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Adiposity, type 2 diabetes and Alzheimer's disease

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Abstract

This manuscript provides a comprehensive review of the epidemiologic evidence linking the continuum of adiposity and type 2 diabetes (T2D) with Alzheimer's disease (AD). The mechanisms relating adiposity and T2D to AD may include hyperinsulinemia, advanced products of glycosilation, cerebrovascular disease, and products of adipose tissue metabolism. Elevated adiposity in middle age is related to a higher risk of AD but the data on this association in old age is conflicting. Several studies have shown that hyperinsulinemia, a consequence of higher adiposity and insulin resistance is also related to a higher risk of AD. Hyperinsulinemia is a risk factor for T2D, and numerous studies have shown a relation of T2D with higher AD risk. The implication of these associations is that a large proportion of the world population may be at increased risk of AD given the trends for increasing prevalence of overweight, obesity, hyperinsulinemia, and T2D. However these associations may present a unique opportunity for prevention and treatment of AD. Several studies in the prevention and treatment of T2D are currently conducting or have planned cognition ancillary studies. In addition, clinical trials using insulin sensitizers in the treatment or prevention of AD are under way.

Keywords

adiposity; overweight; obesity; hyperinsulinemia; insulin; glucose; type 2 diabetes; alzheimer's disease; cognitive impairment

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Introduction

Burden of Alzheimer's disease

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 AD can 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 type 2 diabetes (T2D) and hyperinsulinemia [7,8]. Current treatment options for AD only address symptoms, and no treatments are available that focus on delaying the actual disease process [9]. One of the currently accepted hypotheses of the pathogenesis of AD is that the main culprit is the accumulation of amyloid β in the brain, resulting in synapse disruption and neuronal destruction [4,10]. Mild Cognitive impairment (MCI) has been used to describe a transitional state between normal cognitive function and AD dementia [11,12], and has thus been targeted for interventions [13]. Individuals with MCI do not have dementia but have memory complaints without loss of function in their daily activities [12]. While general cognitive performance is well preserved, memory performance on standardized tests falls below expectations for age and education. Persons with MCI progress to AD at the rate of nearly 10% to 15% per year [11] compared to 1 to 2% in elderly persons with normal cognition [12]. MCI can be classified in amnesic and non-amnesic MCI. It is believed that amnesic MCI is an early stage of AD, while non-amnesic MCI, such as executive MCI, is less specific to AD [11]. The prevalence of amnesic MCI varies between 3% and 20% depending on the criteria applied [14], and increases from about 1% in persons 60 years old to 25% at age 85 [15]. AD can be studied in epidemiologic studies through the outcomes of memory impairment or decline, amnesic MCI, and Alzheimer's dementia, and this review will cover evidence examining these outcomes.

The continuum of adiposity, hyperinsulinemia, and type 2 diabetes

There is a concerning epidemic of obesity, insulin resistance and T2D in the world [16]. With the aging of the population and greater longevity, the long term consequences of these conditions will have a significant public health impact in elderly populations. Adiposity refers to the amount of adipose (fat) tissue in the body [17]. Adiposity is a continuum, and the normal or ideal threshold of adiposity is not clear. However, as adiposity increases it is associated with higher risk of insulin resistance, T2D, hypertension, dyslipidemia, cardiovascular disease, degenerative joint disease, cancer, and respiratory diseases [18,19]. Definitions of a elevated levels of adiposity have been devised using existing measures and according to their relationship with adverse outcomes [20]. Adiposity is usually measured indirectly with anthropological measures [21] such as the body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m^2). BMI is strongly correlated with total body fat tissue and is a good indirect measure of adiposity [19], although this correlation decreases in older age [22]. Another commonly used measure of adiposity is waist circumference. Waist circumference is meant to measure the accumulation of adipose tissue in the abdomen, the largest depot of adipose tissue, and thus, perhaps it is a more direct measure of adiposity compared to BMI [21,23].

Elevated waist circumference is also related to a higher risk of T2D, hypertension, dyslipidemia, and heart disease, and some studies have shown that it is a better predictor of

adverse cardiovascular outcomes compared to BMI [24], and some have advocated its use as the best measure of adiposity [21]. A commonly used cutoff to define elevated waist circumference is 102 cm for men and 88 cm for women [24]. Other less frequently used anthropologic measures of adiposity include skinfolds and waist to hip ratio [21]. Overweight and obesity [25] and elevated waist circumference [26] are increasing in adults in the United States. More concerning, these trends are also observed in children and adolescents [27]. Two thirds of the United States population are overweight or obese [27]; 30% are obese, and the prevalence of obesity is higher in women than men.

Insulin sensitivity is the ability of insulin to dispose of a glucose load. Insulin resistance refers to the resistance of tissues that dispose of glucose to the actions of insulin. Insulin resistance results in an increase in insulin secretion in the pancreas in order to overcome that insulin resistance. Fasting insulin levels are used in epidemiological studies as indicators of the risk of T2D [28-31]. Fasting insulin is accepted as a measure of insulin resistance that is highly correlated with more complicated measures of insulin resistance such as the euglycemic clamp [32], and the homeostasis model assessment [33].

Glucose intolerance and T2D are abnormal elevations of blood glucose that put people at risk for microvascular (nephropathy, neuropathy, retinopathy) and macrovascular disease (coronary artery disease, cerebrovascular disease, peripheral vascular disease) [34]. It is important to point out that this review addresses type 2 diabetes, not type 1 diabetes. The American Diabetes Association currently defines diabetes as a fasting glucose elevation > 126 mg/dl, and glucose intolerance as an elevation of glucose between 110 and 126 mg/dl [35]. It is difficult to establish an absolute threshold for the definition of glucose intolerance and diabetes. Previously, the definition of diabetes was a fasting glucose > 140 mg/dl, and people currently defined as having diabetes were then considered non-diabetic [36]. The fasting glucose threshold for the diagnosis of diabetes will change again and persons currently considered to have glucose intolerance will be considered to be diabetic. This underlines the caveats of using cutoffs to define conditions that have continuous (linear or non-linear) associations with disease: depending on the cutoff use, persons at risk may be classified as normal or abnormal (and vice versa). This is true for measures of adiposity, insulin resistance, and measures of glucose tolerance.

Adiposity, hyperinsulinemia, glucose intolerance, and T2D, are often treated as separate constructs. However, they are related sequentially and often occur simultaneously, and understanding this relationship is fundamental in the study of the role of adiposity, insulin resistance, and T2D in Alzheimer's disease. Keeping glucose in normal levels is achieved by the balance between the ability of peripheral tissues (muscle, adipose tissue, liver) to take glucose into cells, and the pancreas' ability to secrete insulin, the hormone in charge of glucose tissue uptake [34]. Thus, abnormal glucose levels are caused by a resistance of tissues to the action of insulin (insulin resistance), and by the pancreas' inability to secrete enough insulin at normal levels or higher than normal insulin levels (hyperinsulinemia) to overcome insulin resistance in tissues [37]. Insulin resistance increases with age, and the organism maintains normal glucose levels as long as it can produce enough insulin (hyperinsulinemia). Some individuals are less capable than others to mount sustained hyperinsulinemia and will develop glucose intolerance and T2D [37]. Other individuals with insulin resistance will maintain normal glucose levels at the expense of hyperinsulinemia but their pancreas will eventually "burn out", will not be able to sustain hyperinsulinemia, and will develop glucose intolerance and T2D [37]. Others will continue having insulin resistance, may have or not have glucose intolerance, will not develop T2D, but will have hyperinsulinemia and suffer its consequences. The most frequent modifiable determinant of insulin resistance and hyperinsulinemia is elevated adiposity [17,38], although adipose tissue is not the only factor. Insulin resistance can reside in other tissues, including muscle, liver, and the pancreas itself [39]. The susceptibility

to adiposity, that is, the risk of developing insulin resistance and T2D in response to adiposity, varies by gender [19] and particularly by ethnicity. For example, Chinese and southeast Asians are more susceptible than Europeans to developing insulin resistance with comparable increases of adiposity [17]. The distribution of factors related to insulin resistance and the metabolic syndrome, including adiposity, is different in Whites and Blacks [40]. Thus, conventional ways to classify adiposity may not capture its relation with adverse outcomes and this should be taken into account. High adiposity and hyperinsulinemia are both accompanied by dyslipidemia, hypertension, and inflammation [38], and these should also be taken into account.

An implication of the continuum described above is that when an epidemiologic study finds a relation between the components of this continuum and AD we cannot be certain if we are looking at a surrogate marker of one of the other components (e.g. T2D is a marker of past adiposity or hyperinsulinemia, obesity is a marker of hyperinsulinemia) or if the important exposure is the one we are examining. The answer could be that there is an aggregate effect of all the components of the continuum. The metabolic syndrome, an increasingly popular term in clinical practice and research, and reported to be associated with a higher risk of cognitive decline [41] is a constellation of adiposity, hypertension, glucose intolerance, and dyslipidemia, that is associated mainly with insulin resistance and hyperinsulinemia [42,43]. However, the definition of the metabolic syndrome is somewhat arbitrary, intended to capture the clustering of cardiovascular risk factors particularly in middle aged populations, and its validity in elderly populations at risk for AD is not clear [43]. The difficulty of arriving at precise metabolic syndrome criteria is reflected by the fact that over the years at least 6 different definitions have been developed that share several characteristics [42].

Summary of prospective epidemiological studies linking adiposity, hyperinsulinemia, and diabetes to Alzheimer's disease

Adiposity

Elevated BMI in middle age may be associated with higher dementia risk [44,45]. A recent study showed that central adiposity in middle age was related to a higher risk of dementia in older age [46]. Higher BMI at ages 70, 75 and 79 years may also predict higher dementia risk [47]. However, there have been reports of no association at mid-life [48] and of lower BMI related to higher AD risk [49,50] 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 [48,51], and may precede diagnosis by decades [52]. Understanding the reverse causality observed for adiposity parameters in relationship to dementia onset, [53], is critical for interpretation of study findings. Third, the inclusion of different birth cohorts across studies introduces the possibility of cohort effects. According to developmental origins hypotheses early life events related to birth cohort may influence both adult adiposity and cognition throughout adult life [54]. 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 [48]. A study in Northern New York City [55] 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[56] and underscores the difficulty in studying the effects of adiposity in older age[57]. This study also found that higher waist circumference is related to higher AD risk in the younger elderly, but not in the oldest old. The Cardiovascular Health Study recently reported that elevated self-reported BMI at age 50 years was associated with a higher risk of dementia, while BMI at age 65 or older in the same individuals did not[58]. This study underscores the importance of the period in life at which adiposity is ascertained in relation to dementia. The most important explanation for the paradox linking low weight in old age to dementia seems to be weight loss. The mechanisms for this are not entirely clear. They may include loss of olfaction[59,60], one of the earliest manifestations of AD, which may lead to decreased caloric intake, forgetfulness of meals[54], and metabolic changes related to AD that are not well understood. In this regard, AD is accompanied by abnormalities in brain insulin signaling[61] which could affect appetite and food intake. It is not clear if weight loss is a consequence of AD, a parallel process, or if it is related to potential causes of AD, such as insulin resistance[62]. The role of weight loss and nutritional supplementation in the progression of AD is beyond the scope of this review and can be found elsewhere[63-66].

Hyperinsulinemia

Several cross-sectional studies show an association between hyperinsulinemia and an increased risk of AD [67-69]. Two longitudinal studies, one in elderly Japanese Americans in Hawaii [70], and another in elderly Black, Caribbean Hispanic, and Non-Hispanic Whites in New York City [8] found that the risk of incident AD was higher in persons with hyperinsulinemia. These studies also found that the risk of AD related to hyperinsulinemia was higher among persons with the APOE-ε4. The Nurses' health study found that higher C-peptide levels, a measure of insulin secretion [71], and fasting insulin levels are related to cognitive decline in women [72-74]. There is a paucity of prospective epidemiologic studies exploring the relation between markers of hyperinsulinemia and AD and more are needed.

Type 2 diabetes

T2D has been related to a two-fold higher risk of developing MCI among postmenopausal women [75]. A multiethnic study in elderly from New York city found that T2D was related to a higher risk of cognitive impairment-no dementia with stroke although the effect on cognitive impairment-no dementia without stroke was not evident after adjusting for demographic variables and the presence of Apo E-ε4 allele [76]. An Italian study showed a non-statistically significant increase of MCI with T2D in an elderly population[77], while a Canadian study found that T2D was related only to vascular cognitive impairment-no dementia [78]. A study in New York City found that T2D was related to a higher risk of both amnesic and non-amnesic MCI, underlining the importance of T2D for both AD related and vascular cognitive impairment [79]. A recent study in Olmstead county, Minnesota found that presence of T2D was not related to MCI risk, but longer T2D duration and treatment with insulin, a surrogate marker of T2D duration, were related to higher MCI risk[80].

T2D has been found consistently to be related to vascular dementia (VD) but its relation to AD is less clear. A study of Japanese subjects aged 65 years and older found that T2D was related to a higher risk of both AD and VD [81]. A longitudinal study from the Netherlands in over 5,000 subjects aged 55 years and older without dementia at baseline found a higher risk of AD in persons with T2D [82]. This association was stronger in subjects with T2D who reported insulin treatment. Another European study found that the risk of all cause-dementia was

increased by T2D but this relation was weaker with AD [83]. A study from Rochester, Minnesota found a doubling of AD risk in relation to T2D [84], similar to the study from the Netherlands. A study of catholic nuns, priests, and brothers 55 years and older found that T2D was associated with a higher risk of AD [85]. The Honolulu Asia Aging Study also found that T2D in old age was related to a higher risk of AD and AD pathology on autopsy, particularly in subjects with the APOE- ϵ 4 allele [7]. A study from Canada found that T2D had a weak non-statistically significant relation to AD, but was related to VD. A Swedish study found a similar non-significant relation to AD, and a significant relation to a higher risk of VD [86]. A prospective study in over 1,000 subjects from New York City who were mostly African American and Caribbean-Hispanic, with a mean age of 75 years, and without dementia at baseline found a higher risk of AD in relation to T2D which was not statistically significant after adjustment for other variables, but T2D was significantly related to higher risk of a composite outcome of AD and cognitive impairment-no dementia [76]. The risk of AD was also increased in those treated with insulin, indicating a higher risk of AD in subjects with long-standing T2D. This study also found a stronger association between T2D and VD. A recent reanalysis of these data with longer follow-up showed that the risk of AD associated with T2D was stronger than previously reported independent of other vascular conditions (hypertension, heart disease, stroke) and not explained by misclassification of VD cases as AD [87]. A study in Sweden found that T2D increased the risk of VD but not of AD [86], and that this risk was higher in the presence of hypertension and heart disease. The same study recently reported that borderline T2D was associated with a higher risk of AD in persons without the APOE- ϵ 4 allele [88].

Few studies have examined if T2D in middle age leads to the development of dementia in older age. One study in the United States [89] and another in Israel [90] found that T2D at midlife increased the risk of dementia in the elderly. A study in Japanese-Americans found no association between T2D in middle age and dementia [91].

The diagnosis of T2D is somewhat arbitrary and many cases go undetected. Few studies have examined the relation between continuous measures of glycemia and dementia. One study in postmenopausal women found that the risk of MCI and dementia increased with each 1% elevation in glycosylated hemoglobin, a stable measure of glucose levels, even in women without T2D [92]. Glycosylated hemoglobin in persons without T2D correlates with both glucose intolerance and insulin resistance, and this study underscores the continuous nature of the relation between these constructs and higher dementia risk.

Metabolic syndrome

There is limited evidence on the association between the metabolic syndrome and dementia in the elderly. One study in 2,632 black and white elders found that the metabolic syndrome was associated with a higher risk of cognitive decline, particularly among those with high inflammatory markers [41]. A cross-sectional study in Europeans found that AD prevalence was higher in persons with the metabolic syndrome [93]. In Northern New York City the metabolic syndrome was not related to AD risk, while T2D and hyperinsulinemia were [94]. The discrepancy between these studies could be due to the fact that the study in New York City was conducted in an older population, ethnically diverse, and with a high prevalence of vascular risk factors [87]. In Japanese Americans the metabolic syndrome in middle age was associated with VD, but not AD [95].

Potential mechanisms linking adiposity, hyperinsulinemia and diabetes to Alzheimer's disease

This section includes a brief description of mechanisms. It is important to point out that these mechanisms overlap and may be highly correlated. Figure 1 attempts to depict the sequence and interrelation of these mechanisms.

Hyperinsulinemia

As described previously, one of the main consequences of adiposity is insulin resistance and hyperinsulinemia [17]. The role of insulin in AD is attracting increasing attention [96]. Insulin can cross the blood brain barrier from the periphery to the central nervous system and compete with A β for insulin degrading enzyme (IDE) in the brain, including in the hippocampus [97]. Insulin is also produced in the brain, and may have, alternatively, a beneficial effect on amyloid clearance [98]. Peripheral hyperinsulinemia may also inhibit brain insulin production which, in turn results in impaired amyloid clearance and a higher risk of AD [98]. 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 T2D treatment which decreases insulin resistance and decreases peripheral insulin levels may also be beneficial in AD [99]. Interestingly, intranasal insulin, delivered with direct access to the brain without accessing the periphery has a similar effect [98]. Manipulation of blood insulin levels in humans has been demonstrated to affect cognition and levels of amyloid β in the cerebrospinal fluid [100,101], supporting the potential direct role of insulin in AD.

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 [102]. 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 [102].

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 [103], leptin [104], and resistin [104], and of inflammatory cytokines include Tumor Necrosis Factor- α , and Interleukin-6 [104]. 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. Systemic inflammation may be important and AD [41,105,106]. However, it is not clear whether systemic inflammation could just be a marker of cardiovascular disease [107], or be a marker and cause of insulin resistance [108]. However, some evidence links adipokines directly to cognition. Blood leptin levels are directly correlated with adiposity, [109,110] 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 [111] and potentially on brain health in cognition and aging, affecting the function of the hypothalamus, and learning and memory processes controlled by the hippocampus. [112] 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.

[113] Presence of the leptin receptor in the hippocampus, hypothalamus, amygdala, cerebellum, and brain stem indicates potentially linked regulatory mechanisms.[111,112] Recent experimental data show that leptin and adiponectin interact directly with hypothalamic nuclei and regulate energy expenditure and hyperphagic responses.[114,115] Leptin, may even shape the hypothalamus in the earliest stages of development and enhance cognition.[111] Direct leptin administration has been shown to improve memory processing in mice and enhance NMDA receptors.[111] However, other roles of leptin and related adipose-derived factors in the Alzheimer brain are not clear.[116-118] 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.[119]

Microvascular and macrovascular complications of type 2 diabetes

Microvascular complications of T2D include renal and retinal disease. It is thought that white matter disease in the brain visualized as white matter hyperintensities or leukoaraiosis are due to microvascular disease[120] and these have been found to be common in persons with T2D [121]. Brain infarcts are macrovascular complications of T2D. The role of white matter hyperintensities and infarcts in the amyloid cascade that leads to AD is not clear. However, it is thought that cerebrovascular disease at least lowers the threshold for the clinical manifestation of AD[122]

Other vascular risk factors

Hypertension and dyslipidemia accompany adiposity and T2D and cause cerebrovascular disease[123]. As previously mentioned, Cerebrovascular disease is related to a higher risk of AD [124,125]. An autopsy study showed that large vessel cerebrovascular disease, but not small vessel disease or infarcts, were related to a higher frequency of senile plaques [126], the pathologic hallmark of AD [5].

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 T2D, and health of the brain.[127,128] Human brain and adipose tissue express a full RAS. Adipose RAS is involved in adipocyte growth, differentiation, and metabolism.[129] 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.[127] In the brain, angiotensin II continues conversion to angiotensin IV, which, acting through angiotensin receptor 4 (also known as insulin-regulated aminopeptidase, IRAP),[130,131] enhances learning and memory in animal models.[131]

Implications for the prevention and treatment of Alzheimer's disease

There is very strong evidence that adiposity, hyperinsulinemia, and T2D are related to AD. However, this evidence comes short of being considered as proof of causation until we understand the mechanisms. If the relation between these conditions 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. Epidemiologic studies suggest that adiposity in middle age is important as a predictor of AD risk. With increasing life expectancy we are likely to increasingly see the cognitive consequences of increased adiposity, hyperinsulinemia, and T2D in old age. We estimated that in New York City the presence of T2D or hyperinsulinemia in elderly people could account for 39% of cases of AD [8]. However, the other implication is that a large proportion of cases of AD could be preventable or treatable.

The Finnish Diabetes Prevention Study (FDPS) [132] demonstrated that T2D can be prevented with lifestyle interventions. The Diabetes Prevention Program (DPP) in the United States demonstrated that T2D can be prevented through lifestyle interventions or metformin[133] and this effect was largely mediated by improvements in insulin sensitivity and reductions in insulin levels[134]. Cognition ancillary studies are planned for both the FDPS and DPP. These cognition ancillary studies will be unique opportunities to answer whether the prevention of T2D through improvement in adiposity and insulin sensitivity are related to improvements in the risk of cognitive impairment. Rosiglitazone, and insulin sensitizer used in the treatment of T2D but also shown to be effective in prevention[135] have shown preliminary promise [136] in the treatment of AD, particularly in persons without the APOE-ε4 allele[99]. Phase III trials of rosiglitazone are under way although concerns about its safety may make limit this drug's usefulness [137,138]. The potential mechanisms linking the continuum of adiposity, hyperinsulinemia, and T2D are multiple, overlapping, and highly correlated. Thus, it may be difficult to elucidate that a single mechanism is the culprit. Importantly, the potential therapeutic interventions mentioned above impact virtually all potential mechanisms. That is, weight loss through lifestyle interventions or medications alters adipokine activity, improves hyperinsulinemia, inflammation, glucose tolerance, blood pressure, lipids, and the risk of cerebrovascular disease. One of the pitfalls of the clinical diagnosis of AD is that it may detect a heterogenous disease with overlapping vascular and amyloid pathologies in a continuum. This may explain the observation of relations of adiposity, hyperinsulinemia, T2D with AD. It is possible that these relations are explained mostly by cases of dementia with cerebrovascular disease misclassified as AD, or that are cases of mixed dementia. However, the possibility of misclassification does not reduce the potential public health importance of these observations and the potential for prevention and treatment.

Another important question is whether intense treatment can decrease the risk of cognitive impairment and AD in persons with T2D. Moreover, it is important to answer whether treatment of T2D with drugs that increase insulin levels vs. insulin sensitizers affect cognitive impairment. Some of these questions will be answered by a cognition ancillary study in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial [139]. Elucidating the mechanisms linking adiposity, hyperinsulinemia and T2D to AD will help identify specific targets for treatment and more research is needed in this regard.

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Figure 1.

Mechanism linking the continuum of adiposity, insulin resistance and type 2 diabetes to the manifestation of Alzheimer's disease. Elevated adiposity leads to insulin resistance which precedes most cases of glucose intolerance and type 2 diabetes. Each of these conditions is related to specific mechanistic intermediaries, but most mechanisms are shared. For example, elevated adiposity, insulin resistance, and type 2 diabetes are all accompanied by hypertension and dyslipidemia. In addition, some of these mechanisms are bidirectional. For example, insulin resistance due to elevated adiposity results in increased inflammation which in turn increases insulin resistance. These mechanisms overlap and are highly correlated. In theory, these mechanistic intermediaries result in increased amyloid beta deposition and cerebrovascular disease. Cerebrovascular disease is thought to decrease the threshold at which amyloid deposition causes the manifestations of Alzheimer's disease, which starts with memory impairment, reaching the threshold of mild cognitive impairment, and eventually dementia.