resistance, inflammation, effects on predisposing conditions such as gastro-oesophageal reflux disease,[262] Barrett's oesophagus,[263] gallbladder disease,[9] and colorectal adenomas,[264] and through effects on the immune system.[265] There is also evidence for an association between adiposity and a wide range of other chronic disease outcomes, which can also lead to complications and death.[10-13] On the other hand, there is some indication that being underweight can increase the risk of chronic pulmonary disease and other respiratory diseases,[2 18 20 266] though reverse causality and confounding might at least partly explain these findings as weight loss can be an indicator of progressive chronic obstructive pulmonary disease and because smoking is so strongly related to these conditions.[267] For several outcomes, including coronary heart disease, hypertension, hypercholesterolemia, type 2 diabetes, gallstones, gout, colon, and endometrial cancer, there is evidence of increased risk even within the high end of the normal BMI range,[7 9 10 247] and this might explain the slightly increased risk of all cause mortality observed among never smokers even at a BMI of 24-25 in the current meta-analysis, when restricted to studies with ≥20 or ≥25 years follow-up.

Policy implications and future research

The current analysis provides strong evidence that overweight and obesity increases the risk of all cause mortality and therefore reinforces previous concerns regarding the adverse health effects of excess weight. Previous recommendations regarding body weight for prevention of chronic diseases such as cancer and cardiovascular disease have recommended a BMI within the normal range of 18.5-24.9, as defined by the WHO.[120] Some recommendations stated that it would be best to stay as lean as possible within the normal range as there is evidence of increased risk of cardiovascular disease, cancer, diabetes, and some other diseases even within the high normal range (22-24.9).[4 9 10 247] The current results support these recommendations but suggest that the lowest mortality is observed with a BMI of 22-24 (depending on whether prevalent disease is excluded or not), although we cannot entirely rule out the possibility that this might be a slight overestimate if the increased risk observed among people with a BMI of 20 is non-causal, as indicated by the studies with longer durations of follow-up. Any further studies should investigate in more detail the association between BMI and other adiposity measures and specific causes of death, including less common diseases contributing to all cause mortality, and take into account the important methodological issues that have been highlighted in the current meta-analysis.

Conclusions

In conclusion, both overweight and obesity increases the risk of all cause mortality with a J shaped dose-response relation, and the nadir of the dose-response curve seems to be in the BMI range of 23-24 among never smokers and

22-23 among healthy never smokers. With longer duration of follow-up the nadir of the dose-response curve is in the BMI range of 20- 22. There is some evidence of increased mortality in underweight people, but we cannot exclude the possibility that this could partly be because of residual confounding from prediagnostic disease. Lack of exclusion of ever smokers, people with prevalent disease, and early follow-up and inclusion of studies with lower study quality could bias the associations between BMI and mortality towards a more U shaped association.

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Ethical approval: Not required.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been disclosed.

Data sharing: No additional data available.

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Appendix 1: Details of searches
Appendix 2: Supplementary tables A-L
Appendix 3: Supplementary figures A-Q