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Impact of obesity on mortality in patients with diabetes: Meta-analysis of 20 studies including 250,016 patients

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Keywords
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ABSTRACT

Aims/Introduction: The impact of body mass index on mortality among patients with diabetes remains controversial. Therefore, we carried out a meta-analysis of pertinent studies.

Materials and Methods: We searched OVID/MEDLINE, EMBASE and Cochrane databases for all reported studies, which investigated the relationship between body mass index and mortality in patients with diabetes. Summary estimates of hazard ratios (HRs) were obtained with a random effects model. Univariate meta-regressions were carried out.

Results: A total of 20 studies including 250,016 patients with diabetes were identified. The results of the present study showed a significantly reduced risk of all-cause mortality in overweight patients (HR 0.82, 95% CI: 0.74–0.91, $P < 0.0001$, and $I^2 = 91.6\%$) as compared with normal weight patients. The survival benefits of obesity were only observed in the elderly patients (HR 0.69, 95% CI: 0.63–0.75, $P < 0.0001$, and $I^2 = 50.4\%$), but not in the younger patients (HR 1.01, 95% CI: 0.84–1.20, $P = 0.96$, $I^2 = 80.1\%$). Furthermore, the beneficial prognostic impacts on overweight (coefficient = 0.030, $P = 0.041$) and obesity (coefficient = 0.032, $P = 0.010$) were attenuated with clinical follow-up duration.

Conclusions: The present meta-analysis showed a significantly lower risk of all-cause mortality in overweight patients with diabetes compared with normal weight patients. However, the survival benefits of obesity were only observed among the elderly patients.

INTRODUCTION

Obesity is a growing healthcare concern worldwide. Epidemiological studies show that >85% of patients with type 2 diabetes are overweight or obese[1,2]. The detrimental effects of obesity on metabolism and insulin resistance have been well documented, and obesity is also closely tied to the etiology of type 2 diabetes[2,3]. Losing weight has been proven to improve insulin sensitivity and metabolic control for overweight or obese patients, and thus has been recommended in the treatment of diabetes[4,5]. Recently, the phenomenon of the 'obesity paradox,' which refers to a lower risk of mortality for overweight or obese patients assessed by body mass index (BMI), has been reported in a variety of populations, such as patients with cardiovascular disease[6,7], heart failure[8] and chronic kidney disease[9]. However, the influence of BMI on mortality among patients with diabetes remains controversial. Although several studies have also shown an inverse correlation of weight with mortality among patients with diabetes[10–12], some studies suggest no correlation or a direct correlation[13,14]. Heterogeneity of the study population, follow-up duration, varied obesity measurements and a limited number of events in some studies are all considered to contribute to the controversy among these studies. Among various obesity measurements, BMI assessment is cheap, simple and widely used across the globe. Therefore, in order to thoroughly appraise the relationship of BMI and the mortality for patients with diabetes, we carried out a meta-analysis of pertinent studies.

METHODS

Two investigators (FG, ZJW) independently searched OVID/MEDLINE, EMBASE and the Cochrane library databases (Cochrane Central Register of Controlled Trials) for all reported studies, published before December 2014, with English-only citations, which investigated the relationship between body mass index (BMI) categories and mortality in patients with

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diabetes. The search terms and their synonyms related to bodyweight (e.g., 'obesity,' 'overweight,' 'body weight,' 'body mass index'), diabetes (e.g., 'diabetes mellitus,' 'diabetes,' 'diabetics,' 'hyperglycemia') and relevant clinical end-points (e.g., 'mortality,' 'death,' 'survival rate') were combined with terms related to study design (e.g., 'cohort study,' 'longitudinal study,' 'clinical trial'). We also used the Science Citation Index to cross-reference for studies that met our criteria. Citations were initially screened at the title level, followed by the abstract level and finally were retrieved as full texts. Studies were excluded if they met any one of the following criteria: (i) duplicate publication; (ii) ongoing/unpublished study; (iii) publication only as an abstract or as conference proceedings; or (iv) trials only assessed the BMI as the continuous variable. A flow diagram as to the process of study selection is shown in Figure 1. The study was carried out according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group for the conduct of meta-analyses of intervention studies[15].

The classifications of BMI were based on the World Health Organization's criteria[16], normal weight as 18.5–25, overweight as 25–30 and obesity as >30. However, the standard categories were not used by some studies. To avoid missing important information, we included the studies in which BMI categories were within 2 kg/m^2 of the standard categories. Studies evaluating the risk of mortality for overweight/obese patients vs normal weight or non-overweight patients were included as well. Separate analyses were carried out to compare the results for studies with or without standard BMI classifications. The Newcastle–Ottawa scale was used to assess the risk of bias in individual studies[17]. This scale rates studies based on eight criteria. We made a modification by removing the criterion of 'demonstration that outcome of interest was not present at start of study.' The primary outcome of the meta-analysis was all-cause mortality. The secondary outcome was cardiovascular mortality.

Statistical analysis

Individual study hazard ratios (HRs) and 95% confidence intervals (95% CI) were extracted for each article. Summary estimates of HRs were obtained with a random effects model if significant heterogeneity was found (I^2 > 50%). The heterogeneity across the trials was calculated with the I^2 statistic[18]. Sensitivity analyses were examined by excluding one study at a time. Univariate meta-regressions were carried out, and variables included the total number of patients, total number of mortality events, mean age, incident or prevalent diabetes, standard or non-standard BMI classifications and follow-up period. Publication bias was explored by visual inspection of a funnel plot and the Begg and Mazumdar's rank correlation test[19]. Analyses were carried out using the Comprehensive Meta Analysis Version 2.0 (Biostat, Englewood, NJ, USA). The statistical level of significance for the summary treatment effect estimate was a two-tailed *P*-value <0.05.

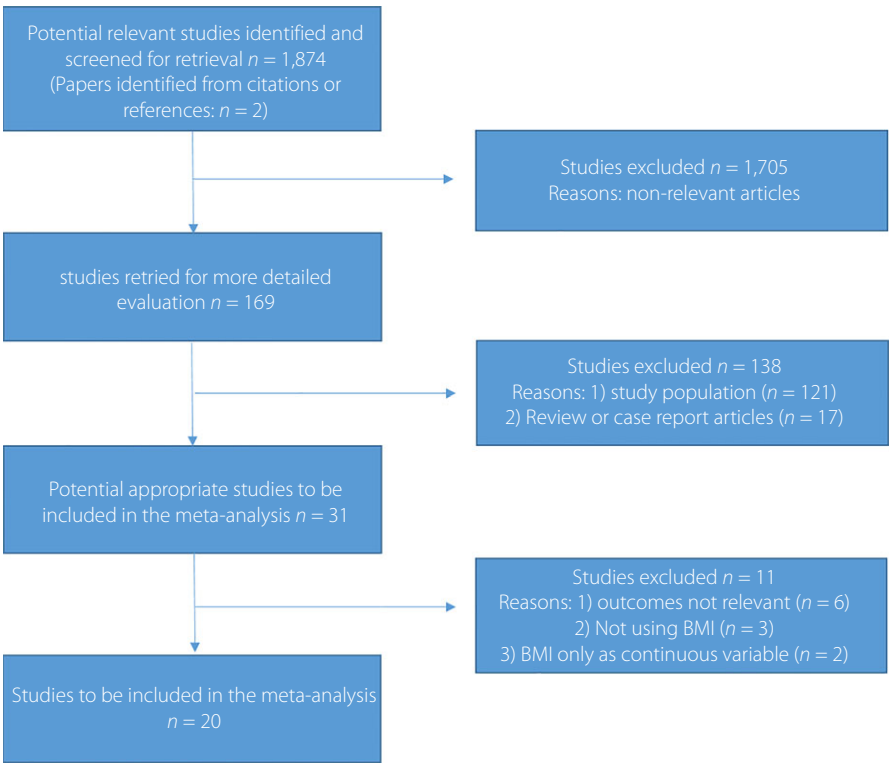


Figure 1 | Flow chart of the meta-analysis. BMI, body mass index.

RESULTS

From 1,874 potentially relevant citations, 20 studies[10–14,20–34], including 250,016 patients with diabetes, met the criteria for the analysis. Quality assessment of each included study is listed in Table S1. The follow-up duration of these studies ranged from 2.9 to 16.7 years. The baseline characteristics of the studies are shown in Table 1.

The results of the present meta-analysis showed a trend toward a lower risk of all-cause mortality for obese patients as compared with normal weight patients, but it did not attain statistical significance (HR 0.87, 95% CI: 0.75–1.01, $P = 0.058$, $I^2 = 91.8\%$; Figure 2a). Significant heterogeneities were observed among studies. Sensitivity analysis showed that no individual study unduly influenced the effect estimates. To further investigate the heterogeneity among studies, subgroup analysis was carried out, and it showed that the significantly lower risk of mortality was only observed in the elderly patients (HR 0.69, 95% CI: 0.63–0.75, $P < 0.0001$, $I^2 = 50.4\%$), as well as in studies with <10 years of clinical follow up (HR 0.78, 95% CI: 0.65–0.93, $P = 0.0006$, $I^2 = 85.5\%$), but not observed for younger patients and studies with >10 years of follow-up (Table 2). In addition, meta-regression analyses also showed that the survival benefit for obese patients was more pronounced along with the increased age, whereas it attenuated as the follow-up duration increased. In obese patients, HR of all-cause mortality decreased by 2.5% with increased per-year of age ($P = 0.018$), whereas it increased by 3.2% with increased per-year of follow-up ($P = 0.010$; Figure 3). No significant modification was observed for the number of patients, number of mortality events, incident or prevalent diabetes and standard or non-standard BMI classifications during meta-regression analysis. No significant publication bias was observed by funnel plots (Begg's test: $P = 0.88$, funnel plot in Figure 4).

In terms of overweight patients, there was a significantly reduced risk of all-cause mortality in comparison with normal weight patients (HR 0.82, 95% CI: 0.74–0.91, $P < 0.0001$, $I^2 = 91.6\%$; Figure 2b). Sensitivity analysis showed that no individual study unduly influenced the estimates. Separate analysis showed that the results were consistent across trials except for the follow-up duration (Table 2). The survival benefits of being overweight disappeared among studies with >10 years of clinical follow up (HR 0.97, 95% CI: 0.78–1.21, $P = 0.78$, $I^2 = 95.5\%$). Meta-regression analysis also confirmed this finding, and it showed no modification of the estimated effect sizes assessed by the number of patients, number of mortality events, mean age, incident or prevalent diabetes and standard or non-standard BMI classifications. However, HRs of all-cause mortality were raised by 3.0% ($P = 0.041$) as per-year of follow-up duration increased (Figure 3b). There was no apparent systematic bias as estimated by funnel plots (Begg's test: $P = 0.53$, funnel plot in Figure 4). In further analysis, we included the two studies[10,19] evaluating the risk of mortality for overweight/obesity vs normal weight patients, and the results of the meta-analysis remained consistent (HR 0.84, 95% CI: 0.77–0.91, $P < 0.0001$, $I^2 = 91.5\%$).

There were five studies[22,26,31–33], with 19,643 patients, which evaluated the relationship of BMI and cardiovascular mortality for patients with diabetes. Meta-analysis of these studies showed that overweight patients were associated with 15% reduced risks of cardiovascular mortality compared with those who were normal weight (HR 0.85, 95% CI: 0.74–0.97, $P = 0.015$, $I^2 = 12.9\%$). However, no significant difference was found for the risk of cardiovascular mortality between obese and normal weight patients (HR 0.95, 95% CI: 0.70–1.28, $P = 0.72$, $I^2 = 69.4\%$).

DISCUSSION

Although the link between obesity and mortality has been extensively investigated in a variety of clinical conditions, the prognostic value of obesity for patients with type 2 diabetes remains controversial. The present meta-analysis represents the largest data on this topic, including 20 studies of >250,000 individuals, and the results of the present study showed a significantly lower risk of mortality in overweight patients compared with normal weight patients; however, the survival benefits were attenuated with longer follow-up durations. In addition, the beneficial prognostic impact of obesity was only observed among the elderly patients, whereas the discrepancy on age was not found among overweight patients.

The inverse relationship between BMI and mortality as shown in the present study is generally consistent with a prior meta-analysis carried out by Liu *et al.*[5], which enrolled nine studies and 161,984 participants. In their study, the relative risks (RRs) of all-cause mortality in overweight (RR 0.81, 95% CI: 0.74–0.90) and obese (RR 0.72, 95% CI: 0.63–0.81) patients with diabetes were also significantly reduced compared with the normal or non-overweight patients. However, some studies only reported the hazard ratio of BMI on mortality, but did not report the events rate[29–33], and therefore these studies were not included in the prior meta-analysis. However, the present meta-analysis included all these studies, and we found a wide range of follow-up durations for these enrolled studies. Therefore, we also carried out meta-regression analyses to further investigate the heterogeneity of studies, and we found that the lower risk of mortality for overweight or obesity attenuated with longer follow-up durations. To avoid unintentional or intentional weight loss secondary to diabetes development and diagnosis, several recent studies only enrolled patients with incident diabetes, and they found the inverse relationship of BMI and mortality also existed for incident diabetes[10,12]. The results from the present meta-analysis confirmed this finding. Separate analysis showed that the survival benefits of overweight remained consistent irrespective of incident or prevalent diabetes (Table 2).

Notably, subgroup as well as meta-regression analysis in the present study showed that the survival benefits of obesity were more pronounced among elderly patients. In fact, it has been

Table 1 | Characteristics of included studies

Study	Publication time	Location	Population	Incident or prevalent diabetes	No. patients	Follow-up duration (years)	Age, mean (years)	BMI category (kg/m^2)	Outcomes
Thomas *et al.*[12]	2014	UK	Type 2 diabetes Two cohorts: with prior CVD; without prior CVD	Incident	47,509 (37,272 + 10,237)	5	60 (without prior CVD) 67 (with prior CVD)	18.5–24.9; 25.0–29.9; ≥30	All-cause mortality
Lajous *et al.*[20]	2014	France	Women with type 2 diabetes	Incident	2,421	16.7	–	<25 ≥25	All-cause mortality
Bozorgmanesh *et al.*[14]	2014	Iran	Type 2 diabetes	Incident	1,322	9.1	53.6	Tertiles (median) 24.9 28.9 33.8	All-cause mortality
Jackson *et al.*[33]	2014	US	Diabetes	Prevalent	4,740	9	50.1	22.84–25.09; 25.10–27.46; 27.47–31.02; 31.03–54.92	All-cause mortality
Murphy *et al.*[11]	2014	Iceland	Type 2 diabetes	Prevalent	637	6.7	76	18.5–24.9; 25.0–29.9; ≥30	All-cause mortality
Tobias *et al.*[13]	2014	USA	Type 2 diabetes	Incident	11,427	15.8	62	18.5–22.4; 22.5–24.9; 25.0–27.4; 27.5–29.9; 30.0–34.9; ≥35.0	All-cause mortality
Waring *et al.*[20]	2011	USA	Type 2 diabetes	Prevalent	1,644	5	74	18.5–24.9; 25–29.9; 30–34.9; 35–39.9; ≥40	All-cause mortality
Perotto *et al.*[21]	2013	Italy	Type 2 diabetes Two cohorts: <65 years ≥65 years	Prevalent	1,475	15	–	<24.2; 24.3–26.7; 26.8–30.0; >30.0	All-cause mortality, Cardiovascular mortality
Eeg-Olofsson *et al.*[22]	2009	Sweden	Type 2 diabetes With no prior CVD or stroke	Prevalent	13,087	5.6	60.3	<25; 25–29.9; ≥30;	All-cause mortality
Weiss *et al.*[23]	2009	Israel	Diabetes	Prevalent	121	3.7	79	<22.1; 22.11–24.95; 24.96–27.5; ≥27.51	All-cause mortality
Tseng[24]	2013	Taiwan	Type 2 diabetes Two cohorts: female; male	Prevalent	89,056	12	61.4 (female) 59.7 (male)	18.5–22.9; 23.0–24.9; 25.0–29.9; ≥30	All-cause mortality
Carnethon *et al.*10	2012	USA	Type 2 diabetes	Incident	2,625	–	41–76	18.5–24.9; ≥25.0	All-cause mortality
Sluik *et al.*[25]	2010	Europe	Diabetes	Prevalent	5,435	9.3	57.4 (male) 57.6 (female)	≤24.9; 25.0–27.1; 27.2–29.1; 29.2–31.8; ≥31.9	All-cause mortality Cardiovascular mortality

Table 1 | (*Continued*)

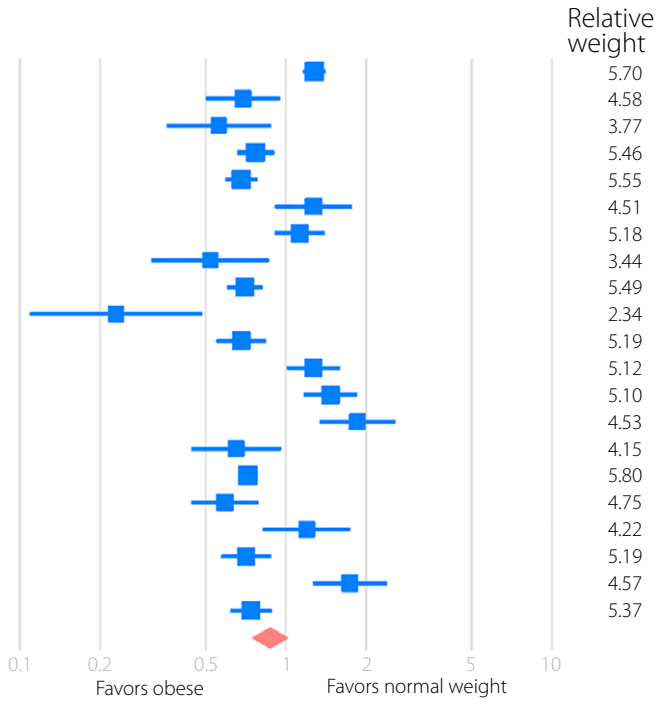
Study	Publication time	Location	Population	Incident or prevalent diabetes	No. patients	Follow-up duration (years)	Age, mean (years)	BMI category (kg/m^2)	Outcomes
Mulnier *et al.*[26]	2006	UK	Type 2 diabetes	Prevalent	44,230	7	65.8	20–24; 25–29; 30–34; 35–54	All-cause mortality
Church *et al.*[27]	2004	USA	Diabetes	Prevalent	2,196	14.6	49.3	<25.0; 25.0–29.9; ≥30.0	All cause mortality
Doehner *et al.*[28]	2012	Europe	Type 2 diabetes	Prevalent	5,202	2.9	62	22–25; 25–30; 30–35; ≥35	All-cause mortality
Kokkinos *et al.*[29]	2012	USA	Type 2 diabetes	Prevalent	4,156	7.5	60	18.5–24.9; 25.0–29.9; 30.0–34.9; >35	All-cause mortality
Ford *et al.*[30]	1991	USA	Diabetes	Prevalent	602	10	–	<27.8; 27.8–31.1; ≥31.1 (male) <27.3; 27.3–32.3; ≥32.3 (female)	All-cause mortality Cardiovascular mortality
McEwen *et al.*[31]	2007	USA	Diabetes	Prevalent	8,733	3.7	61	<26; ≥26 to <30; ≥30 to <35; ≥35	All-cause mortality Cardiovascular mortality
Zoppini *et al.*[32]	2003		Type 2 diabetes	Prevalent	3,398	10	66	≤25.4; 25.5–27.9; 28.0–30.9; ≥30.9 (<65 years) ≤24.6; 24.7–26.9; 27.0–29.8; ≥29.9 (≥65 years)	All-cause mortality Cardiovascular mortality

CVD, cardiovascular disease.

(a) Hazard ratios (HR) for all-cause mortality with obesity versus normal weight in patients with diabetes

Study name	Hazard ratio	Lower limit	Upper limit	*P*-value	Relative weight
Tobias et al. (2014)	1.280	1.161	1.411	0.000	5.70
Murphy et al. (2014)	0.690	0.501	0.951	0.023	4.58
Bozorgmanesh et al. (2014)	0.560	0.356	0.881	0.012	3.77
Thomas et al. (2014)	0.770	0.654	0.906	0.002	5.46
Thomas et al. (2014)	0.680	0.591	0.782	0.000	5.55
Sluik et al. (2010)	1.270	0.911	1.771	0.159	4.51
Sluik et al. (2010)	1.130	0.908	1.407	0.274	5.18
Jackson et al. (2014)	0.520	0.312	0.866	0.012	3.44
Warning et al. (2011)	0.700	0.599	0.818	0.000	5.49
Weiss et al. (2009)	0.230	0.109	0.485	0.000	2.34
Perotto et al. (2013)	0.680	0.547	0.845	0.001	5.19
Mulnier et al. (2006)	1.270	1.009	1.598	0.042	5.12
Eeg-Olofss on et al. (2009)	1.470	1.164	1.856	0.001	5.10
Church et al. (2004)	1.860	1.338	2.586	0.000	4.53
Doehner et al. (2012)	0.650	0.440	0.960	0.030	4.15
Tseng (2013)	0.720	0.681	0.761	0.000	5.80
Kokkinos et al. (2012)	0.590	0.440	0.791	0.000	4.75
Ford et al. (1991)	1.200	0.821	1.753	0.346	4.22
Mc Ewen et al. (2007)	0.710	0.571	0.882	0.002	5.19
Zoppini et al. (2003)	1.740	1.261	2.401	0.001	4.57
Zoppini et al. (2003)	0.740	0.618	0.887	0.001	5.37
Overall effects	0.867	0.748	1.005	0.058	

Heterogeneity (I^2 = 91.8%, P < 0.0001)



(b) Hazard ratios (HR) for all-cause mortality with overweight versus normal weight in patients with diabetes

Study name	Hazard ratio	Lower limit	Upper limit	*P*-value	Relative weight
Tobias et al. (2014)	1.110	1.001	1.231	0.048	5.98
Murphy et al. (2014)	0.720	0.502	1.033	0.075	3.59
Bozorgmanesh et al. (2014)	0.590	0.347	1.002	0.051	2.39
Thomas et al. (2014)	0.680	0.600	0.770	0.000	5.82
Thomas et al. (2014)	0.630	0.560	0.709	0.000	5.87
Sluik et al. (2010)	0.880	0.620	1.250	0.475	3.68
Sluik et al. (2010)	0.910	0.728	1.137	0.407	4.91
Jackson et al. (2014)	0.600	0.391	0.922	0.020	3.04
Warning et al. (2011)	0.800	0.698	0.917	0.001	5.72
Weiss et al. (2009)	0.370	0.191	0.715	0.003	1.78
Perotto et al. (2013)	0.950	0.820	1.100	0.494	5.64
Mulnier et al. (2006)	0.970	0.912	1.032	0.335	6.22
Eeg-Olofss on et al. (2009)	1.080	0.865	1.348	0.496	4.93
Church et al. (2004)	1.230	0.929	1.628	0.148	4.34
Doehner et al. (2012)	0.750	0.652	0.863	0.000	5.70
Tseng (2013)	0.680	0.660	0.700	0.000	6.32
Kokkinos et al. (2012)	0.710	0.541	0.932	0.014	4.42
Ford et al. (1991)	1.030	0.744	1.427	0.859	3.90
Mc Ewen et al. (2007)	0.670	0.552	0.813	0.000	5.20
Zoppini et al. (2003)	1.130	0.888	1.437	0.319	4.74
Zoppini et al. (2003)	0.860	0.757	0.977	0.020	5.80
Overall effects	0.824	0.743	0.914	0.000	

Heterogeneity (I^2 = 91.6%, P < 0.0001)

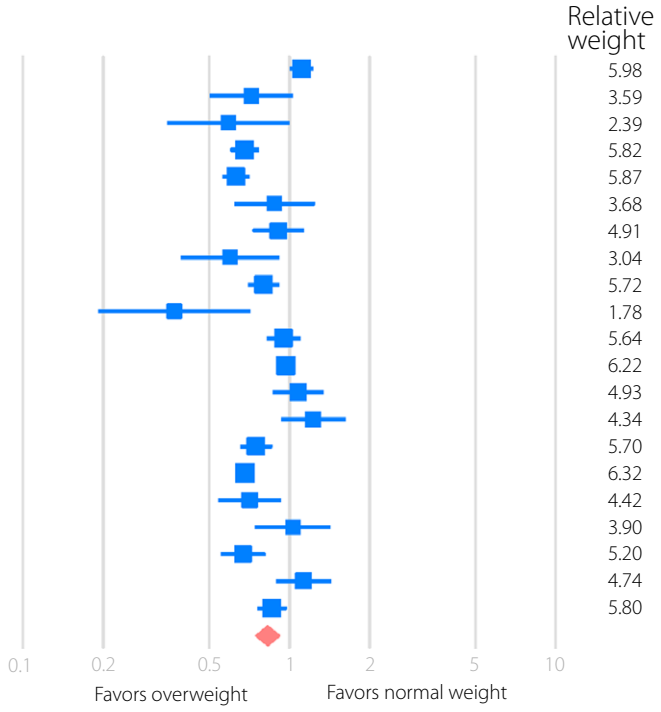


Figure 2 | Hazard ratios (HR) for (a) all-cause mortality with obesity or (b) overweight vs normal weight in patients with diabetes. CI, confidence interval.

Table 2 | Subgroup analyses of overweight and obesity, and the risk of all-cause mortality in patients with diabetes

Separate analysis	No. studies	Hazard ratios (95% CI)	*P*-value	Heterogeneity, I^2 (%)	Heterogeneity *P*-value
Overweight *vs* normal weight					
Elderly	6	0.78 (0.73–0.84)	0.001	69.7%	0.005
Non-elderly	5	0.83 (0.72–0.96)	0.009	67.2%	0.016
Female	3	0.87 (0.64–1.19)	0.40	93.9%	<0.0001
Male	3	0.88 (0.58–1.32)	0.54	96.2%	<0.0001
No. patients ≥5,000	8	0.81 (0.70–0.94)	0.006	95.2%	<0.0001
No. patients <5,000	10	0.85 (0.75–0.96)	0.012	65.4%	0.001
Follow-up duration (≥10 years)	6	0.97 (0.78–1.21)	0.78	95.5%	<0.0001
Follow-up duration (<10 years)	12	0.76 (0.67–0.85)	<0.0001	83.6%	<0.0001
Incident diabetes	4	0.75 (0.54–1.04)	0.08	95.1%	<0.0001
Non-incident diabetes	14	0.84 (0.75–0.94)	0.003	90.7%	<0.0001
Standard BMI category	12	0.82 (0.72–0.93)	0.002	93.6%	<0.0001
Non-standard BMI category	6	0.83 (0.70–0.99)	0.041	73.3%	0.001
Non-smoking	4	0.81 (0.53–1.23)	0.33	76.3%	0.005
Obese *vs* normal weight					
Elderly	6	0.69 (0.63–0.75)	<0.0001	50.4%	0.073
Non-elderly	5	1.01 (0.84–1.20)	0.96	80.1%	0.008
Female	3	1.06 (0.67–1.67)	0.80	97.3%	<0.0001
Male	3	0.97 (0.65–1.46)	0.88	94.7%	<0.0001
No. patients ≥5,000	8	0.95 (0.77–1.16)	0.61	94.5%	<0.0001
No. patients <5,000	10	0.78 (0.61–1.01)	0.058	87.2%	<0.0001
Follow-up duration (≥10 years)	6	1.07 (0.78–1.42)	0.67	96.0%	<0.0001
Follow-up duration (<10 years)	12	0.78 (0.65–0.93)	0.006	85.5%	<0.0001
Incident diabetes	4	0.80 (0.55–1.18)	0.26	95.7%	<0.0001
Non-incident diabetes	14	0.88 (0.75–1.04)	0.14	89.3%	<0.0001
Standard BMI category	12	0.91 (0.76–1.09)	0.30	93.4%	<0.0001
Non-standard BMI category	6	0.77 (0.57–1.04)	0.087	86.3%	<0.0001
Non-smoking	5	0.77 (0.50–1.20)	0.25	99.7%	<0.0001

BMI, body mass index.

reported by some prior studies. Zoppini *et al.*[33] investigated 3,398 patients with type 2 diabetes, followed up for 10 years, and 1,212 deaths occurred during the follow-up period. They found that the obesity paradox was only observed among elderly patients, but not for those younger patients (aged <65 years). Additionally, there were two studies (Weiss *et al.*[24] and Murphy *et al.*[11]) that only enrolled elderly patients with diabetes. Weiss *et al.*[24] showed that BMI was inversely associated with all-cause (RR 0.89, 95% CI: 0.83–0.96, $P = 0.002$) and cardiovascular mortality (RR 0.83, 95% CI: 0.74–0.93, $P = 0.002$) among hospitalized elderly patients with type 2 diabetes. Murphy *et al.*[11] compared the mortality of obesity and normal weight with overweight in the elderly patients with diabetes. They used overweight as the reference, and found an increased risk of mortality among normal weight compared with overweight participants (HR 1.72, 95% CI: 1.12–2.64). One possible explanation is that obesity usually clusters with several cardiovascular risk factors, such as dyslipidemia, hypertension and so on, and these disorders tend to be more frequently developed in elderly patients, even without overweight or obesity[33,35]. However, in younger patients, these disorders are less frequently observed, and their existence might not be considered as mere confounders, but possible intermediate mechanisms of the obesity-related damage, and therefore the detrimental effects of these disorders might be more apparent among younger patients[33]. Additionally, in younger patients, other factors, such as genetic background, latent autoimmune diabetes in adults and so on might play an important role in the development of diabetes, which might link to poorer prognosis. Third, previous studies suggest muscle mass is inversely associated with insulin resistance[10,11,36,37], and age-related loss of lean muscle mass could result in a lower bodyweight in elderly patients, and thus contribute to the worse outcome.

Another interesting finding of the present study was the late 'catch-up' phenomenon. We found the survival benefits of overweight and obesity were time-dependent, which were attenuated with time, and eventually, disappeared after 10 years of follow-up. A possible explanation for this decrescendo effect might be related to the underlying chronic disease or frailty, both of which can cause weight loss and elevate the risk of death[13], and studies with short follow-up duration are more likely to be affected by this problem.

Several limitations of this meta-analysis need to be addressed. First, BMI suffers from the inability to discriminate body fat

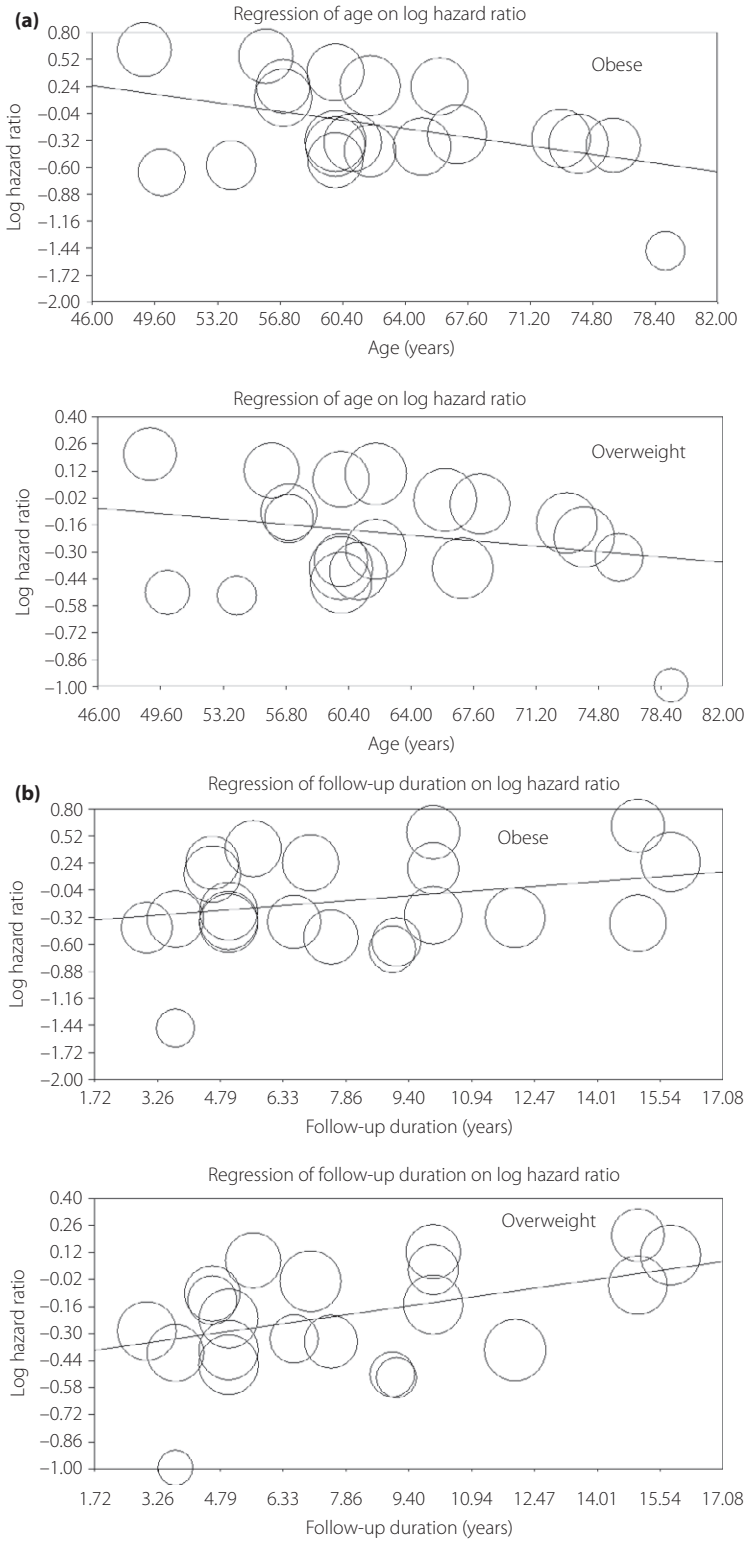


Figure 3 | Meta-regression on hazard ratios of all-cause mortality for (a) age, as well as (b) follow-up duration in overweight and obese patients vs normal weight patients (the size of the circles represents the individual study weights). (a) The meta-regression was carried out among all studies with estimates of all-cause mortality with the mean age of each study. *P* for obesity = 0.018, coefficient = 0.025; *P* for overweight = 0.31, coefficient = 0.008. (b) The meta-regression was carried out among all studies with estimates of all-cause mortality with the follow-up duration of each study. *P* for obesity = 0.010, coefficient = 0.032; *P* for overweight = 0.041, coefficient = 0.030.

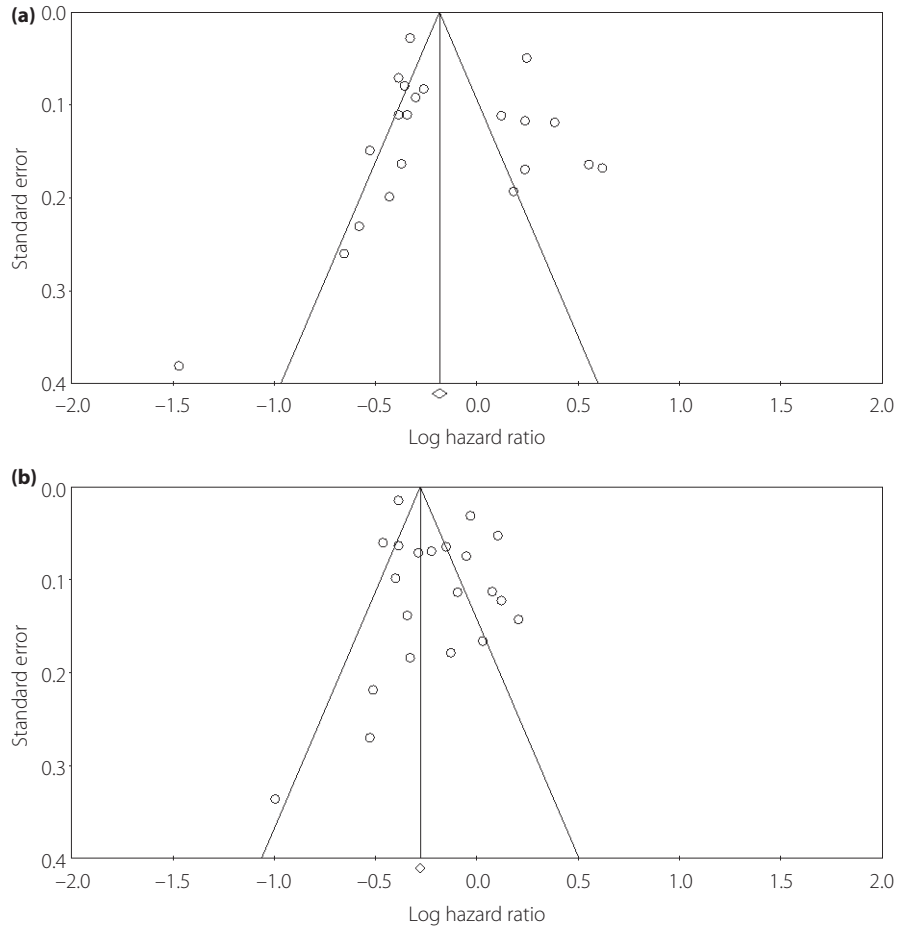


Figure 4 | Funnel plot based on log hazard ratio of all-cause mortality with (a) obese and (b) overweight patients vs normal weight patients. Begg's test: $P = 0.88$ for obese; Begg's test: $P = 0.53$ for overweight vs normal weight patients.

from lean body mass. Second, individual patient data were not available for the meta-analysis, and therefore, there might be potential variables that cannot be adjusted across studies. Third, the majority of existing studies only provided baseline BMI values, so the influence of weight change during the follow-up period cannot be taken into account. Fourth, standard BMI classifications were not used by some studies, although we carried out a separate analysis for studies with or without standard classification, it might still introduce bias into the results. Fifth, substantial heterogeneity was found in the present meta-analysis; although several attempts have been made to investigate the sources of heterogeneity through various sensitivity analyses and meta-regression, we did not find a simple explanation or method to account for this variability. The inconsistency of follow-up duration across individual studies can partly explain the heterogeneity, but a high level of heterogeneity still exists within different subgroup analyses. Additionally, 6 out of 20 studies in the meta-analysis were unable to determine whether participants had type 2 diabetes or other less common forms of diabetes in adults. However, because the studies were carried out in adults where the vast majority (>95%) of diabetes can be assumed to be type 2, the findings should apply to persons with type 2 diabetes[2]. Finally, only BMI was evaluated in the present analysis. Other modalities associated with bodyweight, including body composition and fitness[11], were not included because of insufficient data on these parameters.

In conclusion, the results from the present meta-analysis showed a lower risk of mortality in overweight/obese patients with diabetes compared with normal weight patients, and the beneficial prognostic impact of obesity was more pronounced among elderly patients, but attenuated with longer follow-up durations. However, caution should be taken in interpreting the results, as the design of the present study did not permit any verification of the causal relationship between bodyweight and prognosis in patients with diabetes. To definitively answer this question, prospective randomized controlled studies assessing the survival benefits of supervised weight-control programs across different BMI categories in patients with diabetes are urgently required.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Narayan KM, Boyle JP, Thompson TJ, *et al.* Lifetime Risk for Diabetes Mellitus in the United States. *JAMA* 2003; 290: 1884–1890.
2. Carnethon MR1, Rasmussen-Torvik LJ, Palaniappan L. The obesity paradox in diabetes. *Curr Cardiol Rep* 2014; 16: 446.
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; 37: 1595–1607.
4. Bantle JP, Wylie-Rosett J, Albright AL, *et al.* Nutrition recommendations and interventions for diabetes: a position statement of the American diabetes association. *Diabetes Care* 2008; 31: S61–S78.
5. Liu XM, Liu YJ, Zhan J, *et al.* Overweight, obesity and risk of all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol* 2015; 30: 35–45.
6. Angerås O, Albertsson P, Råmunddal T, *et al.* Evidence for obesity paradox in patients with acute coronary syndromes: a report Swedish Coronary Angiography and Angioplasty Registry. *Eur Heart J* 2013; 34: 345–353.
7. Wang ZJ, Zhou YJ, Zhao YX, *et al.* Effect of obesity on repeat revascularization in patients undergoing percutaneous coronary intervention with drug-eluting stents. *Obesity (Silver Spring)* 2012; 20: 141–146.
8. Padwal R, McAlister FA, McMurray JJ, *et al.* Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes (Lond)* 2014; 38: 1110–1114.
9. Schmidt D, Salahudeen A. The obesity-survival paradox in hemodialysis patients: why do overweight hemodialysis patients live longer? *Nutr Clin Pract* 2007; 22: 11–15.
10. Carnethon MR, De Chavez PJ, Biggs ML, *et al.* Association of weight status with mortality in adults with incident diabetes. *JAMA* 2012; 308: 581–590.
11. Murphy RA, Reinders I, Garcia ME, *et al.* Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). Adipose tissue, muscle, and function: potential mediators of associations between body weight and mortality in older adults with type 2 diabetes. *Diabetes Care* 2014; 37: 3213–3219.
12. Thomas G, Khunti K, Curcin V, *et al.* Obesity paradox in people newly diagnosed with type 2 diabetes with and without prior cardiovascular disease. *Diabetes Obes Metab* 2014; 16: 317–325.
13. Tobias DK, Pan A, Jackson CL, *et al.* Body-mass index and mortality among adults with incident type 2 diabetes. *N Engl J Med* 2014; 370: 233–244.
14. Bozorgmanesh M, Arshi B, Sheikholeslami F, *et al.* No Obesity Paradox-BMI Incapable of Adequately Capturing the Relation of Obesity with All-Cause Mortality: an Inception Diabetes Cohort Study. *Int J Endocrinol* 2014; 2014: 282089.
15. Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
16. Global database on body mass index. Body mass index classification of WHO. Available from: http://wwwwhoint/bmi/indexjsp?introPage=intro_3html Accessed May 6, 2015.
17. Wells GA, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2011. Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed May 6, 2015.
18. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
20. Lajous M, Bijon A, Fagherazzi G, *et al.* Body mass index, diabetes, and mortality in French women: explaining away a "paradox". *Epidemiology* 2014; 25: 10–14.
21. Waring ME, Saczynski JS, McManus D, *et al.* Weight and mortality following heart failure hospitalization among diabetic patients. *Am J Med* 2011; 124: 834–840.
22. Perotto M, Panero F, Gruden G, *et al.* Obesity is associated with lower mortality risk in elderly diabetic subjects: the Casale Monferrato study. *Acta Diabetol* 2013; 50: 563–568.
23. Eeg-Olofsson K, Cederholm J, Nilsson PM, *et al.* Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia* 2009; 52: 65–73.
24. Weiss A, Boaz M, Beloosesky Y, *et al.* Body mass index and risk of all-cause and cardiovascular mortality in hospitalized elderly patients with diabetes mellitus. *Diabet Med* 2009; 26: 253–259.
25. Tseng CH. Obesity paradox: differential effects on cancer and noncancer mortality in patients with type 2 diabetes mellitus. *Atherosclerosis* 2013; 226: 186–192.
26. Sluik D, Boeing H, Montonen J, *et al.* Associations Between General and Abdominal Adiposity and Mortality in Individuals With Diabetes Mellitus. *Am J Epidemiol* 2011; 174: 22–34.
27. Mulnier HE, Seaman HE, Raleigh VS, *et al.* Mortality in people with type 2 diabetes in the UK. *Diabet Med* 2006; 23: 516–521.
28. Church TS, Cheng YJ, Earnest CP, *et al.* Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 2004; 27: 83–88.
29. Doehner W, Erdmann E, Cairns R, *et al.* Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and

cardiovascular co-morbidity: an analysis of the PROactive study population. *Int J Cardiol* 2012; 162: 20–26.
30. Kokkinos P, Myers J, Faselis C, *et al*. BMI–Mortality Paradox and Fitness in African American and Caucasian Men With Type 2 Diabetes. *Diabetes Care* 2012; 35: 1021–1027.
31. Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Am J Epidemiol* 1991; 133: 1220–1230.
32. McEwen LN, Kim C, Karter AJ, *et al*. Risk Factors for Mortality Among Patients With Diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care* 2007; 30: 1736–1741.
33. Zoppini G, Verlato G, Leuzinger C, *et al*. Body mass index and the risk of mortality in type II diabetic patients from Verona. *Int J Obes Relat Metab Disord* 2003; 27: 281–285.
34. Jackson CL, Yeh HC, Szklo M, *et al*. Body mass index and all cause mortality in US adults with and without diabetes. *J Gen Intern Med* 2014; 29: 25–33.
35. Krauss RM, Wiston M, Fletcher BJ, *et al*. Obesity. Impact on cardiovascular disease. *Circulation* 1998; 98: 1472–1476.
36. Folsom AR, Rasmussen ML, Chambless LE, *et al*. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. *Diabetes Care* 1999; 22: 1077–1083.
37. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab* 2011; 96: 2898–2903.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Quality assessment of included studies.