The Global BMI Mortality Collaboration (2016). Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. The Lancet, 388(10046), 776-786. DOI: 10.1016/S0140-6736(16)30175-1

Body-mass index and all-cause mortality:

Individual-participant-data meta-analysis of 239 prospective studies in four continents

The Global BMI Mortality Collaboration (investigators listed in **eAppendix 1**)

Emanuele Di Angelantonio*[1], MD; Shilpa N Bhupathiraju*[2], PhD; David Wormser*[1], PhD; Pei Gao*[1,3], PhD; Stephen Kaptoge*[1], PhD; Amy Berrington de Gonzalez*[4], PhD; Benjamin J. Cairns*[5], PhD; Prof Rachel Huxley*[6], PhD; Chandra L. Jackson*[7], PhD; Grace Joshy*[8], PhD; Sarah Lewington*[5], DPhil; Prof JoAnn E Manson*[2,7], MD; Neil Murphy*[9], PhD; Alpa V. Patel*[10], PhD; Prof Jonathan M. Samet*[11], MD; Prof Mark Woodward*[5,12,13], PhD; Wei Zheng*[14], MD; Maigen Zhou*[15], MSc; Narinder Bansal[1], PhD; Aurelio Barricarte[16,17], MD; Brian Carter[10], MPH; Prof James R Cerhan[18], MD; Prof Rory Collins[5], FRS; Prof George Davey Smith[19], MD; Xianghua Fang[20], PhD; Prof Oscar H. Franco[21], MD; Prof Jane Green[5], DPhil; Jim Halsey[5], BSc; Janet S. Hildebrand[10], MPH; Keum Ji Jung[22], MPH; Rosemary J. Korda[8], PhD; Dale F. McLerran[23], MS; Steven C. Moore[4], PhD, MPH; Linda M. O'Keeffe[1], PhD; Ellie Paige[1], PhD; Anna Ramond[1], DPharm; Prof Gillian K. Reeves[5], PhD; Betsy Rolland[4], PhD, MPH; Carlotta Sacerdote[24], PhD; Prof Naveed Sattar[25], FRCP; Eleni Sofianopoulou[1], PhD; Prof June Stevens[26], PhD; Michael Thun[10], MD; Prof Hirotsugu Ueshima[27], MD; Ling Yang[5], PhD; Young Duk Yun[28], MD; Peter Willeit[1,29], PhD; Prof Emily Banks*[8], PhD; Prof Valerie Beral*[5], FRS; Prof Zhengming Chen*[5], MD; Susan M. Gapstur*[10], PhD; Marc J. Gunter*[30], PhD; Patricia Hartge*[4], ScD; Prof Sun Ha Jee*[23], PhD; Prof Tai-Hing Lam*[31], FRCP; Prof Richard Peto*[5], FRS; Prof John D. Potter*[32], PhD; Prof Walter C. Willett*[2,7], MD; Prof Simon G. Thompson*[1], FMedSci; Prof John Danesh*[1], FMedSci; Prof Frank B. Hu*[2,7] MD.

* Equal contribution

[1] University of Cambridge, Cambridge, UK
[2] Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[3] Peking University, Beijing, China
[4] National Cancer Institute, Bethesda, Maryland, USA
[5] University of Oxford, Oxford, UK
[6] University of Queensland, Brisbane, Australia
[7] Harvard Medical School, Boston, Massachusetts, USA
[8] Australian National University, Canberra, Australia
[9] Imperial College London, London, UK
[10] American Cancer Society, Atlanta, Georgia, USA
[11] University of Southern California, Los Angeles, California, USA
[12] The George Institute for Global Health, University of Sydney, Australia
[13] Johns Hopkins University, Baltimore, Maryland, USA
[14] Vanderbilt University Medical Center, Nashville, Tennessee, USA
[15] Chinese Center for Disease Control and Prevention, Beijing, China
[16] Navarre Public Health Institute, Pamplona, Spain
[17] Consortium for Biomedical Research in Epidemiology and Public Health, Spain
[18] Mayo Clinic, Rochester, Minnesota, USA
[19] MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK
[20] Capital Medical University, Beijing, China
[21] Erasmus MC, University Medical Center Rotterdam
[22] Yonsei University, Seoul, Korea
[23] Fred Hutchinson Cancer Research Center, Seattle, USA
[24] University of Turin, Center for Cancer Prevention, Turin, Italy
[25] University of Glasgow, Glasgow, UK
[26] University of North Carolina, Chapel Hill, North Carolina, USA
[27] Shiga University of Medical Science, Shiga, Japan
[28] Health Insurance Policy Research Institute, Seoul, Korea
[29] Medical University Innsbruck, Innsbruck, Austria
[30] International Agency for Research on Cancer, Lyon, France
[31] School of Public Health University of Hong Kong, Hong Kong, China
[32] Massey University, Wellington, New Zealand

Correspondence: Professor John Danesh

Department of Public Health and Primary Care

University of Cambridge

Cambridge, England

gbmc@phpc.cam.ac.uk

Abstract 298 words

Text 3307 words

2 tables and 4 figures

39 eTables/eFigures/eAppendices

SUMMARY

Background: Overweight and obesity are increasing worldwide. To help assess their relevance to mortality in different populations we conducted individual-participant-data meta-analyses of the prospective studies of body mass index (BMI), limiting confounding and reverse causality by restricting analyses to never-smokers and excluding prior disease and the first 5 years of follow-up.

Methods: Of 10,625,411 participants in Asia, Australia/New Zealand, Europe, and North America from 239 prospective studies (median follow-up 13·7 [IQR: 11·4-14·7] years), 3,951,455 in 189 studies were never-smokers without specific chronic diseases at recruitment who survived 5 years, of whom 385,879 died. The primary analyses are of these deaths, using age and sex-adjusted hazard ratios (HRs).

Findings: All-cause mortality was minimal (HR=1) at BMI (kg/m^2) 20-25, and increased significantly both just below this range (BMI 18·5-<20: HR=1·13, 95%CI 1·09-1·17; BMI 15-<18·5: HR=1·51, 1·43-1·59) and throughout the overweight range just above it (BMI 25-<27·5: HR=1·07, 1·07-1·08; BMI 27·5-<30: HR=1·20, 1·18-1·22). Continuing upwards, HRs for obesity grade I, II, and III (BMI 30-<35, 35-<40, 40-<60) were 1·45 (1·41-1·48), 1·94 (1·87-2.01), and 2·76 (2·60-2·92), respectively. For BMI>25, mortality increased approximately log-linearly with BMI; HR per 5 units higher BMI was 1·31 (1·29-1·33) in all regions; 1·39 (1·35-1·43) in Europe; 1·29 (1·26-1·32) in North America, 1·39 (1·34-1·44) in East Asia, and 1.31 (1.27, 1.35) in Australia/New Zealand. This HR per 5 units higher BMI (for BMI>25) was greater in younger than older people (1.52 at 35–49 years vs 1·21 at 70-89 years; $P_{heterogeneity}$<0·0001), greater in men than women (1·51 vs 1·30; $P_{heterogeneity}$<0·0001), but similar in studies with self-reported and measured BMI.

Interpretation: The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents. This supports strategies to combat the entire spectrum of excess adiposity in many populations.

Funding: UK MRC, BHF, NIHR; US NIH

INTRODUCTION

The worldwide prevalence of overweight and obesity is high and increasing.[1] The World Health Organization (WHO) estimates that more than 1·3 billion adults worldwide are overweight (defined by WHO as a body mass index [BMI weight in kg/the square of height in m] of 25-<30 kg/m^2), and a further 600 million are obese (BMI ≥30 kg/m^2).[2] Analyses of large-scale prospective studies with prolonged follow-up generally indicate that both overweight and obesity are associated with increased mortality, as is underweight (defined conservatively by the WHO as BMI <18.5 kg/m^2). However, it is not known how such associations vary across major global regions, an uncertainty relevant to international strategies on overweight and obesity.[3] Most previous analyses have focused on people living in one particular country or continent,[4-11] even though relationships of overweight and underweight might differ from one population to another.

Estimation of the relationships between BMI and mortality in various populations can help assess the adverse physiological effects of excessive adiposity (and the adverse physiological effects of various determinants of low BMI). However, reliable estimates of the relevance of BMI to mortality need to limit the effects of reverse causality, because chronic disease and smoking can themselves affect BMI. To help achieve more valid estimates, prospective studies of BMI and mortality should where possible exclude smokers, exclude participants who already had some chronic disease at recruitment that could affect BMI, and those dying within 5 years of recruitment. [12-15]

The Global BMI Mortality Collaboration was established to provide a standardised comparison of associations of BMI with mortality across different populations. It includes individual-participant data on 10·6 million adults in 239 prospective cohort studies in 32 countries, mainly located in Australia/New Zealand (NZ), East Asia, Europe, or North America, about 4 million of whom were non-smokers without chronic disease at recruitment who were still being followed up 5 years afterwards.

METHODS

In 2013, over 500 investigators (**eAppendix 1**) from over 300 institutions in 32 countries agreed an analysis plan for combining individual-participant data from contributing studies. This pre-specified analysis plan is provided in **eAppendix 2**. The goal was to produce reliable estimates of associations of overweight and obesity with all-cause mortality using data from studies in several regions. The pre-specified analysis methods were designed to maximize the internal validity by reducing the scope for bias. This paper follows PRISMA-IPD reporting guidelines (**eAppendix 3**).[16]

Data Sources

We sought data from large prospective studies (≥100,000 participants at baseline) or large multi-cohort consortia (total ≥100,000 participants at baseline). We identified studies from 1970 to January 2015 through systematic literature searches and discussion with investigators (**eAppendix 4**). Prospective cohort studies or consortia thereof were eligible if they: 1) had information on weight, height, age and sex; 2) did not select participants on the basis of having previous chronic disease; 3) recorded overall or cause-specific deaths; and 4) had accrued ≥5 years of median follow-up. We identified only two eligible studies that were unable to contribute (**eFigure 1**).[17,18] **eTables 1-2** provide details of studies. The contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause), on the basis of coding from the *International Classification of Diseases*, revisions 8 through 10, to at least three digits (**eTable 3**), or according to study-specific classification systems. Ascertainment of outcomes was based on death certificates, supplemented in some studies by additional data.

Statistical methods

eFigure 1 describes inclusion and exclusion criteria. We excluded participants with a BMI <15 or ≥60kg/m^2, or baseline age <20 or ≥90 years. To limit residual confounding by smoking and bias due to effects of pre-existing disease on baseline BMI (i.e., reverse causality), the primary analysis was restricted to never-smokers without certain known chronic diseases at baseline (e.g., cardiovascular disease, cancer, or respiratory diseases), and omitted the first 5 years of follow-up.

Associations of all-cause mortality with BMI depend not only on the associations of specific causes of death with BMI in different regions (which might differ quantitatively), but also on how relatively

common each specific cause of death is in the particular region (which can differ substantially by region and over time). Hence, the association of all-cause mortality with BMI may differ in regions with different underlying mortality patterns. Therefore, the pre-specified primary analysis was stratified by 5 major geographical regions, 3 with extensive data (East Asia, Europe, North America) and 2 with more limited data (Australia/NZ and South Asia). Data from some or all regions are shown separately, in the main text or the extensive online Supplementary Analyses.

Each study (or consortium of studies) analysed individual-participant data according to a common analytical plan (SASv9·3 [SAS Institute, Cary, NC] or Statav12 [StataCorp, College Station, TX]) provided by the coordinating centres. These separate results were then meta-analysed at Cambridge University, UK. To facilitate standardised comparisons with other meta-analyses, we calculated hazard ratios (HRs) for mortality in the 6 WHO-defined baseline BMI categories: underweight (15·0-<18·5 kg/m^2), normal (18·5-<25 kg/m^2, the reference category for analyses of 6 BMI groups), overweight (25-<30 kg/m^2), and obesity grades I (30-<35 kg/m^2), II (35-<40 kg/m^2), and III (40-<60 kg/m^2).[19] As, however, most people are of normal weight or overweight, these two categories were subdivided, yielding 9 fine groups: 15·0-<18·5, 18·5-<20, 20-<22·5, 22·5-<25·0 (the reference category for analyses of 9 BMI groups), 25·0-<27·5, 27·5-<30, 30-<35·0, 35·0-<40, and 40-<60 kg/m^2.

Study-specific log HRs in particular BMI categories were pooled by inverse-variance-weighted random-effects meta-analyses (an extension of the DerSimonian and Laird procedure) and plotted against mean BMI value within each category. To make comparisons across BMI groups irrespective of the choice of a reference group, a floating variance estimate (reflecting independent variability within each group, including the reference group) was attributed to each category using Plummer's method and used to calculate group-specific confidence intervals (CIs).[20]

To estimate BMI levels at which mortality risk was lowest (i.e., the nadir), weighted linear regression yielded the best-fitting second-degree fractional polynomial model relating pooled log HRs to pooled mean BMI levels (weighted by the inverse of the floating variance of the log HR), and the minimum of this polynomial was the nadir.

We assessed all-cause mortality and its main components, coronary heart disease, stroke, cardiovascular disease, cancer, and respiratory disease (**eTable 3**). HRs were calculated separately within each study using Cox regression models stratified for age and sex (**eAppendix 2**). Attained age was used, with participants contributing from the baseline survey in crude analyses or from year 5 in the primary analyses. HRs in sex- and age-specific groups (and, where appropriate, by trial arms) were combined across studies.[21] To avoid over-fitting of statistical models, studies with ≤10 deaths from a particular cause were excluded from meta-analyses of that cause.[22,23]

Because BMI-mortality associations were approximately log-linear above a BMI of 25 kg/m^2, we calculated HRs per 5 kg/m^2 increase by inverse-variance-weighted regression of the pooled log HRs on mean BMI values in each category.[16] For all-cause mortality we estimate population-attributable fractions (PAFs) for underweight, overweight and obese by combining the proportional excess mortality versus normal weight (HR-1) in these BMI categories (X_0, X_1 and X_2 respectively) with the corresponding prevalences (P_0, P_1 and P_2, taken from Global Burden of Disease[24] region-specific prevalences). The PAFs for overweight and obesity are then P_1X_1/k and P_2X_2/k, where $k=1+P_0X_0+P_1X_1+P_2X_2$. Between-study heterogeneity was quantified by the I^2 statistic.[25] We used 2-sided P-values and 95% CIs.

Role of funders

No sponsor had any role in study design, conduct analysis or interpretation; in manuscript preparation, review, or approval; or in deciding to submit for publication.

RESULTS

Of 10,625,411 participants from 239 studies (median follow-up 13·7 [IQR 11·4-14·7] years), 3,951,455 were never-smokers without specific chronic diseases at recruitment who survived 5 years, of whom 385,879 died. To limit bias, the pre-specified primary analyses involve this restricted population. To avoid merging importantly different risks, many of these primary analyses further subdivide the WHO-defined normal and overweight BMI categories, yielding 9 BMI groups rather than 6.

Table 1 shows the substantial relevance of successively stricter exclusions, going from crude analyses of 10·6 million to pre-specified analyses of 4 million adults. With BMI in only 6 groups the whole range from 18.5 to <25 kg/m^2 is the reference group, and HRs were: underweight 1·47 (95% CI 1·39-1·55), overweight 1·11 (1·10-1·11), and grade I, II, III obesity 1·44 (1·41-1·47), 1·92 (1·86-1·98), and 2·71 (2·55-2·86), respectively. With normal and overweight more finely subdivided, however, BMI 22·5-<25 becomes the reference group, and mortality was minimal at BMI 20-<25, and was significantly increased just below this range (BMI 18·5-<20: 1·13, 1·09-1·17; 15-<18·5: 1·51, 1·43-1·59) and *throughout* the overweight range just above it (BMI 25-<27·5: HR=1·07, 1·07-1·08; BMI 27·5-<30: HR=1·20, 1·18-1·22). With this more precise reference group, the HRs for grade I, II, III obesity increased to 1·45 (1·41-1·48), 1·94 (1·87-2.01), and 2·76 (2·60-2·92).

In these pre-specified analyses of 4 million adults, the HRs for overweight and for obesity grade I were broadly similar across different geographic regions (Europe, North America, East Asia, and Australia/NZ; numbers of deaths in South Asia were too small to be reliable), but the HRs for underweight and grade III obesity appeared somewhat higher in Europe than in East Asia (**Figure 1, Table 2**, **eTables 4-9**).

Combining all regions, the HRs for overweight and obesity were higher in men than women, and higher at younger than older ages (**Figures 2-3**); this held in each major geographic region (**eFigures 2-4, eTables 10-11**). In each region, BMI was non-linearly associated with all-cause mortality, with nadir at BMI 20-<25 and excess mortality in underweight, overweight, and at BMI

18.5-<20, at the lower end of the WHO-defined normal range. The nadir depended on age: it was BMI=22 for age 35-49 years, BMI=23 for 50-69 years, and BMI=24 for 70-89 years).

Population-attributable fractions for all-cause mortality due to overweight or obesity were 18% North America, 15% Europe, 10% Australia/NZ, but only 5% East Asia (**eTable 12**). For BMI≥25, the association of BMI with all-cause mortality was approximately log-linear, and of similar strength in each region (except perhaps South Asia, where numbers were limited), with HR per 5 units higher BMI 1·31 (1·29-1·33) overall, 1·39 (1·34-1·44) in East Asia, 1·39 (1·34-1·43) in Europe, 1·29 (1·26-1·32) in North America, and 1.31 (1.27, 1.35) in Australia/NZ. It was 1·51 (1.46-1.56) for men as against only 1·30 (1.26-1.33) for women, heterogeneity P<0·0001, and it decreased with age from 1·52 (1·47-1·56) for ages 35–49 years at baseline to 1·21 (1·17-1·25) for ages 70-89 years, trend P<0·0001 (**eTable 13**).

For each major cause of death, BMI was non-linearly associated with mortality in each major region we studied (**Figure 4, eFigure 5, eTables 14-15**). Above 25 kg/m^2, it was strongly positively related to coronary, stroke and respiratory mortality, and moderately related to cancer mortality. Findings for overweight and obesity were broadly similar in Europe, North America and East Asia. Within the WHO's wide normal BMI range (18.5-<25 kg/m^2) the main geographic difference was that in East Asia mortality from coronary heart disease was steeply lower with decreasing BMI (having nadir at 18.5-<20 kg/m^2), but in other regions it was not (**eTable 15**). In all regions, underweight was associated with substantially higher respiratory mortality and somewhat higher mortality from coronary heart disease, stroke, and cancer. HRs comparing underweight versus normal weight cardiovascular mortality were more extreme in Europe than elsewhere.

Compared with the strict primary analyses noted above, crude analyses that ignored smoking, ignored any effects of prior disease at baseline and failed to exclude the first 5 years of follow-up yielded different (presumably substantially biased) results, with exaggerated HRs for underweight, no apparent HRs for overweight and less than half of the less-biased HRs for grade I obesity (**Table 1, eFigure 6**). In sensitivity analyses (**eFigures 7-11, eTables 17-23**), HRs were little

changed in analyses that: used fixed effect models or restricted follow-up to years 5-15; considered age at risk rather than age at baseline; used contemporary mortality rates; adjusted additionally for race or excluded participants with diabetes at baseline; used only studies that included both sexes; used only studies with baseline data on heart disease, stroke and cancer; or subdivided studies by mean baseline BMI or median recruitment year (HRs were somewhat higher in studies starting before than since 1990, but meta-regression of HRs on year of recruitment was not significant). HRs did not vary substantially between larger and smaller studies, between studies with measured and self-reported BMI, or between occupational and other studies.

DISCUSSION

Associations between BMI and mortality can help estimate the public health impact of excess adiposity only if the estimated relationships are not substantially distorted by the effects of smoking or ill health on BMI. Hence, our primary analyses were of non-smokers without prior disease who survived at least 5 years. We conducted standardised comparison of associations of BMI with mortality across prospective studies in four continents. Both overweight and obesity were associated with all-cause mortality. In the BMI range above 25 kg/m^2 (the upper limit of the WHO's normal range) the relationship to mortality was steep in every global region we studied, except perhaps South Asia where numbers were small.[26]

Our primary analyses challenge previous suggestions that overweight (25-<30) and grade I obesity (30-<35) are not associated with higher mortality,[27] bypassing speculation about hypothetical protective metabolic effects of increased body fat in apparently healthy individuals.[28] In particular, the findings here contrast with those of a recent review of published data which found that, relative to normal weight, grade I obesity was not associated with higher mortality and overweight was associated with lower all-cause mortality.[27] That review could not, however, control for the biases controlled for in the current analysis. Indeed, the results of the current analysis (eg, Table 1 and eTables 4-5) show how that literature-based review's limited ability to control for bias could have accounted for its misleading findings. Our study was able to reproduce such findings when conducting crude analyses with inadequate control of reverse causality, but not when we conducted appropriately strict analyses.

Despite broadly similar overall findings across different continents, we found some differences. HRs per 5-unit increment of BMI above 25 kg/m² were higher in Europe than in North America. HRs were higher in males than females, consistent with previous observations that, at equivalent BMI levels, men have greater insulin resistance, ectopic (e.g., liver) fat levels and type 2 diabetes prevalence.[29] In each major region we studied, HRs were substantially higher at younger than at older ages, although the absolute excess mortality rate was higher in older people.

Partly because the prevalence of obesity differs by region, for all-cause mortality there was wide variation across regions in the approximate population-attributable fraction due to overweight and obesity: North America 18%, Europe 15%, Australia/New Zealand 10%, and East Asia 5%. These findings suggest that if the entire population had ideal levels of BMI this would avoid about 1 in 5 premature deaths in North America, 1 in 7 in Europe,1 in 10 in Australia/New Zealand, and 1 in 20 in East Asia, assuming that the associations of overweight and obesity with mortality in our primary analyses largely reflect causal effects. Instead, however, BMI is increasing in many populations, so the pattern of high mortality from adiposity in North America may become typical elsewhere unless this increase in overweight and obesity can be halted.[30] At the opposite extreme, there was a substantially higher mortality rate not only among those in WHO's underweight category, but also in those with BMI 18.5-<20 kg/m^2, suggesting that in excessively lean populations underweight remains a cause for concern. We have no information on whether the BMI in underweight individuals was always low.

Our primary analyses used three main approaches to help avoid bias. First, we restricted analysis to never-smokers to avoid as fully as possible residual confounding by smoking because merely adjusting for smoking habits would be unlikely to eliminate important residual biases due to the effect on BMI of different intensity of smoking.[12] Second, we excluded people known to have certain pre-existing chronic diseases (although full information on this was often unavailable). Finally, we omitted the initial five years of follow-up from the analysis because conditions at baseline that might cause death over the next 5 years, could result in reverse causation (where lower BMI at recruitment is the result, rather than the cause, of the underlying pathology).[13-15]

Our findings are consistent with other (albeit less precise) studies that have used effective methods to reduce potential bias in evaluations of a causal relationship between excess BMI and mortality, such as Mendelian randomisation analyses,[31,32] other instrumental variable analyses,[33] and a meta-analysis of randomised trials.[34] Our findings are also broadly consistent with the stricter analyses done in a recent study of 12 million Korean adults.[35]

The most important limitation is that our only measure of adiposity was BMI, so we could not address aspects of body composition such as visceral fat or fat distribution,[36,37] nor could we consider modification of HRs by metabolic factors.[38] Such factors may have different effects in different populations as, given the same BMI, people of Asian ancestry may have higher amounts of body fat and greater risk of developing metabolic diseases than people of European ancestry.[39] Moreover, South Asia, Africa, and Latin America were either unrepresented or poorly represented, and large studies in those areas might yield somewhat different findings. The study-specific results were in general not adjusted for ethnicity, or for socioeconomic status. We did not adjust for regression dilution because previous surveys have reported high levels of concordance in replicate BMI measures taken from the same adults some years apart.[40]

There are, however, particular strengths. Compared with single-country studies, we enhanced generalisability by combining findings from 239 studies across four continents. We had access to data for about 97% of the participants in the studies eligible for this analysis (giving large numbers and negligible bias from unavailability of particular studies), we used a pre-specified analysis plan, we analysed individual-participant data to avoid the potentially important limitations of literature-based reviews,[41] we analysed clinically relevant subpopulations reliably, exploiting the considerable statistical power of the study. We avoided potential "over-adjustment" by not adjusting for variables (e.g, diabetes status, physical activity) that could mediate associations between BMI and mortality.[42] Finally, our results were robust to a variety of sensitivity analyses.

We conclude that wherever overweight and obesity are common their associations with higher all-cause mortality are positive and broadly similar, supporting strategies to combat the entire spectrum of excessive adiposity worldwide.

Dedication: This paper is dedicated to the memory of Gary Whitlock, who contributed much to developing this collaboration.

Funding: http://www.phpc.cam.ac.uk/ceu/research/global-bmi-mortality-collaboration/ provides links to websites of the component studies (or consortia), many of which describe their funding. The coordinating centre at the University of Cambridge was funded by the UK Medical Research Council (G0800270), British Heart Foundation (SP/09/002), British Heart Foundation Cambridge Cardiovascular Centre of Excellence, and UK National Institute for Health Research Cambridge Biomedical Research Centre. The work of the coordinating center at the Harvard T.H. Chan School of Public Health was funded by grants P01 CA87969, UM1 CA176726, UM1 CA167552, DK58845, P30 DK046200, and U54 CA155626 from the National Institutes of Health. This research has been conducted using the UK Biobank resource.

References

1. Ng M, Fleming T, Robinson M et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766-781.

2. World Health Organization. Obesity and overweight. *Fact sheet N°311 (Updated January 2015)*. 2015.

3. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157-163.

4. Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *International Journal of Epidemiology*. 2004;33(4):751-758.

5. Berrington de Gonzalez A, Hartge P, Cerhan JR et al. Body-Mass Index and Mortality among 1.46 Million White Adults. *N Engl J Med*. 2010;363(23):2211-2219.

6. Jee SH, Sull JW, Park J et al. Body-Mass Index and Mortality in Korean Men and Women. *N Engl J Med*. 2006;355(8):779-787.

7. Patel AV, Hildebrand JS, Gapstur SM. Body Mass Index and All-Cause Mortality in a Large Prospective Cohort of White and Black U.S. Adults. *PLoS ONE*. 2014;9(10):e109153.

8. Pischon T, Boeing H, Hoffmann K et al. General and Abdominal Adiposity and Risk of Death in Europe. *N Engl J Med*. 2008;359(20):2105-2120.

9. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083-1096.

10. The Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377(9771):1085-1095.

11. Zheng W, McLerran DF, Rolland B et al. Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians. *N Engl J Med*. 2011;364(8):719-729.

12. Bamia C, Trichopoulou A, Lenas D, Trichopoulos D. Tobacco smoking in relation to body fat mass and distribution in a general population sample. *Int J Obes Relat Metab Disord*. 2004;28(8):1091-1096.

13. Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: A reassessment. *JAMA*. 1987;257(3):353-358.

14. Singh PN, Wang X. Simulation Study of the Effect of the Early Mortality Exclusion on Confounding of the Exposure-Mortality Relation by Preexisting Disease. *American Journal of Epidemiology*. 2001;154(10):963-971.

15. Willett WC, Hu FB, Thun M. Overweight, obesity, and all-cause mortality. *JAMA*. 2013;309(16):1681-1682.

16. Stewart LA, Clarke M, Rovers M. Preferred reporting items for a systematic review and meta-analysis of individual participant data: The prisma-ipd statement. *JAMA*. 2015;313(16):1657-1665.

17. Park SY, Wilkens L, Murphy S, Monroe K, Henderson B, Kolonel L. Body mass index and mortality in an ethnically diverse population: the Multiethnic Cohort Study. *Eur J Epidemiol*. 2012;27(7):489-497.

18. Lin WY, Tsai SL, Albu JB et al. Body mass index and all-cause mortality in a large Chinese cohort. *Canadian Medical Association Journal*. 2011;183(6):E329-E336.

19. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res*. 1998;6 Suppl 2:51S-209S.

20. Plummer M. Improved estimates of floating absolute risk. *Statist Med*. 2004;23(1):93-104.

21. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Statist Med*. 2010;29(12):1282-1297.

22. Preston SH, Mehta NK, Stokes A. Modeling Obesity Histories in Cohort Analyses of Health and Mortality. *Epidemiology*. 2013;24(1):158-66.

23. Thompson S, Kaptoge S, White I, Wood A, Perry P, Danesh J. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol*. 2010;39(5):1345-1359.

24. Stevens G, Singh G, Lu Y et al. National, regional, and global trends in adult overweight and obesity prevalences. *Population Health Metrics*. 2012;10(1):22.

25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.

26. Jensen MD, Ryan DH, Apovian CM et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 suppl 2):S102-S138.

27. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *JAMA*. 2013;309(1):71-82.

28. Doehner W, Clark A, Anker SD. The obesity paradox: weighing the benefit. *European Heart Journal*. 2010;31(2):146-8.

29. Sattar N. Gender aspects in type 2 diabetes mellitus and cardiometabolic risk. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2013;27(4):501-507.

30. Gillman MW, Ludwig DS. How Early Should Obesity Prevention Start? *N Engl J Med*. 2013;369(23):2173-2175.

31. Nordestgaard BG, Palmer TM, Benn M et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PLoS Med*. 2012;9(5):e1001212.

32. Hagg S, Fall T, Ploner A et al. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. *International Journal of Epidemiology*. 2015;44(2):578-586.

33. Davey Smith G, Sterne JA, Fraser A, Tynelius P, Lawlor DA, Rasmussen F. The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study. *BMJ*. 2009;339:b5043.

34. Kritchevsky SB, Beavers KM, Miller ME et al. Intentional Weight Loss and All-Cause Mortality: A Meta-Analysis of Randomized Clinical Trials. *PLoS ONE*. 2015;10(3):e0121993.

35. Yi SW, Ohrr H, Shin SA, Yi JJ. Sex-age-specific association of body mass index with all-cause mortality among 12.8 million Korean adults: a prospective cohort study. *International Journal of Epidemiology*. 2015;44(5):1696-1705.

36. Bohm A, Heitmann BL. The use of bioelectrical impedance analysis for body composition in epidemiological studies. *Eur J Clin Nutr*. 2013;67(S1):S79-S85.

37. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol*. 2013;62(10):921-925.

38. Kramer CK, Zinman B, Retnakaran R. Are Metabolically Healthy Overweight and Obesity Benign Conditions? A Systematic Review and Meta-analysis. *Annals of Internal Medicine*. 2013;159(11):758-769.

39. Chan JN, Malik V, Jia W. Diabetes in asia: Epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301(20):2129-2140.

40. Wormser D, White IR, Thompson SG, Wood AM. Within-person variability in calculated risk factors: Comparing the aetiological association of adiposity ratios with risk of coronary heart disease. *International Journal of Epidemiology*. 2013;42(3):849-859.

41. Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med*. 1995;14(19):2057-2079.

42. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444(7121):875-880.

476 **Table 1: Effects of successively stricter precautions against bias on analyses of BMI vs all-cause mortality**
477

	Underweight (BMI 15 to <18·5)	Normal weight (18·5 to <25)	Overweight (25 to <30)	Obesity Grade I (30 to <35)	Obesity Grade II (35 to <40)	Obesity Grade III (40 to <60)
6 WHO BMI groups: Crude analysis with no exclusions (237 studies; 10,622,450 participants; 1,601,774 deaths)						
Participants / deaths	292003 / 68455	5586892 / 810838	3467617 / 526098	946257 / 144871	237223 / 36113	92458 / 15399
HR (95% CI)	1·82 (1·74, 1·91)	1·00 (0·98, 1·02)	0·95 (0·94, 0·97)	1·17 (1·16, 1·18)	1·49 (1·47, 1·51)	1·95 (1·90, 2·01)
6 WHO BMI groups: Participants without known disease at baseline (236 studies; 9,104,247 participants; 1,210,250 deaths)						
Participants / deaths	255000 / 52789	4922817 / 631488	2916978 / 388781	756075 / 102315	183689 / 24556	69688 / 10321
HR (95% CI)	1·81 (1·72, 1·91)	1·00 (0·98, 1·02)	0·95 (0·95, 0·96)	1·18 (1·16, 1·20)	1·52 (1·48, 1·55)	2·05 (1·98, 2·13)
6 WHO BMI groups: Participants without known chronic disease at baseline, adjusting for smoking status (234 studies; 8,801,617 participants; 1,185,728 deaths)						
Participants / deaths	245080 / 51170	4751019 / 618881	2826687 / 381617	733108 / 100113	178130 / 23945	67593 / 10002
HR (95% CI)	1·70 (1·61, 1·80)	1·00 (0·98, 1·02)	0·99 (0·98, 1·00)	1·25 (1·23, 1·27)	1·63 (1·59, 1·66)	2·24 (2·15, 2·33)
6 WHO BMI groups: Participants without known chronic disease at baseline, adjusting for smoking status, and excluding the first 5 years of follow-up (213 studies; 7,805,434 participants; 949,010 deaths)						
Participants / deaths	208044 / 33817	4234052 / 496310	2513128 / 312450	641237 / 80037	152741 / 18737	56232 / 7659
HR (95% CI)	1·60 (1·51, 1·70)	1·00 (0·98, 1·02)	1·03 (1·01, 1·04)	1·31 (1·29, 1·33)	1·70 (1·67, 1·74)	2·36 (2·27, 2·45)
6 WHO BMI groups (a primary pre-specified analysis): Never-smokers without known chronic disease at baseline, excluding the first 5 years of follow-up (189 studies; 3,951,455 participants; 385,879 deaths)						
Participants / deaths	114091 / 12726	2145550 / 192523	1250103 / 130293	330840 / 37318	80827 / 9179	30044 / 3840
HR (95% CI)	1·47 (1·39, 1·55)	1·00 (0·98, 1·02)	1·11 (1·10, 1·11)	1·44 (1·41, 1·47)	1·92 (1·86, 1·98)	2·71 (2·55, 2·86)

9 BMI groups (strictest precautions against bias: a primary pre-specified analysis): As above, but with normal weight and overweight further subdivided (189 studies; 3,951,455 participants; 385,879 deaths)									
BMI categories	**15 to <18.5**	**18.5 to <20**	**20 to <22.5**	**22.5 to <25**	**25 to <27.5**	**27.5 to <30**	**30 to <35**	**35 to <40**	**40 to <60**
Participants/deaths	114091/12726	230749/20989	838907/72701	1075894/98833	821303/84952	428800/45341	330840/37318	80827/9179	30044/3840
HR (95% CI)	1.51 (1.43, 1.59)	1.13 (1.09, 1.17)	1.00 (0.98, 1.02)	1.00 (0.99, 1.01)	1.07 (1.07, 1.08)	1.20 (1.18, 1.22)	1.45 (1.41, 1.48)	1.94 (1.87, 2.01)	2.76 (2.60, 2.92)

478
479 All analyses are adjusted for age and sex
480

Table 2: Strictest pre-specified analyses, in geographic regions with >1 million participants: Nine BMI groups vs all-cause mortality among never-smokers, excluding chronic disease at baseline and 5 years follow-up

BMI categories	15 to <18.5	18.5 to <20	20 to <22.5	22.5 to <25	25 to <27.5	27.5 to <30	30 to <35.0	35 to <40	40 to <60
Europe (89 studies; 1,135,600 participants; 56,477 deaths)									
Participants/deaths	13398/675	42584/1508	199369/7449	306566/13278	249929/12850	153147/8935	127536/8386	32749/2424	10322/972
HR (95% CI)	1.79 (1.63, 1.97)	1.25 (1.14, 1.38)	1.02 (0.97, 1.07)	1.00 (0.97, 1.03)	1.07 (1.06, 1.09)	1.21 (1.18, 1.25)	1.52 (1.45, 1.58)	1.99 (1.87, 2.12)	3.04 (2.84, 3.27)
North America (40 studies; 1,415,087 participants; 219,922 deaths)									
Participants/deaths	22028/3846	67114/8597	274883/36200	359022/54995	317721/53464	168183/28471	149807/25348	39379/6299	16950/2702
HR (95% CI)	1.51 (1.34, 1.70)	1.09 (1.02, 1.16)	1.01 (0.96, 1.06)	1.00 (0.97, 1.03)	1.06 (1.04, 1.07)	1.17 (1.12, 1.22)	1.39 (1.30, 1.49)	1.93 (1.74, 2.13)	2.58 (2.26, 2.93)
East Asia (46 studies; 1,074,385 participants; 100,784 deaths)									
Participants/deaths	46979/7178	94409/10206	301242/27537	336758/28755	194857/17070	72133/6950	25658/2753	1941/231	408/104
HR (95% CI)	1.36 (1.25, 1.49)	1.11 (1.04, 1.18)	0.99 (0.97, 1.02)	1.00 (0.97, 1.03)	1.07 (1.04, 1.11)	1.28 (1.21, 1.35)	1.54 (1.42, 1.67)	2.01 (1.59, 2.54)	2.38 (1.33, 4.24)
P-value for heterogeneity	0.0045	0.28	0.42	-	0.89	0.46	0.20	0.48	<0.0001

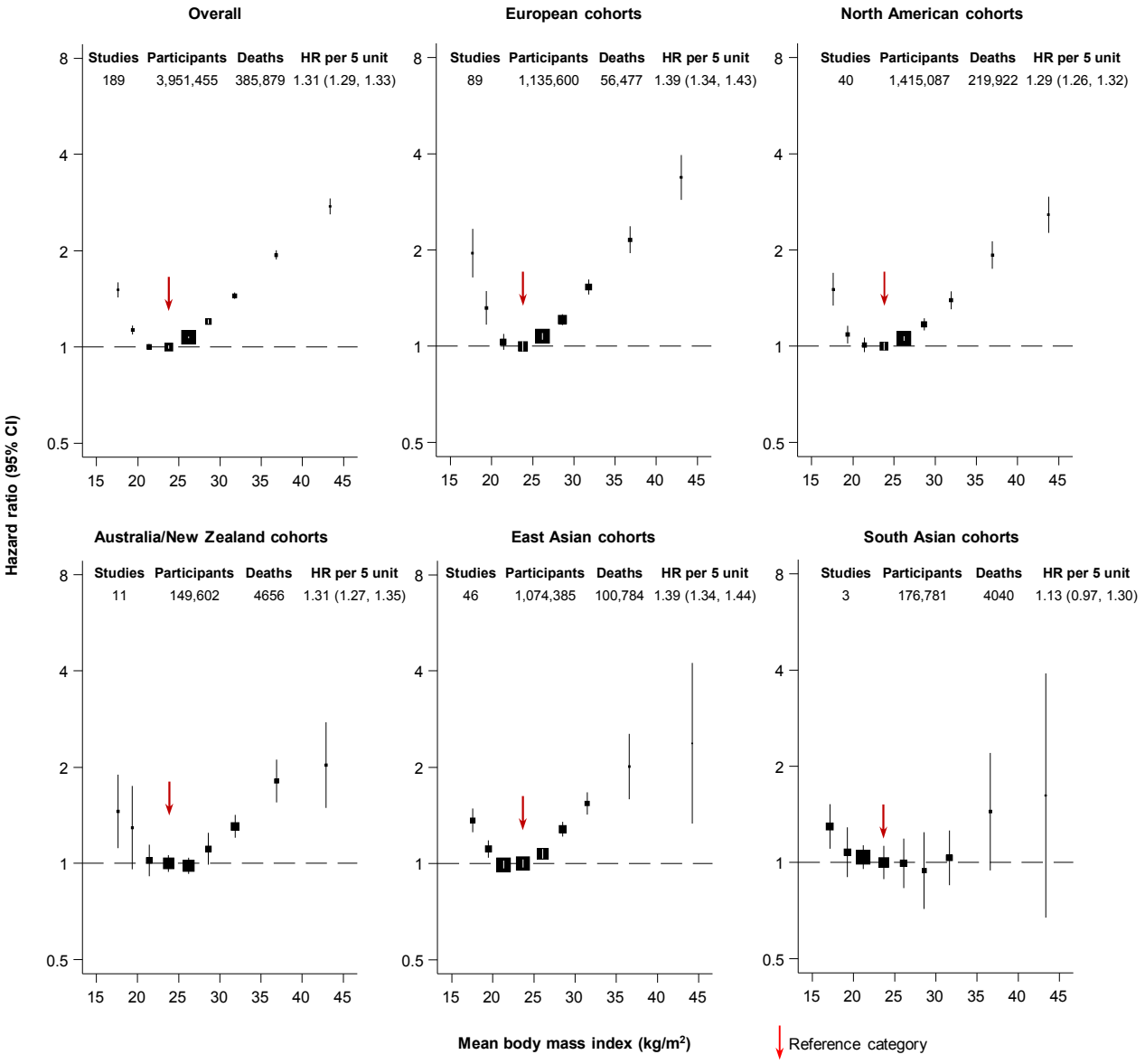
Normal weight and overweight are subdivided, and the reference category is BMI 22·5 to <25 kg/m^2.

Numbers of studies, participants and deaths are after exclusions from these pre-specified principal analyses.

CIs were calculated using floating variance estimates (reflecting independent variability within each group, including the reference group).

Results from studies in South Asia and Australia/New Zealand are in Figure 1, with details in eTable 8 of the Supplementary Material.

Figure 1: Association of BMI with all-cause mortality, by geographical region



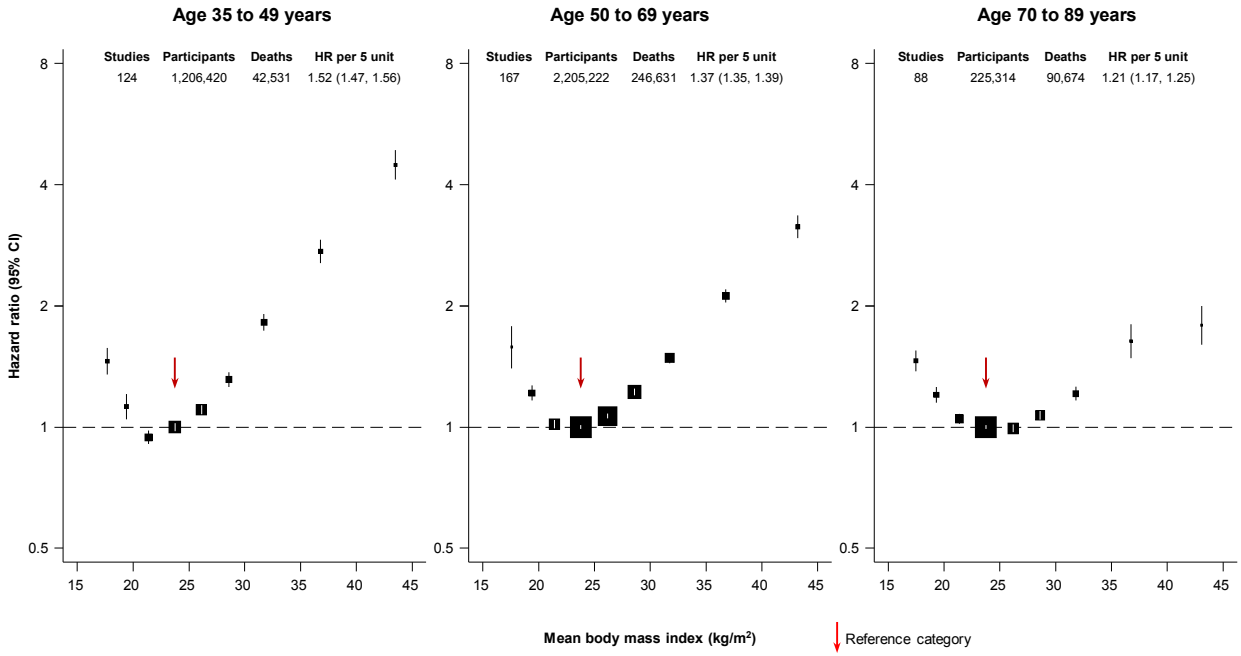
HR, hazard ratio per 5 kg/m^2 unit of BMI in the range BMI >25 kg/m^2 (and 95% CI).

Analyses restricted to never-smokers without pre-existing chronic disease, and excluding the first 5 years of follow-up, and include data from all geographical regions.

BMI groups: 15.0 to <18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30, 30 to <35.0, 35.0 to <40, and 40 to <60 kg/m^2. Reference category (arrow) is 22.5 to <25 kg/m^2.

CIs are from floating variance estimates (reflecting independent variability within each category, including reference). Areas of squares are proportional to the information content.

Figure 2: Association of BMI with all-cause mortality, by baseline age group



HR, hazard ratio per 5 kg/m^2 unit of BMI in the range BMI >25 kg/m^2 (and 95% CI).

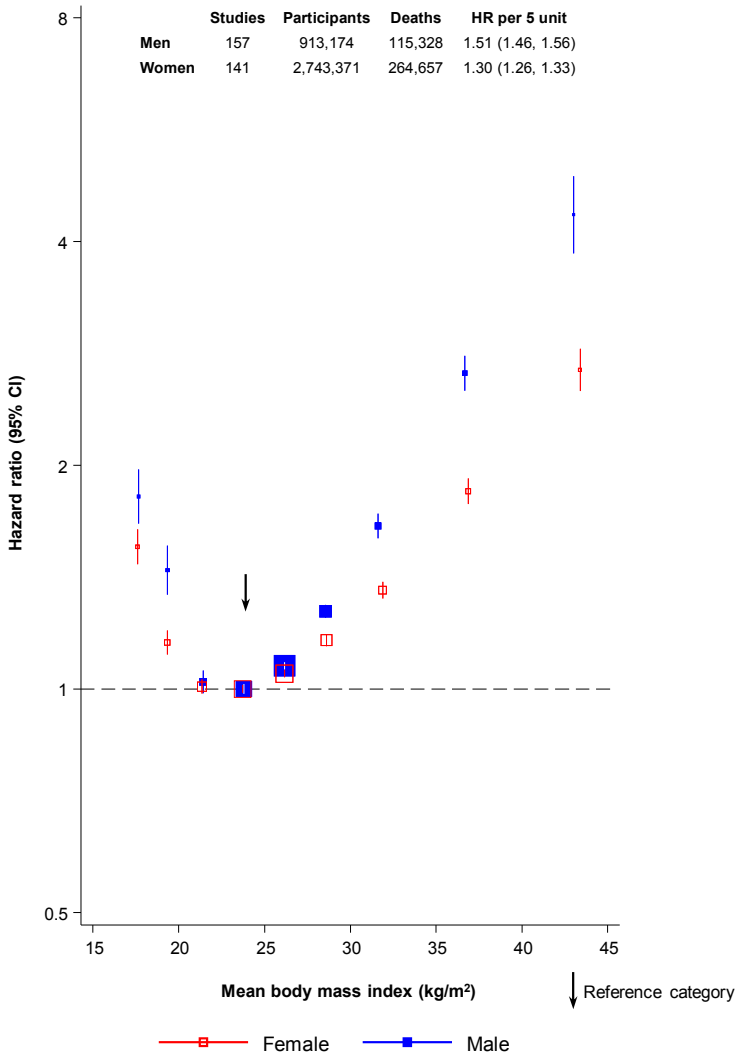
Analyses restricted to never-smokers without pre-existing chronic disease, and excluding the first 5 years of follow-up, and include data from all geographical regions.

BMI groups: 15.0 to <18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30, 30 to <35.0, 35.0 to <40, and 40 to <60 kg/m^2. Reference category (arrow) is 22.5 to <25 kg/m^2.

CIs are from floating variance estimates (reflecting independent variability within each category, including reference). Areas of squares are proportional to the information content.

Analyses by age and the 3 main geographic regions are in eFigure 2.

Figure 3: Association of BMI with all-cause mortality, by sex



HR, hazard ratio per 5 kg/m^2 unit of BMI in the range BMI >25 kg/m^2 (and 95% CI).

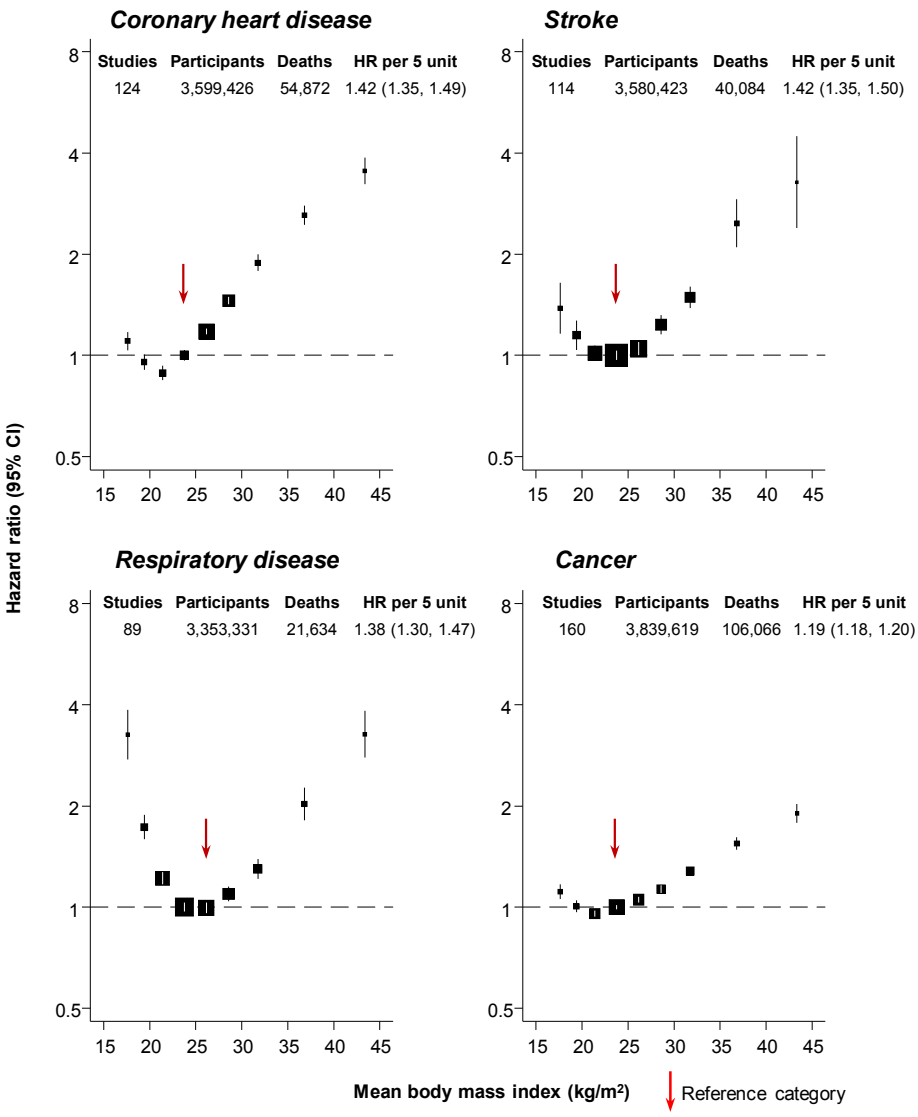
Analyses restricted to never-smokers without pre-existing chronic disease, and excluding the first 5 years of follow-up, , and include data from all geographical regions.

BMI groups: 15.0 to <18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30, 30 to <35.0, 35.0 to <40, and 40 to <60 kg/m^2. Reference category (arrow) is 22.5 to <25 kg/m^2.

CIs are from floating variance estimates (reflecting independent variability within each category, including reference). Areas of squares are proportional to the information content.

Analyses by sex and the 3 main geographic regions are in eTable 10 and eFigures 3-4.

Figure 4: Association of BMI with mortality, by major underlying cause



HR, hazard ratio per 5 kg/m^2 unit of BMI in the range BMI >25 kg/m^2 (and 95% CI). Analyses restricted to never-smokers without pre-existing chronic disease, and excluding the first 5 years of follow-up, and include data from all geographical regions.

BMI groups: 15.0 to <18.5, 18.5 to <20, 20 to <22.5, 22.5 to <25.0, 25.0 to <27.5, 27.5 to <30, 30 to <35.0, 35.0 to <40, and 40 to <60 kg/m^2. Reference category (arrow) is 22.5 to <25 kg/m^2.

CIs are from floating variance estimates (reflecting independent variability within each category, including reference). Areas of squares are proportional to the information content.

Analyses of cause-specific mortality by 3 geographic regions are in eTable 15 and eFigure 5.