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## A Systematic Review of Body Fat Distribution and Mortality in Older People

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### ABSTRACT

We conducted a systematic review investigating body fat distribution in older adults and its association with morbidity and mortality. Our search yielded 2,702 citations. Following three levels of screening, 25 studies were selected to evaluate the association between body fat distribution and comorbidity, and 17 studies were used in the mortality analysis. Most of the selected studies in our analyses used anthropometric measures, e.g., body mass index (BMI), waist circumference, and waist-hip ratio; relatively few studies used direct measures, such as body fat/lean mass, and percentage body fat. Studies reported inconsistent findings regarding the strongest predictor(s) of morbidity and mortality. However, the majority of studies suggested that BMI per se was not the most appropriate predictor of morbidity and mortality in the elderly because of its inability to discern or detect age-related body fat redistribution. In addition, studies using BMI found that the optimal BMI range for the lowest mortality in the elderly was overweight ( $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ ) or mildly obese ( $30 \text{ kg/m}^2 \leq \text{BMI} < 35 \text{ kg/m}^2$ ). Our findings suggest that the current clinical guidelines, recommending that overweight and obesity are major risk factors for increased morbidity and mortality are not applicable to this population. Therefore, the central message of this review is to admonish the government to establish new guidelines specifically for this population, using a combination of body fat distribution measurements, and to certify that these guidelines will not be applied to inappropriate populations.

**Keywords:** body fat distribution; visceral fat; central obesity; morbidity; mortality; elderly

**Abbreviations:** BMI, body mass index; WHR, waist-hip ratio; WC, waist circumference; VF, visceral fat; SAD, sagittal abdominal diameter; BIA, bioelectrical impedance analysis ; DXA: Dual energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; CT: computed tomography; CVD, cardiovascular disease; MS, metabolic syndrome.

## 1. INTRODUCTION

While overweight and obesity are associated with increasing risk of morbidity and mortality in middle-aged adults, relatively few studies focus on older populations, among which, most found that overweight was protective. Based on these conflicting findings, it appears that the change of the role of overweight from being a risk factor for younger adults to being a protective factor for older adults is due to the influence of aging, which may be related to differences in fat distribution in the aging process.

As individuals age, bone mineral density and lean mass decrease, while body fat mass<sup>1</sup> increases and is distributed specifically in the abdominal region [1]. A preferential increase in visceral fat (VF), combined with a decrease in lower body subcutaneous fat can occur independent of changes in body weight, total adiposity, or waist circumference (WC) [2]. Lifestyle factors that contribute to these age-associated changes in body fat distribution include dietary changes, with higher intakes of saturated fats and simple sugars, and reduced physical activities, with less skeletal muscle mass and reduced strength [3].

Increases in VF is strongly associated with many adverse health conditions, such as metabolic syndrome, inflammation, dyslipidemia, insulin resistance, type-2 diabetes, cardiovascular diseases, some cancers [4-9], and, ultimately, death [10]. Consequently, for an older population, body fat distribution seems to be a better indicator to predict morbidity and mortality.

Current clinical guidelines [11] were almost exclusively based on studies that predominantly included young and middle-aged populations and concluded that overweight and obesity<sup>2</sup> were major risk factors for increased morbidity and mortality for adults aged 18 years and older without recommending age-specific cut points. Therefore, recommendations on optimal body shape and body weight specifically for the elderly are lacking and in need.

We performed a systematic review to determine the strength of evidence with regards to the existing findings for the relationship between body fat distribution and mortality in the elderly. The objective of this systematic review is to gain a better understanding of the complex relationship between mortality and morbidity risks associated with changes in body composition during the aging process. This knowledge will not only clarify the discordant evidence on BMI-based mortality risks for middle-aged adults, but also inform policy makers of the direction of prevention and control in current guidelines for this population.

## 2. MATERIALS AND METHODS

This systematic review was conducted and reported according to established guidelines [12]. A detailed research protocol was prepared a priori and was followed throughout.

### 2.1 Data sources and literature search

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<sup>1</sup> Fat mass consists of essential fat and storage fat, the former being the fat necessary to sustain normal physiological function and the latter comprising primarily adipose tissue. Lean mass includes muscle, water, bone, connective tissue and internal organs.

<sup>2</sup> Overweight and obesity were defined as body mass index (BMI, weight in kilograms divided by the square of height in meters)  $\in$  (25, 30] kg/m<sup>2</sup> and  $\geq$  30 kg/m<sup>2</sup>, respectively.

A search strategy was created by a MLIS qualified librarian. Databases, such as MEDLINE, EMBASE, CENTRAL, SCOPUS, COCHRANE, and CINAHL were searched to March 1st, 2012, using the following search terms: body fat (distribution), body composition, adiposity, waist circumference, waist-hip ratio, adipose tissue, fat tissue, subcutaneous fat, VF, or waist in conjunction with aged, old/older individuals/adults/people/persons/subjects/population, or elderly. We also reviewed references from retrieved articles when necessary.

## **2.2 Screening criteria**

Search results were put through three levels of screening. The first screening level involved scanning abstracts for the following exclusion criteria: animal studies; languages other than English; duplicate studies; and studies not containing at least one type of relevant information (measurement of body fat distribution, morbidity, and mortality). After removing abstracts that fit the exclusion criteria during the first level of screening, full articles were obtained and studies were screened at the second level based on the following inclusion criteria: (i) studies needed to report at least one outcome of interest, including mortality and morbid conditions, focusing on insulin resistance, type-2 diabetes mellitus, cardiovascular disease, hypertension, and cancer; (ii) studies included subjects whose age is older than 55 years; (iii) studies used at least one clearly defined measurement of body fat distribution.

## **2.3 Study selection**

In the third screening level, articles were selected to be included in both comorbidity and mortality analyses based on a second set of inclusion criteria: (i) the conclusion was based on stratified analysis and/or adjusted for appropriate covariates; (ii) studies included a minimum of 100 participants to boost statistical power; and (iii) for the mortality analysis, studies had to have 3 or more follow-up years, studies including BMI had to include at least one other measurement of body fat distribution, study subjects had to be non-institutionalized, and studies had to report the relationship between body fat distribution measurements and mortality.<sup>3</sup> Three investigators independently reviewed the studies, abstracted outcomes, and resolved disagreements by consensus.

## **3. RESULTS**

### **3.1 Data Retrieval**

A flow diagram outlining the systematic review process is provided in Figure 1. The initial search resulted in 2,702 articles. After removing duplicate studies and reviewing all abstracts at the first level of screening, 1,128 abstracts remained. Full articles were retrieved, and after a second level of screening for exclusion and inclusion criteria, 228 articles were left for further selection. One hundred and eighty-seven studies did not meet the second set inclusion criteria. Among the selected studies, 25 were selected for comorbidity analysis and 17 were selected for mortality analysis.

### **3.2 Study and Sample Characteristics**

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<sup>3</sup> Less stringent criteria at level 3 were applied to the studies for comorbidity analysis to include more articles due to the limited number of studies for the elderly.

Among the studies extracted for this article, 10 articles were published prior to the year 2002, and 31 articles were published during or after 2002 (Table 1). Eighteen studies initiated recruitment before the year 1995. The remaining 18 studies began recruitment during or after 1995. In 13 studies, the follow up period was equal to or greater than 5 years. Four studies had a follow up period of less than 5 years. The studies were carried out primarily in Europe (n= 17) and North America (n=13). Eight studies were conducted in Asian and only 1 was carried out in Brazil.

We included 868,910 individuals from the 41 extracted studies in our analysis. In studies reporting sex, 52% of participants were female and 48% were male. Among the articles that reported race, 71% of study participants were white, 19% were black, and about 10% were Asian. For the articles that reported comorbidities, 6 studies involving 155,036 participants discussed type-2 diabetes and insulin resistance, 6 targeted hypertension, 10 considered cardiovascular disease, and 5 studies investigated cancer.

### **3.3 Measurements of Body Fat Distribution**

While the commonly used BMI provides a measure that allows comparison between individuals of different heights and weights, it cannot capture the differences in body composition and body fat distribution. Nonetheless, different mathematical formulae across studies were provided to relate BMI to body fat [13-15]. Therefore, BMI is often seen as a comparator among various measurements of body fat distribution in the literature. For the elderly population, BMI is known as an inappropriate measure of body fat and is limited in its predictive ability for mortality [16, 17] due to three reasons: (i) it does not differentiate between fat and lean body mass, and the latter is progressively lost with increasing age [18, 19]; (ii) height measurement is unreliable due to shrinkage and vertebral collapse [19]; (iii) height and weight information is often recalled and self-reported rather than measured, causing spurious and inaccurate BMI estimates in the elderly.

Anthropometric<sup>4</sup> measurements include circumferences of various body parts, e.g., waist, hip, thigh, calf, and sagittal abdominal diameter, as well as skinfold thickness. Circumference measurements are often used alone or in combination with other measures, e.g., waist-hip ratio (WHR), waist-height ratio. Skinfold thickness is measured by calipers at standardized skin pinch points to determine the subcutaneous fat layer thickness.

Direct measures of body fat distribution include hydrodensitometry, air displacement plethysmography and bioelectrical impedance analysis (BIA) which provide information on the two-compartment model (fat mass and fat-free mass) of body composition [20]. Dual energy X-ray absorptiometry (DXA) adds a third compartment, bone mineral content, to the body composition model. Imaging methods, such as computed tomography (CT) and magnetic resonance imaging scanning can differentiate between subcutaneous and visceral adipose tissue and between subcutaneous and intermuscular adipose tissue [21]. These are suitable for smaller detailed research studies but not broader population health studies.

### **3.4 Body Fat Distribution and Risk of Morbidity in the Elderly**

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<sup>4</sup> The term “anthropometric” refers to measurements made of various parameters of the human body.

Adipose tissue is an endocrine organ that secretes inflammatory and immune mediators. Consequently, in evaluating body fat distribution, it is important to note that hepatic fat accumulation is more important than total body fat mass. Visceral adipose tissue (abdominal obesity) places individuals at a greater risk of metabolic syndrome disorders than adipose tissue located in the lower body or subcutaneously [22]. The accumulation of fat in the viscera is associated with a plethora of health conditions namely cardiovascular disease (CVD), insulin resistance and type-2 diabetes mellitus, metabolic syndrome (MS) and cancers. Its association with these diseases is due to its strong pro-inflammatory characteristics [23], and its close proximity to the portal vein, which carries blood from the intestinal area to the liver. Free fatty acids and other substances released by VF enter through the portal vein and travel to the liver, where they can influence the production of blood lipids [24].

VF also secretes several inflammatory hormones, cytokines, immune system chemicals, namely, tumor necrosis factor and interleukin-6 [24], which increases the risk of CVD by promoting insulin resistance, and low-level chronic inflammation. Moreover, evidence suggests that VF may have deleterious effects on cells' sensitivity to insulin, blood pressure, and blood clotting [25]. Table 2 lists the selected studies reporting comorbidity outcomes of the elderly and associations with body fat distribution, using various methods of measurements described in Section 3.3. For studies that also included sample younger than 55 years, only the information and analysis concerning those 55 years and older were included. Twenty five studies [6, 26-47] were included in the comorbidity analysis, of which 5 focused on women only [31, 34, 41, 42, 45] and 4 focused on men [27, 32, 33, 43].

#### **3.4.1 Insulin resistance and type-2 diabetes**

Body fat distribution is associated with numerous metabolic alterations in old age such as insulin resistance and type-2 diabetes. In the Iowa Women's Health Study cohort, of 30,000 women aged 55-69 years BMI and WHR were significantly associated with incident diabetes and hypertension [48]. Passos et al. reported similar findings indicating central adiposity expressed in terms of WHR having greater predictive ability in diabetes development in the elderly and also possibly a better predictor than BMI [38]. Consistent with these reported findings, central obesity was predictive of other disorders important in the clinical development of insulin resistance and diabetes, such as lipid profile, blood pressure, and glycemic indices [37].

To the best of our knowledge, the literature on body fat distribution and insulin resistance/diabetes is sparse when looking at elderly  $\geq 55$  years. Nonetheless, surrogate anthropometric measures of abdominal fat appear to be better predictors of insulin resistance and type-2 diabetes than BMI [46]. It is possible that BMI is unable to detect increases in abdominal adiposity related to the aging process [49]. This may explain the reduced predictive ability of BMI to detect risk for insulin resistance and type-2 diabetes in the elderly. BMI does not appear to be as important a measure for predicting the development of these diseases.

#### **3.4.2 Hypertension**

Differences in adipose distribution tend to also influence hypertension. Gosh et al. investigated Bengalee Hindu elderly  $\geq 55$  years [27]. They reported that there were significant differences between

normotensive and hypertensive individuals in the mean values for BMI, WC, hip circumference, and WHR. They found that the aforementioned indices had consistently higher values when compared with persons in the normotensive group. Moreover, in a study of 60-year-old men and women, a WC  $\geq 95$  cm in men and  $\geq 88.5$  cm in women was associated with incident high blood pressure. Newly diagnosed hypertensives in the study had a large WC, high BMI, high fasting glucose and insulin values. Similar findings of surrogate measures of abdominal fat being associated with blood pressure have been observed in other studies [37]. Again in older adults measures of central adiposity appear to be better predictors of disease risk.

### **3.4.3 Metabolic syndrome**

Body fat is strongly correlated with MS. It has been postulated that it is a cardiovascular risk factor by acting through other risk factor states, such as dyslipidemia, hypertension, insulin resistance, inflammation and prothrombotic states. Adipocytes release non-esterified fatty acids and inflammatory cytokines that can increase insulin resistance, promoting atherogenic dyslipidemia which is associated with prothrombotic and proinflammatory states [50, 51]. MS is also considered the primary risk factor for diabetes and cardiovascular disease [6]. It is defined as a cluster of 3 or more characteristics, namely WC  $> 102$  cm in men  $> 88$  cm in women, triglycerides levels  $150$  mg/dl, high density lipoprotein cholesterol  $< 40$  mg/dl in men and  $< 50$  mg/dl in women, blood pressure  $130/85$  mmHg and fasting serum glucose  $110$  mg/dL [29].

In studies investigating distribution of body fat and MS, one study did not observe a high prevalence of WC among persons with MS [29]. In contrast, in a cohort of 70-79 year old men and women, subcutaneous abdominal adipose tissue was associated with MS in normal weight men. Intermuscular adipose tissue was associated with MS in normal weight and overweight men. However, subcutaneous thigh adipose tissue was inversely associated with MS in obese men and women [6]. Similarly, another study reported the odds of having two or more MS clinical disorders increased with incremental increases in anthropometric measures [35]. In the Health Aging and Body Composition Study, individuals with MS had significantly more abdominal visceral fat and less thigh subcutaneous fat. Moreover, per standard deviation higher visceral fat, the odds of developing MS increased in women [40]. The present studies of older adults indicated that abdominal fat and intermuscular fat was associated with MS and that thigh subcutaneous fat was more protective.

### **3.4.4 Cardiovascular disease**

Several studies reported that odds of developing CVD increased significantly with incremental increases in WC, WHR, and BMI [7, 52, 53]. WC was associated with CVD risk factors to a greater extent compared to BMI and WHR in Taiwanese [35]. Turcato et al. also reported similar findings in 229 men and women aged 67-78 years. Indicators of body fat distribution were associated with CVD risk factors independent of BMI [36]. In contrast one study noted a negative association between BMI and heart disease [54].

It is clear from the literature that certain specific body fat distribution indices may confer a greater risk for adverse health outcomes in the elderly. In particular, measures of central adiposity consistently

appear to be stronger predictors of CVD risk compared to other measures [33]. These findings confirm that possibly VF more so than total fat is the main correlate of CVD.

### **3.4.5 Cancers**

Studies of body fat distribution and cancer have produced inconsistent results. In the European Prospective Investigation into Cancer and Nutrition Study, anthropometric measurements were associated with endometrial cancer. Specific measures associated with cancer were BMI, WC, and WHR. The authors reported a two-fold increased risk in postmenopausal women with a BMI greater than 30 kg/m<sup>2</sup> and three-fold increased risk for morbidly obese women, compared with women in other BMI categories [45]. In contrast to the previous results, higher BMI was associated with significantly reduced incidence of prostate cancer but associated with a risk of dying from prostate cancer [32]. Folsom et al. also reported both positive and negative associations between anthropometric measures and cancer [48]. They found that BMI and WC were moderately associated with incident breast cancer and colon cancer; BMI was negatively associated with lung cancer; BMI was not but WC and WHR were associated with incident ovarian cancer; and BMI and WC were strong predictors of incident uterine cancer.

Studies of body fat distribution and cancer have produced mixed results, indicating that specific measures of body fat may not confer a greater risk for some cancers, but higher anthropometric measures are still associated with other deleterious health outcomes [41].

## **3.5 Body Fat Distribution and Mortality in the Elderly**

The associations between aging, central obesity, and chronic conditions, and mortality are depicted in Figure 2. The former association was explained in Section 3.4 and the latter will be described in this section. Table 3 lists the selected studies reporting mortality outcomes of the elderly and associations with body fat distribution. For studies that also included participants younger than 55 years, only the information and analysis concerning those 55 years and older were included. Seventeen studies [17, 19, 55-69] were selected for mortality analysis, of which, 3 studies [64, 68, 69] focused on men only and 2 studies focused on women only [55, 59]. In terms of measurements of body fat distribution, all of the studies used BMI; 13/8/2 studies used WC/WHR/ skinfold thickness; 5 studies [57-59, 62, 66] used direct measurements of body fat distribution (BIA, DXA, or CT) ; 2 studies [60, 64] used mathematical formulas transforming body weight or potassium to body fat.

### **3.5.1 The Best predictor of all-cause mortality**

Different studies used different sets of measurements of body fat distribution to look at the relationship between mortality and body fat distribution in different samples of old subjects. Therefore, the conclusions of the best predictor of mortality are inconsistent across studies. Most of the studies found association between body fat distribution and mortality. Folsom et al., analyzing finding from the Iowa Women's Health Study, claimed that WHR was the best anthropometric predictor in women [55]. Han et al. in a study consisting of all Asian elderly (aged 65-98 years) argued that lean body mass should be the best predictor of mortality for Asians [62].



Some studies found that a combination of measurements most effectively predict mortality. In a study that only recruited men, Wannamethee et al. concluded that a composite measure of midarm muscle circumference and WC (>102 cm) was the best predictor of mortality for a male older population [68]. In the Cardiovascular Health Study, Janssen et al. found that after controlling for both WC and BMI, BMI was a negative predictor, whereas WC was a positive predictor [65].

Among those studies including body composition measures, Han et al. found lean body mass was the strongest predictor for Asian men and women, as previously mentioned. Looking also at the older Asian population, Auyeung et al. reported that in older men, mortality was related to body composition, whereas in women, no corresponding relationship could be revealed, except in WHR [57]. Kuk et al. found that low percentage body fat ( $\leq 24.3$  % for women and  $\leq 15$  % for men) is strongly associated with a high mortality risk (4/2 folds higher than that for women with percentage body fat  $\in [24.4, 35.9]$  %/men with percentage body fat  $\in [15.1, 24.0]$  %) [66]. On the other hand, Dolan et al. contended that body composition measures were not better predictors than BMI or WC [59]. Cesari et al. also found that no body composition parameters were significantly associated with mortality [58].

In summary, the contradictory conclusions across different studies can be attributed to variations of the following: (i) study populations; (ii) statistical models; (iii) measurement of body fat distribution; and (iv) accuracy of the measurements.

### **3.5.2 Optimal BMI, WC, WHR, and body fat composition for the elderly**

Thirteen out of 17 articles gave information about optimal ranges of body fat distribution for mortality for elderly populations.<sup>5</sup> In terms of BMI, 8 studies provided optimal BMI range for the elderly. With the exception of one study using a sample aged 90+ suggested a range [25, 30) kg/m<sup>2</sup>, the rest of the studies all suggested higher ranges. Six studies had this information on WC. For men, Wannamethee et al., Hays et al., and Visscher et al. suggested WC should be < 102 cm, within (99.5, 106.6) cm, and within (86, 90) cm, respectively; for women, Dolan et al., Hays et al., and Visscher et al. had the optimal ranges of (80, 85.7] cm, (88.4, 95.6] cm, and <79 cm, respectively. Srikanthan et al. and Folsom et al. suggested 87-92 cm and 80-87.3 cm, respectively, for older populations in general. WHR, on the other hand, appears to be the smaller the better. Srikanthan et al. and Folsom et al. showed that older adults in their samples with WHR  $\leq 0.75$  and < 0.762, respectively, had the lowest mortality. Two studies provided optimal percentage body fat. Kuk et al. found that the lowest mortality occurred at [24.1, 29.4] % for men and [42.5, 46.4] % for women. Dolan also found that percentage body fat in the range of (40.91, 44.25] % is the most beneficial.

### **3.5.3 Other-cause mortality**

Three studies discussed cause-specific mortality [19, 55, 60]. Gale et al. and Folsom et al. did not find associations between any of their measurements of body fat distribution and cancer mortality in elderly women, but an inverse association of percentage body fat as well as BMI and cancer mortality in elderly

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<sup>5</sup> If the studies used models with body fat distribution measurements in a continuous fashion, then the information on the optimal value is not available.

men was observed by Gale et al. For the cardiovascular mortality, WC has the worst predictive power in both men and women. Price et al. and Folsom et al. both showed that WHR was positively associated with circulatory- and cardiovascular-related death, respectively. Without including WHR as one of their measurements of body fat distribution, Gale et al. concluded that only BMI (neither fat free mass nor percentage body fat) showed positive association with cardiovascular mortality in women. However, Price et al. contradictorily found that BMI was negatively associated with circulatory mortality in women.

### **3.5.4 Obesity paradox**

Although obesity is a risk factor for the aforementioned comorbidities, studies have shown that when overweight and obese people develop these diseases they have better survival outcomes than their normal weight counterparts. This has been termed the “obesity paradox” [70]. The obesity paradox was found in the elderly in most of the studies investigating BMI threshold as a risk factor in the older population [17, 19, 71-75]. However, the National Institutes of Health guidelines [11] on overweight and obesity define adults with a BMI  $\geq 25$  kg/m<sup>2</sup> as being at risk, and recommend treatment for people with a BMI  $\geq 30$  kg/m<sup>2</sup> or for those with a BMI  $\in [25, 30)$  kg/m<sup>2</sup> and either  $\geq 2$  comorbidities or a high WC. The obesity paradox suggests that these recommendations are inappropriate for older adults [19, 74, 76].

### **3.6 Economic Burden**

Death is only part of the picture of the burden of chronic diseases caused by body fat redistribution for the elderly. These conditions can cause tremendous economic burden on the health care system. The comorbidities associated with body fat redistribution in the process of aging will be a focus of medical care as the population continues to age and live longer than ever before. According to a report by Centers for Disease Control and Prevention [77], currently about 80% of Americans older than 65 years are living with at least one chronic condition. And the older population is growing due to longer life spans and aging baby boomers. However, the cost of providing health care for an older adult is three to five times greater than the cost for an adult younger than 65. As a result, by 2030, the U.S. health care spending is projected to increase by 25% due to the demographic shifts.<sup>6</sup>

Although premature death caused by those comorbidities associated with age-related body fat redistribution, ironically, generates a direct medical savings [78], the improved medical care and prevention efforts have prolonged life expectancy. To the extent that the age-associated fat deposition contributes to those comorbidities but does not hasten death, which translates to marked health care costs that greatly outperform the savings, the financial impact on the health care system is substantial. In a study that included 3,789 individuals aged  $\geq 65$  years, it was found that abdominal obesity was associated with 15% higher costs controlling for age, sex, race/ethnicity, and other factors [79].

## **4. DISCUSSION**

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<sup>6</sup> It is projected that there will be 71 million older adults by 2030, accounting for roughly 20% of the U.S. population.

We performed a comprehensive search and conducted a systematic review of the literature to examine the existing findings on the relationship between body fat distribution and mortality. We found that the majority of studies conducted body fat distribution and mortality in a general population context; relatively few studies focused on the elderly.<sup>7</sup> Our review included 25 studies in the analysis of comorbidities associated with age-related body fat redistribution and 17 studies in the analysis of mortality.

Our review revealed several important findings. As fat tissue increases toward the center of the body in the process of aging, central adiposity becomes one of the major risk factors of chronic diseases, including type-2 diabetes, hypertension, cardiovascular diseases, and some cancers, and, ultimately, death.<sup>8</sup> We found that the commonly used measures for body fat distribution in the literature were anthropometric measures, e.g., BMI, WC, and WHR, and direct measures, e.g., body fat/lean mass, and percentage body fat. Among these measures, studies have had inconsistent conclusions with regard to the strongest predictor(s) of incidence of the aforementioned comorbidities and mortality. But almost all of the studies alluded to the fact that BMI per se was not the most appropriate predictor for this population due to the age-related body fat redistribution. Furthermore, studies using BMI found that the optimal BMI range for the lowest mortality in the elderly was overweight and mildly obese. These suggest that the current National Institutes of Health guidelines [11] advising that overweight and obesity are major risk factors for increased morbidity and mortality are not applicable to this population.

There are at least four reasons that can explain the inconsistent findings regarding the best predictor of morbidity/mortality across different studies: (i) although the study samples belong to an older population, findings may be very different across different age subgroups, e.g., the youngest old and oldest old, even though age is controlled for; (ii) pre-baseline weight loss, the extent of which increases with age, can confound the estimation of risk due to adiposity at baseline in a cohort study [80]; (iii) the measurements of body fat distribution deviate from study to study, e.g., fat mass could be measured by DXA, BIA, and even from body weight; and (iv) the selections of covariates vary across studies, making back-to-back comparisons difficult. The heterogeneity in the studies and in the measurements of body fat distribution was one of the reasons that a systematic review is preferred over a meta-analysis in this paper.

Our study is restrained by the limitations of the quality of the selected studies for the following reasons. First, some of the studies used self-reported information, which might result in biased estimation and erroneous conclusion. Second, although we excluded those studies that only reported unadjusted estimates or raw correlations, bias still exist in the adjusted model due to important risk factors that were left out in the model. Third, quite a few studies reported insignificant individual tests results, which should be noted that the insignificance may not result from the weak correlation between the target covariates and the outcome; rather, the insignificance came from the strong correlation between covariates, which could be resolved by using a joint test.

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<sup>7</sup> Even though a lot of studies cover the range of our target age group, they did not stratify in terms of age, so the estimates that they reported were mixed and not applicable to our analyses.

<sup>8</sup> We focused on these major diseases and did not cover other conditions attributable to age-related body fat redistribution, e.g., sarcopenia, left ventricular mass, pulmonary disease, and disability.

Nevertheless, our review has several strengths. First, we performed a systematic review with a priori criteria to determine the strength of evidence in relevant studies and selected the studies of highest quality to synthesize their findings. Second, our conclusions help readers gain a better understanding of the complex relationship between mortality and the morbidity risks associated with age-related body fat composition. Third, our findings help clarify the misleading BMI-based mortality risks for middle-aged adults.

In conclusion, our findings have provided evidence supported by existing literature suggesting that the current clinical guidelines require updated recommendations using combinations of body fat distribution measurements, including height, weight, waist and hip circumferences, direct measurements, and so on, specifically for older adults. At the same time, the updated version should make itself clear that it will not be misapplied back to a general population or younger populations. As the demographic shifts toward an aging society, it is imperative to establish new guidelines for the older population in terms of optimal body fat distribution for chronic disease prevention and control.

### **Contributors**

S.-H. Chang: study design, data extraction, data synthesis and analysis, interpretation of results, and writing of the manuscript; T. Beason: study design, data extraction, data synthesis and analysis, interpretation of results, and writing of manuscript; J. Hunleth: data extraction, interpretation of results, and writing of manuscript; G. Colditz: study design, interpretation of results, and critical review of manuscript. All authors approved the final version.

### **Competing interest**

None declared.

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