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Review

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Recent Updates on Associations among Various Obesity Metrics and Cognitive Impairment: from Body Mass Index to Sarcopenic Obesity

Chan-Hee Jung, Ji-Oh Mok*

Division of Endocrinology and Metabolism, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea

Obesity and obesity-associated morbidity continues to be a major public health issue worldwide. Dementia is also a major health concern in aging societies and its prevalence has increased rapidly. Many epidemiologic studies have shown an association between obesity and cognitive impairment, but this relationship is not as well established as other comorbidities. Conflicting results related to the age and sex of participants, and the methodology used to define obesity and dementia may account for the uncertainty in whether obesity is a modifiable risk factor for dementia. More recently, sarcopenia and sarcopenic obesity have been reported to be associated with cognitive impairment. In addition, new mediators such as the muscle-myokine-brain axis and gut-microbiota-brain axis have been suggested and are attracting interest. In this review, we summarize recent evidence on the link between obesity and cognitive impairment, especially dementia. In particular, we focus on various metrics of obesity, from body mass index to sarcopenia and sarcopenic obesity.

Key words: Obesity, Cognitive dysfunction, Dementia, Sarcopenia

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*Corresponding author
Ji-Oh Mok

https://orcid.org/0000-0003-4882-1206

Division of Endocrinology and Metabolism, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine,
170 Jomaru-ro, Wonmi-gu,
Bucheon 14584, Korea
Tel: +82-32-621-5156
Fax: +82-32-621-5016
E-mail: hanna@schmc.ac.kr

INTRODUCTION

According to the 2021 Obesity fact sheet, the prevalence of obesity (body mass index [BMI] ≥25kg/m^2) in Korean adults over the age of 20 years in 2019 was 36.3%.[1] The prevalence of obesity has steadily increased over the past 11 years.[2] Dementia is a major health concern in aging societies and its prevalence has increased rapidly.[3] Dementia affects approximately 10.3% of adults over the age of 65 years, according to data from National Health Insurance.[4] Alzheimer disease has become one of the top 10 leading causes of death and the associated death rate increased exponentially over the past 20 years in Korea.[4] The rapid rise in obesity and dementia is causing a substantial public health burden for both the current aging society and the projected future super-aged society.

Individuals with obesity are at higher risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and some cancers, whereas the role of obesity on the risk of dementia remains unclear.[5] Although many epidemiologic studies have shown an association between obesity and cognitive impairment since 2003, relatively less attention has been paid to the role of obesity on dementia than other comorbidities.

Previous studies reported inconsistent results regarding the rela-

tionship between obesity and cognitive function. Some reported that higher BMI tended to be a risk factor for cognitive impairment,[6-8] while others observed a reduced risk of higher BMI in cognitive decline.[9,10] The majority of earlier studies used BMI as an assessment tool of obesity. Unfortunately, BMI does not reflect location or amount of body fat nor alterations in body composition. Therefore, measurement of central adiposity indices such as waist circumference (WC) and waist-hip ratio (WHR) have been used to elucidate the association between obesity and cognitive impairment.[11]

In addition, sarcopenia characterized by loss of muscle mass and strength is aging-related changes in body composition and closely linked to dementia.[12-14] Obesity often coexists with poor muscle mass and function, which is called sarcopenic obesity (SO).[15,16] The role of sarcopenia and SO on various diseases has been extensively explored. As a similar motivation, there have been increasing studies regarding the role of and mechanistic links between sarcopenia and SO and cognitive impairment.[14,17-19]

Herein, we present recent evidence on the link between various obesity metrics and cognitive impairment, especially dementia. We discuss data ranging from earlier studies on BMI to very recent research on body weight (Bwt) variability, sarcopenia, and SO.

BMI AND RISK OF COGNITIVE IMPAIRMENT

Mid-life BMI and cognitive impairment

The evidence for the association between higher BMI in mid-life and dementia is relatively consistent. A meta-analysis including 19 studies on 589,649 participants revealed that mid-life obesity (age 35–65 years, BMI ≥ 30 kg/m^2, with long-term follow-up to 42 years) was associated with dementia in late-life (relative risk [RR], 1.33).[20] Another meta-analysis of 15 prospective studies with 25,624 participants (follow-up ranging from 3.2 to 36.0 years) showed a J-shaped relationship between mid-life BMI on dementia.[21] Underweight, overweight and obesity in mid-life were associated with 1.96, 1.35, and 2.04 times the risk of developing Alzheimer dementia.[21] A recent study of 6,582 participants from the English Longitudinal Study of Ageing (age 50 years, mean follow-up period of 11 years) showed that overweight or obese participants were more likely to develop dementia (RR, 1.3).[22] This study included apolipoprotein E-e4 (APOE-e4) as one adjustment variable. Previous studies conducted in younger participants at baseline with longer follow-up periods showed an even stronger association between higher BMI and cognitive impairment.[23,24]

On the other hand, some studies contradict the hypothesis that obesity in mid-life could increase the risk of dementia in old age. A retrospective study of 2 million electronic records of patients from the UK Clinical Practice Research Datalink showed that mid-life obesity (median follow-up of 9.1 years) was associated with substantially reduced dementia risk.[9] Very obese subjects (BMI > 40 kg/m^2) had a 29% lower dementia risk than subjects with normal BMI and the incidence of dementia continued to fall for every increase in BMI category. A cohort of 5,125 adults with normal cognitive function showed that obesity over the age of 45 (BMI ≥ 25 kg/m^2, 6-year follow up) was associated with lower risk of cognitive decline.[10] Based on these studies, it seems that relatively shorter follow-up (less than 10 years) may affect the detection of associations between higher BMI in mid-life and cognitive impairment.

Late-life BMI and cognitive impairment

Higher BMI in late-life has been considered as a possible protective factor against dementia in many epidemiological studies. The association between obesity and dementia may be modified by age. A 28-year follow-up in the Whitehall II study examined whether obesity (BMI ≥ 30 kg/m^2) at ages 50, 60, and 70 years was associated with subsequent dementia.[25] This study showed a higher risk of dementia for obesity at age 50, but not at ages 60 or 70 years. In a longitudinal study by Sun et al.,[26] individuals with higher BMI in late-life experienced a slower decline in cognitive function. Higher late-life BMI was associated with larger hippocampus, entorhinal cortex, and middle temporal lobe volume at baseline. In addition, lower baseline BMI (mean age, 77.9 years) in older adults was related to a faster decline in global cognition.[10,27] These findings suggest that the obesity paradox is also observed in the field of cognition and dementia.

Several hypotheses are proposed to explain the obesity paradox in terms of late-life BMI and dementia. The protective role of high BMI on cognitive impairment might be related to changes in body composition with age. Aging is characterized by loss of lean body

mass.[28] Therefore, low lean body mass can appear as low BMI and high lean body mass as high BMI. If an old person has a high BMI, they are likely to have a high proportion of lean body mass. High BMI suggesting high lean body mass may be involved in reducing the risk of cognitive impairment in an older population.[29] In addition, high BMI may also result from increased accumulation of fat in regions other than the abdominal area, such as the legs, which could contribute to a lower risk of cognitive impairment.[30] Low BMI may be indicative of malnutrition for older people and malnutrition and cognitive status are closely correlated.[28]

Nonetheless, there is some evidence that contradicts the above results.[7,31-33] In a study by Karlsson et al.,[34] higher BMI contributed to a sharp decline in cognitive function in both mid-life and late-life. The study indicated that the detrimental effects of higher BMI persist from mid-life through late-life. West et al.[35] reported that long-term adiposity may have an unfavorable impact on the volume of brain regions related to cognitive functioning in older adults with type 2 diabetes.

CENTRAL OBESITY AND RISK OF COGNITIVE IMPAIRMENT

Obesity has traditionally been defined using BMI, but WC or WHR as an indicator of abdominal obesity might be a more sensitive unhealthy adiposity marker than BMI.[36] In a prospective evaluation by West and Haan,[37] increased central adiposity was associated with a faster rate of cognitive decline during a 5-year follow-up, but BMI was not strongly associated with cognitive scores. In 32 years of longitudinal WHR data from the Prospective Population Study of Women in Sweden,[38] a mid-life WHR greater than 0.80 increased risk for dementia approximately two-fold among survivors to age 70 years. A cross-sectional study by Anand et al.[39] found that higher visceral adipose tissue (VAT) and total percentage of body fat were significantly associated with reduced cognitive scores among adults with no prior history of clinical cardiovascular disease. For each one-standard-deviation-increase in adiposity equivalent to 36 mL of VAT or a 9.2% increase in body fat, 1-year cognitive aging was reduced. Subjects in the highest quartile of adiposity compared with those in the lowest quartile had a commensurate with 3 years of cognitive aging.

A study by Cho et al.[40] investigated whether a positive association exists between WC and dementia according to baseline BMI and WC categories. This study comprised 872,082 participants over the age of 65 who participated in a Korean national health screening examination. WC was significantly associated with increased risk of dementia after adjustment for BMI. Normal weight men and women with abdominal obesity had a prominently increased risk of dementia compared with those without abdominal obesity. WHR per 0.1 increase had 1.39 times higher risk of cognitive impairment in those with BMI > 25.3 kg/m^2.[40] In contrast, in a cohort study of Australians (12,047 men with aged 65-84 years),[41] men with WHR ≥ 0.9 who were overweight had a lower risk of dementia than those with WHR < 0.9 who were normal weight.

Older people tend to have more body fat and less lean mass than younger people with a same BMI. Therefore, BMI is a less suitable measurement for total body adiposity in older persons. In addition, BMI does not provide a measure of muscle or of specific fat components such as visceral and subcutaneous fat[15] and may not provide the detail necessary to determine whether a person's weight is healthful.

Only a few studies have analyzed visceral and subcutaneous fat separately as adiposity parameters.[42] In the AGES-Reykjavik study (mean age, 76 years),[42] there was a decreased probability of dementia per standard deviation increase in subcutaneous fat (odds ratio [OR], 0.72), thigh subcutaneous fat (OR, 0.81), and thigh muscle (OR, 0.63), but not visceral fat. Higher amounts of abdominal and thigh subcutaneous fat were associated with a lower probability of dementia in women only, whereas higher amounts of thigh muscle were associated with a lower probability of dementia in both men and women. Most studies[43] revealed an inverse association between increased VAT and cognitive function in both younger and older subjects but a few studies[44] showed no relevant associations.

BODY WEIGHT VARIABILITY AND COGNITIVE IMPAIRMENT

Growing evidence has suggested that Bwt variability, weight fluctuations within a specific period, may lead to poorer body-fat distribution, preferential abdominal adiposity, and adverse health outcomes, independent of the extent of obesity.[45,46] Although there have

been many studies about the association between Bwt variability and health status, very few studies have assessed the effects of Bwt variability on dementia.[47-49]

A retrospective cohort study of 19,987 participants with a mean age of 73 years using Korean National Health Insurance Service data revealed that high Bwt variability was associated with increased risk of dementia in the elderly.[47] Low Bwt variability and obese BMI was associated with decreased risk of dementia. Another study of elderly women demonstrated that instability in Bwt over 5 years between ages 40 and 70 years was associated with increased risk for dementia independently of the direction of weight change.[48] In a very recent study,[49] participants with significant changes in BMI (increase or decrease of ≥ 5%) or who had greater variability in BMI, experienced faster cognitive decline. This pattern was consistent irrespective of BMI at baseline. Unstable Bwt can lead to alterations in adipose tissue structure and function that tend to favor abdominal fat accumulation and produce adipokines.[45,50,51] In addition, low-grade inflammation may develop in those with higher Bwt variation.[52] These mechanisms could negatively affect the brain.

SARCOPENIA/SARCOPENIC OBESITY AND COGNITIVE IMPAIRMENT

Age-related sarcopenia is characterized by decreased muscle mass, decreased muscle strength, and decreased functional performance.[12] Weak handgrip strength and lower muscle mass are more prevalent in patients with dementia compared with healthy subjects of the same age.[53,54] Epidemiologic evidence suggests that sarcopenia is associated with accelerated cognitive changes and cognitive impairment.[19] A recent met-analysis demonstrated that the significant association between sarcopenia and cognitive impairment (OR, 2.2) was independent of the study population, definition of sarcopenia, and degree of cognitive impairment.[15] In particular, the association between muscle and cognition may originate from muscle strength or performance versus muscle mass.[55,56] Poor muscle performance such as low gait speed and low handgrip strength was found to be significantly associated with cognitive decline.[57-62]

SO is a condition characterized by co-existence of excess fat mass and low skeletal muscle mass and function.[16] In recent decades, greater attention has been paid to SO due to the greater associated disability and morbidity,[63] with numerous studies on the role of SO in the association with cognitive dysfunction and dementia.[64,65] A very recent study by Someya et al.[65] investigated whether SO is associated with cognitive impairment in 1,615 older Japanese participants (aged 65–84 years; mean age, 73.1 years). They divided participants into four groups according to sarcopenia (handgrip strength < 28 kg in men and < 18 kg in women) and obesity status (BMI ≥ 25 kg/m^2). Only the SO group was independently associated with mild cognitive impairment versus an obese and a control group. In terms of dementia, the SO group had the greatest risk of dementia. Sarcopenia alone was also significantly associated with dementia only in women, and not in men. Obesity alone was not associated with either mild cognitive impairment or dementia. An earlier study by Tolea et al.[64] consisted of 353 patients aged 69 years on average divided into three groups: obesity without sarcopenia, SO, and sarcopenia without obesity. The SO group showed a greater degree of cognitive impairment than other groups. Sarcopenia is a more potent predictor of loss of cognitive function than obesity. Strong handgrip strength was associated with less likelihood of developing cognitive impairment compared to weak handgrip strength in obese women (adjusted OR, 0.23). Handgrip strength has been suggested to be a useful marker for predicting future cognitive impairment among obese women. These results are in line with a previous report that showed a stronger association between weak handgrip strength and cognitive impairment in women than in men.[66] It remains unclear why sarcopenia or SO is more strongly associated with cognitive impairment in women than in men.

The coexistence of obesity with sarcopenia accelerates loss of muscle mass and function and reduces physical performance through multiple suggested pathogeneses.[67] Suggested pathogeneses such as dysfunction of adipose tissue, adipocytokines, oxidative stress, inflammation, insulin resistance, mitochondrial dysfunction, and endothelial dysfunction may contribute to other disorders (Fig. 1).[17,63,68,69] Therefore, it is possible that SO can cause significant cognitive impairment compared with obesity or sarcopenia alone.

However, considering the obesity paradox, obesity could also be a protective factor in older adults with sarcopenia. A recent study by Bahat et al.[70] demonstrated that SO was associated with a lower prevalence of impaired functional health status than that of sarcopenia alone. This suggests that obesity might have a protective ef-

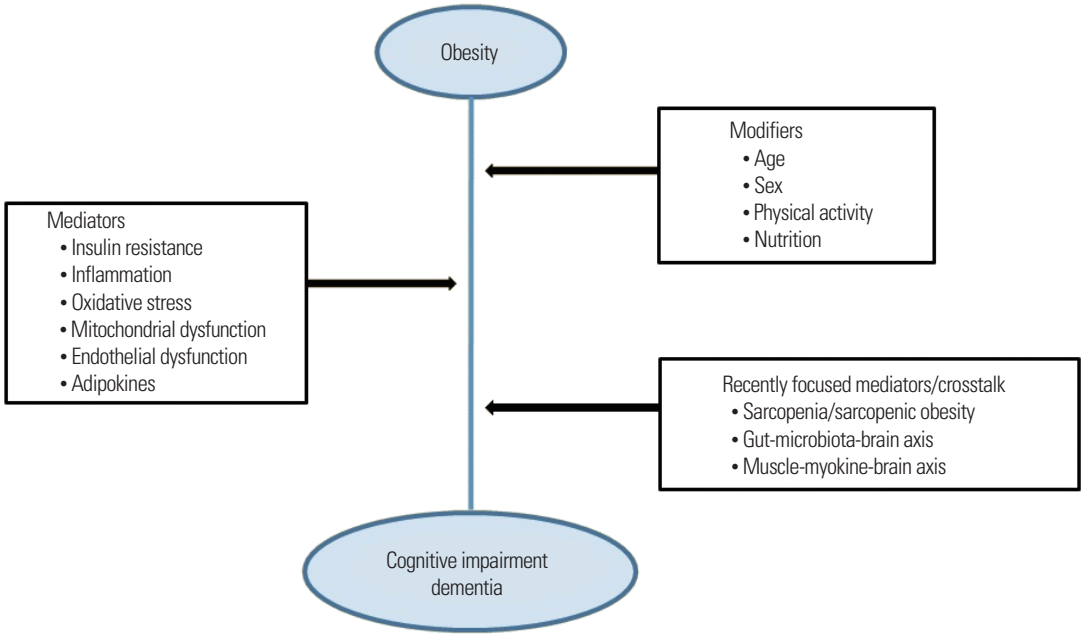

Figure 1. Association between obesity and cognitive impairment. The risk of dementia or cognitive impairment is associated with obesity and age-related body composition changes. Insulin resistance, inflammation, oxidative stress, mitochondrial dysfunction, and endothelial dysfunction are commonly related to these conditions. Moreover, the gut-microbiota-brain axis and muscle-myokine-brain axis are recently identified mediators.

fect in sarcopenic subjects. Perna et al.[71] proposed the existence of two phenotypes: osteosarcopenic visceral obesity and osteosarcopenic subcutaneous obesity. Among these two phenotypes, osteosarcopenic subcutaneous obesity seems to be in line with findings regarding the obesity paradox.

There is evidence that muscle-derived myokines play an important role in regulating muscle mass and function.[18,19] Myokine abnormalities may underlie the pathogenesis of age-related diseases such as obesity, sarcopenia, and SO. Myokines act as a mediator between skeletal muscle and the brain, termed the "muscle-brain axis" (Fig. 1).[18,19] In addition, the gut microbiota has been suggested to play a part in the mechanistic link between obesity and impaired cognition, termed the "gut-brain axis" (Fig. 1).[18,72]

LIMITATIONS OF EXISTING STUDIES AND UNRESOLVED ISSUES

Discrepancies between studies may stem from differences in the populations studied (sex and age at baseline, different age criteria for comparison groups) and methodologies applied (parameters of obesity, follow-up period, method of diagnosis for dementia or cognitive impairment, and definition used for sarcopenia or SO). Ascertaining obesity as an independent risk factor for dementia requires careful adjustment of confounding variables, for example, *APOE-e4*. *APOE-e4* is the strongest risk factor gene for Alzheimer disease.[73] Nonetheless, many articles did not adjust for that variable. In addition, most studies linking SO to cognitive impairment have been carried out in patients over 65 years of age. Therefore, further studies are needed to evaluate the relationship between SO and cognitive function in younger individuals. Also, mechanisms for the sex differences in the relationship between obesity and cognitive impairment need to be explored. Most of all, intervention studies are needed to reveal whether weight loss or improvement in SO can prevent cognitive impairment.

CONCLUSION

Dementia is a major public health concern. We presented the association between various metrics of obesity and cognitive impairment or dementia by reviewing prior evidence (Fig. 2). Cognitive impairment is an obesity-related comorbidity. However, based on numerous reported studies, the relationship between obesity and

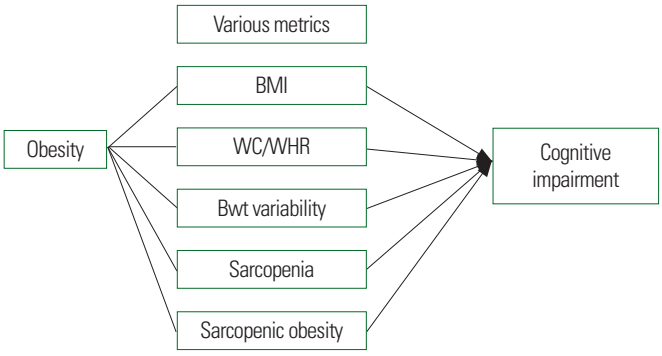

Figure 2. Association between various metrics of obesity and cognitive impairment. The relationship between various obesity indices and cognition is complex. BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; Bwt, body weight.

cognition is complex and partially modified by age and sex. With the use of various methodologies and study populations, inconsistent results have been reported. Nevertheless, the evidence for the association between higher BMI in mid-life and higher risk of late-life dementia is fairly consistent across various measures of obesity. On the other hand, it is unclear whether the risk of dementia is associated with obesity at older age. Protective effect, namely, obesity paradox or negative effect of obesity on cognition varies with sex and fat components. In the last decade, there has been considerable interest in sarcopenia and SO and related health concerns, particularly cognitive impairment. Among the components of sarcopenia, the association between muscle strength or performance and cognitive impairment showed more consistent results than muscle mass. In addition, there has been increasing evidence for the role of SO compared with obesity or sarcopenia alone in cognitive dysfunction. The high prevalence of cognitive impairment with aging and obesity as a potentially modifiable risk factor warrants further investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: JOM; analysis and interpretation of data: CHJ; drafting of the manuscript: CHJ; critical revision of the manuscript: all authors; and study supervision: JOM.

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