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Adiposity and Alzheimer's Disease

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Abstract

Purpose of the review—Alzheimer's disease (AD) is the most common form of dementia. There are no known preventive or curative measures. There is increasing evidence for the role of total adiposity, usually measured clinically as body mass index (BMI), and central adiposity, measured in AD. This topic is of enormous public health importance given the global epidemic of high adiposity and its consequences.

Recent findings—Salient publications in 2007 and 2008 showed that a) central adiposity in middle age predicts dementia in old age; b) the relation between high adiposity and dementia is attenuated with older age; c) waist circumference in old age, a measure of central adiposity, may be a better predictor of dementia than BMI, d) lower BMI predicts dementia in the elderly; e) weight loss may precede dementia diagnosis by decades, which may explain seemingly paradoxical findings.

Summary—The possibility that high adiposity increases AD risk is alarming given global trends of overweight and obesity in the general population. However, prevention and manipulation of adiposity may also provide a means to prevent AD. Treatment of weight loss in AD may also be important but is beyond the score of this review.

Keywords

Alzheimer's disease; dementia; adiposity; overweight; obese; body weight

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Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for between 70% to over 90% of all cases(1), and its prevalence is expected to quadruple by the year 2047 in the United States (2). As much as 50% of the population aged 85 years and older, the fastest growing segment of the population, may have AD (3). The risk factors for ADcan be classified as genetic and non-genetic. Three genes have been identified in familial early onset AD, Amyloid Precursor Protein (APP), Presenilin 1, and Presenilin 2 (4). These genes affect less than 5% of cases of AD, have full penetrance and expressivity, and usually affect persons in middle age (5). This review will address risk factors for late onset AD. Robust risk factors that have been identified for late onset AD include older age, lower education, and the APOE-ε4 allele(5). Importantly, APOEε4 has been found to modulate the effect of other putative risk factors (6), such as diabetes and hyperinsulinemia (7,8). It is thought that the main culprit in AD is the accumulation of amyloid β in the brain, resulting in synapse disruption and neuronal destruction (4,9). Thus, putative treatments or prevention measures for AD must target the deposition of Aβ and have the potential of preventing or delaying the onset of disease, not just symptoms (10). There are no established preventive or curative measures for AD. Thus, there is an intense search for modifiable risk factors. High adiposity is an established modifiable risk factor for several diseases(11) and has gathered interest as a risk factor for AD. This manuscript is a brief review of the evidence linking adiposity to AD.

Definition and burden of adiposity

Adiposity refers to the amount of adipose (fat) tissue in the body (12). Some refer to adiposity as "fatness", overweight, or obesity. Adiposity is a continuum, the normal or ideal threshold of adiposity is not clear, and is affected by factors such as age, sex and ethnic group. In general, as adiposity increases it is associated with higher risk of insulin resistance, diabetes, hypertension, dyslipidemia, cardiovascular disease, degenerative joint disease, cancer, and respiratory diseases (11,13). Definitions of a high level of adiposity have been devised using simple anthropometric measures and in relationship with adverse outcomes(14). Anthropometric measures(15) such as body weight and height are used to calculate body mass index (BMI), which is defined as weight in kilograms divided by height in meters squared (kg/m^2). A BMI of 25 – 29.9 kg/m2 is considered overweight, and BMI≥ 30 kg/m2, obese(16). BMI is strongly correlated with total body fat tissue and is a good indirect measure of adiposity (11), although this correlation decreases in older age (17). Thus, there is controversy over whether BMI cutoffs used for adults should be used in the elderly(18).

Another commonly used measure of adiposity is waist circumference (WC). WC is meant to measure the accumulation of adipose tissue in the abdomen, the largest depot of adipose tissue in some individuals, particularly as they age. WC is thus, perhaps, a better marker of potential adverse metabolic effects of high adiposity compared to BMI (15,19). Elevated WC is also related to a higher risk of diabetes, hypertension, dyslipidemia, and heart disease. Most studies show that it is a better predictor of adverse cardiovascular outcomes compared to BMI (20), and have therefore advocated its use as the best measure of the detrimental effects of adiposity (15). A commonly used cutoff to define elevated waist circumference is 102 cm for men and 88 cm for women (20). Other less frequently used anthropologic measures of adiposity include skinfolds and waist to hip ratio (15).

There is a concerning epidemic of high adiposity in the world (21). With the aging of the population and greater longevity, the long term consequences of these conditions are serious and burdensome. Overweight (BMI ≥ 25) and obesity (BMI≥ 30) (22) and elevated waist

circumference(23) are increasing in adults in the United States. More concerning, these trends are also observed in children and adolescents (24). Two-thirds of the United States population are overweight or obese (24).

Potential mechanisms linking adiposity to Alzheimer's disease

There are a number of potential mechanisms linking high adiposity to AD. Mechanisms summarized below include hyperinsulemia, advanced glycosylation products, adipocyte-derived hormones (adipokines and cytokines), and the influence of adiposity on vascular risk and cerebrovascular disease.

1. Hyperinsulinemia

As described previously, one of the main consequences of adiposity is insulin resistance and hyperinsulinemia (12). The role of insulin in AD is attracting increasing attention (25). Insulin can cross the blood brain barrier from the periphery to the central nervous system and compete with Aβ for insulin degrading enzyme (IDE) in the brain, including in the hippocampus (26). Insulin is also produced in the brain, and may have, alternatively, a beneficial effect on amyloid clearance (27). Peripheral hyperinsulinemia may also inhibit brain insulin production which, in turn results in impaired amyloid clearance and a higher risk of AD (27). Thus, it is possible that decreasing peripheral hyperinsulinemia and increasing brain insulin levels have the same beneficial effect on AD. A study found that rosiglitazone, a drug used in diabetes treatment which decreases insulin resistance and decreases peripheral insulin levels may also be beneficial in AD (28). Interestingly, intranasal insulin, delivered with direct access to the brain without accessing the periphery has a similar effect (27). Manipulation of blood insulin levels in humans has been demonstrated to affect cognition and levels of amyloid β in the cerebrospinal fluid (29,30), supporting the potential direct role of insulin in AD.

2. Advanced glycosylation end products (AGEs)

AGEs result from impaired glucose tolerance and diabetes, which often accompany or follow high adiposity and are responsible for their related end organ damage (31). AGEs can be identified immunohistochemically in senile plaques and neurofibrillary tangles, the pathologic hallmarks of AD (5). Glycation of amyloid β enhances its aggregation in vitro. Furthermore, receptors for AGEs have been found to be specific cell surface receptors for amyloid β, thus potentially facilitating neuronal damage (31).

3. Adipokines and cytokines

Adipose tissue has been traditionally viewed as a passive energy-dense depot. As a dietary component, fat contains the most energy per gram than any other dietary component. Recent evidence shows that adipose tissue is active and produces a series of substances that are important in metabolism (adipokines), and inflammation (cytokines). Examples of adipokines include adiponectin (32), leptin(33), and resistin (33), and of inflammatory cytokines include Tumor Necrosis Factor-α, and Interleukin-6 (33). All are correlated with insulin resistance and hyperinsulinemia. It is unclear at this point whether adipokines and cytokines produced by adipose tissue are directly related to AD or whether they are only markers of insulin resistance and hyperinsulinemia. However, some evidence links adipokines directly to cognition. Blood leptin levels are directly correlated with adiposity, (34,35) and the CA1 nucleus of the hippocampus, which may be affected in AD, is directly affected by adipose-derived hormones such as leptin. Leptin has been shown to have numerous effects on brain development (36) and potentially on brain health in cognition and aging, affecting the function of the hypothalamus, and learning and memory processes controlled by the hippocampus.(37) In adults with a recessive mutation in the *ob* gene

(homologous to *ob/ob* mice), leptin replacement is trophic for the brain, and increases gray matter tissue in the anterior cingulate gyrus, the inferior parietal lobe, and cerebellum.(38) Presence of the leptin receptor in the hippocampus, hypothalamus, amygdala, cerebellum, and brain stem indicates potentially linked regulatory mechanisms.(36,37) Recent experimental data show that leptin and adiponectin interact directly with hypothalamic nuclei and regulate energy expenditure and hyperphagic responses.(39,40) Leptin, may even shape the hypothalamus in the earliest stages of development and enhance cognition.(36) Direct leptin administration has been shown to improve memory processing in mice and enhance NMDA receptors.(36) However, other roles of leptin and related adipose-derived factors in the Alzheimer brain are not clear.(41-43) Fasting plasma leptin has been inversely correlated with grey matter volume in areas of the brain in which obese have reduced grey matter in comparison with lean individuals.(44)

4. Vascular risk factors and cerebrovascular disease

Cerebrovascular disease and stroke are related to a higher risk of AD (45,46). It is not clear whether cerebrovascular disease has a direct action on the amyloid cascade. Cerebrovascular disease may cause brain damage in additionto amyloid neurotoxicity that may lower the threshold for the clinical manifestation of AD (47). An autopsy study showed that large vessel cerebrovascular disease, but not small vessel disease or infarcts, were related to a higher frequency of brain neuritic plaques (48), the pathologic hallmark of AD (5). Adiposity, hyperinsulinemia, and diabetes (13), and related vascular risk factors such as hypertension and dyslipidemia are related to a higher risk of cerebrovascular disease(49). Thus, adiposity, may affect AD risk indirectly through vascular risk factors and cerebrovascular disease.

Another potential link of adiposity, vascular disease and AD is the renin-angiotensin system (RAS). The classical function of the RAS is blood pressure regulation, but RAS may also provide a link between obesity, hypertension, and vascular syndromes, such as type 2 diabetes, and health of the brain.(50,51) Human brain and adipose tissue express a full RAS. Adipose RAS is involved in adipocyte growth, differentiation, and metabolism.(52) The RAS is activated in response to low levels of blood pressure, when angiotensin is converted by renin to angiotensin I, which is subsequently converted to angiotensin II by ACE. Angiotensin II interacts with angiotensin receptors 1 and 2, to mediate major cardiovascular effects of the RAS, such as increasing blood pressure.(50) In the brain, angiotensin II continues conversion to angiotensin IV, which, acting through angiotensin receptor 4 (also known as insulin–regulated aminopeptidase, IRAP),(53,54) enhances learning and memory in animal models.(54)

Dementia and weight regulation

Thus far this review has covered how high adiposity may affect AD. However, the inverse relationship, that AD affects adiposity, may also occur. Brain regions and processes important for dementia are also important for the neural regulation of food intake and energy metabolism. Emotional learning, memory and complex cognition affect eating behavior and are affected in dementia. A classic example is as memory impairment is a first symptom in AD, individuals with memory impairments may forget to eat, and thus experience declines in body weight. However, ‘body memory’ related to food intake in general, may also influence obesity susceptibility. Numerous hypotheses relating memory, a hippocampal function, and control of energy intake, a hypothalamic function, have been brought forward.(37,55,56) One interesting hypothesis relating establishment of body weight set points and feeding behavior to late-life body weight disturbances in AD, is related to common involvement of hippocampal subregions, for example CA1. In early AD, neuropathological lesions appear to be selectively located in medial temporal lobe structures, including the

transentorhinal cortex, entorhinal cortex, and CA1 area of the hippocampal formation.(57,58) The entorhinal cortex within the temporal lobe, is an area of neuropathological, ischemic and other insults in early dementia.(59,60) Temporal atrophy, an early hallmark of dementia and cognitive decline, is a manifestation of neuronal degeneration,(61,62) and has been related to higher BMI levels 24 years before an atrophy measurement using computed tomography (CT),(63) and cross-sectionally to lower MRI measures of global brain volume in a study of women and men aged 40-66 years.(64) Higher BMI has also been shown to predict a higher rate of atrophy progression measured using serial MRI.(65) Central adiposity (high waist-to-hip ratio) has been cross-sectionally related to temporal atrophy using MRI.(66) High BMI may lead to atrophy, or alternatively, some level of atrophy or susceptibility to atrophy may be present among those with a higher BMI due to involvement of common brain structures related to energy metabolism and dementia. Having a smaller temporal lobe volume early on may contribute to dysregulatory events leading to both higher levels of BMI throughout life and/or are reflective of diminished cognitive reserve.

Review of prospective epidemiological studies linking adiposity to Alzheimer's disease

Few studies have explored the association between adiposity and AD, and several reveal conflicting findings. Elevated BMI in middle age may be associated with higher dementia risk (67,68). A recent study showed that central adiposity in middle age was related to a higher risk of dementia in older age(69). Higher BMI at ages 70, 75 and 79 years may also predict higher dementia risk (70). However, there have been reports of no association at mid-life (71) and of lower BMI related to higher AD risk(72) (73) at older ages. There are several explanations for this apparent paradox. First, age of the adiposity measure in relationship to clinical dementia onset varies across studies. Throughout life, there may exist critical periods in which risk or protective factors may have more or less impact. Second, several studies have reported weight loss preceding dementia onset(71,74), and may precede diagnosis by decades(75). Understanding the reverse causality observed for adiposity parameters in relationship to dementia onset, (76), is critical for interpretation of study findings. Third, the inclusion of different birth cohorts across studies introduces the possibility cohort effects. According to developmental origins hypotheses early life events related tobirth cohort may influence both adult adiposity and cognition throughout adult life(77). Fourth, anthropometric characteristics of populations vary around the world. If baseline BMI, whether measured at mid-life or late-life, is within a healthy range (e.g., < 25 kg/m2), with low prevalence of overweight and obesity, the risky effects of high adiposity may be less likely observed. Fifth, diagnosis of dementia is not the same across epidemiologic studies. For example, some studies use neuropsychiatric interviews, some registry data, and others, screening criteria prior to diagnosis. Related to this is that demented populations are heterogeneous and identified at different levels of severity. Given the potentially rapid changes that occur in BMI throughout the dementia process, these nuances may translate to differences in observations, and thus data interpretation. Sixth, dementia is a syndrome. Metabolic alterations occurring with dementia may vary based on expression of the syndrome. Finally, another potential explanation is ethnicity. One study in Japanese Americans showed no association of high adiposity with AD (71). A study in Northern New York City (78) found that in younger elderly (65 to 76 years of age), the association between BMI quartiles and AD resembles a U shaped-curve, while in the oldest old (> 76 years) higher BMI is related to a lower AD risk. This U-shaped association has been reported for the relation between adiposity and cardiovascular mortality(79) and underscores the difficulty in studying the effects of adiposity in older age(80). This study also found that higher waist circumference is related to higher AD risk in the younger elderly, but not in the oldest. In late life, low BMI may also be a sign of frailty due to

sarcopenia (81,82) or the consequence of hyperinsulinemia (83), one of the putative mechanisms linking adiposity and AD. Table 1 describes salient publications from 2007 and 2008 relating adiposity and AD. Curiously, these publications encapsulate the paradoxes mentioned above, but also seem to explain them. The study by Whitmer et al found that central adiposity in middle age is a predictor of dementia. The study by Luchsinger et al had similar findings for persons 65 to 75 years, but not persons 76 years and older. The study by Luchsinger el al also found that BMI in persons 65 to 75 years had a U-shape association with dementia, while there was an inverse association in persons 76 years and older. Similarly, the study by Atti et al found an inverse association between BMI and dementia in persons 75 years and older. Finally, these findings could be explained by the study by Knopman et al, which found that weight loss may precede dementia by more than 10 years.

Conclusions Implications of the evidence linking adiposity to AD

There is compelling evidence that high adiposity, particularly in middle age and in younger elderly, is related to AD. However, this evidence comes short of being considered as proof of causation until we understand the mechanisms and some of the caveats discussed in this review. It is also important to point out that AD causes weight loss. A discussion of how weight loss in AD affects outcomes is beyond the scope of this review but can be found elsewhere(84-87). If the relation between high adiposity and AD were to be causal, the public health implications are enormous. As explained before, 2/3 of the adult population of the United States are overweight or obese, and the short term trend is for this to worsen. These trends are also being observed worldwide. With increasing life expectancy we are likely to increasingly see the cognitive consequences of increased adiposity in old age. However, the other implication is that a large proportion of cases of AD could be preventable or treatable. There is existing evidence that interventions for elevated adiposity or that improve insulin sensitivity can positively affect cognition. There is a body of literature showing that aerobic exercise can improve cognition, particularly executive-frontal abilities, in elderly people (88,89), and some of this effect could be mediated by weight loss. A small trial of diet and exercise in middle aged Japanese Americans with glucose intolerance showed improvement in memory at 6 months(90). Rosiglitazone, a potent insulin sensitizing medication with effects similar to those of exercise and weight loss, has been shown to prevent memory decline in persons with Alzheimer’s disease(91). Most of these studies are short term, and the long term effects of weight loss are not clear. Furthermore, the right age group in which these interventions would be effective is not clear. The epidemiologic data seems to suggest that middle age is a critical period. Large intervention studies with lifestyle interventions(92) and drugs like metformin(93) that result in weight loss have shown that it is feasible and safe to decrease hyperinsulinemia and the risk of diabetes in middle aged populations in the long term (e.g. after 3 or more years). It is possible that these interventions could extend to decreasing the risk of AD in old age. Thus, it is necessary to add AD biomarkers and clinical predictors to trials that include adiposity interventions. In this regard, there are ongoing efforts to add cognitive measures to the Finnish Diabetes Prevention Study(92), and the Diabetes Prevention Program Outcomes Study(94), 2 landmark studies of interventions to lose weight and prevent type 2 diabetes. This would help clarify the mechanisms linking adiposity and AD and may reveal a strategy to prevent an important common disease for which there is no cure. For the moment, and pending the results of these studies, it seems reasonable to postulate that maintaining a healthy weight over the life course is a ‘best’ strategy for optimizing both body and brain health. There are numerous clinical trials showing that weight loss lowers blood pressure, improves blood lipids and insulin resistance, and positively affects other factors that lower not only cardiovascular, but dementia risk.

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Table 1

Summary of salient studies published in 2007 and 2008 relating adiposity and dementia. Authors are in alphabetical order.

First author (reference)	Study setting and description	Findings
Atti, AR (72)	The Kungsholmen Project in Sweden, a prospective study of 1255 persons 75 years and older with body mass index (BMI) information at baseline followed for 3, 6, and 9 years. Incident dementia was ascertained using standard research criteria.	Persons with a BMI of 25 kg/m^2 or higher had a lower risk of dementia than persons with a BMI of 20 to 24.9 kg/m^2.
Knopman, DS (75)	The Rochester Epidemiology Project in Rochester, MN, United States. Dementia was ascertained by a medical records linkage system. Cases of dementia were matched to controls without dementia. Weight and weight change was abstracted from medical records	There were no differences in weight between cases and controls 21 to 30 years before dementia onset. Women with dementia had lower weight than controls starting at 11 to 20 years before diagnosis.
Luchsinger, JA (78)	The Washington Heights Inwood Columbia Aging Project, a cohort study of persons 65 years and older followed for 5 years on average in New York City, United States; 893 had information on BMI, and 907 had information on waist circumference at baseline. Incident dementia was ascertained using standard research criteria.	Compared with persons in the first quartile of BMI, persons in the third quartile had a lower dementia. The association between BMI and dementia resembled a U shape in those younger than 76 years, while dementia risk decreased with higher BMI in those 76 years and older. The fourth quartile of waist circumference was related to a higher Alzheimer disease risk in persons younger than 76 years.
Whitmer, RA. (69)	A cohort study of of 6,583 members of Kaiser Permanente of Northern California, United States, who had their sagittal abdominal diameter (SAD) measured . Diagnoses of dementia were from medical records an average of 36 years later	Compared with those in the lowest quintile of SAD, those in the highest had nearly a threefold increased risk of dementia. Those with high SAD (>25 cm) and normal BMI had nearly a doubling of dementia risk compared to those with low SAD (<25 cm) and normal BMI (18.5-24.9 kg/m^2). Those with obesity (BMI >30 kg/m^2) and high SAD over a tripling of dementia risk