Obesity and Cognitive Aging

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Obesity is a health problem that has reached epidemic proportions. Given the high prevalence of obesity, even a small adverse impact of obesity on cognitive aging might have a serious effect on public health. The purpose of this systematic review was to examine the relation between obesity and cognitive function in late life among persons not diagnosed with dementia and to evaluate the evidence for a causal association. Medline was used to search for the following terms: obesity, overweight, cognition, cognitive, age, and aged. To be included, studies must have had a population-based, dementia-free sample and a 5-year minimum interval between measurement of the predictor and the outcome. Only 11 studies met the criteria. Of these, 7 studies assessed obesity in midlife and cognitive function in later life, and 4 studies assessed obesity and cognitive function in late life. The reviewed studies showed clear evidence that midlife obesity was associated with cognitive aging, whereas this association was weaker in late life; thus, no firm conclusions could be drawn. The findings of this review suggest that, although there is evidence for an association between midlife obesity and low cognitive abilities in late life, the direction of the association and the causality remain to be clarified.

adiposity; aged; aging; body mass index; body weight; cognition; obesity; overweight

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index; SATSA, Swedish Adoption/Twin Study of Aging; VISAT, the Vieillissement, Santé, Travail (Aging, Health, Work) Study.

INTRODUCTION

Intact cognitive function is one of the single most important contributors to health, quality of life, and survival in old age. Although the main threat to cognitive function in late life is dementia, even old persons with no evidence of dementia experience cognitive decline. This age-related change usually is referred to as “cognitive aging” (and will be referred to as such in the present study). On average, cognitive abilities remain stable through adulthood and start to decline around the age of 65 years (1, 2). Some cognitive abilities are considered more sensitive to aging than others; in general, fluid abilities are more age sensitive than are crystallized abilities (3). Nonetheless, there are large intra-individual differences in cognitive aging. Some people show a steep decline, some stay fairly constant, and some even improve (4, 5), although it is most common that cognitive abilities decrease with increasing age. Several factors have been suggested to affect cognitive aging, ranging from biologic factors, such as genes, to social factors, such as education and television watching. The level of evidence for the contributions of various risk and protective factors ranges from very strong to weak. In the present review, we will evaluate the evidence for an association between obesity and cognitive aging.

During the past decade, attention has been paid to the potential negative effect of obesity on late-life cognitive abilities. Several reviews (6–10) have shown that obesity in midlife is associated with an increased risk of dementia, both of vascular origin and Alzheimer’s disease. Less is known about the association between obesity and cognitive aging. In general, persons gain weight over the life span, but this weight increase is considered to level off around the age of 65–70 years (11), and weight loss is associated with an increased risk of death in late life (12). However, older adults today are heavier and have been overweight for a longer period of time than in previous generations. Given that excess body weight is a global health problem that has reached epidemic proportions (13), with more than 60% of the US and European adult populations being overweight
or obese (14, 15), including persons aged 65 years or older, even a small adverse effect on cognitive abilities might have a detrimental effect on public health.

To the best of our knowledge, there are only 2 previous review articles on obesity and cognitive functions in late life (16, 17). However, neither of these makes a clear distinction between cognitive aging and cognitive changes due to dementia. In the review by Smith et al. (16), the authors concluded that the relation between obesity and cognitive function was uncertain in the elderly. Smith et al. also found that low cognitive abilities in early life, especially executive functions, were associated with a higher risk of becoming obese, which shows the need for a discussion about a bidirectional relation between obesity and cognition. These findings illuminate the complexity of this association. In aging research, a causal pathway from obesity to cardiovascular disease and further to cognitive decline often is assumed; however, despite the great number of studies reporting an association between obesity and cognition, the question of directionality remains unsolved and often is not even discussed.

In this context, we systematically reviewed all available prospective studies assessing various cognitive functions in late life and obesity from midlife to late life. Several studies show that underweight persons perform at a lower level than do people within the normal weight range (18–21). Poor cognitive function in underweight persons most often is explained by underlying severe diseases that are responsible for both the underweight and the poor cognitive function; in the elderly, this underlying disease is usually dementia. Because both cognitive function and weight are thought to decrease several years before the clinical onset of dementia (22–24), only studies that measured obesity at least 5 years before the measure of cognitive function were included. For the same reason, only studies that excluded persons with known dementia were included, to reduce the potential risk that preclinical dementia would blur the association.

METHODS

Medline was used to search for the terms obesity, overweight, cognition, cognitive, age, and aged, resulting in 1,024 hits (1946 to January 2012) when the search was limited to studies with human samples and articles written in English. A similar search was performed in CINAHL (Cumulative Index to Nursing and Allied Health Literature), resulting in 305 hits, 80% of which also appeared in Medline. The remaining 62 hits from CINAHL were evaluated together with the 1,024 hits from Medline. In total, 1,086 abstracts were reviewed. The studies that were included were required to have used population-based samples and to have had prospective designs with a 5-year minimum time period between the obesity measure and the cognition measure, and accordingly, all studies with shorter follow-up times and all cross-sectional studies were excluded. The purpose of these restrictions was to limit the influence of preclinical weight loss and dementia-related cognitive changes on the obesity-cognition association.

Obesity usually was assessed with body mass index (BMI; weight (kg)/height (m)²), and most studies either used the World Health Organization’s cutoffs for underweight, normal weight, overweight, and obesity or categorized on the basis of the distribution of the sample, where the top tertiles or similar categories indicated obesity. Furthermore, studies including other anthropometric measures such as waist circumference and waist-hip ratio were included because these measures are considered better indicators of abdominal fat. Last, because the primary aim was to study the association between obesity and cognitive function, the effect of obesity had to be reported separately in joint analyses, for example, when the joint effect of obesity and other cardiometabolic factors was studied.

Studies were required to have assessed cognitive function after subjects reached the age of 60 years. Shorter screening tests such as the Mini-Mental State Examination (25) were not allowed to be the outcome because they are a crude measure of cognitive ability and the variation in test scores is small. Given that the focus of the present review was cognitive aging within the normal range, we excluded all studies examining mild cognitive impairment, which is not considered to represent cognitive changes within the normal range (26), and all studies examining dementia. Furthermore, studies that did not explicitly state that persons diagnosed with dementia had been removed from the analyses were excluded. However, studies in which it was unclear if persons with dementia were included were allowed only if the mean age at the assessment of cognitive function was younger than 65 years, because the prevalence of dementia before that age is very low. All review articles, commentaries, and experimental and clinical trials were excluded. Experimental and clinical trials were excluded because they target persons with specific conditions and hence cannot be considered representative of the population at large. Finally, several of the selected studies also reported associations between underweight and cognitive function; however, given the aim of the present review, these findings will not be discussed.

After an initial screening of titles and abstracts, 41 articles remained for the analysis. Of these, 14 studies were excluded after a more detailed reading of the abstracts. Most of the studies that were excluded at this step either were based on clinical trials or had imaging or dementia as the outcome measure. Twenty-seven studies were then read in detail, and, in cases of uncertainty, both authors (A. K. D. and L. B. H.) read the article and discussed whether it should be included on the basis of the selection criteria. Most of these studies were based on a cross-sectional design, had a follow-up time shorter than 5 years, or failed to exclude persons with dementia. Finally, 11 articles remained for the analysis. The characteristics of these studies are summarized in Tables 1 and 2.

RESULTS

Midlife obesity and late-life cognitive abilities

Seven studies assessed obesity 1 or more times before subjects reached the age of 60 years (18, 19, 27–31) (Table 1).
<table>
<thead>
<tr>
<th>First Author, Year (Reference)</th>
<th>Study</th>
<th>No. of Participants</th>
<th>Age, years</th>
<th>Study Design</th>
<th>Adiposity Measures</th>
<th>Cognitive Measures</th>
<th>Covariates</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cournot, 2006 (30)</td>
<td>Aging and Health at Work</td>
<td>2,223</td>
<td>32–62 at baseline (32 years, 28%; 42 years, 32%; 52 years, 27%; 62 years, 13%)</td>
<td>BMI measured at baseline in midlife. Cognition measured at baseline and at 5 years’ follow-up.</td>
<td>BMI (in quintiles)</td>
<td>Longitudinal assessments of verbal memory, processing speed, and attention</td>
<td>Age, sex, education, blood pressure, diabetes, baseline cognitive ability, and psychosocial factors (i.e., stress and self-reported health)</td>
<td>Cross-sectionally, higher BMI was associated with lower cognitive function across domains. Prospectively, higher BMI was associated with a steeper decline in all domains, but the effect remained significant only for verbal memory in the fully adjusted model. Increase in BMI was found to be associated with poorer attention only.</td>
</tr>
<tr>
<td>Dahl, 2010 (27)</td>
<td>Swedish Adoption/Twin Study of Aging</td>
<td>781</td>
<td>Mean = 42; range, 25–63</td>
<td>BMI measured at baseline in midlife. Cognition assessed longitudinally with a first assessment 21 years later.</td>
<td>BMI (continuous)</td>
<td>Longitudinal assessments of general cognitive ability</td>
<td>Age, sex, education, cardiometabolic factors, alcohol use, smoking, twinness, and cohort</td>
<td>Persons with higher midlife BMI scores had lower mean level general cognitive ability and steeper decline across the longitudinal follow-ups.</td>
</tr>
<tr>
<td>Dahl, 2012 (18)</td>
<td>Swedish Adoption/Twin Study of Aging</td>
<td>657</td>
<td>Mean = 40 (range, 25–49.9) and 63 (range, 50–75)</td>
<td>Multiple BMI measures in midlife. Cognition measured longitudinally with a first measure at 21 years from baseline.</td>
<td>BMI (WHO categories)</td>
<td>Longitudinal assessments of verbal and spatial abilities, memory, and perceptual speed</td>
<td>Age, sex, education, cardiometabolic factors, alcohol use, smoking, twinness, cohort, exercise, general physical health, and baseline verbal abilities</td>
<td>Persons who were obese in early midlife had significantly lower cognitive performance across domains in late life and significantly steeper decline in perceptual speed. Obesity in late midlife was associated with lower cognitive abilities in late life. Being obese across midlife was associated with worse cognitive performance.</td>
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<td>First Author, Year (Reference)</td>
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<tr>
<td>Gunstad, 2010 (28)</td>
<td>Baltimore Longitudinal Study of Aging</td>
<td>1,703</td>
<td>Mean = 55 (range, 19–93) at baseline</td>
<td>BMI, WC, and WHR measured in midlife. Cognitive abilities measured longitudinally every 2–3 years since baseline.</td>
<td>BMI, WC, and WHR</td>
<td>Longitudinal assessments of MMSE, Blessed Information-Memory-Concentration test, memory, attention, executive function, language, and spatial ability</td>
<td>Age, sex, education, blood pressure, diabetes, glucose intolerance, and anti-lipid treatment</td>
<td>Higher BMI scores were in general associated with lower mean level cognitive test performance across domains and with steeper decline in global functioning, tests of attention/executive functions, and memory. Higher WC and WHR were to a smaller extent than BMI associated with lower mean level cognitive performance and with a more rapid decline in some tests of attention/executive functions, memory, and spatial ability.</td>
</tr>
<tr>
<td>Hassing, 2010 (29)</td>
<td>Origins of Variance in the Old-Old Study</td>
<td>417</td>
<td>Mean = 52 (range, 50–60) at baseline</td>
<td>BMI measured at baseline in midlife. Cognition measured longitudinally with a first measure 30 years later.</td>
<td>BMI (continuous)</td>
<td>Longitudinal assessments of long- and short-term memory, speed, verbal, and spatial ability</td>
<td>Age, sex, education, alcohol use, smoking, blood pressure, diabetes, stroke, exercise, baseline verbal abilities</td>
<td>Higher BMI in midlife predicted lower test performance across domains 30 years later; however, a higher midlife BMI was not associated with a steeper cognitive decline.</td>
</tr>
<tr>
<td>Knopman, 2009 (36)</td>
<td>Atherosclerosis Risk in Communities Study</td>
<td>1,130</td>
<td>Mean = 59 (range, 47–70) at first assessment of cognitive abilities</td>
<td>BMI measured about 3 years before the first assessment of cognitive abilities. Cognitive abilities measured 4 times during a 14-year period.</td>
<td>BMI (continuous)</td>
<td>Longitudinal assessments of memory, verbal fluency, and processing speed</td>
<td>Age, sex, education, and race</td>
<td>BMI was not significantly associated with either mean level cognitive performance or change in cognitive abilities.</td>
</tr>
</tbody>
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Table 1. Continued

<table>
<thead>
<tr>
<th>First Author, Year (Reference)</th>
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</tr>
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<tbody>
<tr>
<td>Sabia, 2009 (19)</td>
<td>Whitehall II Study</td>
<td>5,131</td>
<td>Mean = 25 at baseline</td>
<td>BMI measures from 3 occasions across early midlife. Cognition measured at 36 years’ follow-up.</td>
<td>BMI (WHO categories and quartiles)</td>
<td>MMSE, memory, and executive function</td>
<td>Age, sex, education, smoking, alcohol use, diet, and activity</td>
<td>Overweight in early adulthood was associated with poor memory. Obesity in early midlife was associated with lower executive function. In late midlife, overweight/obesity was associated with lower MMSE, memory, ability, and executive function. Being obese and underweight across midlife was associated with worse performance across domains. Increase in BMI across midlife was associated with lower executive function.</td>
</tr>
<tr>
<td>Wolf, 2007 (31)</td>
<td>Framingham Offspring Cohort</td>
<td>1,814</td>
<td>Mean = 53</td>
<td>BMI and WHR measured once at baseline in midlife. Cognition measured at 8 years’ and 12 years’ follow-up.</td>
<td>BMI and WHR</td>
<td>Verbal memory, spatial ability, and executive function</td>
<td>Blood pressure</td>
<td>Adiposity measured by WHR was associated with poorer executive function and spatial ability but not with verbal memory.</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio.

a Weight (kg)/height (m)².
### Table 2. Late-Life Obesity and Late-life Cognitive Abilities

<table>
<thead>
<tr>
<th>First Author, Year (Reference)</th>
<th>Study</th>
<th>No. of Participants</th>
<th>Mean Age at Baseline, years</th>
<th>Study Design</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Brubacher, 2004 (32)</td>
<td>Basel Cohort Study</td>
<td>531</td>
<td>69.4</td>
<td>BMI(^a) measured on 2 occasions at baseline and 10 years' follow-up. Cognition measured at 10 years' follow-up.</td>
<td>BMI and change in BMI</td>
<td>Composite score based on CERAD-NAB</td>
<td>Age, sex, blood pressure, diabetes, apolipoprotein E, and health status</td>
<td>Change in BMI predicted lower cognitive function. Neither BMI at baseline nor BMI at follow-up predicted cognitive function.</td>
</tr>
<tr>
<td>Buchman, 2005 (33)</td>
<td>Religious Order Study</td>
<td>820</td>
<td>74</td>
<td>BMI measure at baseline and follow-up. Cognition measured at baseline and at 5.5 years' follow-up.</td>
<td>BMI and change in BMI</td>
<td>Composite score based on 19 tests</td>
<td>Age, sex, education, and chronic health conditions</td>
<td>Lower BMI at baseline and decline in BMI were associated with lower general cognitive ability at follow-up.</td>
</tr>
<tr>
<td>Elias, 2003 (34)</td>
<td>Framingham Heart Study</td>
<td>1,423</td>
<td>65.7 (men) and 67.2 (women) (range, 55–86)</td>
<td>BMI measure at baseline. Cognition measured at 4–6 years' follow-up.</td>
<td>BMI; normal/overweight were compared to obese</td>
<td>Learning, memory, executive functioning, and abstract reasoning</td>
<td>Age, education, occupation, smoking, alcohol, cholesterol, and diabetes</td>
<td>Obesity was associated with lower performance in working memory, spatial abilities, and global cognitive function in men but not in women.</td>
</tr>
<tr>
<td>Sturman, 2008 (35)</td>
<td>The Chicago Health and Aging Project</td>
<td>3,885</td>
<td>73.8</td>
<td>BMI measured at baseline and at 6.4 years' follow-up. Cognition measured at baseline and at follow-up</td>
<td>BMI both continuous and dichotomized at 25</td>
<td>Composite measure of general cognitive ability</td>
<td>Age, sex, education, race, blood pressure, diabetes, heart disease, and stroke</td>
<td>No significant associations between BMI and cognitive function in a cognitively intact sample (MMSE score &gt;24)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CERAD-NAB, Consortium to Establish a Registry for Alzheimer’s Disease-Neuropsychological Assessment battery; MMSE, Mini-Mental State Examination.

\(^a\) Weight (kg)/height (m)\(^2\).
The follow-up time between the obesity measure and the cognitive assessment ranged from 5 to 37 years. In general, midlife obesity was associated with lower cognitive ability in late life, across domains and after adjustment for various covariates. It also should be mentioned that some studies reported an association between overweight and lower cognitive functions and that some studies showed a linear association. The association between obesity and cognitive abilities did not change substantially when cardiometabolic factors and diseases were controlled for. Most studies measured obesity with BMI. Only 2 studies, the Framingham Offspring Cohort (31) and the Baltimore Longitudinal Study of Aging (28), included other measures. In the Framingham Offspring Cohort, the waist-hip ratio measure of obesity gave stronger associations with cognitive aging than did BMI. On the contrary, in the Baltimore Longitudinal Study of Aging, BMI was generally a better predictor of cognitive performance than were waist-hip ratio and waist circumference.

Five studies based on 4 samples assessed cognitive function longitudinally, enabling conclusions about changes in cognitive function (18, 27–30). In accordance with studies that assessed cognitive abilities at only one time point, these 5 studies showed that midlife obesity was associated with lower mean levels of cognitive performance across domains. The results of change in cognitive function were less conclusive.

In the Swedish Adoption/Twin Study of Aging (SATSA), early midlife obesity was associated with a steeper decline in general cognitive ability (27) and perceptual speed, with a tendency for a steeper decline in verbal and spatial abilities (18). Late midlife obesity, on the other hand, was associated with a steeper decline in only verbal ability, similar to the findings from the Origins of Variance in the Old-Old (29) and the Vieillissement, Santé, Travail (VISAT; Aging, Health, Work) studies (30). Except for verbal ability, no evidence for obesity-related cognitive decline was reported in the Origins of Variance in the Old-Old or VISAT studies. In the Baltimore Longitudinal Study of Aging, associations between obesity and cognitive decline were reported for some single tests measuring attention/executive functions and spatial ability, but the majority of the tests were nonsignificant, although in the same direction, reflecting a tendency for obesity-related cognitive decline across tasks (28).

With regard to whether gaining weight and being stably obese for a long time are associated with lower cognitive function, 3 studies evaluated the effects of obesity across midlife (i.e., cumulative effects and change) on cognitive functions; these studies were VISAT (28), SATSA (18), and the Whitehall II Study (19). Both the Whitehall II Study and SATSA evaluated the effect of being stably obese across midlife (across 2 observations compared with only 1 observation) and reported a stronger negative association with cognitive function across domains in those who were stably obese than in those who were obese at 1 observation, which indicates a cumulative effect of long-term obesity. Furthermore, an increase in BMI in the Whitehall II Study was associated with a lower Mini-Mental State Examination score and poorer memory and executive function. The VISAT study reported similar findings in attention but not in the other domains. The VISAT findings were supported by findings from SATSA, in which no association between weight increase and low cognitive function was reported.

**Late-life obesity and late-life cognitive abilities**

Four prospective studies assessing obesity in late life were identified (32–35). The follow-up time between the first obesity measure and cognitive testing ranged from 5 to 10 years (Table 2). Among these studies, only the Framingham Heart Study reported results for specific cognitive domains (memory, executive function, and abstract reasoning) (34). The remaining studies used a single measure of global cognitive ability or a composite score. In general, the studies found no association (35) or found that low BMI (33) and change in BMI (32, 33) were related to lower cognitive function. Only the Framingham Heart Study (34) reported that obesity was associated with lower global cognitive ability or cognitive decline, but this was found only among men (34).

**DISCUSSION**

The purpose of the present systematic review was to examine the relation between obesity and cognitive function in late life and to evaluate the evidence for a causal association. The general pattern of the findings reflects that obesity in midlife is related to lower cognitive function across domains in late life (18, 19, 27–31). The only exception from this pattern was the Atherosclerosis Risk in Communities (ARIC) Study (36). A possible explanation for this seemingly contradictory finding is that BMI was assessed at a higher mean age (59 years) in the ARIC Study than in the other studies assessing BMI in midlife. As will be discussed subsequently, the association between late-life BMI and cognitive abilities is less clear cut, and there seems to be a shift in the association from early to late life. Hence, it is possible that the participants in the ARIC Study had passed this threshold.

Moreover, being stably obese over a longer period of time was associated with lower cognitive function in late life (18, 19). On the other hand, the evidence that obesity in midlife was related to cognitive decline was weak. Despite that there was generally only a weak association between obesity and the trajectories of cognitive abilities, the association between obesity and verbal ability followed a different pattern. Three studies, SATSA (18), the Origins of Variance in the Old-Old Study (29), and VISAT (30), all of which assessed BMI in late midlife, consistently showed a negative association between obesity and the trajectories of verbal abilities. Again, the findings from the ARIC study were different (36). However, the association between BMI and steeper decline in verbal abilities was supported by the Lothian Birth Cohort 1936, in which late-life obesity was related to lower verbal ability (37) even when childhood mental ability was controlled for. The observed effect of obesity on the decline in verbal abilities is interesting because verbal abilities represent the cognitive domain.
considered most resistant to aging (2). It could be hypothesized that because there is less change in verbal abilities due to normal aging, it might be easier to pinpoint factors, such as obesity, that cause changes in this domain.

When obesity was measured in late life only, the Framingham Offspring Cohort study (34) showed that obesity was related to lower cognitive ability, whereas 2 other studies (32, 33) showed that low weight or weight change in late life was associated with lower cognitive function. In the present review, we applied the exclusion criterion of a minimum of 5 years’ follow-up time between the obesity measure and the cognitive assessment to avoid interference of preclinical dementia. Given that weight and cognitive functions are believed to decline more than 10 years before the clinical onset of dementia, it cannot be excluded that these findings were due to preclinical dementia. This notion is supported by the findings from the Chicago Health and Aging Project, in which the U-shaped association between BMI and global cognitive ability became nonsignificant when persons with a Mini-Mental State Examination score <24 were excluded (35).

The direction of the association

Although there is no doubt that a link exists between obesity in midlife and lower cognitive function in late life, less is known about the direction of this association. A causal relation between obesity and cognitive aging would be supported by an effect of obesity on the trajectories of cognitive decline; however, the reviewed studies report either no effect or only small effects in some domains or small effects on single tests. It is possible that the negative effect of obesity on cognitive function is small and that cognitive function needs to be studied over a long period of time to show changes. This is supported by the fact that the study with the longest surveillance period of cognitive function showed the most consistent effect of obesity on cognitive decline, although these effects were small to moderate (18). Other support for obesity possibly causing cognitive aging comes from the findings of 2 studies showing that persons who are obese over long time periods have lower cognitive function than that of persons who are obese over shorter time periods (18, 19).

It also has been hypothesized that the association between cognitive function and obesity might go in the reverse direction—that is, low cognitive function might be associated with an increased risk of obesity. Studies assessing cognitive function in childhood have linked low cognitive function to an increased risk of becoming obese in midlife (38, 39). In addition, research using cross-sectional analyses in midlife (30, 40) sometimes indicated that higher BMI was associated with lower cognitive test performance. Further support for the theory that the association between obesity and cognitive functions begins in early life comes from the Lothian Birth Cohort 1936 study, in which the negative association between late-life obesity and cognitive ability almost completely disappeared when controlled for early-life cognitive ability; the association remained significant only for verbal ability. However, high BMI was reported to be only weakly inversely associated with intelligence among 1 million Swedish men around the age of 18 years (41). Likewise, 2 reports included in the present review showed that when verbal ability was used as a proxy of early-life cognitive ability, the association between obesity and cognition was not substantially attenuated (18, 29). The rationale for using verbal ability as a proxy for early-life cognitive ability is that verbal ability remains stable over the adult life span until very old age (1), although it cannot supplement a proper assessment of cognitive functions in early life. Taken together, this can be seen as evidence that obesity does in fact cause cognitive decline.

Causal pathways

Because obesity is associated with an increased risk of cardiometabolic factors such as hypertension and diabetes that in turn are associated with lower cognitive functions in old age, the cardiometabolic pathway usually is proposed as a potential pathway from obesity to low cognitive function. Accordingly, all studies except the Religious Order Study controlled for the prevalence of 1 or more cardiometabolic factors. Because the presence of several cardiometabolic risk factors, often referred to as the metabolic syndrome, is suggested to have a cumulative negative effect on various health outcomes, it would not have been surprising if studies with more measures of cardiovascular factors had been more likely to find a mediation effect of cardiometabolic factors. However, the association between obesity in midlife and lower cognitive function in late life generally was not attenuated by controlling for various cardiometabolic factors, either alone or in combination, or if cardiovascular events such as stroke or ischemic heart attack had occurred.

It should be emphasized that the assessment of these cardiometabolic factors is difficult. The lack of mediation of these effects might be because a) undiagnosed type II diabetes mellitus, hypercholesterolemia, and hypertension are common in the general population (although they should be less common in longitudinal studies in which participants generally receive feedback on their health); b) the effects of the preclinical phase were not assessed; and c) treatment and treatment adherence usually were not captured. Furthermore, if cardiometabolic factors were assessed only at baseline, it is possible that the negative effects of obesity had not yet occurred, and hence the mediating effect might not have been captured.

In future studies, other potential causal pathways also should be explored. For example, one proposed causal pathway is through inflammatory processes. Obese persons have higher levels of inflammation than do normal-weight persons (42). In longitudinal studies, serum C-reactive protein and proinflammatory cytokines like interleukin-6 have been associated with cognitive decline (43, 44). Another pathway is through hormones, cytokines, and growth factors that are produced in adipose tissue. These factors could interact directly with blood vessels (45, 46) or can cross the blood-brain barrier (47) and contribute to disruption of homeostasis. Leptin and adiponectin are suggested as possible pathways between obesity and brain health (10). For
example, leptin, a hormone that increases with obesity, has been shown to enhance memory functions in rodents. Accordingly, leptin has been suggested to be one of the potential explanations for the reversed association between obesity and better cognitive abilities in later life (35), but this hypothesis does not hold true for the negative association between obesity and cognitive function in early life.

A third alternative is that there might be underlying shared etiologies between obesity and low cognitive function. A great deal of the obesity epidemic is attributed to lifestyle factors, but around 70% of the variation in body weight is still thought to be due to genetic factors (48). Because the main variations in obesity and cognitive function are estimated to originate from a genetic disposition, it would be interesting to further evaluate whether obesity and cognitive function share a common genetic variance, as suggested by the Finnish Twin Cohort Study (49), and if obesity-related genes, such as the fat-associated gene (FTO), and genes associated with cognitive function, such as apolipoprotein E4 and SORL1, modify the association between the 2 constructs.

Limitations and future directions

First, there is never a guarantee that all relevant papers have been included in a literature search. However, we tried to limit this risk by using broad search terms and by using some of the key words used in the most relevant publications. By doing this, we believe that we have limited the selection bias. However, we cannot guarantee that we have not missed some studies in which obesity was not the key feature of the paper.

All the included studies were based on well-known and well-characterized samples with sufficient numbers of participants. All studies assessed obesity with BMI, but the cutoffs varied across studies, which made it harder to compare the results. BMI is often criticized for not differentiating between fat and muscle mass, and this is more pronounced among the elderly (50). Future studies should include other measures of obesity. The range of cognitive domains assessed varied from study to study, but all studies used well-known cognitive tests with high validity and reliability.

The main limitations of the studies in this research area are failure to exclude persons with dementia and short follow-up times, which make it impossible to distinguish between cognitive aging and cognitive decline due to dementia. A substantial number of studies were excluded on the basis of these limitations. Another limitation is that no study that we are aware of has access to cognitive assessments and weight assessments in early life, midlife, and late life. Access to assessments of these factors across the life span would make it possible to elucidate the direction or directions of the association between overweight in midlife and lower cognitive function.

Conclusion

This systematic review shows clear evidence that midlife obesity was associated with cognitive aging, whereas this association was weaker in late life; thus, no firm conclusions could be drawn. The findings of this review suggest that, although evidence exists for an association between midlife obesity and low cognitive abilities in late life, the direction of the association and the causality remain to be clarified.

Hence, the possibility that the association between obesity and low cognitive function in old age has been present for a long time (i.e., before a person enters old age) cannot be excluded. To better understand the direction of the association between obesity and cognitive aging, longitudinal studies are needed to assess adiposity and cognitive function, as well as potential biologic and psychological mechanisms, at multiple occasions over a long period of time, preferably starting in early life.

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