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REVIEW

Age-dependent decline of association between obesity and mortality: A systematic review and meta-analysis

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KEYWORDS
Obesity;
Mortality;
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Summary
Objective: It is debatable if the strength of obesity—mortality association depends on age. The objective of this study was to investigate the influence of age on the obesity—mortality association in men and women, and to assess if adjusting for major confounding factors altered the age-dependent trend of the obesity—mortality association.
Design and methods: Articles were identified by searches of PubMed through 15 August 2013. Twenty studies which reported two or more age-specific effect estimates were identified. A random-effect approach was applied to estimate pooled effect sizes for different age groups.
Results: There was a significant heterogeneity among studies within each age group in the effect estimates for the association between obesity and mortality. The pooled hazard ratio estimates decreased with increasing age from 1.59 (95% confidence interval, 1.46—1.72) for men and 1.60 (1.49—1.72) for women under 35 years to 1.11 (1.08—1.15) for men and 1.11 (1.09—1.14) for women 75 years or older. On average, the effect estimate was decreased by about 10% with every 10 years increase in age.
Conclusions: Adjusting for known confounding factors of smoking, pre-existing illness, hypertension and diabetes has little impact on the age-dependent decline trend of the obesity—mortality association. Therefore, the strength of the association between obesity and mortality weakens with increasing age.

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Introduction

It is well accepted that obesity is associated with significantly higher risk of all-cause mortality [1,2]. It is still debatable if the strength of obesity—mortality association depends on age. Increasing evidence suggests that the association between obesity and mortality declines with advancing age [3—5]. A diminishing association with age has also been reported between obesity and cardiovascular disease [6,7]. However, in a recent study, Masters et al. argued that the weakening obesity and mortality association with age was derived from biased estimates of the relationship because the models of those studies failed to account for confounding influences [8]. They suggested that the estimates of the obesity—mortality relationship became stronger with increasing age, which contradicted the findings from previous reports.

Understanding whether the obesity—mortality association is modified by age is important for defining optimal weight and for guiding weight control efforts among people of different ages. Individual reports about age effects on the obesity—mortality association have often attracted criticisms mainly about biases due to uncontrolled confounding [9—13]. Although there are a number of review articles examining the association between obesity and mortality [1,2,14], the literature reporting the effect of age on the obesity—mortality association has not been systematically reviewed. Studies on this topic require large samples to generate and compare age-specific effect estimates. Confounding has been considered as one of the major threats to the validity of those observational studies. Generally, different sets of potential confounding factors were controlled for in different studies even though smoking and pre-existing illness have generally been considered as confounding factors. On the other hand, adjusting for some intermediate variables in the causal pathway may diminish the estimates of the true association between obesity and mortality (over-adjusting) [15].

The objective of this study was to review evidence about the influence of age on the obesity—mortality association in men and women. To achieve this objective, we compiled and summarised the published age specific hazard (or risk) ratios of all-cause mortality for obesity in cohort studies that had provided age specific risk ratios for two or more age groups. Since confounding is the focus of the debate, we also compiled confounding factors adjusted for in those studies and assessed whether adjusting for smoking and pre-existing illness provided different age trends of the obesity—mortality association.

Methods

Study search and selection

Articles were identified by searches of PubMed through 15 August 2013. Searching the following combinations of key words in titles: ''Weight or BMI or Body mass index or Obesity) and (Mortality), not (patient*, adolescen*, child*, neonat*, infant*, pregnant*, cancer*), we retrieved 564 articles as shown in Fig. 1. Reading through the titles and abstracts of those articles, we excluded 394 papers focusing on special groups of patients and animals. The remaining170 manuscripts were reviewed to identify those articles which used BMI categories to define obesity in prospective cohort studies and assessed the association between obesity and all-cause mortality in either men or women or both. We identified twenty research articles which reported age specific hazard (or risk) ratios for two or more age groups in the same study for the final analysis of this review [4,5,8,16—32].

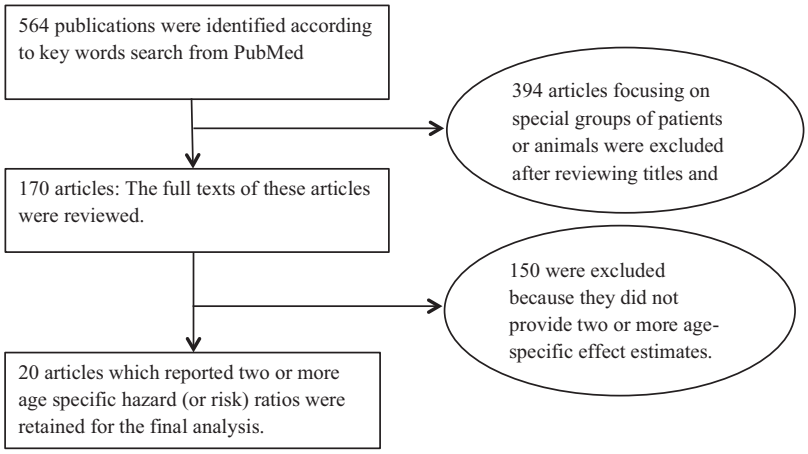

Figure 1 A flow chart of study selection process.

Obesity

BMI cutoff values were used to define obesity in those studies. If available in the original reports, we chose BMI $\geq 30\,kg/m^2$ to define obesity as it is the most commonly used definition, which was used in 14 studies. When multiple BMI categories were used to assess the association between BMI and mortality, BMI cutoff closest to $30\,kg/m^2$ was chosen for the analysis in this study, and all BMI groups higher than $30\,kg/m^2$ were combined as one group. BMI $\geq 27\,kg/m^2$ was used to define obesity in two studies of Asian populations [16,18]. To focus on our research objective, we did not include the overweight group (BMI 25—29.9 kg/m^2) in this study.

Effect estimates: hazard (risk) ratios of all-cause mortality for obesity

The hazard (risk) ratios of all-cause mortality for obesity were calculated with normal weight (BMI within 18.5—24.9 kg/m^2) as the reference group. Two studies used the lowest BMI group as reference to estimate hazard ratios [18,29]. To make their results comparable to those of other studies, we recalculated the hazard ratios using the normal BMI group as reference.

Some studies directly reported hazards ratios for obesity as one group while most studies divided obese participants into multiple subgroups according to BMI levels and reported 2 or more hazard ratios for different BMI groups [8,17—19,21—23,26,28,30]. For those latter studies, a pooled effect estimate for BMI $\geq 30\,kg/m^2$ was calculated for each age and sex specific group using the Mantel—Haenszel method [33].

Assessing influence of age on obesity—mortality association

From each individual study, we obtained age-specific hazard ratios of mortality for obesity. To examine if the obesity—mortality association increased or decreased with age, we plotted effect estimates against age. Different studies had different age categories with different age intervals. To obtain approximately summary effects, we re-categorised age as <35, 35—44, 45—54, 55—64, 65—74 and 75+ years according to the lower bound of age range for each age group. For example, an age group of 50—60 years in the original article was assigned to the new 45—54 year group as we were unable to split those original participants into different groups. The pooled log-transformed hazard ratios and their 95% confidence intervals were calculated using two meta-analytic methods: a fixed effects model with inverse-variance weighting and a random effects model with DerSimonian—Laird weighting [34]. We calculated the quantity I^2 to describe the degree of heterogeneity among studies within each age group [35].

The trends of effect estimates with age were assessed using the multilevel mixed-effects linear regression with Stata *xtmixed* command. The dataset was set up as panel data with each individual study as a panel and age as a time variable. This age variable was centred to 50 years in the unit of 10 years as (age − 50)/10. The dependent variable of the mixed effects regression model was the logarithmic scale of hazard ratio, log(HR). The coefficient of age was used to estimate the linear change in log(HR) corresponding to every 10-year increase in age. Therefore, the exponentiated value of this coefficient was presented as the ratio of hazard ratios corresponding to 10-year

Table 1 Summary of papers reporting age-specific hazard (or risk) ratios of mortality for obesity in men and women.

Author	Location	Sample size	Deaths	Follow-up time (years)	Age categories	BMI (kg/m^2)		Confounding factors
						Obesity	Reference	
Masters et al. [8]	USA	373,185 (M) 416,908 (F)	64,443 (M) 58,937 (F)	Up to 21	25–34, 35–44, 45–54, 55–64, 65–74, 75–84, ≥85	≥30	18.5–29.9	Age, education, income, marital status, region of residence, race
Pan et al. [18]	Taiwan	53,177 (M) 58,772 (F)	3211 (M) 2134 (F)	~10	20–39, 40–59, ≥60	>27	18.5–23.9	Age, age squared, smoking
Tsai and Hsiao [16]	Taiwan	2357 (M) 2083 (F)	–	4	53–64, 65–74, ≥75	>27	21–27	Age, smoking, drinking, exercise, hypertension, diabetes, heart disease, stroke, cancer and kidney disease
Park et al. [17]	USA	83,200 (M) 100,011 (F)	19,678 (M) 15,986 (F)	12.5 (mean)	45–54, 55–64, 65–75	≥30	23–24.9	Age, drinking in never smokers without pre-existing diseases
Fontaine et al. [19]	USA	16,798 (M & F)	5186 (M & F)	5–18	18–59, 60–69, ≥70	≥30	18.5–24.9	Sex, smoking
Nagai et al. [20]	Japan	21,038 (M) 22,934 (F)	3685 (M & F)	12	46–64, 65–79	≥30	23–24.9	Age, weight change, smoking, alcohol drinking, physical activity, liver disease, kidney disease, hypertension, diabetes
Berrington de Gonzalez et al. [21]	USA	1.46 million (M & F)	160,089 (M & F)	10 (median) 5–28	20–49, 50–59, 60–69, 70–84	≥30	22.5–24.9	Sex, alcohol drinking, education, marital status, physical activity
Kuk te al [22]	USA	4437 (M) 5166 (F)	1045 (M) 599 (F)	8.7 (mean)	18–64, 65–74, ≥75	≥30	18.5–24.9	Income, ethnicity, smoking, alcohol intake, physical activity, and dietary fat content
Reuser et al. [23]	USA	16,192 (M & F)	–	7.8 (mean) 1–10.8	55–79, ≥80	≥30	18.5–24.9	Smoking and education
Moore et al. [25]	USA	50,186 (F)	5201 (F)	10–	40–64, 65–93	≥30	21–23.4	Age, menopausal hormone use, income, education, race, smoking, physical activity
Pednekar et al. [24]	India	88,658 (M) 59,515 (F)	9589 (M) 3412 (F)	5–6	35–59, ≥60	≥30	18.5–24.9	Age, education, mother tongue and tobacco use
Adams et al. [26]	USA	313,047 (M) 54,925 (F)	42,173 (M) 19,144 (F)	Up to 10	50–55, 56–60, 61–65, 66–71	≥30	23.5–24.9	Age, race, education, smoking, physical activity, alcohol intake
Corrada et al. [5]	USA	13,451 (M & F)	11,203 (M & F)	Up to 23	59–69, 70–74, 75–79, ≥80	≥30	18.5–24.9	Age, smoking, physical activity, hypertension, angina, myocardial infarction, stroke, diabetes, arthritis and cancer

Thorpe and Ferraro [32]	USA	4679 (M & F)	—	About 20	25—47, 50—74	≥30	18.5—24.9	Age, sex, race, live alone, widowed, education, income, private medical insurance, medicaid, regular physician, smoking, exercise, heart failure, hypertension, diabetes, cancer, non-serious illness
Stevens et al. [27]	USA	62,116 (M) 262,965 (F)	8946 (M) 22,465 (F)	—	30—39, 40—49, 50—59, 60—69, 70—79	≥30	18.5—24.9	Never smokers, pre-existing cancer and heart disease excluded
Bender et al. [4]	Germany	1591 (M) 4602 (F)	663 (M) 365 (F)	14.8 (Median)	18—29, 30—39, 40—49, 50—74	Obese	Standard population	Age standardised
Calle et al. [28]	USA	457,785 (M) 588,369 (F)	113,517 (M) 88,105 (F)	14	30—64, 65—74, ≥75	≥30	23.5—24.9	Age, education, physical activity, alcohol use, marital status, aspirin use, fat, vegetable consumption, use of oestrogen in women, never smokers, no history of cancer, heart disease, stroke, respiratory illness, and no current illness
Lindsted and Singh [29]	USA	12,576 (F)	3280 (F)	26	30—54, 55—74	>27.4	23.0—24.8	Age, alcohol use, education, marital status, never smokers
Rissanen et al. [30]	Finland	17,159 (F)	898 (F)	12	25—54, ≥55	Quintile IV & V	Quintile II	Age, region, smoking
Rissanen et al. [31]	Finland	22,995 (M)	8146 (M)	12	25—54, ≥55	≥31	22.0—24.9	Age, region, smoking

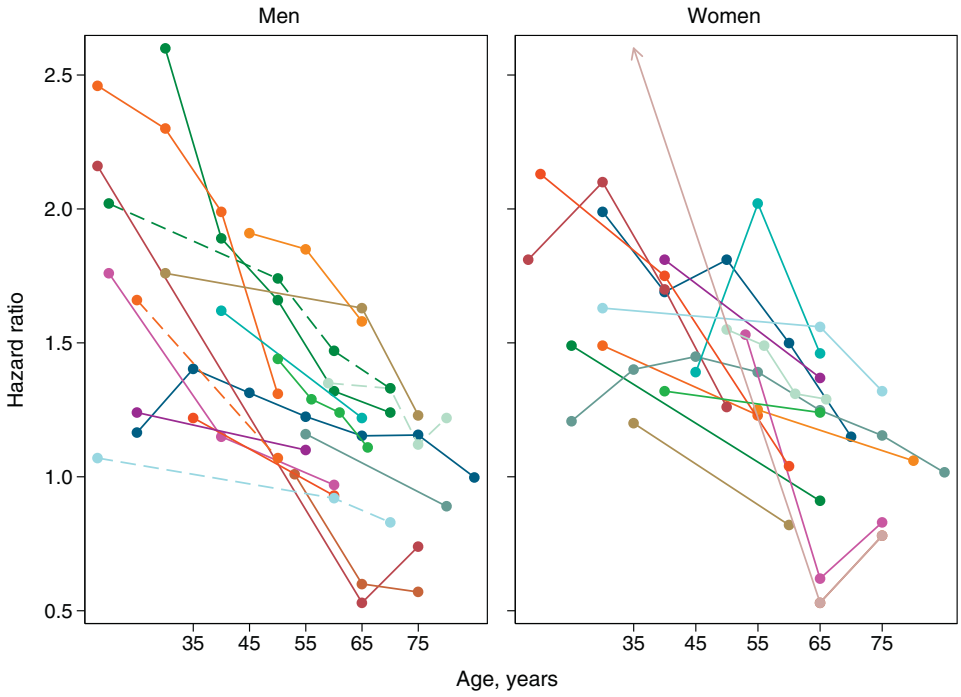

Figure 2 Hazard ratios estimates of all-cause mortality for obesity by age and sex. Each line represents one study. Dashed lines represent studies only reported data of men and women combined. Age represents the lower bound of age range for each age group in the original studies.

increase in age. Since the US populations were over represented in those published studies, we also calculated the trend separately for the non-US and US populations.

Assessing the impact of confounding

To assess if adjusting for major confounding factors produced different age-dependent trends of the obesity—mortality association estimates, we performed several subgroup analyses. Smoking and pre-existing illness have been considered as major confounding factors. As hypertension and diabetes have been considered as intermediates in the causal pathway between obesity and mortality, adjusting for those variables might dilute the true obesity—mortality association [15]. We stratified all identified studies into subgroups according to whether those variables were taken into consideration either by limiting study participants to a homogenous status such as non-smokers or those free from pre-existing illness, or by including those potential confounding variables in the Cox proportional hazards regression. The average trend was expressed as ratio of effect estimates over 10 year increase in age. We calculated the age trends in the obesity—mortality association for subgroups with different confounding variables controlled for. All analyses were performed with Stata SE 12 [36].

Results

Among twenty studies, 12 studies included both men and women and reported age specific effect estimates for men and women separately, 4 studies only reported age specific estimates for a combined group of men and women, 3 studies included women only and 1 study men only. Thirteen studies were conducted in the USA [5,8,16,17,19,21—23,25—29], and 2 in Taiwan [16,18], 2 in Finland [30,31], 1 in Germany [4], 1 in India [24], and 1 in Japan [20], with a total sample size of 4.6 million participants with various follow-up times (Table 1). The identified studies generally had large sample sizes to be able to estimate multiple age specific associations, eight of the 20 studies with more than 100,000 participants each. Different sets of confounding factors were adjusted for in different studies and commonly adjusted variables included age, smoking, and pre-existing illness.

Fig. 2 shows the hazard ratios of mortality for obesity by age and sex in different studies. Fifteen studies reported age specific hazard (or risk) ratios for women and thirteen studies for men. Four studies did not separate two genders. There was a clear weakening trend with increasing age in the strength of the association between obesity and mortality in both men and women. Only in one study, the middle age group women had a

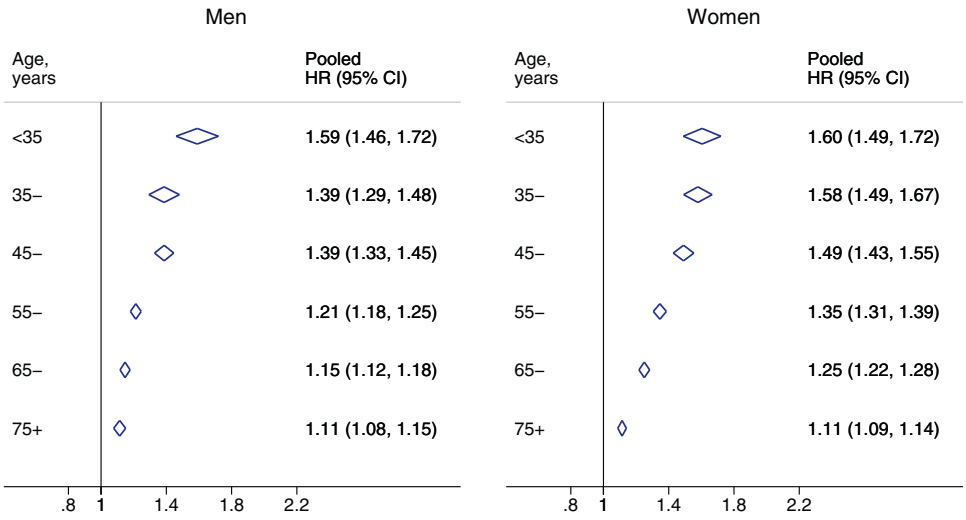

Figure 3 Pooled hazard ratios by age and sex: fixed effect estimates.

stronger association than younger and older age groups [17].

Pooled effect estimates were calculated for the regrouped age categories: <35, 35—44, 45—54, 55—64, 65—74, and 75+ years. The fixed effects and random effects estimates are presented in Figs. 3 and 4, respectively. The fixed hazard ratio estimates declined with increasing age in both sexes, from 1.59 for men and 1.60 women under 35 years to 1.11 for both men and women 75 years or older. A similar pattern was observed in random effect estimates. The between-study heterogeneity was statistically significant ($P < 0.05$) within each age category: as indicated by the values of I^2: 75.7, 78.2, 64.2, 81.4, 89.4, and 82.5 for <35, 35—44, 45—54, 55—64, 65—74, and 75+ age categories, respectively, for men. For women, the corresponding I^2 values were 51.7, 71.7, 85.7, 90.2, 89.3 and 91.8, respectively. Even if the point estimates from several individual studies suggest the obesity might have protective effect (Fig. 2) for those in the oldest age group with hazard ratio <1, the pooled estimate was significantly higher than the null effect value for both men and women in fixed effects estimates.

As shown in Table 2, the trend in the effect estimates of obesity—mortality association decreased 12% for men (ratio: 0.88) and 11% for women (ratio: 0.89) with 10 year-increase in age. The studies in which the confounding effects of smoking were taken into consideration produced a similar trend level. In six studies, smoking was controlled for by only including never smokers in the analysis while in other 12 studies smoking was adjusted for using multiple regression techniques (such as Cox proportional hazards model). The similar declining trend was observed in both groups of studies regardless which method was used. Only two studies did not control for smoking in which the decreasing trend over age was also observed. Controlling for pre-existing illness did not change the decreased trend with age. The age trend estimates remained the same, about 10% decrease in effect estimates with 10 year increase in age, regardless whether diabetes and hypertension were adjusted for or not. The trend estimates were also similar for US and non-US populations.

Discussion

This study presents comprehensive assessment of the effect of age on the obesity—mortality association. Our analysis supports the weakening trend of obesity—mortality association with increasing age. Such a trend commonly exists in different populations and cannot be fully explained by the confounding effects of smoking and pre-existing illness. Those findings have implications for future research, health policy and health education.

It has been debated about over decades on whether the excess mortality associated with obesity declines with age. Early studies have been criticised for failure to control for confounding effects [15,37—39]. Major confounding factors include cigarette smoking and pre-existing illness (or weight loss due to existing illness). Recently, an increasing number of studies have controlled for cigarette smoking and pre-existing illness on the obesity—mortality association. Previous reviews have shown that neither smoking nor pre-existing illness confound the association between obesity

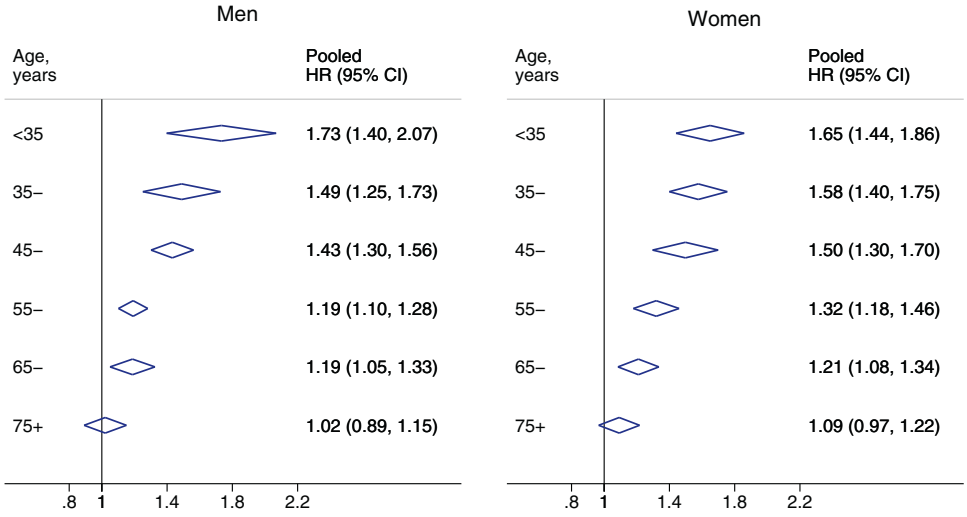

Figure 4 Pooled hazard ratios by age and sex: random effect estimates.

and mortality [1,40—42]. Our study focused on the age dependent trend of obesity—mortality association. We found that controlling for cigarette smoking did not alter the declining trend with age regardless the techniques being used: by including never smokers only in the study or by using multiple regression techniques. Again further adjusting for pre-existing illness did not weaken the declining trend with age. Therefore, our study does not support the suggestion that smoking and pre-existing illness are major causes of bias on the age-dependent decline of the obesity—mortality association.

Another potential criticism on the age-trend of obesity—mortality association is over-adjustment. The relation between obesity and mortality is partially mediated by other risk factors including hypertension, glucose intolerance, hyperlipidaemia and diabetes [15]. Adjusting for those factors may reduce the strength of the association between obesity and mortality. In our study, adjusting for diabetes and hypertension did not alter the

Table 2 Age trend: random effect estimates of ratio of hazard ratios corresponding to 10 year increase in age in different groups.

Groups	Number of studies	Ratio change per 10 years in age	95% CI	*P*[a]
Sex				
Men	13	0.88	0.84, 0.92	<0.001
Women	15	0.89	0.85, 0.94	<0.001
Population				
Non-USA	7	0.88	0.83, 0.93	<0.001
USA	13	0.90	0.86, 0.94	<0.001
Smoking				
Controlled for	18	0.89	0.86, 0.92	<0.001
Not controlled for	2	0.91	0.84, 0.99	0.022
Methods				
Never smokers only	6	0.91	0.88, 0.95	<0.001
Multiple regression	12	0.89	0.84, 0.94	<0.001
Diabetes and hypertension				
Controlled for	4	0.88	0.80, 0.96	0.0028
Not controlled for	16	0.90	0.87, 0.93	<0.001
Pre-existing illness				
Controlled for[b]	11	0.89	0.85, 0.94	<0.001
Not controlled for	9	0.90	0.85, 0.94	<0.001

[a] *P* values for testing the null hypothesis: ratio change = 1.
[b] Smoking was also controlled for in those studies.

age-dependent decline of the obesity—mortality association. Due to limited published data available on other variables, we could not assess all possible variables. However, over-adjustment could have little impact on the age trend in obesity—mortality association. Several studies reported hazard ratios from different models adjusting for different sets of variables [5,20,23,32]. Those studies consistently showed a declining trend with age in all models. Third, an age dependent decline was also observed in studies in which the possible intermediate variables in the causal pathway were not controlled for. Therefore, it is unlikely that over-adjustment can explain the weakening trend in obesity—mortality association over age.

Our study has shown significant heterogeneity in the obesity—mortality association across reviewed studies within each age group. These differences can be at least partly explained by differences in age and BMI distributions among studies. Nevertheless, the weakening obesity—mortality association appears to be a common phenomenon in all studies. In addition, several studies which assessed age trend of obesity—mortality association were not included in this review because those studies provided insufficient data in the original reports or used fundamentally incomparable methods [3,39,43—45]. However, all those studies also show an age-dependent decline trend based on the reported point effect estimates for different age groups.

In a recent study, Masters et al. concluded that when confounding factors were accounted for in the Cox survival models, the obesity—mortality relationship became substantially stronger with increasing age [8]. They suggested that the findings by others showing the weakening obesity—mortality association with age in the United States stemmed from survival models that incorrectly estimated the obesity—mortality relationship. Masters et al. might have misinterpreted their coefficients from the Cox proportional hazards model because coefficients of interaction terms between age and obesity were ignored. When interaction terms were taken into consideration, their data also showed a decreasing trend with increasing age [46], a similar age-dependent decline as in other studies.

One of the strengths of our study is the large sample size included to produce robust age specific effect estimates. Additionally, studies adjusting for various sets of confounding factors were included in this review and we performed subgroup analyses to assess impact of adjusting for major confounding factors on the age-dependent decline of the obesity—mortality association. Our study has limitations. First, although the normal weight group according to BMI values was used as reference to calculate effect estimates, the BMI range for the reference group varied among studies, and so did the obesity cutoff values. Second, studies in this area were predominately conducted in the United States, and data overlapping was possible among some studies. For example, three studies used the data from the Third National Health and Nutrition Examination Survey (NHANES III) [19,22,27]. However, excluding those studies had little impact on our results. Although those studies are over represented by data from the USA, the trend is likely to be true in other populations as a similar trend was observed in non-US studies. Third, since the age range and age grouping varied substantially among those studies, our pooled effect ratios for different subgroups were only rough estimates. The pooled effect in this study for those 75 years or older was still significantly higher than 1, suggesting overall obesity still increases the risk of mortality in this age group. However, several studies reported effect estimates less than 1 for oldest age group, suggesting that obesity might be protective for some subgroups of seniors in those studies. With significant heterogeneity among studies with this age group, further analysis with more detailed age grouping is needed to assess if obesity is a protective or risk factor for those older than 75 years. Finally, only four known factors as potential confounders were assessed in this study. Residual confounding and confounding due to other factors could still influence the age trend of obesity—mortality association.

In summary, the obesity—mortality association decreases considerably with age in both sexes. The age-dependent decline of obesity—mortality association has been observed consistently in different populations. This decline cannot be explained by known confounding effects, neither can be explained by over adjustment for intermediate variables in the causal pathway. Therefore, obesity may play a more important role in the elevated mortality risk in younger people than in older people.

Conflict of interest

None.

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References

[1] 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.

[2] Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. Obes Rev 2007;8:41—59.

[3] Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. N Engl J Med 1998;338:1—7.

[4] Bender R, Jockel KH, Trautner C, Spraul M, Berger M. Effect of age on excess mortality in obesity. JAMA 1999;281:1498—504.

[5] Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A. Association of body mass index and weight change with all-cause mortality in the elderly. Am J Epidemiol 2006;163:938—49.

[6] 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;377:1085—95.

[7] Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 1995;141:1117—27.

[8] Masters RK, Powers DA, Link BG. Obesity and US mortality risk over the adult life course. Am J Epidemiol 2013;177:431—42.

[9] Willett WC, Hu FB, Thun M. Overweight, obesity, and all-cause mortality. JAMA 2013;309:1681.

[10] Welborn TA, Dhaliwal SS. Body-mass index and mortality among white adults. New Engl J Med 2011;364, 781-.

[11] Pesola GR. Age, body-mass index, and mortality. N Engl J Med 1998;338:1159.

[12] Redberg RF. Age, body-mass index, and mortality. N Engl J Med 1998;338:1159.

[13] Abhyankar S, McDonald CJ. Overweight, obesity, and all-cause mortality. JAMA 2013;309:1680—1.

[14] Chen Z, Yang G, Offer A, Zhou M, Smith M, Peto R, et al. Body mass index and mortality in China: a 15-year prospective study of 220 000 men. Int J Epidemiol 2012;41:472—81.

[15] Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity. A reassessment. JAMA 1987;257:353—8.

[16] Tsai AC, Hsiao ML. The association of body mass index (BMI) with all-cause mortality in older Taiwanese: results of a national cohort study. Arch Gerontol Geriatr 2012;55:217—20.

[17] Park SY, Wilkens LR, Murphy SP, Monroe KR, Henderson BE, Kolonel LN. Body mass index and mortality in an ethnically diverse population: the Multiethnic Cohort Study. Eur J Epidemiol 2012;27:489—97.

[18] Pan WH, Yeh WT, Chen HJ, Chuang SY, Chang HY, Chen L, et al. The U-shaped relationship between BMI and all-cause mortality contrasts with a progressive increase in medical expenditure: a prospective cohort study. Asia Pac J Clin Nutr 2012;21:577—87.

[19] Fontaine KR, McCubrey R, Mehta T, Pajewski NM, Keith SW, Bangalore SS, et al. Body mass index and mortality rate among hispanic adults: a pooled analysis of multiple epidemiologic data sets. Int J Obes (Lond) 2012;36:1121—6.

[20] Nagai M, Kuriyama S, Kakizaki M, Ohmori-Matsuda K, Sugawara Y, Sone T, et al. Effect of age on the association between body mass index and all-cause mortality: the Ohsaki cohort study. J Epidemiol 2010;20:398—407.

[21] Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211—9.

[22] Kuk JL, Ardern CI. Influence of age on the association between various measures of obesity and all-cause mortality. J Am Geriatr Soc 2009;57:2077—84.

[23] Reuser M, Bonneux L, Willekens F. The burden of mortality of obesity at middle and old age is small. A life table analysis of the US Health and Retirement Survey. Eur J Epidemiol 2008;23:601—7.

[24] Pednekar MS, Hakama M, Hebert JR, Gupta PC. Association of body mass index with all-cause and cause-specific mortality: findings from a prospective cohort study in Mumbai (Bombay), India. Int J Epidemiol 2008;37:524—35.

[25] Moore SC, Mayne ST, Graubard BI, Schatzkin A, Albanes D, Schairer C, et al. Past body mass index and risk of mortality among women. Int J Obes (Lond) 2008;32:730—9.

[26] Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 2006;355:763—78.

[27] Stevens J, Cai J, Juhaeri Thun MJ, Williamson DF, Wood JL. Consequences of the use of different measures of effect to determine the impact of age on the association between obesity and mortality. Am J Epidemiol 1999;150:399—407.

[28] Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath Jr CW. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097—105.

[29] Lindsted KD, Singh PN. Body mass and 26-year risk of mortality among women who never smoked: findings from the Adventist Mortality Study. Am J Epidemiol 1997;146:1—11.

[30] Rissanen A, Knekt P, Heliovaara M, Aromaa A, Reunanen A, Maatela J. Weight and mortality in Finnish women. J Clin Epidemiol 1991;44:787—95.

[31] Rissanen A, Heliovaara M, Knekt P, Aromaa A, Reunanen A, Maatela J. Weight and mortality in Finnish men. J Clin Epidemiol 1989;42:781—9.

[32] Thorpe Jr RJ, Ferraro KF. Aging, obesity, and mortality misplaced concern about obese older people? Res Aging 2004;26:108—29.

[33] Sterne JAC, Bradburn MJ, Egger M. Meta analysis in Stata. In: Egger M, Davey Smith G, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. 2nd ed. Wiley Online Library; 2008. p. 336—47 [chapter 18].

[34] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177—88.

[35] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557—60.

[36] StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.

[37] Beasley JW. Body weight and longevity. JAMA 1987;257:1895—6.

[38] Simopoulos AP, Van ITB. Body weight, health, and longevity. Ann Intern Med 1984;100:285—95.

[39] Stevens J. Studies of the impact of age on optimal body weight. J Nutr Biochem 1998;9:501—10.

[40] BMI in Diverse Populations Collaborative Group. Effect of smoking on the body mass index-mortality relation: empirical evidence from 15 studies. Am J Epidemiol 1999;150:1297—308.

[41] Allison DB, Faith MS, Heo M, Townsend-Butterworth D, Williamson DF. Meta-analysis of the effect of excluding early deaths on the estimated relationship between body mass index and mortality. Obes Res 1999;7:342—54.

[42] Flegal KM, Graubard BI, Williamson DF, Gail MH. Impact of smoking and preexisting illness on estimates of the fractions of deaths associated with underweight, overweight, and obesity in the US population. Am J Epidemiol 2007;166:975—82.
[43] Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011;377:1085—95.
[44] Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083—96.
[45] Mehta T, McCubrey R, Pajewski NM, Keith SW, Allison DB, Crespo CJ, et al. Does obesity associate with mortality among hispanic persons? Results from the national health interview survey. Obesity (Silver Spring) 2013;21:1474—7.
[46] Wang Z. Re: ''Obesity and US mortality risk over the adult life course''. Am J Epidemiol 2014;179:529—30.