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Obesity Comorbidity

A dose-response meta-analysis of the impact of body mass index on stroke and all-cause mortality in stroke patients: a paradox within a paradox

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Summary

The obesity paradox is often attributed to fat acting as a buffer to protect individuals in fragile metabolic states. If this was the case, one would predict that the reverse epidemiology would be apparent across all causes of mortality including that of the particular disease state. We performed a dose-response meta-analysis to assess the impact of body mass index (BMI) on all-cause and stroke-specific mortality among stroke patients. Data from relevant studies were identified by systematically searching PubMed, OVID and Scopus databases and were analysed using a random-effects dose-response model. Eight cohort studies on all-cause mortality (with 20,807 deaths of 95,651 stroke patients) and nine studies of mortality exclusively because of stroke (with 8,087 deaths of 28,6270 patients) were evaluated in the meta-analysis. Non-linear associations of BMI with all-cause mortality ($P < 0.0001$) and mortality by stroke ($P = 0.05$) were observed. Among overweight and obese stroke patients, the risk of all-cause mortality increased, while the risk of mortality by stroke declined, with an increase in BMI. Increasing BMI had opposite effects on all-cause mortality and stroke-specific mortality in stroke patients. Further investigations are needed to examine how mortality by stroke is influenced by a more accurate indicator of obesity than BMI.

Keywords: Body mass index, dose-response meta-analysis, obesity, paradox, stroke.

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Introduction

Among otherwise healthy subjects, increasing body mass index (BMI), generally reflecting an increased level of obesity (1) above a threshold value of around BMI = 23 to 25, is associated with increasing risk of various non-communicable diseases such as type 2 diabetes (2), hypertension and cardiovascular disease (CVD) (3), non-alcoholic fatty liver disease (4) and some forms of cancer (5,6). Consequently, large epidemiological surveys reveal that there is an increasing risk of all-cause mortality with increasing BMI above the threshold level (7–9). Following the onset of some disease states, however, it has been observed that it is the more obese subjects with greater BMI who survive the longest (10). This effect, variously called 'reverse epidemiology' or the 'obesity paradox' has been demonstrated to occur in stroke patients (11–13), as well as sufferers from chronic kidney disease (14,15), CVD (16) and specifically heart failure (HF) patients (17), general surgery patients in intensive care (18), patients with surgically induced peritonitis (19) and patients following bone fractures (20).

The widespread nature of this effect across a variety of seemingly unrelated disorders has led to speculation that it may be an artefact of biased subject selection and hence contributes to biased estimates of obesity-related mortality (21,22). Yet another interpretation, however, is that in the fragile metabolic state following various traumatic events, elevated body fat levels may act as a buffer protecting the individual and therefore facilitating recovery (11,12,23,24). If this latter interpretation is correct then it would be predicted that the mortality paradox would be observed with respect to all causes of mortality among patients with specific disease states and not just in the mortality because of each particular disease. Yet, this distinction has been rarely addressed. To address this topic, we performed a dose-response meta-analysis of studies of stroke patients separating the effects of BMI on all-cause and stroke-specific mortality.

Methods

Search strategy and data extraction

PubMed, OVID and Scopus databases were searched to identify the papers written in English published up to 7 July 2014. Further studies were identified by hand-searching the reference lists of the relevant reviews and meta-analysis. The following key words were used to extract the prospective articles pertinent to the study objectives: 'obesity' OR 'overweight' OR 'Body Mass Index' OR 'BMI' OR 'body weight' OR 'adiposity' OR 'fat mass' OR 'body fat' OR 'body size' OR 'body composition' AND 'death' OR 'survival' OR 'mortality' OR 'prognosis' OR 'paradox' AND 'stroke' OR 'prestroke' OR 'poststroke' AND 'follow-up' OR 'cohort' OR 'prospective studies' OR 'retrospective studies' OR 'longitudinal studies' OR 'observational studies'. The criteria used for study selection included a prospective design, a study population covering adult aged >18 years, assessment of BMI as the exposure of interest, assessment of mortality by stroke or all-cause mortality in stroke patients as the outcome of interest, measurement of the relative risk (RR) or hazard ratio (HR) with corresponding 95% confidence intervals (CIs), measurement of the number of patients and number of cases in each BMI category. The studies were excluded if they were reviews, commentaries, research notes, letters or conference proceedings and if they were conducted on pregnant populations. When duplicate records on the same study population were identified, the bigger sample size study was considered for inclusion in the review. Authors were contacted by email in case extra data were required.

The Newcastle-Ottawa Scale was used to assess the study quality on the bases of parameters including selection, comparability and outcome. Mortality risk estimates were extracted from each study independently by two reviewers. The extracted data included first author's last name, publication year, country, study design, follow-up length, sex, mean age, number of patients and number of cases, adjusted RR/HR with the corresponding 95% CI, case ascertainment, stroke subtype and variable adjusted for in the multivariable analysis. Disagreements in data extraction were settled by consensus with a third reviewer.

Statistical analysis

We calculated HRs related to five-unit increases in BMI for each study by transforming supplied category-specific risk estimates with the use of generalized least squares for trend estimation described by Orsini *et al*. (25).

When the lowest group was not the referent, HRs and CIs were estimated as relating to the referent for which data were required (26). In studies with stratified analyses by sex, the combined estimates of HRs and CIs were calculated using a fixed-effects model.

For the dose-response meta-analysis (25,27), the midpoint of each BMI category was utilized if BMI mean or median for the category was not provided in the study. The open-ended categories were assumed to have the same amplitude as their neighbouring categories.

A two-stage hierarchical regression model (28) was administered to estimate the non-linear dose-response relation across different BMI levels. In this model, the difference between the midpoints of category-specific and reference-specific quadratic terms for BMI, based on studies with non-zero BMI level as reference, was examined. Then, the dose-response relationship, considering within- and between-study variances, was estimated using spline transformations. Random-effects dose-response models using logarithms of HRs and CIs, the number of deaths and the number of participants across BMI categories were performed assuming linearity in the potential relationships.

The Q and I^2 statistics were used for exploring statistical heterogeneity among the included studies. The values of 25%, 50% and 75% were regarded as low, moderate and high heterogeneity, respectively. Stratified analyses by sex, mean or median years of follow-up, the study quality and the time of BMI measurement were conducted to evaluate the potential sources of heterogeneity. We also performed a sensitivity analysis in which a single study was excluded from the analysis at a time to investigate whether different results were obtained. To detect publication bias, the Egger's regression test was applied.

All statistical analyses were performed by Stata v12 software (StataCorp, College Station, TX, USA). Statistical significance was considered at two-sided $P < 0.05$.

Result

The number of articles identified through database searching and other sources was 4,391. Among 2,016 records remaining after duplicates were excluded, 1,907 were removed after looking through the abstracts. Of the 102 full-text articles evaluated, 30 were considered for inclusion in the meta-analysis. Of these records, 13 lacked sufficient data and therefore we contacted the authors of the relevant studies to request the data needed. The authors of three studies shared the requested data (29–31). Thus, eight publications on BMI and total mortality among stroke patients (11–13,30–34) and nine publications on BMI and mortality by stroke (29,35–42) were finally selected for the meta-analysis (Fig. 1).

Study characteristics

All of the papers dealt with either 'all-cause' or 'by stroke' mortality. The cohort studies investigating the association of BMI with all-cause mortality consisted of eight records published from 2009 to 2014 and included 95,651 stroke patients of whom 20,807 patients died. There were two studies performed in the United States (31,32), one in Denmark (11), one in Greece (13), one in Germany (33), two in Korea (12,34) and one in Sweden (30). The participants were prospectively followed for less than 10 years in four studies (11,12,33,34) while the follow-up duration was 10 years and more in the others (13,30–32). BMI was measured by professional staff in all studies except for three (12,33,34) in which no information was provided concerning who made the measurement. There was one study (31) with self-reported and two (30,33) without reported case ascertainment. When the Newcastle-Ottawa scoring system was used to assess the quality of the studies, three records (13,32,34) were of moderate quality and the other five (11,12,30,31,33) were of high quality.

The nine studies on mortality by stroke were published between 2001 and 2014 with the length of follow-up ranging from 1 month to 40 years. There were two publications performed in Japan (36,41), two in China (35,39), one in Denmark (37), one in the United Kingdom (29), one in Scotland (40), one in Norway (38) and one in Korea (42). In total, 28,6270 patients were included and 8,087

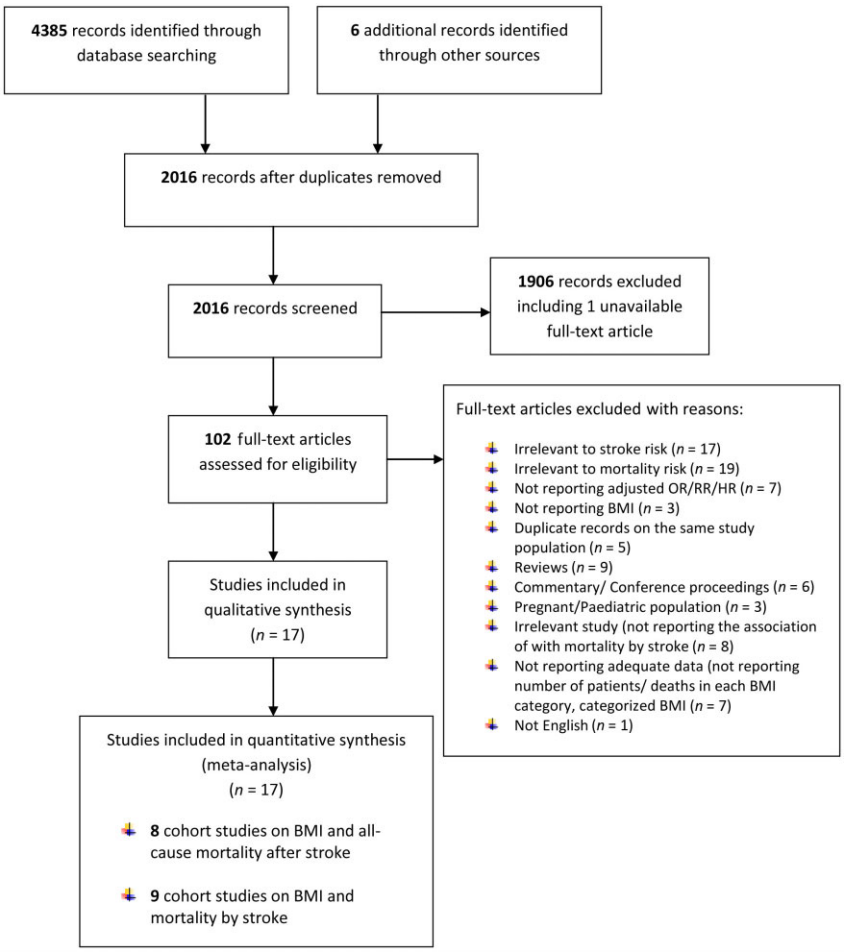

Figure 1 Flow diagram for the study selection.

patients died of stroke. Information on the source of the BMI measurement was not provided in two records (37,40); however, in the remaining (29,35,38,39,41,42), BMI was measured by trained staff except for one (36) in which it was self-reported. Case ascertainment was reported only in two studies (35,39). In quality assessment with the use of the Newcastle-Ottawa scale, three publications (36,37,40) were of moderate quality and the remaining publications (29,35,38,39,41,42) were of high quality.

The findings of the included papers were presented in different BMI categories. In fact, some studies (12,30,31,34,36,38,39,41,42) did not describe patients according to the World Health Organization quartiles. The mean BMI value of 33 kg m^{-2} was the highest assessed in the studies examining the association of BMI with mortality by stroke. Thus, we were not able to yield results over a BMI of >35 kg m^{-2}. This observed heterogeneity in exposure across the studies needed to be accounted for and therefore a generalized least squares for trend estimation method was administered to minimize the existing heterogeneity. As a result, with the use of this method, the clinical consequences of BMI across the entire range could be predicted.

All-cause mortality after stroke

When the random-effects dose-response analysis was used, a significant non-linear relationship ($P < 0.0001$) was found between BMI and all-cause mortality after stroke with the estimate in the correlation matrix of 0.72 and the estimated between studies Standard Deviations (SDs) of 0.03 and 0.01. BMI values lower than 25 kg m^{-2} had a protective effect on overall death rates demonstrating that the risk of all-cause mortality after stroke decreased with the BMI increase up to 21 kg m^{-2}, but increased with a steep slope at BMI levels higher than 23 (Fig. 2a). Comparing the findings with a linear trend using a two-stage random-effects model, we observed that the risk of mortality for every five units of BMI linearly declined by 17% (HR: 0.83, 95% CI: 0.76–0.91, $P < 0.0001$) at BMI below 25. Furthermore, the large goodness-of-fit P-value ($Q = 80.95$, $P < 0.0001$) and the result from I^2 statistics ($P < 0.0001$, $I^2 = 89.1\%$) showed that between-study heterogeneity in the assumed linear relationship was detected. It was also found that no publication bias (Egger's regression test P-value = 0.66) was present among the studies.

To detect the sources of heterogeneity, we carried out subgroup analyses by sex, follow-up years, the score of the study quality and the time when BMI was measured. Despite that heterogeneity was still present, no variations in the shapes of the slopes were observed in all subgroup analyses. For sensitivity analysis, a single study was removed at a time and the analysis as repeated on the remaining studies to assess whether our findings were

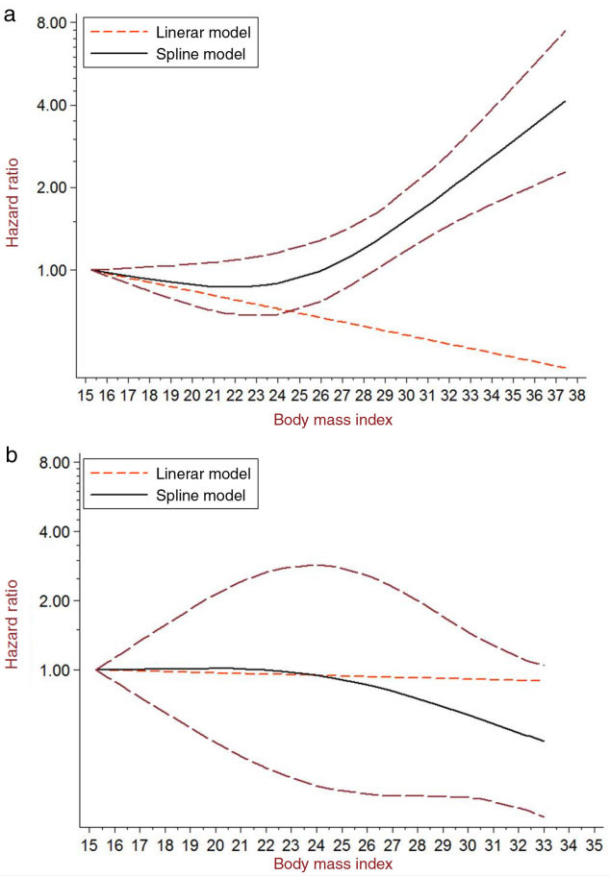

Figure 2 Dose-response associations of body mass index (BMI) with mortality among stroke patients. (a) Non-linear dose-response relationship between BMI and all-cause mortality ($P < 0.0001$). (b) Non-linear dose-response relationship between BMI and mortality by stroke ($P = 0.05$). Non-linear and linear plots are displayed with continuous black and medium-dashed orange-red lines, respectively. Long-dashed maroon lines depict 95% confidence intervals. The log-scale of the hazard ratios are presented on vertical axes.

affected by the excluded studies. When the study by Doehner *et al.* (33) was removed, the slope of mortality rate at BMI higher than 23.5 kg m^{-2} increased and at BMI ranging from 15.2 to 21.5 kg m^{-2}, the risk was reduced with a nadir at 21.5–23.5 kg m^{-2} (Fig. 3a). Leaving out the study by Silventoinen *et al.* (30) substantially increased HRs of all-cause mortality after stroke at BMI higher than 25 kg m^{-2}; in fact, a highly steep slope was observed in the shape of the dose-response plot with the increase in BMI level among overweight and obese individuals (Fig. 3b). As it was suggested that heterogeneity in a dose-response meta-analysis related to the shape of the relationship (25), a better dose-response model ($Q = 10.21$, $P = 0.12$) might be fitted if this particular study was removed. Our result was consistent with the main outcome when other studies were excluded in the sensitivity analysis.

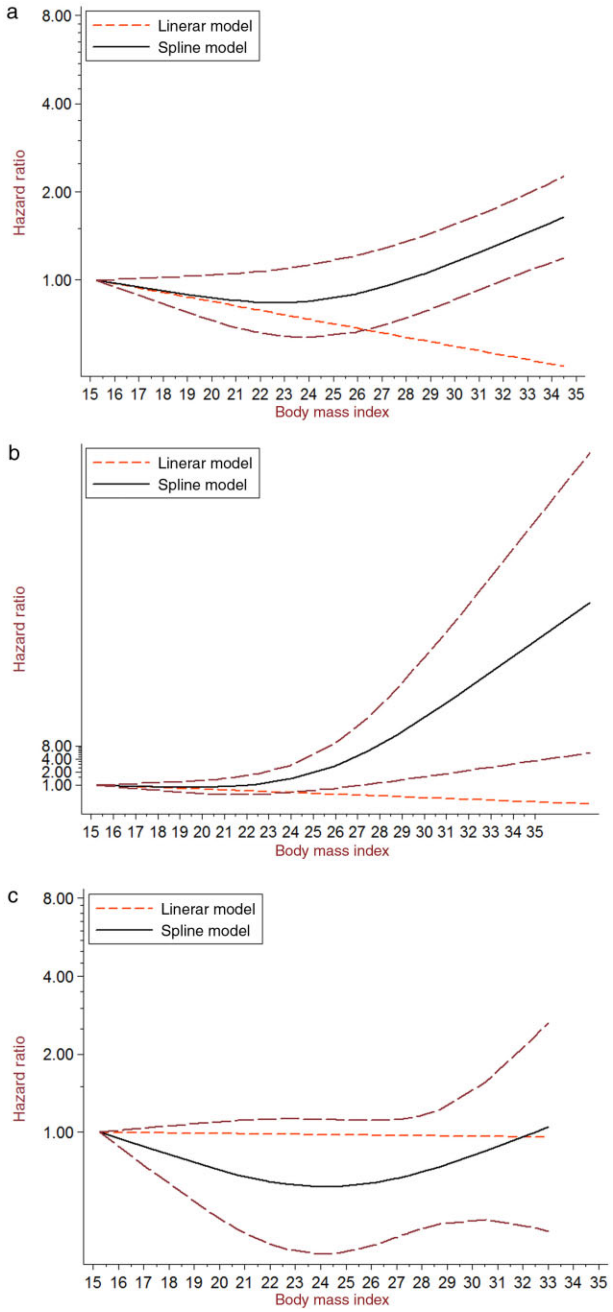

Figure 3 Sensitivity analyses plots displaying non-linear dose-response relationships between body mass index (BMI) and all-cause mortality after stroke with the removal of the studies by Doehner *et al.* (33) (a), Silventoinen *et al.* (30) (b) and non-linear dose-response relationship between BMI and mortality by stroke with the exclusion of the study by Li *et al.* (39). (c). Non-linear and linear plots are displayed with continuous black and medium-dashed orange-red lines, respectively. Long-dashed maroon lines depict 95% confidence intervals. The log-scale of the hazard ratios are presented on vertical axes.

Mortality by stroke

A non-linear relationship was suggested between BMI and mortality by stroke in the random-effects dose-response analysis ($P = 0.05$) with the estimate in the correlation matrix of −1 and the estimated between studies SDs of 0.05 and 0.02 (Fig. 2b). A two-stage random-effects model which was tested to compare the obtained results with the linear trend suggested that every 5 kg m^{-2} increase in BMI was not significantly associated with a decreased risk of mortality by stroke (HR: 0.97, 95% CI: 0.86–1.1, $P = 0.62$). Results from goodness-of-fit ($Q = 117.06$, $P < 0.0001$) and I^2 statistics ($P < 0.0001$, $I^2 = 92.1\%$) showed that potential sources of heterogeneity should be identified. Egger's regression test detected no small study effects ($P = 0.83$) indicating that there was no publication bias among the studies exploring the association of BMI with the risk of mortality by stroke.

The subgroup analyses were conducted to explore the potential sources of heterogeneity. In stratifying analyses on the basis of sex, follow-up duration and the study quality score, it was found that the shapes of dose-response plots were consistent with the main findings in all stratified analyses. In the sensitivity analysis, removal of the study by Li *et al.* (39), accounting for 10.55% of the total sample size, non-significantly altered our main finding ($P = 0.1$) yielding decreasing HRs, with BMI ranging from 15.2 to 24.5 kg m^{-2} and increasing HRs, with BMI levels higher than 24.5 kg m^{-2} (Fig. 3c). Significant non-linear trends similar to the main plot were detected in other sensitivity analyses demonstrating that our main result was not influenced by other studies assessing the association of BMI with the risk of mortality by stroke.

Discussion

In the present dose-response meta-analysis, we observed a non-linear significant association of BMI with total mortality among stroke survivors; with the BMI increase, the risk of overall death increased among overweight and obese individuals. However, BMI levels higher than 24.5 kg m^{-2} was suggested to be inversely and significantly associated with mortality by stroke in a non-linear trend. To our knowledge, our study is the first dose-response meta-analysis to address and comprehensively analyse the findings on BMI and mortality after stroke and present separate analyses on overall death among stroke survivors and mortality by stroke. Following stroke, it is likely that the probability of mortality from further stroke events is diminished because of secondary prevention measures and a 'Hawthorne' effect (special attention) (43). However, it would not be expected that such effects would occur differentially with respect to patient BMI. That is, one would not anticipate a greater Hawthorne effect or greater secondary

prevention effects in more obese relative to less obese patients. Such effects might then be anticipated to change the position of the mortality curve for stroke in relation to BMI, relative to the curve for all-cause mortality in relation to BMI, but would not be anticipated to change the direction of the slope of the relationship as observed in our analysis.

Consistent with our findings on the association of BMI with mortality by stroke, several meta-analyses have been published to summarize and evaluate the available evidence regarding BMI and the risk of mortality by a number of diseases. Overweight and obese patients with chronic HF compared with those with normal weight were reported to be less likely to die of HF (44). Likewise, results from a meta-analysis exploring the effect of BMI on survival of patients with renal cell carcinoma demonstrated less mortality in patients with higher BMI than those with normal levels (45). Furthermore, records of the influence of BMI on CVD mortality supported the existence of an obesity paradox (46). On the other hand, there are reports indicating that death by some particular diseases including coronary heart disease (CHD), CVD and cancer increased among patients with higher BMI levels (47).

Although evidence from a meta-analysis showed that the highest total mortality existed among underweight patients (46), a meta-analysis by Flegal *et al*. suggested that BMI of ≥35 kg m^{-2} was directly related to all-cause mortality compared with BMI within normal range (9). Similarly, overall death was indicated to be associated with BMI by a meta-analysis performed on 26 observational studies (47). Obesity is not only associated with CHD and CVD, the leading causes of death, but it is also the prominent risk factor for hypertension, dyslipidaemia, obstructive sleep apnoea, diabetes and cancer (48), which by themselves lead to numerous complications.

Variations in the findings from meta-analyses assessing BMI-mortality associations might be due to differences in the ages of the examined populations, causes of death and the range of the BMI examined; overweight was associated with lower all-cause mortality and mortality rates from non-cancer and non-CVD causes, while higher overall death and mortality rates from CVD, some cancers, diabetes and kidney diseases were reported among obese patients (49). The age-related explanations proposed for reverse epidemiology, which mediates the relationship between obesity and prolonged survival of elderly patients, might be regarded as a potential mechanisms explaining the better prognosis of overweight and obese stroke patients whose mean age was 60.4 years in our review. First, patients with higher visceral fat accumulation are less likely to die earlier than those with increased less risky lower-body fat mass. This phenomenon demonstrates that among individuals with higher BMI levels, better prognosis belongs to those who are metabolically healthy and therefore do not bear adverse outcomes of obesity (23,24). Furthermore, evidence supporting the age-associated accumulation of subcutaneous fat mass rather than visceral adipose tissue, even a decline in the latter, was linked to a reduction in insulin resistance and type 2 diabetes (23). It has been suggested that the obesity paradox may also be explained using the phenomenon of reverse causation indicating that higher death rate among underweight stroke patients may be due to some age-related illnesses which lead to weight loss and malnutrition in the elderly (24,50). This seems unlikely, however, as it would also be observed in the 'all-cause' mortality data. Other age-linked explanations include ameliorated antioxidant protection caused by decreased oxidation in obese patients with loss of skeletal muscle mass and lower risk of artherosclerosis in survived patients with lower-body obesity (23,24).

Along with age-connected explanations, improved nutritional status and energy reservoirs serving as a protection against mortality and following a healthy lifestyle, to reduce adverse outcomes associated with obesity in patients with higher BMI, may contribute to the obesity paradox in mortality by stroke (11,12,23,24). However, our findings suggested that the pattern of mortality because of stroke and overall mortality rates among obese stroke patients were radically different. If factors such as greater sources of energy or metabolites related to obesity mediated the paradoxical increase in survival of obese stroke patients (12), an obesity paradox would be observed concerning not only stroke but also all-cause mortality.

The strengths of our meta-analysis include examining the probability of non-linear relationships, assessing the studies with various BMI categories with the use of generalized least squares for trend estimation, exploring cohort records exclusively to decrease likelihood of heterogeneity, analysing the impact of BMI separately on all-cause mortality after stroke and mortality by stroke, summarizing homogeneous studies on the basis of the time of BMI measurement in the association of BMI with mortality by stroke, using adjusted risk of death and performing the sensitivity analyses. The present study, however, contains a number of limitations which are worthy of attention. Our main findings might be influenced by confounding factors which existed in the original cohort studies. However, the effect of potential confounding variables on the study outcomes is likely to be limited by excluding studies which reported unadjusted HRs. Furthermore, different follow-up durations in the records evaluated in this review might contribute to heterogeneity across studies. But the shape of the plots did not differ in subgroup analyses by years of follow-up in both of the separate meta-analyses carried out in this study. BMI is an inaccurate and imperfect indicator of body fat (51) and abdominal obesity was suggested to be a more precise predictor of stroke than BMI (52). Thus,

results on the association of BMI with stroke mortality might not best address the research question.

In conclusion, significant non-linear trends exist in both of our dose-response sub-meta-analyses, with 20,807 deaths in eight cohort studies assessing the effect of BMI on overall mortality among stroke patients and the other with 8,087 deaths in nine cohort studies evaluating how mortality by stroke was influenced by BMI. Our findings on the association of BMI with total mortality show a non-linear, increased risk at BMI levels higher than 23 kg m^{-2} and a decreased non-linear trend at BMI ranging from 15.2 to 21 kg m^{-2} with a nadir at 21–23 kg m^{-2}. The results on the other sub-meta-analysis, however, indicate that BMI levels higher than 24.5 kg m^{-2} was inversely associated with mortality by stroke. To evaluate the effect of adiposity on stroke mortality, further research is required using direct measurement of body fat rather than BMI. Whether this paradox within a paradox pertains for other disease states, and its causes, remains unknown.

Conflict of interest statement

No conflict of interest was declared.

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References

1. Romero-Corral A, Somers VK, Sierra-Johnson J *et al*. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)* 2008; **32**: 959–966.
2. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994; **17**: 961–969.
3. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. *Obes Res* 2002; **10**(S12): 97S–104S.
4. Browning JD, Szczepaniak LS, Dobbins R *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387–1395.
5. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003; **348**: 1625–1638.
6. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; **4**: 579–591.
7. 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**: 2211–2219.
8. Prospective Studies Collaboration, Whitlock G, Lewington S *et al*. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373**: 1083–1096.
9. 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**: 71–82.
10. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; **81**: 543–554.
11. Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. *Int J Stroke* 2015; **10**: 99–104.
12. Kim BJ, Lee S-H, Ryu W-S, Kim CK, Lee J, Yoon B-W. Paradoxical longevity in obese patients with intracerebral hemorrhage. *Neurology* 2011; **76**: 567–573.
13. Vemmos K, Ntaios G, Spengos K *et al*. Association between obesity and mortality after acute first-ever stroke the obesity–stroke paradox. *Stroke* 2011; **42**: 30–36.
14. Abbott KC. Reverse epidemiology and obesity in maintenance dialysis patients. *Kidney Int* 2003; **64**: 1138–1138.
15. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 2004; **80**: 324–332.
16. Uretsky S, Messerli FH, Bangalore S *et al*. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med* 2007; **120**: 863–870.
17. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008; **156**: 13–22.
18. Hutagalung R, Marques J, Kobylka K *et al*. The obesity paradox in surgical intensive care unit patients. *Intensive Care Med* 2011; **37**: 1793–1799.
19. Utzolino S, Ditzel CM, Baier PK, Hopt UT, Kaffarnik MF. The obesity paradox in surgical intensive care patients with peritonitis. *J Crit Care* 2014; **887**: e1–887. e5.
20. Prieto-Alhambra D, Premaor MO, Avilés FF *et al*. Relationship between mortality and BMI after fracture: a population-based study of men and women aged ≥40 years. *J Bone Miner Res* 2014; **29**: 1737–1744.
21. Masters RK, Powers DA, Link BG. Obesity and US mortality risk over the adult life course. *Am J Epidemiol* 2013; **177**: 431–442.
22. Banack HR, Kaufman JS. The 'obesity paradox' explained. *Epidemiology* 2013; **24**: 461–462.
23. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. *Diabetes Care* 2013; **36**(Suppl. 2): S276–S281.
24. Oreopoulos A, Kalantar-Zadeh K, Sharma AM, Fonarow GC. The obesity paradox in the elderly: potential mechanisms and clinical implications. *Clin Geriatr Med* 2009; **25**: 643–659.
25. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata Journal* 2006; **6**: 40–57.
26. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008; **27**: 954–970.
27. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; **135**: 1301–1309.
28. Liu Q, Cook NR, Bergström A, Hsieh CC. A two-stage hierarchical regression model for meta-analysis of epidemiologic non-linear dose–response data. *Comput Stat Data Anal* 2009; **53**: 4157–4167.
29. Ferrie JE, Singh-Manoux A, Kivimäki M *et al*. Cardiorespiratory risk factors as predictors of 40-year mortality in women and men. *Heart* 2009; **95**: 1250–1257.

30. Silventoinen K, Tynelius P, Rasmussen F. Weight status in young adulthood and survival after cardiovascular diseases and cancer. *Int J Epidemiol* 2014; **43**: 1197–1204.
31. Towfighi A, Ovbiagele B. The impact of body mass index on mortality after stroke. *Stroke* 2009; **40**: 2704–2708.
32. Bell CL, LaCroix A, Masaki K *et al*. Prestroke factors associated with poststroke mortality and recovery in older women in the Women's Health Initiative. *J Am Geriatr Soc* 2013; **61**: 1324–1330.
33. Doehner W, Schenkel J, Anker SD, Springer J, Audebert HJ. Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the TEMPiS trial. *Eur Heart J* 2013; **34**: 268–277.
34. Kim BJ, Lee SH, Jung KH, Yu KH, Lee BC, Roh JK. Dynamics of obesity paradox after stroke, related to time from onset, age, and causes of death. *Neurology* 2012; **79**: 856–863.
35. Bazzano LA, Gu D, Whelton MR *et al*. Body mass index and risk of stroke among Chinese men and women. *Ann Neurol* 2010; **67**: 11–20.
36. Cui R, Iso H, Toyoshima H *et al*. Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC study. *Stroke* 2005; **36**: 1377–1382.
37. Dehlendorff C, Andersen KK, Olsen TS. Body mass index and death by stroke: no obesity paradox. *JAMA Neurol* 2014; **71**: 978–984.
38. Ellekjær H, Holmen J, Vatten L. Blood pressure, smoking and body mass in relation to mortality from stroke and coronary heart disease in the elderly. A 10-year follow-up in Norway. *Blood Press* 2001; **10**: 156–163.
39. Li Y, Sun Y, Sai X *et al*. Factors affecting rate of stroke-related death in elderly male military population a 23-year cohort study of 1 268 cases in Xi'an, China. *Neural Regener Res* 2011; **6**: 1031–1036.
40. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJV. Long-term cardiovascular consequences of obesity: 20-Year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). *Eur Heart J* 2006; **27**: 96–106.
41. Oki I, Nakamura Y, Okamura T *et al*. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-Year follow-up of NIPPON DATA80. *Cerebrovasc Dis* 2006; **22**: 409–415.
42. Yi SW, Odongua N, Nam CM, Sull JW, Ohrr H. Body mass index and stroke mortality by smoking and age at menopause among Korean postmenopausal women. *Stroke* 2009; **40**: 3428–3435.
43. Tajer CD. RAC director's letter. The obesity paradox. Intention of making a reasonable suggestion for secondary prevention. *Rev Argent Cardiol* 2012; **80**: 195–204.
44. Padwal R, McAlister FA, McMurray JJV *et al*. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes* 2013; **38**: 1110–1114.
45. Choi Y, Park B, Jeong BC *et al*. Body mass index and survival in patients with renal cell carcinoma: a clinical-based cohort and meta-analysis. *Int J Cancer* 2013; **132**: 625–634, 45.
46. Sharma A, Vallakati A, Einstein A *et al*. Relationship of Body Mass Index with total mortality, cardiovascular mortality and myocardial infarction after coronary revascularization: evidence from a meta-analysis. *J Am Coll Cardiol* 2014; **63**(12_S): 1080–1100.
47. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* 2005; **15**: 87–97.
48. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular diseaserisk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009; **53**: 1925–1932.
49. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007; **298**: 2028–2037, 49.
50. Löser C, Lübbers H, Mahlke R, Lankisch PG. CME: involuntary weight loss in elderly people. *Dtsch Arztebl* 2007; **104**: 3411–3420.
51. Kennedy AP, Shea JL, Sun G. Comparison of the classification of obesity by BMI vs. dual-energy X-ray absorptiometry in the Newfoundland population. *Obesity* 2009; **17**: 2094–2099.
52. Winter Y, Rohrmann S, Linseisen J *et al*. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. *Stroke* 2008; **39**: 3145–3151.

