Minireview

Body composition and mortality in the general population: A review of epidemiologic studies

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Impact statement

Current understanding of the association of body composition on mortality in the general population is limited. This review evaluated the available epidemiologic studies on body composition and mortality that leveraged diverse approaches to estimate body composition. Although studies showed inconsistent results, there was evidence suggesting that high fat mass and low lean body mass may be independently associated with mortality in the general population. This review may help partially explain the "obesity paradox" phenomenon and facilitate further studies to advance the understanding of the association of body composition on health in the general and patient populations.

Abstract

Numerous studies have examined the association between body mass index and mortality and often observed that risk of mortality was higher in those with lower body mass index than those who were overweight or even obese ("obesity paradox"). One potential explanation of the obesity paradox is the limitation of body mass index as an imperfect measure of adiposity. However, relatively few studies have examined the association between body composition and mortality due to practical issues of assessing body composition in large-scale epidemiological settings. The available epidemiologic studies on this topic were heterogenous with regard to study design, analyses, results, and interpretations. The majority of studies using direct body composition measures such as dual-energy x-ray absorptiometry or computed tomography had relatively small sample size, short follow-up period and restricted study population. Studies have also used other approaches to indirectly estimate body composition to examine the association with mortality in a larger and more representative population. Overall findings were not consistent but suggested that fat mass and lean body mass may play an independent role on mortality in the general population. Various shapes of the associations were observed, but studies generally suggested that high fat mass was associated with increased risk of mortality (especially higher range of fat mass) and low lean body mass was associated with increased risk of mortality (especially lower range of lean body mass). On the other hand, fat mass and lean body mass tended to show either null or inverse association with mortality in elderly populations. Given the complex relationship of two body components as well as with other factors (e.g., age, smoking, disease, etc.), future studies should be conducted and interpreted after careful consideration of potential biases. In summary, the available data suggest independent associations of fat mass and lean body mass on mortality in the general population.

Keywords: Body composition, fat mass, lean body mass, body mass index, mortality, obesity paradox

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Introduction

The global burden of obesity is high and rising at an alarming rate.[1] Currently, body mass index (BMI) is the most widely used measure of adiposity in clinical and research settings. Overweight and obesity, defined by BMI of $\geq$25 kg/m^2, are well established risk factors for many health outcomes including cardiovascular disease, diabetes, and certain type of cancers.[2] A J or U-shaped relationship is often observed, depending on the analytic approach; however, whether a causal benefit of being overweight or obesity for longer survival exists remains controversial ("obesity paradox").[3] Recently, two large meta-analyses have reported conflicting results.[3,4] Many studies attempted to control for potential biases (e.g., residual confounding and reverse causation) and observed attenuation

of the unexpected J or U-shaped relationship, although these corrections may not fully explain the "obesity paradox" phenomenon.

One critical but underexplored area of obesity research is on body composition and mortality. Previous studies using BMI have acknowledged the major limitation of BMI being an imperfect measure of adiposity because it cannot discriminate fat mass and lean body mass.[5] Thus, understanding body composition may provide new insights into the relationship between obesity and mortality. However, a limited number of studies have used body composition because it is difficult to conduct in a large epidemiological setting. Here, we conducted a narrative review of the literature and summarized the evidence to understand the association of body composition on mortality in the general population.

Body composition assessment in epidemiologic studies

Human body composition has been of great interest as inadequate lean body mass and excess fat mass are major risk factors related to many health outcomes. Numerous body composition measurement methods have been developed and used in clinical and epidemiological settings.[6–8] The available body composition methods have a wide range of validity, reproducibility, and feasibility; thus, it is important to understand principles, strengths and limitations of the commonly used body composition methods in research to evaluate studies on body composition and health outcomes. Herein, we briefly describe the body composition methods used in the current epidemiologic studies to estimate body composition.

Dual-energy x-ray absorptiometry (DXA) is one of reference methods that are commonly used to validate or calibrate field methods for assessing body composition. DXA estimates body composition by using two different x-ray beams which attenuate differently by fat tissue, lean tissue, and bone mineral. DXA has the advantage of high accuracy and reproducibility and it provides estimates of regional body composition. However, DXA has an upper body weight limit and is not suitable for pregnant women. Moreover, it is expensive and not portable to be widely used in a large-scale study. Imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) are also known as reference methods. These techniques are the most accurate methods for the assessment of overall and regional body composition at tissue and organ levels. However, CT causes substantially higher level of radiation exposure than DXA. Furthermore, both CT and MRI are expensive, unportable and incapable of accommodating large individuals. There are other direct body composition methods such as densitometry, air-displacement plethysmography, and dilution method that are available, but these methods have been rarely used in epidemiologic studies. Details of these methods are described elsewhere.[6,8]

Although the aforementioned direct body composition methods provide more accurate estimates of body composition, they are expensive, complicated, and time consuming to be used in a large-scale setting. Therefore, alternative "indirect" but more practical body composition methods have been more preferably used. Bioelectrical impedance analysis (BIA) measures the impedance or resistance to a small electrical current as it passes through body tissues. Then prediction models are used to estimate fat mass and fat-free mass. Of note, the difference between fat-free mass and lean body mass is that essential body fat is included in lean body mass (total body mass − storage fat mass) but not fat-free mass (total body mass − (storage fat mass + essential fat mass)). BIA has advantages of being relatively simple, portable, and inexpensive compared to direct body composition methods. However, its validity can be influenced by age, sex, race, body structure, disease state, and hydration status.

Skinfold and circumference measures are commonly used as an indirect measure of body fat distribution or central obesity because they are inexpensive and portable. Skinfold measure technique involves a caliper to measure the thickness of two layers of skin and the underlying fat in the area of triceps, biceps, subscapular, abdomen, and thighs. However, this method requires technical skill and has relatively high interobserver errors. Compared to skinfold measure, circumference measure such as waist circumference (WC) and waist to hip circumference ratio (WHR) are easier to obtain in epidemiological settings and has lower measurement errors in general. However, circumference measures are not entirely standardized and the interpretation of certain measures such as WHR is less clear. Lastly, anthropometric prediction equations are another practical approach that has potential to be used in large-scale studies. This method calculates predicted body composition (i.e., fat mass and lean body mass) based on simple demographic and anthropometric information (e.g., height, weight, and waist circumference). If the equations are validated and applied cautiously, this method can be used with relatively high precision in a population level. The disadvantage is that the developed equations may not be applicable to study populations with different characteristics.

In epidemiologic studies, to remove extraneous variation due to body size, fat mass and lean body mass are adjusted for height by either including height as a covariate in the model or directly incorporating height such as fat mass index (fat mass/height^2) and lean body mass index (lean body mass/height^2).

Epidemiologic studies

A number of epidemiologic studies have investigated the association between body composition and mortality in the general population. However, relatively few studies have used direct measures of body composition due to practical issues of using expensive technologies in a large epidemiological setting. In addition, studies have applied indirect measures of body composition to estimate body composition using diverse approaches. Epidemiologic studies that used either direct or indirect measures of body composition to examine the relationship with

mortality in the general population are briefly summarized in Tables 1 and 2.

Studies using direct measures of body composition

Small cohort studies of elderly populations. The majority of studies that used direct measures of body composition have been conducted in relatively small samples of elderly populations over 65 years old (approximate mean of 75 years). A US study of 2292 elderly enrolled in the Health, Aging and Body Composition Study assessed body composition using both CT and DXA and followed participants for a mean of 4.9 years.[9] This study reported no strong association between lean body mass and mortality. DXA-measured regional lean body mass (i.e., arm or leg) was not associated with mortality but low CT-measured leg muscle area was associated with increased risk of mortality in men only (RR = 1.26, 95% CI = 1.02–1.55 per one SD). An Italian study of 934 elderly from the InCHIANTI study with a mean follow-up of 5.1 years showed null results.[10] CT-measured calf skeletal muscle (density or area) and fat mass were not associated with mortality. Of note, these studies conducted analyses using regional body composition (i.e., arm, leg, or calf); thus, the findings may not represent the total body composition. Further, they were relatively small.

Two larger studies of approximately 4000 older adults reported an inverse association between DXA-measured fat mass and mortality but no association between DXA-measured lean body mass and mortality. A study conducted in Hong Kong found that one quintile increase in fat mass index was associated with reduced risk of mortality in men (HR = 0.87, 95% CI = 0.79–0.97) but not in women.[11] Muscle mass index (muscle mass/height^2) was not significantly associated with mortality in men and women. However, this study did not adjust for important confounders including smoking and chronic diseases, and the shape of the associations were not comprehensively examined due to small number of deaths. A recent French study of older women ($\geq$75 y) with a median of 17.7 years of follow-up examined the shape of the association of fat mass and lean body mass with mortality.[12] This study showed a reversed J-shaped association between fat mass index and mortality and an inverse association between fat percent and mortality (HR = 0.88, 95% CI = 0.84–0.92 per 10% increase). After adjusting for fat mass, lean body mass index and appendicular skeletal muscle mass index (appendicular skeletal muscle mass/height^2) were not associated with mortality.

A few studies reported an inverse association of lean body mass or both lean and fat mass with mortality in older adults. A Chilean study of 1413 older adults showed that low appendicular fat-free mass, not fat mass, was a significant predictor of mortality, although this study could not adjust any other confounders except for age and sex.[13] In a Swedish study of 921 older adults with a mean of 9.2 years follow up, fat mass showed a U-shaped association in men and an inverse association in women.[14] Moreover, lean body mass was inversely associated with mortality in men and women. One SD increase of lean body mass was associated with 31% and 19% decreased risk of mortality in men and women, respectively ($P < 0.01$). One potential limitation of this study included participants admitted for DXA examination which may introduce selection bias or generalizability. Another study from the Netherlands which consisted of 477 community-dwelling older adults have examined the association of region specific fat mass and muscle mass with 12-year mortality.[15] A U-shaped association was found for most analyses of CT-measured leg, arm, and trunk fat mass. However, CT-measured appendicular skeletal muscle showed a linear positive association in women while a reversed J-shaped association in men.

Large cohort studies of general populations. Three recent studies have examined the association between body composition and mortality in the general population including a wide range of age groups. A Canadian study of 54,420 participants aged over 40 referred for bone mineral density testing examined the association of BMI and body fat percent with mortality over a median follow-up of 6.7 years for women and 4.5 years for men.[16] In multivariable adjusted models including both fat percent and BMI, high fat percent was associated with increased risk of mortality in men (HR of quintile 1 vs. 3 = 1.59, 95% CI = 1.28–1.96) and women (HR of quintile 1 vs. 3 = 1.19, 95% CI = 1.08–1.32). In the mutually adjusted models, low BMI was associated with increased risk of mortality in men (HR of quintile 1 vs. 3 = 1.45, 95% CI = 1.17–1.79) and women (HR of quintile 1 vs. 3 = 1.44, 95% CI = 1.30–1.59). Although BMI could be a surrogate of lean body mass when BMI and fat percent are included together in the models, this study did not directly examine the association of lean body mass with mortality. Moreover, residual confounding by smoking and physical activity could be a potential limitation of this study.

Two US studies were conducted in a large representative sample of the National Health and Nutrition Examination Survey (NHANES) (approximately 10,000 participants aged over 20). One study examined the association of DXA-measured total and regional adiposity with mortality.[17] Higher total fat percent was significantly associated with increased risk of total mortality (HR of quartile 4 vs. 2 = 1.48, 95% CI = 1.07–2.04) in multivariable adjusted models. Regional adiposity (i.e., leg or trunk) and fat-free mass index were not significantly associated with total mortality. On the other hand, a recent study using the same cohort reported that muscle mass was inversely associated with mortality.[18] Higher appendicular skeletal muscle index was associated with 18% decreased risk of mortality in US adults (HR = 0.82, 95% CI = 0.73–0.92 per 1 kg/m^2). A stronger inverse association was found for younger adults (HR = 0.63, 95% CI = 0.48–0.83 per 1 kg/m^2) compared to older adults (HR = 0.89, 95% CI = 0.80–0.99 per 1 kg/m^2). Moreover, the observed U-shaped BMI–mortality relationship became more linear when muscle mass was adjusted for in the analyses.

Table 1. Summary of studies on body composition assessed using direct measures and all-cause mortality in the general population.

Reference, country	Study population, Sex, Age	Study period (Follow-up)	No. of deaths	Body composition measure	RR (95% CI)		Confounder adjustment		
					FM measures	LBM measures	Smoking	PA	FM/LBM or BMI
Newman et al.,[9] US	N=2292 Both Age 70–79 y	NA (mean 4.9 y)	286	CT DXA	NA	CT leg muscle area Women No association Men 1.26 (1.02–1.55) per 1 SD decrease DXA leg or arm lean mass No association	Y	Y	Y
Cesari et al.,[10] Italia	N=934 Both Age≥65 y	1998–2006 (mean 5.1 y)	263	pQCT	Calf fat area No association	Calf muscle density or area No association	N	Y	Y
Auyeung et al.,[11] Hong Kong	N=4000 Both Age≥65 y	2001–2008 (mean 5.3 y)	W: 78 M: 242	DXA	FMI Women No association Men 0.87 (0.79–0.97) per quintile increase	Muscle mass index Women No association Men No association	N	N	Y
Rolland et al.,[12] France	N=4574 Women Age≥75 y	1992–2011 (median 17.7 y)	2876	DXA	FMI Reversed J-shaped association FM% Inverse association 0.88 (0.84–0.92) per 10% increase	LBMI No association ASMI No association	Y	Y	Y (only LBM measures)
Bunout et al.,[13] Chile	N=1413 Both Age mean 74.3 y	1995–2008 (median 1594 days)	221	DXA	Total or trunk FM No association	Appendicular FFMI 0.85 (0.74–0.98) per unit increase	N	N	Y
Toss et al.,[14] Sweden	N=921 Both Age 65–89 y	1991–2009 (mean 9.2 y)	397	DXA	FM Women 0.85 (NA), P=0.009 per 1 SD increase Men U-shaped association	LBM Women 0.81 (NA), P<0.001 per 1 SD increase Men 0.69 (NA), P=0.001 per 1 SD increase	N	N	N[a]
Wijnhoven et al.,[15] Netherland	N=477 Both Age 65–85 y	1995–2007 (NA)	W: 92 M: 133	DXA	Leg, arm or trunk FM Mostly U-shaped association	ASM Women Linear increasing association Men Reversed J-shaped association Below mean	Y	N	Y

(continued)

Table 1. Continued

Reference, country	Study population, Sex, Age	Study period (Follow-up)	No. of deaths	Body composition measure	RR (95% CI)		Confounder adjustment		
					FM measures	LBM measures	Smoking	PA	FM/LBM or BMI
						1.31 (0.84–2.06) per 1 SD decrease			
Padwal et al.,[16] Canada	N=54,420 Both Age≥40 y	1999–2013 (median 6.7 y for women, 4.5 y for men)	W: 4965 M: 984	DXA	FM% Women Q1: 1.10 (0.99–1.22) Q2: 1.08 (0.99–1.19) Q3: Reference Q4: 1.02 (0.93–1.12) Q5: 1.19 (1.08–1.32) Men Q1: 0.98 (0.78–1.23) Q2: 0.96 (0.77–1.19) Q3: Reference Q4: 1.19 (0.97–1.47) Q5: 1.59 (1.28–1.96)	BMI Women Q1: 1.44 (1.30–1.59) Q2: 1.12 (1.02–1.23) Q3: Reference Q4: 0.99 (0.90–1.09) Q5: 0.95 (0.85–1.06) Men Q1: 1.45 (1.17–1.79) Q2: 1.14 (0.93–1.39) Q3: Reference Q4: 0.92 (0.74–1.13) Q5: 0.91 (0.72–1.15)	N	N	Y
Zong et al.,[17] US	N=9471 Both Age≥20 y	1999–2010 (mean 8.8 y)	682	DXA	FM% Q1: 1.33 (0.95–1.87) Q2: Reference Q3: 1.13 (0.81–1.56) Q4: 1.48 (1.07–2.04)	FFMI Q1: 0.98 (0.68–1.43) Q2: Reference Q3: 1.02 (0.72–1.45) Q4: 0.90 (0.62–1.32)	Y	Y	Y (only FFMI)
Abramowitz et al.,[18] US	N=11,687 Both Age≥20 y	1999–2011 (median 9.3 y)	1819	DXA	NA	ASMI 0.82 (0.73–0.92) per 1 kg/m^2 increase	Y	Y	Y

ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index (ASM divided by height squared, kg/m^2); BMI: body mass index; CI: confidence interval; CT: computerized tomography; DXA: dual-energy x-ray absorptiometry; FM: fat mass; FMI: fat mass index (FM divided by height squared, kg/m^2); FFM: fat-free mass; FFMI: fat-free mass index (FFM divided by height squared, kg/m^2); LBM: lean body mass; LBMI: lean body mass index (LBM divided by height squared, kg/m^2); NA: not applicable; PA: physical activity; pQCT: peripheral quantitative computerized tomography; RR: relative risk; SD: standard deviation.
[a]In the mutually adjusted model, LBM remained significant and FM weakened slightly.

Table 2. Summary of studies on body composition assessed using indirect measures and all-cause mortality in the general population.

Reference, country	Study population, Sex, Age	Study period (follow-up)	No. of deaths	Body composition measure	RR (95% CI)		Confounder adjustment		
					FM measures	LBM measures	Smoking	PA	FM/LBM or BMI
Bigaard et al.,[19] Denmark	N=57,053 Both Age 50–64 y	1993–2001 (median 5.8 y)	1851	BIA	FMI J-shaped association Per 1 kg/m^2 increase Below 20th percentile Women 0.86 (0.77–0.96) Men 0.89 (0.78–1.01) Above 20th percentile Women 1.05 (1.02–1.09) Men 1.11 (1.06–1.16)	FFMI Reversed J-shaped association Per 1 kg/m^2 increase Below 60th percentile Women 0.77 (0.69–0.86) Men 0.80 (0.73–0.88) Above 60th percentile Women 1.01 (0.91–1.12) Men 1.03 (0.93–1.13)	Y	N	Y
Wannamethee et al.,[20] UK	N=4107 Men Age≥60 y	1998–2005 (mean 6.0 y)	713	BIA MAMC WC WHR	FMI Non-linear association Q4 vs. Q1: 1.29 (1.02–1.63) WC Linear association Q4 vs. Q1: 1.54 (1.21, 1.95) WHR Linear association Q4 vs. Q1: 1.30 (1.04, 1.63)	FFMI No association MAMC Linear association Q4 vs. Q1: 0.71 (0.56–0.88)	Y	Y	Y (only FM measures)
Graf et al.,[21] Switzerland	N=3181 Both Age≥65 y	1990–2011 (NA)	1773	BIA	Women No association Men No association	Women No association Men Inverse association Q4 vs. Q1: 0.72 (0.54–0.96)	Y	N	Y
Batisis et al.,[22] US	N=4652 Both Age≥60 y	1988–2006 (median 14.3 y)	2782	BIA	No association	Women Any sarcopenia/non-obese vs. non-sarcopenic/ non-obese 1.32 (1.04–1.69) Men No association	Y	Y	NA
			3722				Y	N	Y

(continued)

Table 2. Continued

Reference, country	Study population, Sex, Age	Study period (follow-up)	No. of deaths	Body composition measure	RR (95% CI)		Confounder adjustment		
					FM measures	LBM measures	Smoking	PA	FM/LBM or BMI
Allison et al.,[23] US	N=10,169 Both Age 25–75 y	1971–1992 (mean 13.9 y)		Skinfold Circumference	FM indicator 1.03 (1.01–1.06) per unit increase	FFM indicator 0.92 (0.91–0.94) per unit increase			
Simpson et al.,[24] Australia	N=41,313 Both Age 27–75 y	1990–2003 (median 11 y)	2822	BIA WC WHR	Women FM, FM% No association WC U-shaped association WHR Linear positive Men FM, FM%, U-shaped association WC, WHR Linear positive	NA	Y	Y	N
Metter et al.,[25] US	N=1071 Men Age 66.3 y (mean)	1960–1999 (mean 17.5 y)	533	24 h creatinine excretion	NA	Creatinine excretion Inverse association	N	Y	Y
Heitmann et al.,[26] Sweden	N=787 Men Age 60 y	1973–1995 (NA)	460	Total body potassium	FM Linearly increasing association	FFM Linearly decreasing association	Y	Y	Y
Lee et al.,[27] US	N=38,006 Men Age≥40 y	1987–2012 (mean 21.4 y)	12,356	Anthropometric prediction equations	Predicted FM Monotonic positive association Per 1 SD increase Below median 0.99 (0.92–1.06) Above median 1.18 (1.18–1.26)	Predicted LBM U-shaped association Per 1 SD increase Below median 0.87 (0.82–0.92) Above median 1.14 (1.09–1.20)	Y	Y	Y

BIA: bioelectrical impedance analysis; BMI: body mass index; CI: confidence interval; FM: fat mass; FMI: fat mass index (FM divided by height squared, kg/m^2); FFM: fat-free mass; FFMI: fat-free mass index (FFM divided by height squared, kg/m^2); LBM: lean body mass; LBMI: lean body mass index (LBM divided by height squared, kg/m^2); MAMC: midarm muscle circumference (cm); NA: not applicable; PA: physical activity; RR: relative risk; SD: standard deviation; WC: waist circumference (cm); WHR: waist to hip ratio.

Studies using indirect measures of body composition

Bioelectrical impedance analysis studies. BIA has been used as an indirect measure of body composition in several studies. A large Danish study assessed BIA of 57,053 participants aged 50–64 years and followed them for a median of 5.8 years.[19] In the mutually adjusted model including both fat mass index and fat-free mass index, fat mass index showed a J-shaped association with mortality. Higher fat mass index (per 1 kg/m^2 increase) was associated with 11–14% lower risk of mortality in the low range of fat mass index (below 20th percentile) but 5–11% higher risk of mortality in the high range of fat mass index (above 20th percentile). On the other hand, fat-free mass index showed a reversed J-shaped association with mortality in the mutually adjusted model. Higher fat-free mass index (per 1 kg/m^2 increase) was associated with 20–23% lower risk of mortality in the low range of fat-free mass index (below 60th percentile) but there was no association in the high range of fat-free mass index (above 60th percentile).

Other smaller BIA studies also showed some evidence of the influence of body composition on mortality. A study of 4107 UK men reported no association between fat-free mass index and mortality but greater midarm muscle circumference, an indicator of muscle mass, was significantly associated with lower risk of mortality (HR of quartile 4 vs. 1 = 0.71, 95% CI = 0.56–0.88).[20] Of note, fat mass index was not mutually adjusted in the models of fat-free mass index and midarm muscle circumference. Moreover, fat mass index and other obesity related measures such as WC and WHR were not significantly associated with mortality in the multivariable models. However, fat mass index, WC, and WHR showed a strong significant positive association with mortality when muscle mass (i.e., midarm muscle circumference) was further adjusted for. Another study from Switzerland suggested that low fat-free mass index was a strong predictor of mortality in men but not in women.[21] Lastly, a study of 4652 older adults in the NHANES III showed that older women with sarcopenia (total skeletal muscle mass/height^2$\leq$10.75 kg/m^2) may increase the risk of mortality independent of obesity.[22] Compared to non-obese women without sarcopenia, non-obese women with sarcopenia had 32% increased risk of mortality (HR = 1.32, 95% CI = 1.04–1.69). Sarcopenia was not significantly associated with mortality in older men.

Other studies. Simple skinfold and circumference measures have been used as indicators of fat mass and fat-free mass. A US study from the NHANES I/II reported that fat mass indicator showed a monotonic increasing association with mortality while fat-free mass indicator showed a monotonic decreasing association with mortality in the mutually adjusted models.[23] A large study from Australia showed that WC and WHR are better predictors of mortality than fat mass and fat percent, although this study did not mutually adjust for lean body mass.[24] A few other studies have used different approaches such as 24-hour creatinine excretion and total body potassium to estimate lean body mass. A US study of 1071 men found an inverse association between muscle mass assessed by 24 h creatinine excretion and mortality.[25] Another study of 787 men from Sweden used total body potassium to assess body composition. This study found that fat mass was associated with linearly increased risk of mortality while fat-free mass was associated with linearly decreased risk of mortality.[26]

Recently, a large prospective study of US men with a long follow-up introduced a new approach to estimate fat mass and lean body mass using validated anthropometric prediction equations.[27,28] This study found that the shape of the BMI–mortality relationship was determined by the shape of fat mass and lean body mass associations with mortality. There was a J-shaped association between BMI and mortality. When fat mass and lean body mass were separately examined with mortality, predicted fat mass showed a monotonic increasing association with mortality while lean body mass showed a strong U-shaped association with mortality. Although there are inevitable measurement errors in estimating body composition using the anthropometric equations, this new approach allowed the authors to examine the body composition–mortality relationship in a large well-established cohort study accounting for important biases. More specifically, this study had a large number of deaths (including the information on cause of death) over a long follow-up period, detailed and updated information on confounders and repeated measures of body composition to minimize and assess the influence of confounding and reverse causation.

Summary of current studies

A number of studies have examined the association between body composition and mortality in the general population. Overall results were not consistent, but there was clear evidence showing that fat mass and lean body mass may have differential associations with mortality. Studies using direct body composition methods suggested that fat mass was positively associated with mortality, while lean body mass was inversely associated with mortality.[16–18] However, these associations were not consistent in studies restricted to older adults.[9–15] Most studies showed either null or inverse association of both fat mass and lean body mass in relation to mortality. When we further considered the studies using indirect body composition methods, the studies and their results were heterogenous but suggested a positive association with fat mass and a reversed J or U-shaped association with lean body mass. There are several important issues to discuss why we may have observed inconsistent findings of the association between body composition and mortality in the general population.

1. Although studies included generally healthy population without major chronic diseases, participants may have had undiagnosed preexisting diseases. This is problematic because these conditions are not only associated with weight loss plus change in body composition but also increased risk of mortality. This "reverse causation" issue could be more prominent in older adults because they are more likely to have undiagnosed medical conditions than younger adults. In fact, we observed conflicting

results on the fat mass and mortality relationship. In studies limited to older adults, fat mass appeared to have no harmful impact on mortality while fat mass tended to show a positive association with mortality in studies including both young and older adults.

Reverse causation can be a greater concern in studies with a short follow-up period because people with serious undiagnosed medical conditions are more likely to die in a short time. Most studies using direct body composition measures had relatively short follow-up period (less than mean of 10 years) and thus these studies are more susceptible to reverse causation. One study that had repeated measures of body composition (estimated using anthropometric equations) conducted lagged analysis to examine the influence of the reverse causation on obesity–mortality relationship by using different lag times (time between measure of obesity and death).[27] With shorter lag times, fat mass showed a weaker positive association with mortality and lean body mass showed a stronger U-shaped association with mortality. As expected, BMI showed a more pronounced U-shaped association with mortality with shorter lag times. We can infer that the body composition–mortality relationship is prone to reverse causation when study follow-up is short. In addition, this study suggested that the observed U-shaped association between BMI and mortality with short lag times may be largely attributed to lean body mass loss rather than fat mass loss. These findings imply that lean body mass may be inherently a marker of health status (e.g., illness). Many diseases, especially respiratory diseases, can decrease lean body mass (i.e., muscle wasting) through several biological mechanisms (e.g., inflammation, glucocorticoids, myostatin activation).[29,30] Moreover, the high end of lean body mass is driven mostly by obesity, which is far more common than extreme body builders. Thus, it is difficult to completely separate a pure effect of lean body mass on mortality, as low lean body mass may reflect diseases and high lean body mass may indicate obesity. Having a lean body mass within the middle range of the population may most reflect a healthy status.

2. The true shape of the association between body composition and mortality may have been masked for studies that have not examined the potential dose–response relationship. Due to small number of participants and deaths, many studies could not examine the shape of associations by using splines (or at least quintiles) with high precision.[31] If the true shape is not linear, using a linear approach may mask the true relationship between body composition and mortality. Several studies showed some evidence that the relationship of fat mass and lean body mass with mortality may be non-linear. Various shapes of the associations have been observed. Among large studies including both young and older adults, fat mass showed a monotonic positive or J-shaped association with mortality while lean body mass showed a linear inverse, reversed J or U-shaped association with mortality.

For fat mass, we consistently observed a strong positive association with mortality in the higher range of fat mass. In the lower range of fat mass, some studies found lower risk of mortality with higher fat mass but it may be explained by the reverse causation or high correlation of fat mass with lean body mass. If we could ideally address these issues, we might expect to see no inverse association but likely a minimal or monotonic positive association of fat mass with mortality in the lower range. In contrast, we consistently found evidence that lean body mass was inversely associated with mortality in the lower range. The association was less consistent in the higher range of lean body mass.

3. To examine the independent association of fat mass and lean body mass with mortality, mutual adjustment of these two body components as well as other confounders are important. Given the growing literature on body composition and health, fat mass and lean body mass are not only closely correlated each other but also are associated with mortality, presumably independent of each other. Although it is difficult to completely tease out fat mass and lean body mass, it is still important to account for potentially two different body components in the mortality analysis. Moreover, other confounding factors such as smoking, physical activity and diseases can substantially bias the association between body composition and mortality. For example, smoking is inarguably a strong risk factor for mortality and also causes weight loss and changes in body composition. Thus, not adjusting for smoking can seriously distort the association of body composition and mortality.

4. Measurement errors can also affect the results. For studies that used gold standard methods such as DXA or CT, measurement errors should be minimal. However, several studies collected data only from a specific region (e.g., arm, leg or calf) or using various indirect methods described in the previous section thus these data may not reflect the true total fat mass and lean body mass. In addition, because of the complexity and costs of using these techniques, typically only one measurement is made. The measurement error can be random but also systematic depending on the methods used to estimate body composition. Validation of the methods and understanding their assumptions, as well as strengths and limitations, is crucial for the valid application in research.[32] Moreover, it is also possible that detailed body composition at tissue level or quality are more relevant to overall health than total quantity of fat and lean body mass.

Future directions and conclusion

Overall, epidemiological studies on body composition and mortality suggest that fat mass and lean body mass may play an independent role on survival in the general population. The shape of the associations is not conclusive but there was plausible evidence that high fat mass was associated with increased risk of mortality (especially higher range of fat mass) and low lean body mass was associated with increased risk of mortality (especially lower range of lean body mass). These associations appeared to be less consistent in studies with elderly populations, where both fat mass and lean body mass tended to show either null or inverse association with mortality.

Given the inconclusive evidence and limitations of the current studies, future studies with high quality can be helpful. The meaning of fat mass and lean body mass is inherently complex because of the close relationship between (undiagnosed) diseases, comorbid conditions and weight loss, and the correlation of two body components in relatively healthy people.

Future studies should be carefully designed to address potential biases. Studies need to have detailed information on diseases and long follow-up period to reduce the bias due to reverse causation. Exclusion of deaths in the early follow-up is one additional approach to exclude unhealthy individuals with preexisting diseases. Although it is challenging, studies with repeated measures of body composition will be informative to understand the impact of reverse causation. Studies restricted to older adults should be interpreted with more caution as this population is more susceptible to biases (e.g., reverse causation and selection bias). Moreover, residual confounding can affect the overall findings; thus, important confounders such as smoking, physical activity, and diseases should be comprehensively adjusted or stratified in the analysis. Lastly, limited evidence exists on the association of body composition with cause-specific mortality.[27] Due to insufficient power or information, most studies only examined the association between body composition and all-cause mortality, but body composition may play a different role in the cause of death (e.g., cardiovascular disease, cancer, respiratory disease, and others).

It could be practically difficult to conduct an "ideal" study because there are limited well-established cohort studies that have a direct measure of body composition. Thus, understanding strengths and limitations of studies is critical. It is not always true that studies with a gold standard body composition measure provide the most valid evidence. Due to practical issues, these studies have shorter follow-up (e.g., reverse causation), fewer data on covariables (e.g., residual confounding), have a single measure, and tend to be smaller in size, and more restrictive in population (e.g., elderly). The overall quality of the study incorporating all these features, as well as the complex relationships of body composition, should be carefully considered when conducting the study and interpreting the findings.

Although this review focused on the literature in the generally healthy population without apparent major diseases, understanding the influence of body composition on survival among patient populations is an interesting area of research that needs more attention. The "obesity paradox" phenomenon is highly prevalent in diverse patient populations.[33] Recently, several studies showed some evidence that body composition, especially lean body mass (muscle) may play an independent role on survival in patients with disease such as cancer and cardiovascular diseases.[34–36] Body composition has a potential to provide important prognostic information to improve survival among patients, and thus more studies are warranted to better understand this association in diverse patient populations.

AUTHORS' CONTRIBUTION

All authors contributed to the preparation of this manuscript and approved the final version.

DECLARATION OF CONFLICTING INTERESTS

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REFERENCES

1. Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008;**32**:1431
2. Collaborators GO. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;**377**:13–27
3. 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
4. Global BMIMC, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson Ch L, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willeit P, Banks E, Beral V, Chen Z, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;**388**:776–86
5. Rothman KJ. BMI-related errors in the measurement of obesity. *Int J Obes* 2008;**32**:S56
6. B. Heymsfield S, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. *Annu Rev Nutr* 1997;**17**:527–58
7. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care* 2008;**11**:566
8. Wagner DR, Heyward VH. Techniques of body composition assessment: a review of laboratory and field methods. *Res Q Exerc Sport* 1999;**70**:135–49
9. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci* 2006;**61**:72–7
10. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R, Guralnik JM, Ferrucci L. Skeletal muscle and mortality results from the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci* 2009;**64**:377–84
11. Auyeung TW, Lee JS, Leung J, Kwok T, Leung PC, Woo J. Survival in older men may benefit from being slightly overweight and centrally obese—a 5-year follow-up study in 4,000 older adults using DXA. *J Gerontol A Biol Sci Med Sci* 2009;**65**:99–104
12. Rolland Y, Gallini A, Cristini C, Schott A-M, Blain H, Beauchet O, Cesari M, Lauwers-Cances V. Body-composition predictors of mortality in women aged≥ 75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr* 2014;**100**:1352–60
13. Bunout D, de La Maza MP, Barrera G, Leiva L, Hirsch S. Association between sarcopenia and mortality in healthy older people. *Australas J Ageing* 2011;**30**:89–92

14. Toss F, Wiklund P, Nordström P, Nordström A. Body composition and mortality risk in later life. *Age Ageing* 2012;**41**:677–81
15. Wijnhoven HA, Snijder MB, Deeg DJ, Visser M. Region-specific fat mass and muscle mass and mortality in community-dwelling older men and women. *Gerontology* 2012;**58**:32–40
16. Padwal R, Leslie WD, Lix LM, Majumdar SR. Relationship among body fat percentage, body mass index, and all-cause mortality: a cohort study. *Ann Intern Med* 2016;**164**:532–41
17. Zong G, Zhang Z, Yang Q, Wu H, Hu FB, Sun Q. Total and regional adiposity measured by dual-energy X-ray absorptiometry and mortality in NHANES 1999-2006. *Obesity (Silver Spring)* 2016;**24**:2414–21
18. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: a population-based cohort study. *PLoS One* 2018;**13**:e0194697
19. Bigaard J, Frederiksen K, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Body fat and fat-free mass and all-cause mortality. *Obesity Res* 2004;**12**:1042–9
20. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr* 2007;**86**:1339–46
21. Graf CE, Karsegard VL, Spoerri A, Makhlouf A-M, Ho S, Herrmann FR, Genton L. Body composition and all-cause mortality in subjects older than 65 y. *Am J Clin Nutr* 2015;**101**:760–7
22. Batsis J, Mackenzie T, Barre L, Lopez-Jimenez F, Bartels S. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. *Eur J Clin Nutr* 2014;**68**:1001–7
23. Allison DB, Zhu SK, Plankey M, Faith MS, Heo M. Differential associations of body mass index and adiposity with all-cause mortality among men in the first and second National Health and Nutrition Examination Surveys (NHANES I and NHANES II) follow-up studies. *Int J Obes* 2002;**26**:410–6
24. Simpson JA, MacInnis RJ, Peeters A, Hopper JL, Giles GG, English DR. A comparison of adiposity measures as predictors of all-cause mortality: the Melbourne Collaborative Cohort Study. *Obesity* 2007;**15**:994–1003
25. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol A Biol Sci Med SciJ Gerontol A Biol Sci Med Sci* 2002;**57**:B359–65
26. Heitmann B, Erikson H, Ellsinger B, Mikkelsen K, Larsson B. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish menFa 22-year follow-up. The study of men born in 1913. *Int J Obes* 2000;**24**:33–7
27. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, Giovannucci EL. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ* 2018;**362**:k2575
28. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Sun Q, Willett WC, Giovannucci EL. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999–2006. *Br J Nutr* 2017;**118**:858–66
29. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. *Am J Clin Nutr* 2010;**91**:1123S–7S
30. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov* 2015;**14**:58
31. Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables. *J Clin Epidemiol* 2009;**62**:511–7.e1
32. Sinha J, Duffull SB, Al-Sallami HS. A review of the methods and associated mathematical models used in the measurement of fat-free mass. *Clin Pharmacokinet* 2018;**57**:781–95
33. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. *Diabetes Care* 2013;**36**:S276–S81
34. Caan BJ, Feliciano EMC, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, Quesenberry CP, Weltzien EK, Castillo AL, Olobatuyi TA. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol* 2018;**4**:798–804
35. Medina-Inojosa JR, Somers VK, Thomas RJ, Jean N, Jenkins SM, Gomez-Ibarra MA, Supervia M, Lopez-Jimenez F. Association between adiposity and lean mass with long-term cardiovascular events in patients with coronary artery disease: no paradox. *J Am Heart Assoc* 2018;**7**:pii:e007505
36. Lavie CJ, De Schutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease: impact of lean mass index and body fat in the "obesity paradox". *J Am Coll Cardiol* 2012;**60**:1374–80