Review

Body Mass Index and Mortality

Hye Jin Yoo*

Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Korea University, Seoul, Korea

Although the prevalence of obesity, a well-known risk factor for various chronic diseases such as hypertension, type 2 diabetes and dyslipidemia, is rapidly increasing worldwide, the association of obesity with all-cause mortality remains controversial. Many previous epidemiologic studies have demonstrated a U-shaped relationship between obesity and mortality, suggesting that there is an obesity paradox. However, recent large-scale meta-analyses found contradictory results that both overweight and obese subjects exhibited a significant increase in all-cause mortality. This review summarizes the key epidemiologic studies on the association of obesity with mortality and thoroughly examines the causes of the obesity paradox and the precautions needed in the interpretation of this clinical evidence.

Key words: Obesity, Mortality, Body mass index, Waist circumference

INTRODUCTION

The prevalence of obesity, defined as a body mass index (BMI) of 30 or greater, is rapidly increasing, up to 35.5% among adult men and 35.8% among adult women based on findings from the 2009-2010 National Health and Nutrition Examination Survey (NHANES).[1] The Korean Society for the Study of Obesity noted that 32.8% of adult Koreans are obese: 36.1% of men and 29.7% of women.[2] Obesity is defined as a BMI ≥ 25 kg/m^2 in Korea. Obesity, traditionally defined as a high BMI, exhibits an intimate association with incident chronic diseases, including hypertension, type 2 diabetes, cardiovascular diseases (CVD) and cancer.[3] Obesity induces insulin resistance, proatherogenic states, unfavorable hemodynamic burden to the heart[4], and promotes the growth of certain types of cancers such as breast and colorectal cancer.[5] Although obesity is a well-known reversible risk factor for chronic diseases, there is still debate on the relationship between obesity and mortality. Until now, many epidemiological studies have suggested that there is a U-shaped relationship between BMI and mortality.[6-8] Interestingly, the lowest hazard ratios (HR) for mortality have been observed in overweight or mildly obese individuals rather than in normal weight subjects. However, in 2016, large-scale meta-analyses reported results conflicting with these previous studies. Therefore, this review will briefly summarize the recent key meta-analyses on the relationship of elevated BMI with mortality and the potential causes of these contradictory results, focusing on the rationale for the obesity paradox.

Recent key epidemiologic studies on the relationship between elevated BMI and mortality
Association of BMI with mortality in the general population (Table 1)

In 2016, various large-scale clinical studies reported on the relationship of BMI with mortality. One meta-analysis of 239 prospec-

tive studies in four continents, including Asia, Australia and New Zealand, Europe, and North America, showed that all-cause mortality during a median follow-up of 13.7 years was minimal in individuals with a BMI of 20.0-25.0 kg/m^2 and increased significantly both above and just below this range.[9] Importantly, to limit the effects of reverse causality, this meta-analysis excluded smokers, participants with chronic diseases at baseline and those dying within 5 years of recruitment. As a result, both being overweight and obesity were significantly associated with increased all-cause mortality, which contradicted previous results showing a protective effect of overweight and obesity on mortality and which indicated only severely obese people were at an increased risk of mortality.[8] Another recent meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants also showed that the lowest mortality risk was detected at BMI 23-24 kg/m^2 in never smokers, 22-23 kg/m^2 in healthy never smokers and 20-22 kg/m^2 in never smokers with ≥ 20 years of follow-up.[10] In this study, the shape of the dose-response curve between BMI and mortality changed from a U-shape to a J-shape with increasing duration of follow-up, which is overall less influenced by the confounding factor of pre-diagnostic weight loss.

Association of BMI with mortality in individuals with type 2 diabetes

Compared to the general population, subjects with type 2 diabetes exhibit higher mortality, mainly caused by CVD.[11] Although being overweight or obese is one of the modifiable risk factors for type 2 diabetes, the association between obesity and mortality in patients with type 2 diabetes remains controversial. A recent meta-analysis of 414,587 participants with type 2 diabetes showed that all-cause mortality was lowest in individuals with a BMI in the ranges of 31-35 kg/m^2 for men and 28-31 kg/m^2 for women[12], while mortality was higher in normal weight subjects. Similarly, Wang et al.[13] reported that the BMI value associated with the lowest mortality in individuals with type 2 diabetes was within the overweight range at 26.6 kg/m^2, even after adjusting for smoking, underlying diseases such as CVD, cancer, chronic bronchitis and renal disease, and excluding those who died during the first 3 years of follow-up. Thus, being overweight/obese conferred more protective effects against mortality than normal weight[14] in individuals with type 2 diabetes compared to the general population. However,

studies on the association of BMI with mortality in subjects with type 2 diabetes usually have short-term follow-up periods compared to studies of individuals without type 2 diabetes. Therefore, more large-scale studies with long-term follow-up are warranted to clarify the influence of obesity on mortality in diabetic patients.

Association of BMI with mortality in Asians

People in Asia have relatively higher visceral fat compared to members of other ethnic populations with the same BMI[15] which contributes to the development of diabetes and CVD in individuals with relatively lower degrees of obesity.[16] A World Health Organization (WHO) expert consultation proposed that Asians have an increased risk of type 2 diabetes and CVD at a lower BMI than the current WHO cut-off point for being overweight (≥ 25 kg/m^2).[17] In 2000, the Asia-Pacific region redefined obesity as a BMI of ≥ 25 kg/m^2 and overweight as ≥ 23 kg/m^2. However, the use of this cut-off was not directly supported by data on mortality. In a representative group of Chinese subjects, deaths from any cause were lowest among men with a BMI of 24.0 to 24.9 and women with a BMI of 25.0 to 24.9[18,19] both of which are in the current overweight range in the Asia-Pacific guidelines. Yi et al.[20] reported that the gender-age specific optimal BMI value with minimal mortality was higher than the existing normal weight BMI range in Korean adults. Similarly, a 12-year prospective cohort study of 1,213,829 Koreans showed that the risk of death from any cause was lowest among patients with a BMI of 23.0 to 24.9[21], and recently updated data showed the lowest mortality in the 25-27.4 kg/m^2 BMI group (HR 0.88; 95% CI, 0.80-0.97).[22] Taken together, these findings suggest that the cutoff value of < 23 kg/m^2 for normal body weight in Asians might be too strict in terms of mortality.

Causes of the obesity paradox

The obesity paradox refers to the phenomenon that despite the harmful impact of obesity on risk factors associated with chronic diseases, overweight or obese individuals often exhibit a better prognosis than leaner patients.[23] However, the obesity paradox may be due to both the inherent limitations in existing clinical studies, which falsely inflate the comparative survival advantage of patients with obesity, and the critical defects in using BMI to define obesity, which does not differentiate lean versus adipose tissue compart-

Table 1. Large clinical studies about the relationship of BMI with mortality

Author	Study type	Population	Study size	End point	Follow-up duration	Major findings
Flegal et al. (2013)[8]	Meta-analysis	General population	28,800,000	All-cause mortality	1-42 years	OW (25 ≤ BMI < 30) vs NW (18.5 ≤ BMI < 25) subjects (HR 0.94; 95% CI, 0.91-0.96) OB (30 ≤ BMI) vs NW subjects (HR 1.18; 95% CI, 1.12-1.25)
The Global BMI Mortality Collaboration (2016)[9]	Meta-analysis	General population	10,625,411	All-cause mortality	13.7 years	UW grade1 (18.5 ≤ BMI < 20) vs NW subjects (HR 1.13; 95% CI, 1.09-1.17) OW grade 1 (25 ≤ BMI < 27.5) vs NW subjects (HR 1.07; 95% CI, 1.07-1.08) OW grade 2 (27.5 ≤ BMI < 30) vs NW subjects (HR 1.20; 95% CI, 1.18-1.22) OB grade 1 (30 ≤ BMI < 35) vs NW subjects (HR 1.45; 95% CI, 1.41-1.48) OB grade 2 (35 ≤ BMI < 40) vs NW subjects (HR 1.94; 95% CI, 1.87-2.01)
Aune et al. (2016)[10]	Meta-analysis	General population	30,233,329	All-cause mortality	13.8 years	Never smoker: lowest mortality at BMI 23-24 Healthy never smoker: lowest mortality at BMI 22-23 Never smoker with ≥ 20 years follow up: lowest mortality at BMI 20-22
Zaccardi et al. (2017)[12]	Meta-analysis	Type 2 Diabetes	414,587	All-cause mortality	2.7-15.9 years	Lowest mortality at BMI 31-35 (men) and 28-31 (women)
Wang et al. (2016)[13]	Prospective	Non-diabetes Type 2 Diabetes	315,939 25,458	All-cause mortality	2-12 years	Lowest mortality at BMI 26.7 (non-diabetes) and 29.1 (type 2 diabetes)
Gu et al. (2006)[18]	Prospective	Asians	154,736	All-cause mortality Cause specific mortality	8.3 years	U-shaped association of BMI with all-cause mortality 23 ≤ BMI < 23.9 (HR 1.09; 95% CI, 1.01-1.19), Reference BMI: 24.0-24.9 25 ≤ BMI < 26.9 (HR 1.00; 95% CI, 0.92-1.08), 27.0 ≤ BMI < 29.9 (HR 1.15; 95% CI, 1.06-1.24) Cause specific mortality (CVD, cancer and others): similar U-shaped pattern
Yi et al. (2015)[20]	Prospective	Asians	12,832,637	All-cause mortality	9-12 years	Age specific optimal BMI: 23.0-25.9 at 18-34 years (men) 24.0-27.9 at 45-54 years 25.0-28.9 at 65-74 years 15.5-24.9 at 18-34 years (women) 21.0-16.9 at 45-54 years 24.0-28.9 at 65-74 years
Jee et al. (2006)[21]	Prospective	Asians	1,213,829	All-cause mortality Cause-specific mortality	12 years	All-cause mortality: lowest at BMI 23.0-24.9 Risk of death from respiratory causes: higher at a lower BMI Risk of death from CVD and cancer: higher at a higher BMI
Kim et al. (2015)[22]	Prospective	Asians	153,484	All-cause mortality CVD mortality Cancer mortality	7.91 years	Lowest risk of all-cause mortality: BMI 24-26.4 (HR 0.86; 95% CI, 0.77-0.97, reference BMI: 23-24.9) Lowest risk of the elderly and those with chronic diseases: BMI 25-29.9

OW, overweight; BMI, body mass index; NW, normal weight; OB, obese; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular diseases.

ments. Adipose tissue itself can shift its biological characteristics from an unhealthy phenotype towards a healthy phenotype, resulting in a true obesity paradox.

Limitations of epidemiological studies on the obesity paradox

Many methodological limitations of clinical studies such as selection, survival and treatment biases; a lack of controlling for confounding factors such as age, presence of chronic diseases, smoking and unmeasured factors; and inadequate follow-up length can lead to reverse causality and misconceptions about the nature of the obesity paradox.

Aging and sarcopenic obesity

Aging results in a progressive loss of muscle mass known as sarcopenia.[24] Sarcopenic obesity is defined as the relative increase in fat mass and reduction in muscle mass, thereby leading to relative

visceral fat accumulation at the same BMI[25], and is a well-known risk factor for cardiovascular mortality. Because the elderly have a significant decrease in peripheral fat and a relative increase in abdominal fat, BMI adjusted for waist circumference (WC) probably reflects mostly lean mass and has been associated with favorable effects on mortality.[26] In the elderly, BMI represents lean body mass better than body fat, which allows the protective effect of higher BMI on mortality to become more obvious. For example, Jee et al.[21] showed that the highest relative risks associated with a high BMI were observed only in individuals less than 50 years old, whereas an increase in BMI more than 25.0 kg/m² was not associated with the risk of death among subjects who were 65 years older at baseline. Another meta-analysis observed a significant increase in optimal BMI according to age; optimal BMI was 23.0-25.9 kg/m² at 18-34 years of age and 25.0-28.9 kg/m² at 65-74 years of age in men and 15.5-24.9 kg/m² at 18-34 years of age and 24.0-28.9 kg/m² at 65-74

Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is a well-known predictive factor for cardiovascular and all-cause mortality.[27] A major study reported that for every increase in CRF by 1 metabolic equivalent (MET), the incidence of all-cause mortality was reduced by 13% and that of major cardiovascular events was reduced by 15%.[28] Unfit individuals exhibit a higher risk of mortality about two times larger than that of fit normal-weight individuals irrespective of BMI, whereas fit overweight or obese individuals showed a similar risk of mortality compared to that of fit normal-weight individuals.[29] Fitness includes critical contributions of muscle mass, and a high level of body fat indicates increased muscular mass.[30] Therefore, a 'fit and fat' phenomenon might be a potential modifier in the association between BMI and mortality, which attenuates the increased mortality risk associated with higher BMI.[31]

Underlying conditions including smoking history

Underlying diseases result in loss of appetite and increased metabolic demands, causing unintentional weight loss. Because weight loss can precede the diagnosis of disease by many years, the association between low BMI and increased mortality might be caused by an undiagnosed illness.[32] Smoking, which is also related with a lower weight, increases many specific causes of death.[33] Therefore, limiting the analysis within healthy non-smokers usually attenuates the risk of death in underweight individuals and shows a tendency of higher risk of death with increasing BMI values.[6] Stokes et al.[34] demonstrated that overweight/obese never smokers exhibited a significantly higher mortality risk compared to individuals with a normal BMI (HR 1.51; 95% CI, 1.07-2.15), whereas other studies showed that the U-shaped relationship of BMI with mortality did not change even after adjusting for these confounding factors.

Follow-up duration

A follow-up of less than 10 years is not sufficient time to develop obesity-related metabolic disturbances or to influence health. Obesity showed a definite close relationship with a higher risk of critical cardiovascular events with longer follow-up duration.[35] A recent meta-analysis with a total of 299,059 participants reported that metabolically healthy overweight and obese individuals showed an increased risk of having CVD events, which appeared much stronger during a long-term follow-up period of more than 15 years, with pooled HRs of 1.47 (95% CI, 1.37-1.58) in overweight and 2.00 (95% CI, 1.79-2.24) in obese subjects.[36] Therefore, to reduce the effect of reverse causation between BMI and mortality, many researchers performed subgroup analysis according to duration of follow-up and excluded the initial 2-5 years of mortality data.

Limitations of BMI as an obesity index

A generalized obesity index such as BMI cannot fully reflect the risk of obesity-related metabolic complications.[37] Abdominal obesity is more closely associated with the risk of several chronic diseases compared to generalized obesity, and large studies have suggested that the abdominal obesity indicators of WC or the waist-to-hip ratio (WHR) may be better predictors of the risk of disease than BMI.[38] In a meta-analysis of six studies including 15,923 coronary heart disease subjects, central obesity based on tertiles of WHR or WC was associated with mortality (HR 1.70; 95% CI, 1.58 to 1.83), whereas BMI was inversely associated with mortality (HR 0.64; 95% CI, 0.59 to 0.69).[39] Staiano et al.[40] also reported that adults with a high WC had a higher mortality risk regardless of BMI obesity status when compared with low WC non-obese adults. Furthermore, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study showed that the positive association between WC and mortality was stronger in individuals with a lower BMI.[41] In that study, participants in the lowest third of BMI and the highest quintile of WC had the highest relative risk of death. Because of these types of findings, many researchers have asserted that WC should be considered in combination with BMI, even in subjects with normal and low BMIs, in order to accurately assess the risk of obesity related mortality. Therefore, the obesity paradox should not be confused with the BMI paradox, refuting the notion that obesity itself can be healthy in particular situations.

Dynamic changes of adipocytes into healthy adipose tissue

Recent evidence suggests that it is still true that certain obese individuals have a lower cardiometabolic risk. The phenotypes of adipose tissue can be diverse. Adipose tissues of increased infiltration

with M1-polarized macrophages exhibit a pro-inflammatory and insulin resistant status[42], whereas adipose tissues infiltrated with M2 macrophages show favorable adipokine expression and metabolic healthy profiles.[43] Recently, the switch from white adipose tissue to brown or beige adipocytes has been found to provoke beneficial effects with regard to glucose tolerance and lipid homeostasis.[44] In addition to such healthy changes in adipocytes, the location of fat accumulation can determine the overall effect of obesity on health risk. For example, the growth of subcutaneous adipose tissue deposition has advantageous effects on insulin resistance and fatty acid metabolism[45], but epicardial adiposity detrimentally affects cardiovascular health.[46] Therefore, better understanding of the biology, phenotype and function of adipose tissue will provide a pivotal key to clarifying the mechanism by which adipose tissue influences health and helps determine if the obesity paradox actually exists.

CONCLUSION

Obesity, defined as unhealthy adipose tissue accumulation, is a definite risk factor for chronic diseases. BMI may be an inaccurate index for assessing body fat distribution and discriminate between lean and fat mass. Current epidemiological studies have several inherent limitations in clarifying the relationship between obesity and mortality due to the use of BMI as an obesity index, various kinds of bias, lack of controlling for confounding factors, and insufficient follow-up duration. Furthermore, the impact of obesity on health can be very different according to age, gender, patient characteristics and the presence of comorbidities. Therefore, further research to develop a novel anthropometric index and determine its individualized cut-off points to estimate obesity risk should be completed, along with studies on the mechanism underlying adipocyte dysfunction and methods to preserve healthy fat.

CONFLICTS OF INTEREST

The author has no conflicts of interest.

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