

# Obesity and brain illness: from cognitive and psychological evidences to obesity paradox

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**Abstract:** Recent findings showed that obesity represents an additional risk factor to developing brain illness such as cognitive impairments and psychopathological disorders. However, some benefits of overweight in the elderly have been identified and an "obesity paradox" has been shown. Currently, it is still unknown how obesity and brain functioning could be linked, and the process by which body fat independently injures cognitive abilities and psychological well-being remains unclear. To establish the independent role of obesity on cognitive abilities and mental health, clarifying the role played by several factors and understanding their interaction is essential. In this review, we discuss the relationship between obesity and brain illness and underline the role played by confounders and other covariates to determine this link.

**Keywords:** obesity, cognitive decline, mood disorders, obesity paradox

## Introduction

In the past decades, worldwide obesity gradually increased and World Health Organization formally recognized this condition as a global epidemic.<sup>1,2</sup>

Recent readings estimate worldwide incidence of obese adults at 10.8% for men and 14.9% for women, increasing from 857 million in 1980 to 2.1 billion in 2013 for both developing and developed countries. In the same time frame, overweight people increased from 28.8% to 36.9% (men) and from 29.8% to 38% (women). However, different sex and age patterns between countries are observed. The prevalence is also rising in children and adolescents, increasing from 8.1% in 1980 to 12.9% in 2013 in boys and 8.4% to 13.4% in girls.<sup>3</sup>

Obesity negatively affects most bodily systems and boosts the risk of many chronic diseases, including type 2 diabetes, metabolic syndrome, hypertension, dyslipidemia, hyperinsulinemia, coronary artery disease, cardiovascular disease, osteoarthritis, chronic kidney disease, many forms of cancer (e.g., endometrial, esophageal, renal cell, pancreatic, ovarian, breast, colorectal, thyroid, malignant melanoma, etc.), non-alcoholic steatohepatitis, sleep apnea, depression and other psychiatric disorders.<sup>4-9</sup>

Furthermore, recent findings showed that obesity may also affect cognitive function, and higher body mass index (BMI), especially in midlife, might increase the risk of developing dementia, or other cognitive impairments, later in life.<sup>10-13</sup>

However, despite these findings, some benefits of overweight in the elderly have been identified,<sup>14</sup> and an "obesity paradox" in the past years has been shown.<sup>15</sup>

Currently, it is still unknown how weight increase and brain functioning could be linked, and the process by which obesity injures cognitive abilities and psychological well-being remains unclear.

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To establish the independent role of obesity on brain physiology, it is necessary to clarify the role played by several factors and understand their interaction, which is essential to plan future studies.

This review, conducted in line with the American Psychiatric Association practice guidelines, focuses on the relationship between obesity, cognitive decline (CD) and psychological disorders and underlines the role played by confounders and other covariates to determine this link.

## Obesity and CD

To better understand the role played by obesity to affect cognitive functioning is essential to examine how weight increase interacts with brain physiology.

Structural integrity is reflected by brain substructure volumes and represents a major hallmark of underlying neuronal health. Tissue loss occurs with normal aging, but it is more marked in dementia cases.<sup>16,17</sup>

Recent findings showed that obesity additively afflicts the brain structure of cognitively impaired patients and is linked to poor brain volumes even in cognitively normal elderly subjects.<sup>18</sup>

In a longitudinal study group from overweight and obese female patients, temporal lobe atrophy was estimated from 13% to 16% for each BMI unit increase.<sup>19</sup> In a structural brain mapping cohort study of 700 cognitively impaired patients (mild cognitive impairment [MCI] and Alzheimer's disease [AD]), higher BMI was related to decreased brain volume in frontal, temporal, parietal, and occipital lobe regions, proving an additional burden on the brain structure. Further, whole brain analysis estimated brain tissue reduction from 0.5% to 1.5% for each BMI unit increase, even after controlling for relevant confounders (i.e., sex, age, level of education), and AD caused widespread brain volume deficits and ventricular expansion (other features of brain tissue loss) compared with MCI.<sup>20</sup>

Brain scanning studies demonstrated that obese individuals had significantly lower gray matter density in the post-central gyrus, frontal lobe, putamen, and middle frontal gyrus when compared with normal weight.<sup>21</sup>

Greater body adiposity in otherwise healthy subjects was related with lower brain volumes in hippocampus area, orbital frontal cortex and parietal lobes.

Cross-sectional studies showed that elevated waist-hip ratio and greater BMI were linked to reduced hippocampal volume and tissue loss of temporal lobe.<sup>22-24</sup>

A further analysis in over 1400 healthy Japanese showed negative correlation between brain volume and obesity, high-

lighting lower brain gray matter ratio of temporal, occipital and frontal lobes and the anterior lobe of cerebellum.<sup>25</sup>

Several studies have found that obesity in midlife is related with an increased risk of CD in the elderly, and, according to these findings, consistent neuropathological studies showed either hippocampal brain atrophy or executive dysfunction.<sup>26;116-119</sup> It is well recognized that hippocampal formation played a key role in learning and memory,<sup>27,28</sup> it is particularly affected by aging<sup>29-31</sup> and that low volume of this region predicts cognitive impairment and dementia in general people.<sup>32-37</sup>

However, the exact underlying mechanisms by which obesity increases the risk of AD remains to be fully understood, but some explanations are available.

Neuropathological features of AD, such as amyloid plaques and neurofibrillary tangles,<sup>38</sup> are even more stated in elderly obese people when compared with normal-weight subjects. In a cohort study, greater levels of  $\beta$ -amyloid, the main component of amyloid plaques, protein precursor and expression of tau, were present in the hippocampal region of morbidly obese patients without cognitive damage when compared with non-obese controls.<sup>39</sup>

A possible connection between midlife obesity and development of AD in the elderly is represented by increased levels of adipose tissue, which could modify  $\beta$ -amyloid metabolism. Plasma amyloid proteins have been found in obesity,<sup>40,41</sup> and it is suggestive of increased risk of AD.<sup>42</sup>

Furthermore, high-fat diet may independently increase either body fat or dementia risk.<sup>43</sup> In a prospective study from 939 individuals aged  $\geq 65$  years, greater caloric intake was related to higher AD risk in the subsequent 6.3-year follow-up.<sup>44</sup> High-fat diet (fatty acids and sugars) may also interact with brain physiology, harming the integrity of blood-brain barrier (BBB),<sup>45</sup> which plays a key role in protecting the central nervous system (CNS) from blood-borne toxins.<sup>46</sup> AD and vascular dementia (VaD) are linked with BBB dysfunction,<sup>47</sup> and longitudinal study showed that midlife obesity was also correlated with lower BBB integrity.<sup>48</sup>

Higher levels of white adipose tissue could increase systemic inflammation and may provide CD and dementia.<sup>49</sup> Adipocytes, lymphocytes and macrophages leading to production of pro-inflammatory cytokines and subsequent increase in tumor necrosis factor- $\alpha$ .<sup>50-53,115</sup> Indeed, central inflammation is observed after high-fat feeding, especially in the hypothalamus region.<sup>54</sup> Further, systemic inflammation has been shown to be linked to vascular disease,<sup>55</sup> obesity, poorer cognitive performance and dementia.<sup>56,57</sup> It was

demonstrated<sup>58</sup> that the outcomes of metabolic syndrome on cognitive performance were mediated by inflammation, and that combined effects of high inflammation and metabolic syndrome had a greater risk of CD. However, the direction of the associations between inflammation and dementia is unclear.<sup>59</sup>

Finally, the effects of obesity on brain physiology are further observed in principal mediators of the CNS, such as microglia and astrocytes.

## Obesity and psychopathology

Several studies suggest that subjects with severe psychiatric disorders are more likely than general population to be obese.<sup>60</sup> However, the link between body fat and psychiatric illness is widely discussed.

There are several studies that account for the risk of psychiatric disorders in obese individuals such as mood disorders, anxiety disorders, low self-esteem, body dissatisfaction, eating disorders and emotional problems.<sup>61,62</sup> However, an extensive body of literature shows that mood disorders are most frequently related to obesity, and the incident risk of lifetime depression is significantly higher in obese persons when compared with non-obese peers, with a range from 29% to 56%.<sup>63–65</sup>

In a study performed with more than 40,000 people, the relationship between obesity and depression varied by sex and obese men, compared with normal-weight people, reported less symptoms of major depression and suicidal ideation. A different pattern was seen for women that was 37% more likely to report depressive symptom when compared with normal-weight peers.<sup>66</sup>

However, with regard to the direction of relationships between obesity and psychopathology, the studies failed to find clinically significant results. Studies that investigated whether obesity precedes depression or whether an existing mood disturbance predisposed to weight increase showed conflicting results.

In a nationally representative adolescent sample, obesity condition did not increase depression incidence 1 year later. However, depression at baseline doubled the risk of developing obesity at follow-up.<sup>67</sup>

Apparently, results from longitudinal studies suggest that depression precedes obesity in adolescent girls, but not boys, and that obesity precedes depression in older adults. In a sample of 1037 New Zealanders, boys who were depressed at age 18 or 21 were less likely to be obese at age 26. Girls with late adolescent depression, however, were twice as likely to be obese at age 26.<sup>68</sup>

However, other studies showed that obesity is not strongly associated with depression, or any abnormal personality characteristics and psychological traits are more widely varied within the population of obese individuals than between obese and non-obese.<sup>69–73</sup>

The reason for controversial results seems to be a lack of consensus about how to measure psychological functioning, and a growing body of studies reminds us of the importance of considering the role played by co-morbidity of morbid obesity.

Actually, further research on this issue is needed.

## The obesity paradox

Several studies have provided empirical evidence that obesity in midlife represents a risk factor for cognitive diseases later in life, such as MCI, VaD and AD.<sup>74–78</sup>

Higher midlife BMI is heavily predictive of both AD and VaD, independent of other comorbidities (e.g., stroke, cardiovascular diseases and diabetes), and compared with normal-weight individuals, obesity at age 40–45 years increases the risk of developing dementia by 74% in the elderly.

In a prospective cohort study, high BMI assessed in middle age was independently linked with cognitive impairment in a sample aged 33–62 years in the subsequent 5-year follow-up,<sup>79</sup> and subjects with BMI above the third quartile during middle age had 59% greater risk of suffering dementia during old age.

These results collectively suggest that midlife obesity is a strong predictor of dementia in the elderly, and being obese in middle age may increase the risk for functional impairment and brain pathology.<sup>80</sup>

Despite these findings,<sup>81,82</sup> other studies have shown no association or even negative correlations between obesity and cognitive impairment in the elderly.<sup>83–85</sup>

A substantial part of scientific literature in this area underlines that body fat, traditionally considered dangerous for health, might predict survival in the elderly and that even low BMI during middle age could be linked to CD in old age.<sup>86–88</sup>

Some findings support this dissociation, highlighting an “obesity paradox”.<sup>89</sup>

Continuous BMI was not linked to cognitive impairment in some studies,<sup>90–93</sup> and high BMI, assessed in late life, was not related to increased risk of CD.<sup>94</sup> In a sample of 169 adults aged  $\geq 68$  years, greater BMI reduced risk of CD when compared with lower BMI subjects ( $< 23$ ) in a 5-year follow-up.<sup>95</sup> In a sample of 1393 elderly subjects, continuous BMI and MCI were not linked.<sup>96</sup> In an 8-year prospective investigation of 1351 subjects, higher BMI was not associated with

increased dementia risk.<sup>97</sup> In a research study of 1302 patients (mean age  $77.71 \pm 6.86$  years), of which 905 (69.5%) without CD and 397 (30.5%) had CD, higher BMI scores reduced the risk of cognitive disorder.<sup>98</sup> Finally, underweight condition in late life (BMI <20) increased dementia risk by 60%, while being obese (BMI >30) was linked with a reduced risk of cognitive impairments.

To summarize, the studies performed in middle age show a relationship between high BMI and dementia risk, whereas those in the elderly differ. Apparently, risk estimates in middle age reversed when assessed in late life.

A recent meta-analysis performed with extensive follow-up (ranging from 3.2 to 36.0 years) showed that low BMI in midlife, compared with normal BMI, increased 1.96 times the risk of developing AD in the elderly. The relative risk to develop AD for obese midlife BMI was 2.04. Furthermore, compared with normal BMI, overweight midlife could be associated with 35% increased risk of developing AD and 33% of developing VaD in late life. These findings overall suggest that underweight, overweight and obesity in midlife increase dementia risk and that predictive ability of BMI varied over time.

Consistent with previous systematic reviews and meta-analysis from body weight and dementia,<sup>99</sup> the risks appear higher for underweight and obese BMI, suggesting a U-shaped relationship, a curvilinear association between midlife BMI and late-life dementia.

However, these inconsistencies and paradoxical findings may have several explanations.

According to Clinical Guidelines on the identification, evaluation and treatment of overweight and obesity in adults (1998), BMI  $\leq 18.5$  kg/m<sup>2</sup> underweight condition, from 18.5 to 24.9 kg/m<sup>2</sup> normal- or healthy-weight condition, from 25 to 29.9 kg/m<sup>2</sup> overweight,  $\geq 30$  kg/m<sup>2</sup> obesity and  $\geq 40$  kg/m<sup>2</sup> morbid obesity. This index was first described by Adolphe Quetelet but involved some limitations.<sup>100</sup>

Ethnicity and age, for example, affect this index because fat-free mass ratio decreases with age, especially among women.<sup>101</sup> Aging process implied that lean body mass decreases, while adipose tissue increases without weight gain. Therefore, this ratio may not be captured by BMI and not represent, in the elderly, a reliable index of adiposity.<sup>102,103</sup> In other words, BMI may underestimate adiposity because with aging, lean body mass is replaced by fat.<sup>104</sup> Thus, this index is a better measure of adiposity only for younger people while, during old age, it is possible to report low BMI despite relatively high body fat. The link between increased adiposity and dementia may be weaker among older subjects who may

have more body fat despite low body weight and cloud the relationship between obesity and dementia in older samples.

Alternative anthropometric tools to assess obesity in the elderly could be more effective. It has been reported that the highest quintile of sagittal abdominal diameter, evaluated in midlife, was related with a three fold increased dementia risk. Waist circumference and waist: hip ratio have been proposed as a better adiposity marker in old age<sup>105</sup> and are also related to higher dementia risk.<sup>44</sup> Therefore, it has been suggested that low late-life BMI and waist circumference represent potentially useful preclinical markers for MCI and AD.<sup>106</sup>

Another possible explanation of conflicting results is that rapid weight loss could precede diagnosis of AD and general cognitive impairment by several years.<sup>107–109</sup> Clinical data suggest that weight loss precedes dementia diagnosis<sup>92,93</sup> and in dementia onset, obese patients lose ~50% of their pre-dementia weight.<sup>110,111</sup> This implies that BMI effects on dementia may be more accurately estimated at midlife than in old age<sup>7,24</sup> because it would reflect a more valid perspective of a person's lifelong exposure to body fat.<sup>59</sup>

It is now known that underlying neuropathological changes characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles may be observed many years in advance of the onset of clinical symptoms of AD. As a result of AD, BMI may decrease and emerge earlier than cognitive symptoms.

Furthermore, weight loss occurs with a lot of comorbidities in older age<sup>112–114</sup> and reflects poor health. Higher midlife BMI increases dementia risk; in old age, increased BMI could be a global marker of decreased risk. In agreement with these hypotheses, being overweight and obese in later life seems to be a protective factor from dementia. Nevertheless, many studies are required.

## Conclusion

It is unclear whether obesity increases cognitive impairments independently from other risk factors, given that some experimental studies are limited by study design, variable follow-up and limited account of comorbidities.

Although previous findings have shown negative association between obesity and age-related CD, studies performed with appropriate exclusion criteria and accurate adjustment for potential collinearity seem to support the relationship.

Given the need to achieve synergies between research activities, future studies should focus on the independent role of obesity on brain functioning, taking into account a large number of covariates, such as sex, lifestyle factors (diet, physical activity, level of education, smoking, alcohol consumption), neurological disorders, mental diseases, vascular

diseases, inflammatory processes, hypertension, diabetes and leptin dysregulation.

To better understand the exclusive role of obesity in enhancing CD and psychological diseases, there is a need to improve the study design by implementing clear exclusion criteria, adequate comparison groups, multivariate statistical technique and appropriate assessment of cognitive domains and psychological functions.

In this paper, we provided some insights about confounders and emphasized the need for more multivariate research.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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