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# Adipokines: a link between obesity and dementia?

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## Abstract

Being overweight or obese, as measured with body mass index (BMI) or central adiposity (waist circumference), and evolving trajectory of BMI over the life course, have been associated with brain atrophy, white matter changes, blood brain barrier integrity and risk of all-cause late-onset dementia and Alzheimer's Disease (AD). This observation leads us to question what it is about BMI that is associated with health of the brain and dementia risk. If high BMI and central adiposity represent an increase in adipose tissue, then the endocrine aspect of adipose tissue, mediated by adipose tissue hormones and adipokines, may be a clue to understanding the association with dementia and AD. Hundreds of adipokines have been identified, creating a complexity that is challenging to simplify. Nonetheless, adipokines are being investigated in association with clinical dementia outcomes, as well as imaging-based measures of brain volume, structure and function in preclinical and human models of clinical dementia.



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**Authors' contributions** Dr. Gustafson received the invitation to write the review as a follow-up to her 2006 Lancet Neurology review on BMI and dementia. For this review, she conducted literature searches, helped to design the figure and tables, and drafted the text. Ms. Arnoldussen conducted literature searches, helped to design the figure, and drafted parts of the text.
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## Introduction

Since 2003, when the first report was published of a risk association in women between AD and higher body mass index (BMI, kg/m2), a common and simple measure of overweight and obesity,[1] there have been many epidemiologic reports relating higher mid-life and late-life BMI to dementia[1–8] There is an approximate 2-fold higher risk associated with mid-life BMI or central adiposity measures.[3, 4, 6, 7] The levels of mid-life adiposity that are associated with dementia or AD are in overweight and obese ranges based on traditional anthropometric cutpoints for BMI, waist circumference and waist-to-hip ratio (WHR) and used to denote risk for cardiovascular disease and overall mortality. (See Figure 1). Following mid-life, a decrease in BMI tends to occur, such that those who have clinical dementia have lower BMI or body weight compared to those who do not.[9, 10] This reverse epidemiology phenomenon has been a topic of debate. [11] It has been suggested that the higher mid-life adiposity that is associated with higher dementia risk may be due to vascular mechanisms, whereas the decline in BMI and body weight is reflective of neurodegeneration and interruption of homeostatic feedback mechanisms in later life.[11] An overarching challenge in linking anthropometric measures with dementia has been to answer the question, ‘What is BMI, waist circumference or WHR measuring that translates to differences in dementia risk?’ One answer to this is the quantity and secretory capacity of peripheral white adipose tissue (WAT).

WAT is an endocrine tissue that secretes hundreds of compounds, which are called adipokines when WAT is thought to be the major source. The endocrine function of adipose tissue may provide insight as to underlying mechanisms linking adipose tissue to the major neurodegenerative and vascular disease of aging - cognitive impairments and dementia. There are other potential factors associated with risk for dementia and adipose tissue, including physical activity, dietary constituents (nutrients and non-nutrients), dietary patterns, health and disease status, as well as genetic background, but discussion of these is beyond the scope of this review.[12]

In this Review we will define and discuss the role of the adipokines that have shown associations with dementia from human observational and clinical studies. We will also discuss examples of adipokines that may be important for the brain and dementia that have been identified from experimental models and characteristic of the obese condition. (See Figure 2) The hypotheses described are related to selected adipokines, and their potential association with vascular events and neurodegeneration. This review is not comprehensive, but provides an overview for how certain adipokines could be associated with late-onset dementia risk. In light of this evolving literature and the paucity of data on associations between adipokines and dementia and dementia-related brain outcomes, we will also discuss the limitations of the data. Search Strategy and selection criteria

We searched PubMed using the following terms: dementia, Alzheimer, adiposity, body mass index (BMI), and the following adipokines: leptin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), hepatocyte growth factor (HGF), nerve growth factor (NGF), adipsin (Complement Factor D), monocyte chemotactic protein (MCP-1), and interleukins. A comprehensive literature search was performed for studies reporting on associations

between adipokines and dementia with no date restrictions. Studies of biological mechanism focused on 2010–2013.

## ADIPOKINES AND ADIPOSE TISSUE

WAT is a complex tissue consisting of multiple cell types with multiple cellular phenotypes depending on cell composition and location.[13] WAT consists of a stromal layer and a mature adipocyte layer. The stromal layer consists of Adipose Derived Stem Cells (ADSCs) or pre-adipocytes, fibroblasts, blood vessels, and nerve cells. ADSCs are self-renewing and can differentiate along several mesenchymal lineages into adipocytes, osteoblasts, myocytes, chondrocytes, endothelial cells, cardiomyocytes, and even neuronal-like cells.[14] The mature adipocyte layer consists of fully differentiated adipocytes.[15]

Adipokines include hundreds of polypeptides secreted by the different cells of WAT, sometimes referred to as the adipose secretome or adipokinome,[16] In the periphery, adipokine release is fat depot-specific, which is coherent with differences in adipocyte morphology and the local milieu. [14, 17, 18] More adipokines are released from visceral versus subcutaneous WAT. In addition, brown, epicardial and pancreatic adipose tissue appear to have unique adipokine profiles.[19–21] Since the amount of visceral adipose is associated with higher waist circumference or WHR,[22–24] this has been one rationale for using relatively unsophisticated methods of determining body adiposity, such anthropometric measures, to pinpoint mechanisms of action. Similarly BMI grossly reflects total adipose tissue during adulthood, and is a relatively good correlate, regardless of changing body composition with aging [25]

The word adipokine or adipocytokine means ‘adipo-, adipose; -cyto-, cell; -kinos, movement. The term, ‘adipokine’ was derived to refer to immunomodulatory cytokines secreted by adipose tissue. However, the popular use of this term has expanded beyond this to include compounds which are technically not cytokines, adipokine instead refers to[16] cytokines, acute phase reactants, growth factors and other inflammatory mediators, adipose tissue hormones such as leptin, and other chemical messengers.[11, 26, 27] Adipokines act in autocrine, paracrine, or endocrine ways,[28] and many affect processes in the periphery and the central nervous system (CNS).

Leptin, adiponectin, and interleukin-6 (IL-6), are the best known examples of adipokines, broadly defined. In 2011, experiments with isolated human adipocytes, serum, and adipose tissue biopsies from lean and obese individuals, identified 347 protein components (including 44 never before reported) of the adipokinome.[16] However, over 700 adipose tissue-derived proteins have been reported in response to specific chronic or acute stimuli or at rest.[16] One may also surmise that fat in the CNS plays a role, since the CNS has the highest lipid content in the human body after adipose tissue. However, CNS lipid does not exist as adipose tissue, but as layers of fatty acid-containing myelin sheaths that surround the axons of the brain and spinal cord.[29] CNS-derived adipokines are instead, produced in various brain regions, by a variety of cell types[30] and nuclei, such as the arcuate nucleus in the hypothalamus, for specific purposes such as regulating feeding behavior.

Since neurodegenerative and vascular processes observed in dementia affect several brain regions and nuclei,[31] while not proven, the action of adipokines could be altered during neurodegenerative and vascular events and may even feedback to contribute to neurodegeneration. However, much remains to be discovered as to the relative source, brain versus periphery, and mechanistic actions of these adipokines in each compartment.

Adipokine release may be dysregulated in obesity and in aging, possibly because the adipose tissue may be 'diseased'. The terms inflammaging[32] and adiposopathy have been used to describe unhealthy adipose tissue. Adiposopathy describes the excessive hypertrophy of adipocytes[33, 34] that leads to the dysregulated paracrine and endocrine adipose tissue activity that is associated with cardiovascular disease. Alterations in adipose tissue also contribute to the frailty syndromes observed in aging, to encompass physical (e.g., weight loss, sarcopenia) and functional (e.g., diminishing Activities of Daily Living) frailty in the periphery, as well as cognitive frailty in the brain.[35] As such, while not proven, there is potentially a role for dysregulated adipose tissue in the development of dementia, brain pathology and/or clinical symptoms of dementia. While there is no known pharmacologic intervention targeting the link between adipose tissue and dementia, the link is indirectly suggested via the evidence presented in this review.

The adipokines most studied in humans are listed in Table 1. These molecules may be grouped according to primary function as shown; however, each may possess more than one function, and these functions do overlap. For example, leptin, adiponectin, resistin, plasminogen activator inhibitor-1 (PAI-1), hepatocyte growth factor (HGF), and nerve growth factor (NGF) are involved in dysregulation of nutrient utilization as well as inflammation, endothelial dysfunction, hypertension and atherogenesis.[36] In addition, adipose and non-adipose hormones, for example, leptin and insulin, respectively, interact to augment each other.[37] Insulin interacts directly with hypothalamic nuclei, and it appears that both leptin and insulin are mediators in insulin resistance, as illustrated by observations that pro-opiomelanocortin (POMC) neurons in the hypothalamus express both leptin and insulin receptors and regulate energy balance and glucose homeostasis. Experimental mouse models lacking both leptin and insulin receptors in POMC neurons display systemic insulin resistance. Thus, direct action of both insulin and leptin on POMC neurons appears required to maintain normal glucose homeostasis.[38]

We now review eight adipokines or classes of adipokines, grouped according to a primary function: energy balance and metabolism (leptin, adiponectin, and adipsin [Complement Factor D]); thrombosis and hypertension (plasminogen activator inhibitor-1 [PAI-1]); growth factors (HGF1, NGF1); and inflammation (interleukins and monocyte chemotactic protein [MCP-1]). First are the adipokines that have been reported in epidemiologic studies in association with dementia (Table 2); second we present a selection of adipokines that may be associated with dementia due to their biological roles and/or associations with brain processes.

## Energy Balance and Metabolism

**Leptin;—**Leptin is a 16 kDa protein hormone[39–41] that is primarily secreted by adipose tissue and positively correlated with BMI.[42, 43] Correlations of approximately r=0.7 between

BMI and blood leptin levels are observed in adults, even among those with obesity syndromes.[2, 44]

Peripheral leptin enters the CNS and CSF and interacts with specific areas of the brain such as the hypothalamus and hippocampus.[45, 46] However, beside leptin transport into the CSF and other brain regions, several studies indicate that leptin is also produced in human and rodent brains, for example in the hypothalamus, cortex and cerebellum.[47–51] Leptin transport across the BBB occurs via a mechanism involving leptin receptor a (LepRa), and a second, not yet characterized, transport mechanism.[52]

Leptin regulates food intake and energy expenditure, improves insulin sensitivity, facilitates lipolysis, and inhibits lipogenesis.[53, 54] In addition, leptin plays a permissive role in neuroendocrine immune function.[55] Leptin is the most studied adipokine in association with brain structure and function, and has numerous effects on brain development[56] and potentially on brain health in cognition and aging. Leptin affects hypothalamic function, and learning and memory processes controlled by the hippocampus.[56–59] Experimental data show that leptin, and other adipokines, interact directly with hypothalamic nuclei, such as the arcuate nucleus, and regulate energy expenditure and food intake through production of orexigenic (NPY, agrp) and anorectic (aMSH) peptides.[60, 61] In addition, leptin appears to facilitate pre- and postsynaptic transmitter release and sensitivity, respectively, in hippocampal CA1 neurons.[58] This translates to improved performance related to spatial learning and memory function. Leptin may both shape the hypothalamus in the earliest stages of development and enhance cognition.[56] Leptin reduces beta-secretase activity in vitro, increases APOE-dependent Abeta uptake, and via lipolytic mechanisms, affects Abeta turnover in experimental models.[59]

Observations from human population studies in late life suggest that high leptin levels and high BMI are associated with lower dementia risk when measured within 10 years of clinical dementia diagnosis (Table 2).[56, 62] Longer term follow-up and cross-sectional studies show no association between leptin and dementia. Since leptin levels are higher among adults who do not develop dementia during the approximate 10 year prodromal phase, it has been suggested that leptin may be a cognitive enhancer when given at the time of cognitive impairment or dementia.[63] While leptin levels may trend with BMI in relation to dementia, given the ctrong correlation between them,, leptin may also have an independent role in health of the ageing brain.

**Adiponectin;—**Adiponectin (ACRP30) exists as complex multimeric isoforms comprised of High Molecular Weight (HMW) hexamers and trimers.[64] Adiponectin modulates inflammatory responses, energy expenditure in the CNS and periphery, central food intake, and a number of metabolic processes, including glucose regulation and fatty acid catabolism in the periphery. It is an effective insulin sensitizer, and circulating levels are inversely correlated with insulin resistance, metabolic syndrome, obesity, type 2 diabetes, and cardiovascular diseases.[65] HMW adiponectin or the ratio of HMW adiponectin to total adiponectin may be better indicators of insulin sensitivity than total adiponectin in obesity, diabetes, and cardiovascular disease.[64] While adiponectin is produced solely by adipose tissue, its receptors are not.[66] The peripheral effects of adiponectin are mediated mainly via

2 receptors, AdipoR1 and AdipoR2. Expression of these receptors is reported in adipose, brain, ovaries, endometrium, and placenta.[67] Both AdipoR1 and AdipoR2 are widely found throughout the CNS in brain microvessels, hippocampus, hypothalamus and brainstem in humans and rodent models.[51, 68–71] However, in humans, a 1000-fold lower cerebrospinal fluid (CSF)/serum adiponectin ratio is observed.[71] Thus, the origin of brain adiponectin is debated. Trimeric and low molecular weight adiponectins are detectable in the CSF of humans and rodents.[61, 69, 72] In combination with a lack of HMW adiponectin observed in CSF, this may imply that only smaller forms of adiponectin cross the blood brain barrier (BBB).[52, 69, 72]

The Prospective Study of Women in Gothenburg, Sweden show late-life (age 70 years and older) correlations of r= −0.29, between BMI and blood HMW adiponectin levels.[2] Similar correlations are observed in mid-life for women with or at risk for HIV infection.[2] Given the inverse association of adiponectin with BMI in adults, one may expect higher adiponectin levels to be associated with prevalent dementia and AD, since individuals with dementia tend to have lost weight prior to a clinical diagnosis, and subsequently weigh less than those without dementia.[9, 73] Of the studies summarized in Table 2, conclusions are mixed. Adiponectin is suggested to be a visceral adiposity marker [74, 75] and only moderately correlated with BMI (compared to leptin for example), and, as aforementioned, BBB transport mechanisms are unclear. Thus blood levels may not provide adequate indication of potential interaction between adiponectin and the brain.[76] Studies evaluating adiponectin in association with dementia, have reported on total adiponectin levels. Isolating HMW adiponectin and the smaller adiponectin fragments can present problems in the laboratory and inter- and intra-assay variability can be high,[64] making laboratory assay optimization difficult.

**Adipsin (Complement Factor D)—**Plasma adipsin is inversely correlated with age and positively associated with BMI, WHR, and overweight and obesity.[77] There are no observational human studies showing an association between adipsin and dementia. However, it is interesting to note that adipsin is elevated in animal models that have been treated with functional gamma secretase inhibitors.[78] However, gamma secretase inhibition elevates adipsin secretion from ileum crypt cells only (measured via higher levels of fecal adipsin), not from adipose tissue.[78]

## Thrombosis and Hypertension

**PAI-1—**In humans, plasminogen activator inhibitor-1 (PAI-1) is elevated in plasma of obese children, adolescents and adults,[79–82] primarily due to adipocyte secretion. PAI-1 influences vascular health by inhibiting fibrinolysis[83] via inhibition of tissue type plasminogen activator (tPA) and urokinase plasminogen activator (uPA).[83, 84] Furthermore, excess adipose tissue, especially central obesity in adults is associated with decreased fibrinolysis, possibly due to elevated PAI- 1.[85] Despite the association of peripheral PAI-1 with obesity, peripheral PAI-1 may not be capable of affecting brain processes, since no transport mechanism for PAI-1 across the BBB has been discovered. PAI-1 produced within the brain by microglia and astrocytes may regulate apoptosis, survival of neurites and

migration of microglia.[86–89] Moreover, *in vitro* studies show that PAI-1 contributes to the survival of neurites, axons and/or dendrites.[89]

There are several investigations of the interactions between PAI-1 and t-PA in the brain; however, the data are not clear. t-PA is produced by endothelial cells, mediates fibrinolysis, and crosses intact BBB.[11] As aforementioned, PAI-1 inhibits t-PA. Therefore, related to aging and dementia processes, the role of endogenous t-PA in the brain may be protective and includes clot dissolution or amyloid degradation.[90–92] It has also been shown that brain amyloid induces t-PA formation, thus increasing plasmin levels, which may lead to Abeta-42 degradation.[93] However, it has also been suggested that in the brain, t-PA may be neurotoxic, lead to tau hyperphosphorylation, destabilize microtubules, mediate amyloid toxicity, and shift apoptosis in a *stressed* brain, such as observed in strokes without clot formation.[93] Only one study was identified on PAI-1 and vascular dementia (Table 2); and a study of brain tissue from AD and control brains, revealed higher tPA mRNA expression in AD brains.[94]

## Inflammation

A variety of adipokines, particularly interleukins, are associated with inflammatory processes and implicated in dementia. Obesity is characterized by a chronic low inflammation state partly mediated via production of pro-inflammatory adipokines such as IL-1 and IL-6.[95] This has been reviewed extensively.[30] For example, IL-6 is an immunoregulatory cytokine that activates a cell surface signaling assembly composed of IL-6, IL-6RA, and the shared signaling receptor gp130, a common mechanism in inflammation.[96] IL-6 crosses the BBB by a saturable transport mechanism, entering both CSF and brain parenchyma. Approximately 50% of IL-6 in the CSF and 16% in brain parenchyma represent intact peripheral cytokine in male mice.[97] Since there is excessive degradation of IL-6 in the brain, the influence of peripheral IL-6 in the CNS is unclear; small amounts of intact IL-6 may be effective.[97] Rodent studies show that IL-6 is produced in the brain by glial cells, astrocytes and endothelial cells of the brain's microvessels.[98–100] In addition, amyloid deposition, and other neuropathological events in dementia are associated with local inflammatory events in the brain characterized by interleukin release, as well as release of TNF-alpha and other inflammatory agents.[30]

The hippocampus is particularly vulnerable to adverse effects of IL-6, affecting brain functions like synaptic plasticity and neurogenesis.[101–104] In the hypothalamus, IL-6 modifies leptin signaling and other anorexic signals.[105] An early onset of IL-6 elevation due to childhood and adolescent obesity, and its persistence in aging obese adults, has been proposed to negatively affect brain functioning by inhibiting neurogenesis, decreasing synaptic plasticity and subsequently disrupting learning and memory processes, particularly in the hippocampus, which increases the risk of cognitive deficits in obese individuals.[106] In middle-aged adults, higher plasma IL-6 levels are associated with lower hippocampal grey matter volume.[107] Studies of interleukins in association with dementia and mild cognitive impairment (MCI) are summarized in Table 2. While different interleukins are measured across studies, in general, they are suggested to increase with MCI and dementia.

MCP-1 in the blood is another marker of systemic inflammation. Insulin induces substantial expression and secretion of MCP-1 *in vitro* in insulin-resistant adipocytes, and *in vivo* in insulin-resistant obese mice (ob/ob).[108] The MCP-1 gene functionally resembles other genes that are sensitive to insulin in insulin-resistant states, such as PAI-1. MCP-1 is overexpressed in obesity and included in the family of genes like PAI-1 and SREBP-1c that continue to respond to exogenous insulin in insulin resistant mice and adipocytes. Mice remain sensitive to insulin in terms of PAI-1 gene expression, possibly because glucose homeostasis and PAI-1 gene expression are regulated by different insulin signaling pathways.[109] Consistent with this hypothesis, it has been demonstrated that in leptin-deficient states, insulin signaling in murine liver also diverges along two pathways; and the transcription factor SREBP-1c is another gene that remains sensitive to insulin in these IR mice.[108, 110] Similar selective insulin resistance also has been described in human and rodent muscle.[111, 112]

Collectively, these observations raise the possibility that in metabolic insulin resistance accompanied by hyperinsulinemia and obesity, the expression of certain insulin-responsive genes may dramatically increase in insulin target tissues. Higher levels of MCP-1 protein may induce adipocyte dedifferentiation and contribute to pathologic states associated with hyperinsulinemia and obesity, including type 2 diabetes. Increased MCP-1 mRNA in adipose tissue and MCP-1 protein in plasma are observed in genetically obese diabetic (db/db) mice and in wild-type mice with obesity induced by a high-fat diet.[113] Interestingly, plasma MCP-1 is correlated with severity of Traumatic Brain Injury (TBI) and an index of compromised axonal fiber integrity in the frontal cortex. MCP-1 is suggested as a marker of AD risk in TBI.[114]

## Growth Factors

**Hepatocyte Growth Factor (HGF)—**HGF, also known as scatter factor and hematopoietin A, is elevated in obese adults and adolescents.[115] *In vitro*, HGF secretion from adipocytes of obese versus lean individuals is greater.[116] HGF is a multifunctional trophic factor that binds to its receptor, MET, and activates a tyrosine kinase signaling cascade. While HGF is produced by neurons and nonneuronal cells, MET is highly expressed in neurons. During embryogenesis, HGF acts as a neural inducer, an interneuron motogen, axonal chemoattractant, angiogenic factor and as neuroprotective survival factor.[117, 118] In adults, HGF production is induced by ischemic injury[119] and AD.[120]

HGF enhances long-term potentiation[121] and improves memory deficits due to ischemia.[122] HGF mRNA is found in the brain; HGF-like immunoreactivity is observed in both the cerebral cortex and white matter; and confocal microscopy confirms that HGF is present in GFAP positive astrocytes and LN3 positive microglia cells, as well as rare scattered cortical neurons.[120] These studies also indicate that HGF is increased within senile plaques as a function of gliosis and microglial proliferation that occurs in association with AD.[120] HGF and other growth factors are also shown to accelerate neuroprotection, angiogenesis, and regeneration in the brain.[123] However, it is unclear the role of central versus peripheral HGF.

**Nerve Growth Factor (NGF)—**NGF is a neurotrophin secreted by adipose tissue, and associated with neuronal survival, differentiation of target neurons, and growth of nerve fibers and their guidance (tropism) toward the source of production.[124] With application for the brain and important for AD, is that NGF inhibits the amyloidogenic processing of amyloid precursor protein (APP) in vitro.[125, 126] The source of this NGF may be central or peripheral production, since NGF has been shown to cross the BBB. There are few studies evaluating circulating NGF with cognitive outcomes, although it is hypothesized that NGF repletion may be a treatment for AD via protection of the cholinergic system.[127] Serum NGF has been suggested to be lower among those with AD.[128] In contrast, CSF levels of NGF were higher in AD patients versus healthy controls.[129] NGF has also been proposed as a therapy for traumatic brain injury (TBI),[130] a risk factor for dementia.

In relationship to adiposity, a study in China assessing the correlations between anthropometric indices and adipokines, showed that WHR was associated with NGF (r = 0.48), and leptin (r = 0.53) levels. In this study, BMI and WHR were also correlated with mean HGF levels (r = 0.34 and 0.51, respectively) and PAI-1 levels (r = 0.42 and 0.56, respectively).[131]

## CONCLUSION

The association between adipokines and clinical dementia or cognitive impairment is largely unexplored, despite published epidemiologic data supporting associations between adiposity, measured via anthropometry, and dementia and AD.

### Considerations and Limitations

There are several considerations and/or limitations when evaluating the adipokine-dementia literature. 1) Adipokines are not secreted from adipose tissue only. While hundreds of adipokines potentially reflect the adipose tissue exposure and comprise the adipokinome, depending on the mechanisms of action of interest and tissues involved, different adipokines may play a role. In this case, adipokines may function as biomarkers for systems biology approaches or be good statistical markers of risk, but poor indicators of neurodegenerative or vascular mechanisms that are coupled to adipose tissue. Definitive dementia risk estimates remain to be elucidated for any adipokine. 2) Many adipokines are not associated with anthropometric measures of overweight and obesity. Reasons for this may be that anthropometric measures are not be good estimates of amount of adipose tissue during adulthood; adipose tissue is not a primary source of these particular adipokines; or adipokine release is not associated with quantity of adipose tissue. 3) Adipokine functions in the periphery are not necessarily similar to those in the brain, e.g., PAI-1. This has challenged understanding of adipokine actions in each compartment, as well as requiring more research on their movement across the BBB and interactions with other adipokines. 4) There are sex and race/ethnic differences in adult body composition and adipokine levels, and these differences do not correspond to differences in dementia occurrence.[132, 133] 5) Potential influencers of blood adipokine levels, such as medications, type of metabolic syndrome (e.g., in type 2 diabetics, adults with HIV infection), degree of overweight and obesity, and other factors are not well understood. 6) The trajectory of BMI over the life course

suggested in Figure 3,[10] and variations in the relationship of BMI to general aging, dementia, and mortality,[134] emphasize the importance of age of BMI measurements and proximity to occurrence of clinical dementia onset, for example, mid- versus late-life. While higher levels of adult BMI may increase risk for chronic neurodegenerative and vascular diseases of aging, some studies show that the direction of the BMI-dementia relationship changes direction, and declines, later in life.[2, 7, 10] Perhaps higher BMI, and more central adiposity, are mid-life markers of vascular risk dominating the dementia risk equation, while declining, and lower levels of BMI, denote predominant neurodegenerative events in latest life. This latter point is illustrated by data from the National Alzheimer Coordinating Center (NACC) in U.S., showing that among those with MCI, a higher baseline level of BMI is associated with a worse clinical dementia rating, but greater subsequent body weight decline is associated with faster clinical progression.[9] Not all observations, however, evidence a similar trajectory. The Gothenburg Birth Cohort Studies showed that there is lesser BMI increase prior to the inflection point indicated in Figure 3, followed by a similar rate of BMI decline among those with and without dementia.[10] This suggests different biological mechanisms, perhaps mediated by adipokines, underlying the evolution of aging and dementia, as well as heterogeneity in the dementia outcome reflecting both vascular and neurodegenerative processes in the brain. 7) Survival bias may be influencing observed mid-life, late-life obesity-dementia associations, since competing risk analyses tend to show that those who are overweight or obese die before the age at which they are at risk for dementia.[5, 135] However, this may change as survivorship with multiple co-morbidities, many associated with overweight and obesity, increases. These considerations can be best addressed, and limitations overcome, by additional research.

## In summary

The focus of this review has been on adipokines associated with excess adiposity, a risk factor for late-onset dementia. We are unaware of published data on changes in adipokine levels over the life course. As additional chapters on the epidemiology and biological mechanisms linking adipokines and dementia are written, there will be greater understanding of inter- and intra-individual differences in adipokine metabolism; dysregulation of metabolism that occurs with aging, neurodegeneration and/or dementia; and differences in metabolism given differences in diet, physical activity, race/ethnicity and genetics. For example, whether changes in body composition with physical activity interventions among elderly ‘improve’ the adipokine profile for the aging brain, is unknown. Given the vast number of adipokines, one approach for exploration could be directed toward their cumulative role as classes of adipokines versus single adipokines. In addition, therapeutic strategies related to the use of single or combined adipokines may be an avenue for exploration in prevention of cognitive impairments and dementia. This has been suggested for leptin.[63]

Given the immense secretory capacity of adipose tissue, the often acute nature of the adipose secretome in response to various stimuli, and changing body composition with aging, it remains a challenge to unravel the influence of this organ over the life course. From bench to bedside, adipokines as biomarkers may enhance understanding of late-onset dementia risk over the life course, as well as the clinical progression of prodromal and manifest dementias.

This will allow for identification of populations at risk, and for the design of better clinical trials to target vascular and metabolic risk associated with adipose tissue both centrally and peripherally.

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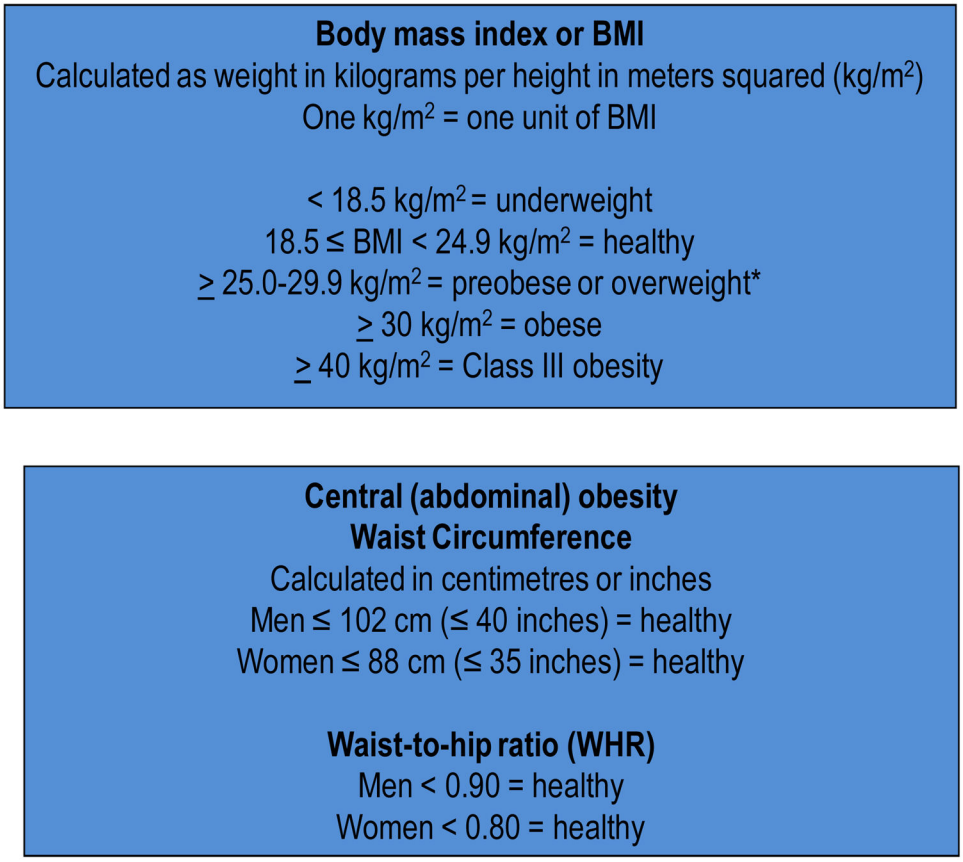


**Figure 1.**
Anthropometric measures and corresponding cutpoints of overweight and obesity in adults.

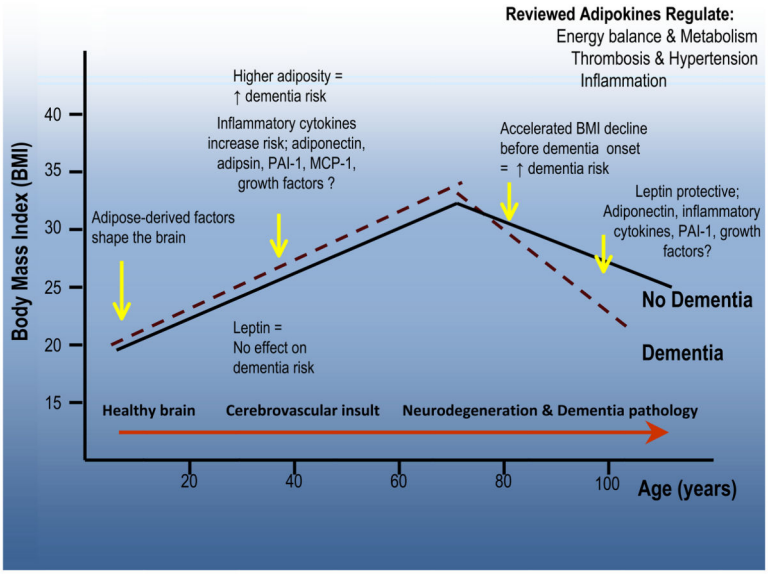


**Figure 2.**

WAT is an endocrine organ that secretes hundred of adipokines that influence multiple physiological processes to maintain homeostasis and respond to injury. WAT exists as subcutaneous, visceral and retroperitoneal depots, and has a stromal layer containing ADSCs. Amount of WAT is measured crudely in humans as BMI. BMI, on average, exhibits a dynamic trajectory with ageing. This trajectory is characterized by an adult life increase, followed by later life decrease. Generally, higher BMI or BMI increase is associated with the vascular risk that is common among overweight and obese adults. BMI decrease is associated with ageing and neurodegeneration. This reverse association is reflected in changing risk associations commonly observed between BMI and dementia/AD over the life course.

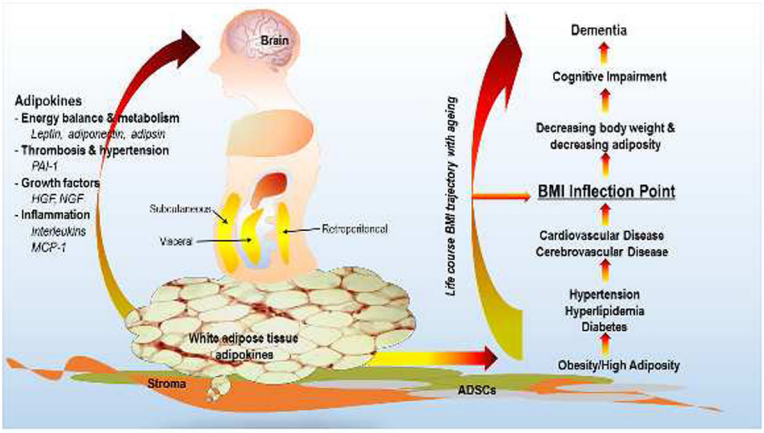


**Figure 3.**

The trajectory of BMI over the life course by chronological age and potential roles of adipokines. Observational data suggest that higher levels of adult BMI may increase risk for late-onset dementia. Mid-life inflammatory cytokine levels measured in blood are higher in relationship to dementia. A null association with blood leptin levels has been reported. The BMI-dementia association changes direction later in life. BMI declines such that lower levels of BMI are observed among those with dementia compared to those without. During this period, lower blood leptin levels have been reported and reports on other adipokines are mixed. Other BMI trajectories have been observed, suggesting perhaps different adipokine-related mechanisms underlying the evolution of aging and dementia, as well as heterogeneity in the dementia outcome.

## Table 1

A sampling of adipokines involved in energy balance and metabolism, inflammation, and thrombosis and hypertension and that may have relevance for AD[119]

| |
|---|
| *Energy balance and metabolism* |
| Adiponectin |
| Adipsin (complement Factor D) |
| Apelin |
| Chemerin |
| Dipeptidyl peptidase-4 (DPP-4) adenosine deaminase complexing protein 2 or CD26 |
| Leptin |
| Lipocalin |
| Omentin |
| Resistin |
| Retinol binding protein-4 |
| Vaspin |
| Visfatin, also pre-B cell enhancing factor (PBEF) |
| *Inflammation* |
| IL-6 |
| IL-1 |
| IL-10 |
| IL-8 |
| monocyte chemotactic protein-1 (MCP-1) |
| TNF-alpha |
| *Thrombosis & hypertension* |
| Serum amyloid A (SAA) |
| CRP |
| PAI-1, total, active |
| Proteins of the Renin Angiotensin System |
| *Growth factors* |
| NGF |
| HGF |
| *Brown fat* |
| fibroblast growth factor-21 |
| interleukin-6 |
| insulin-like growth factor-1 |

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**Table 2**

A selection of epidemiologic studies associating blood adipokine levels with clinical dementia, AD or cognitive impairment.

| Study Name | N | Avg age (y) | Obs time | Study Type | Results |
|---|---|---|---|---|---|
| **Leptin** | | | | | |
| Prospective Population Study in Gothenburg, Sweden [32] | N=1462 | 38–60 | 24y | Long | No association of mid-life leptin with late-onset dementia in women (multivariate adj HR 1.01 95% CI 0.98–1.03, p=0.620) |
| Framingham Heart Study, USA[120] | N=785, no dementia | 79 +/−5 | 8.3y | Long | Higher leptin levels associated with lower risk of incident dementia and AD in multivariable models (HR per 1SD log leptin, 0.68, 95% CI, 0.54–0.87, for all-cause dementia; HR per 1SD log leptin, 0.60, 95% CI, 0.46–0.79, for AD). A 1SD elevation in plasma leptin level associated with higher total cerebral brain volume (p=0.005) |
| Study of Osteoporotic Fractures[121] | N=579 no dementia | 82.6 | 5y | long | Among women with BMI <25 kg/m$^2$ a 1SD difference in log leptin (0.91 ng/mL) was associated with 32% lower odds of dementia/MCI (*OR* =0.68; 95% *CI* = . 46,0.99) compared to those with BMI ≥ 25 kg/m$^2$ |
| Health ABC Study, USA[122] | N=2871 | 73.7 | 4y | Long | Compared to those in the lower leptin groups, elders in the high leptin group had less likelihood of cognitive decline, OR= 0.66 (95% CI 0.480.91). The lowest leptin group: mean leptin 2.3 ng/ml (SD 1.0 ng/ml), range 03.7 ng/ml; the middle leptin group: mean leptin 10.9 ng/ml (SD 5.2 ng/ml), range 3.722.8 ng/ml; the highest leptin group: mean leptin 32.3 ng/ml (SD 8.0 ng/ml), range 22.84.7 ng/ml. |
| Case-control study, in Japan[123] | N=60, 20 Vascular Dementia, 40 age-matched controls | 79 | 0 | XS | Average leptin levels not different between VaD and controls (5.2 ± 0.9 vs 4.5 ± 0.6 ng/ml, p=0.548) |
| **Adiponectin** | | | | | |
| Framingham Heart Study[124] | N=826 | Median 76 | 13y | | Total adiponectin levels associated with increased all- cause dementia risk (HR 1.29; 95% CI, 1.00–1.66; P=0.054) and AD (HR 1.33; 95% CI, 1.00–1.76; P=.050) in women; baseline adiponectin > median at higher risk for all cause dementia (HR 1.63; 95% CI, 1.03–2.56; *P*=.04) and AD (HR 1.87; 95% CI, 1.13–3.10; =.01) |
| Rochester Epidemiology Project, USA[125] | N=890 no dementia | Median 80 | 0 | XS | Total adiponectin not related to MCI in a case-control study; average level MCI 14.4 (9.8, 19.6) mg/L vs no MCI: 14.5 (9.8, 19.6) p=0.97 |
| Case-control study, in Japan, Vascular dementia vs age-matched controls[123] | N=60, 20VaD, 40 controls | 79 | 0 | XS | Average total adiponectin levels not different between VaD and controls (14 ±2 vs 12 ± 1(mcg/ml), p=0.387) |
| Clinical case series in Japan[126] | N=28 controls, 18 MCI, 27 AD | 74.7 | 0 | XS | Higher plasma adiponectin in MCI and AD compared to controls (p<0.05), and higher CSF adiponectin in MCI compared to controls (p<0.05) |
| Clinical case series of MCI and AD, Brazil[127] | N=157; 41 AD, 65 MCI, 51 controls | 71 | 0 | XS | Lower total adiponectin levels among those with MCI and AD (F = 18.2, df = 2, p=0.001); adiponectin did not predict progression of MCI to AD |
| **Interleukins** | | | | | |
| Framingham Heart Study[128] | N=691 | 79 | 7y | long | Compared to the lowest tertile, individuals in the top two tertiles of PBMC production of IL-1 at higher risk for AD: for tertile 2, HR 2.84, 95% CI 1.09, 7.43, p=0.03, for tertile 3, HR 2.61, 95% CI 0.96, 7.07, p=0.06. |

| Study Name | N | Avg age (y) | Obs time | Study Type | Results |
|---|---|---|---|---|---|
| Health ABC Study[109] | N=665 high, N=1967 low inflammation | 73.5 | 4y | long | Among those with metabolic syndrome, “high inflammation” defined as higher than the median for both CRP (≥2.0 mg/L) and IL-6 (≥2.0 pg/mL) associated with risk of developing cognitive impairment (RR = 1.66, 95% CI 1.19–2.32). |
| Rochester Epidemiology Project, USA[125] | N=890 no dementia | Median 80 | 0 | XS | Total IL-6 not related to MCI in a case-control study; average level MCI 4.8 (2.5, 14.0) pg/ml vs 4.0 (2.4, 11.0), p=0 .35 |
| Dutch family study[129] | N=206 children of AD, N=200 children of no AD | 50.3 | 0 | XS | In middle-aged children of late-onset AD cases, higher mean production capacity of IL-1beta (13 091 (380) vs 10 548 (580) pg/ml P < .001), IL-1beta to IL-1ra ratio (1.38 (0.06) vs 1.10 (0.05) P < .001), IL-6 (96 031 (2809) vs 88 226 (2827), P = . 04); production capacity after stimulation with 10-ng/mL lipopolysaccharide. |
| Case-control study, in Japan, Vascular dementia vs age-matched controls[123] | N=60, 20VaD, 40 controls | 79 | 0 | XS | Average IL-6 levels suggested higher among VAD vs controls (7.5 ± 1.7 vs 4.6 ± 0.7 pg/ml, p= 0.078) |
| **PAI-1** | | | | | |
| Case-control study, in Japan, Vascular dementia vs age-matched controls[123] | N=60, 20VaD, 40 controls | 79 | 0 | XS | Average PAI-1 levels suggested higher among VaD vs controls 26 ±5 vs 18 ±2 ng/ml, p=0.064 |

Abbreviations: Obs, observation; avg, average; y, years; RR, relative risk; HR, hazards ratio; OR, odds ratio; VaD, Vascular dementia; vs, versus; Long, longitudinal; XS, cross-sectional;