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Insulin Resistance, Cognition, and Alzheimer's Disease

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Abstract

Chronic diseases of aging are increasingly common. Dementia, often due to multiple etiologies including Alzheimer's disease (AD), is at the forefront. Previous studies reported higher rates of dementia among persons with diabetes, yet less is known about how insulin resistance relates to cognition. We examine recently published data on the relation of insulin resistance to cognition and AD and discuss remaining knowledge gaps in the field. We conducted a structured review of studies over a five-year period, investigating insulin and cognitive function in adults with a baseline mean age ≥65 years. Our search yielded 146 articles, of which 26 met the predetermined inclusion and exclusion criteria. Among the nine studies which specifically examined insulin resistance and cognitive dysfunction and/or decline, eight studies suggest an association, but some only in sub-analyses. Results were mixed in studies relating insulin to structural and functional changes on brain imaging, and data on intranasal insulin for cognition remain unclear. We review gaps in the field and propose future avenues to elucidate the impact of insulin resistance on brain structure and function, including cognition, in persons with and without AD.

Keywords

Insulin; diabetes; cognition; dementia; Alzheimer's disease

INTRODUCTION

Advancements in public health and healthcare in the last century have led to an increase in the average life expectancy, but chronic diseases of aging are now more common. Among the most disabling conditions in aging is dementia, often due to combined Alzheimer's disease (AD) and one or more other neuropathologies. With few treatments and ineffective preventive approaches, biomedical researchers are working to better the understanding of potentially modifiable dementia risk factors. Diabetes has emerged as a modifiable risk factor and has been associated with cognitive impairment, cognitive decline, and dementia, including dementia attributed to AD. Several studies have now shown a 50% increase in dementia risk among persons with diabetes, compared to those without (1, 2). Furthermore, diabetes appears to be associated with cognitive decline in some cognitive domains more than others, notably executive function, working memory, and attention (3–6).

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The global prevalence rate of diabetes was 10.5% in 2021, and is expected to rise to 12.2% by 2045 (7). Type 2 diabetes is the most prevalent form, particularly among older persons, and a large body of literature has examined its' relation to cognition in aging. Insulin resistance is a key defining feature among many persons with type 2 diabetes and is the focus of this paper. Insulin resistance can easily be assessed with a simple blood test, for instance by using the calculated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (8, 9). However, the role of insulin resistance in the development of dementia and cognitive impairment, using HOMA-IR or otherwise, is not well-understood (10–15). Understanding the pathophysiology underlying the relationship of insulin sensitivity/resistance, diabetes, and cognitive dysfunction is important to identify potential molecular pathways and focus diabetes management efforts and dementia therapeutic targets. The objective of this paper on insulin resistance and cognitive function is to review the recent published data derived from human studies, including clinical trials, and offer a perspective on the ongoing knowledge gaps and future directions in the field.

METHODS

We conducted a review of the published literature on April 14, 2021, using PubMed. The search terms were: "Insulin [title] and (brain or cognition or dementia or Alzheimer's disease)." Inclusion criteria were: publication date in the last five years, and baseline ages 65+ years. We chose to focus on studies in older persons, given that both diabetes and dementia are significantly more common among older populations. We reviewed citation titles, abstracts, and full manuscripts when needed, to exclude publications which were not of original research, not directly relevant to the brain and insulin pathways, or with a small sample size and limited power to detect associations (<75 persons in total).

RESULTS

Using the search strategy, 146 articles were retrieved. Upon review of every citation, we excluded 120 articles that were not directly relevant to this review: 28 examined other diseases (type 1 diabetes, cancer, trauma, Down syndrome, atherosclerosis, psychiatric disorders, frailty, sleep disorders, or diseases of the heart, lungs, liver, eyes, or rheumatologic system), 22 focused on other neurological diseases (stroke, Parkinson's disease, Huntington's disease), and 22 were related to other medical topics (medications/supplements, overtreatment, post-operative issues, exercise, symptomatology, genetics/epigenetics, public awareness or individual perspectives, feeding behavior and other). 9 were other types of articles (case report, analytic methods, opinion piece, review, not written in English), and 7 were using animal models. An additional 32 were excluded because of small sample sizes (fewer than 75 subjects) or a baseline mean or median age <65 years (not target age range for conditions of interest). Thus, 26 articles were included in this review.

Part A: Insulin Resistance and Cognition

Cross-sectional studies—Four cross-sectional studies examined insulin resistance, as measured by serum insulin or HOMA-IR, and cognition based on performance (see Table 1). The first two studies assessed cognition using a single test, while the other two utilized a more extensive neurocognitive test battery (two individual tests or more).

A population-based study (16) of 1028 cognitively-normal participants tested cognitive performance using the Digit Symbol Substitution (DSS) subtest of the Wechsler Adult Intelligence Scale, a sensitive measurement of cognitive dysfunction (17). In multivariable linear regressions adjusted for socio-demographics, clinical lab results, and comorbidities, higher insulin resistance as measured by HOMA-IR was associated with worse DSS performance. This result suggests that a simple test of perceptual speed may be informative in clinical practice to detect cognitive dysfunction in older persons with insulin resistance. Strengths include the sample size, representation of the US population, and adjustments for multiple covariates. However, the only cognitive data was the DSS, and there was no consideration for other cognitive domains, mild cognitive impairment (MCI), AD dementia, depression, or *APOEε4,* which is an effect modifier (18).

In a study of 212 patients with type 2 diabetes (19), results showed fasting plasma insulin levels and HOMA-IR were risk factors for lower Mini-Mental State Exam (MMSE). This study shows that greater insulin resistance is associated with worse cognitive performance on a global measure of cognition commonly used in clinical practice. But, this single-institution study was limited to hospitalized patients with diabetes, and cognition was evaluated using only a general crude test.

Secondary analysis of a clinical trial of persons with cognitive impairment utilized a more comprehensive cognitive test battery (20). In 160 participants with vascular Cognitive Impairment, No Dementia (CIND) (21), cognition was assessed using a 45–60 minute battery testing for executive function, verbal memory, and visual memory. Individual tests were used to form composite scores for each cognitive domain. Higher HOMA-IR and plasma leptin levels were associated with lower executive function, suggesting insulin resistance may mediate the relation of obesity to executive function. While the study has expanded cognitive testing and collected multiple metabolic measurements, it has limited generalizability since the participants were obese and sedentary.

A brief report, which showed no difference in insulin resistance between AD (n=40) and controls (n=40), had important weaknesses in the small sample size, biased selection for the controls, lack of baseline characteristics, and limited analyses (22). Interestingly, higher insulin levels correlated with more severe dementia for the subgroup with AD, raising the possibility that insulin resistance may be associated with worse cognition even in individuals with already advanced dementia.

In summary, three (16, 19, 20) of four cross sectional studies suggest that peripheral insulin resistance is inversely associated with cognitive performance on individual tests such as the DSS and MMSE, but also on more comprehensive cognitive testing of executive function. While the fourth study (a brief report) did not find a relation, it had important limitations (22). Two (19, 20) of the four studies measured plasma insulin levels, which were associated with cognitive dysfunction; but whether insulin resistance is involved was unclear. In conclusion, even though the four studies are limited by their cross-sectional study design, overall, they appear to indicate that there is an association between higher insulin resistance with lower levels of cognition.

Longitudinal studies—Longitudinal study design provides the opportunity to assess change in cognitive performance over time and inform on a meaningful health outcome. We identified five studies utilizing a longitudinal design following participants for more than 5 years and examined the relationship between insulin resistance, as assessed by HOMA-IR, with change in cognitive function (see Table 2).

A prospective case-control study of 477 participants (335 with diabetes and 142 without) were divided into three groups based on HOMA-IR (23). Authors examined the change of MMSE and Alzheimer's Disease's Assessment Scale-Cognitive subscale (ADAS-Cog) between baseline and annual follow-up examinations for 7 years. Analysis included 444 subjects, with high follow-up rate (93%). Using multiple regressions, those with the highest insulin resistance had lower MMSE scores and higher ADAS-Cog, suggesting that only high levels of insulin resistance were associated with severe cognitive impairment. This implies that perhaps there is a point at which insulin resistance will negatively affect cognition. A major limitation is the absence of a control group without diabetes. Also, analyses did not consider all cognitive data collected over the years by using mixed effects models. Furthermore, participants were observed to switch between assigned HOMA-IR groups during the study, which was not considered in the analyses.

In 269 adults without dementia from the Cardiovascular Risk Factors, Aging, and Dementia Study, serum insulin, glucose, and HOMA-IR were measured only at baseline (24). Participants were examined at both baseline and 7-year follow-up for global cognition (MMSE), episodic memory, executive function, verbal expression, and psychomotor speed. Adjusted multivariable linear regressions showed no associations between insulin resistance or serum insulin with cognition. However, exclusion of incident dementia cases (n=19) at 7-year follow-up showed that higher baseline HOMA-IR was related to worse performance in global cognition and psychomotor speed. Also, increased insulin levels were related to worse global cognition. There was no significant relationship between serum glucose and other cognitive domains. Detailed cognitive assessment and long follow-up were strengths but having one time point of serum data and using 10-year frozen samples were limitations.

Another study used similar variables with different indices. This prospective cohort, involving 1544 Japanese men without type 2 diabetes or dementia, assessed baseline insulin resistance using HOMA-IR, McAuley, and combined indices (25). McAuley index utilizes fasting insulin and triglyceride values to estimate insulin resistance, but the authors do not explain how combined indices were created (26). The incidence of total dementia and AD was examined 3 years after initial examination, using physician consensus and the Cognitive Abilities Screening Instrument score (27). Subjects were also evaluated for *APOEε4*. In separate adjusted models, HOMA-IR was not associated with incident dementia or AD, but insulin resistance as measured by a McAuley index ≤5.8, was associated with decreased odds of incident dementia (OR=0.61; 95%CI:0.39–0.94). The authors conclude that blood measures of insulin resistance were related with decreased dementia risk. Though insulin resistance as measured by HOMA-IR did not show significance, the McAuley index showed association with dementia, suggesting that the triglyceride levels in the McAuley index formula may be relevant to cognitive decline and the development of dementia. Insulin resistance measurements were not assessed over time and may have fluctuated

in between examinations. Having subjects with similar age, same sex, and ethnicity in a longitudinal timeline is a strength of this study, but these subject characteristics also reduce generalizability.

In a subsample of persons participating in a prospective study, 442 individuals with normal baseline cognition were followed for 6 years (28). HOMA-IR, HbA1C, fasting insulin, and lipid profile were obtained at two visits. Cognition was measured with the Korean version of MMSE. In an adjusted linear regression, elevated insulin resistance (fully adjusted model, p=0.004), and fasting insulin (p=0.001), were associated with a greater decline in MMSE. These results further support the association between insulin resistance and reduced global cognition. Study strengths include cohort size and consideration of multiple covariates, including *APOEε4* status, education, and diabetes. However, the study was limited by having a single measure of cognition and only two time points.

A larger study included 1759 women, who had normal baseline cognition and completed examinations over a 15-year follow-up (29). Participants were assessed for risk factors of metabolic syndrome (MetS: BMI >30kg/m^2, elevated blood pressure, impaired fasting plasma glucose, low HDL, and elevated triglycerides), HOMA-IR, and two short cognitive tests, the Category Fluency Test and Short Blessed Test (30, 31). The odds of cognitive dysfunction on the Category Fluency Test were nearly three times higher in those with all five MetS risk factors compared to those with none (OR=3.09; 95%CI:1.09–8.69). Subjects with insulin resistance had a higher likelihood of cognitive dysfunction with verbal fluency than those without insulin resistance (OR=1.47; 95%CI:1.09–1.99). Overall, the study showed that individuals with poorer metabolic profiles had greater likelihood of developing cognitive dysfunction, suggesting that having higher number of risk factors will increase cognitive impairment, compared to having fewer factors. The large sample size and similarity between the participants' study group and nonparticipants in the population were strengths. The absence of repeated plasma data and a limited cognitive assessment were limitations. *APOEε4* status was a confounding variable that was acknowledged but not considered in analyses.

In conclusion, three (23, 28, 29) of five longitudinal studies suggest that insulin resistance, measured by HOMA-IR, is associated with worsening performance on measures of global cognition (most often using the MMSE), and possibly the specific cognitive domain of verbal fluency. The other two (24, 25) of the five studies showed an association between insulin resistance and cognition in subanalyses, with one showing an association with psychomotor speed after exclusion of incident dementia cases (24), while another showing an association using McAuley index of insulin resistance (25). Furthermore, two (24, 28) of the five longitudinal studies specifically examined plasma insulin levels, and both showed that insulin itself was also associated with lower global cognition. Taken as a whole, the longitudinal studies suggest that insulin resistance and levels are associated with worse global cognition and possibly specific cognitive domains, though inconsistently. Results may have been affected by several sources of bias, including selection bias because cognitive impairment may negatively influence study retention. Though investigators examined baseline and follow-up cognitive measurements (and/or plasma measures), some studies that did not analyze these data over more time points raise the issue of information bias. For

example, cognitive data are prone to various sources of variability, random and non-random (e.g., practice effects with improved scores over time).

Part B: Insulin Medication and Cognition

A line of research in relating insulin resistance to cognition is whether the administration of insulin improves cognition in persons without diabetes. Indeed, intranasal insulin delivery is a relatively new strategy which may restore brain insulin function for older adults with cognitive impairment by circumventing the blood brain barrier without affecting peripheral insulin levels. Using our pre-defined search criteria, we found two recent clinical trials which utilized intranasal insulin therapy to examine change in cognitive performance (see Table 3).

Leveraging the Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF120), a placebo-controlled clinical trial investigated the effect of intranasal insulin (INI) on plasma levels of insulin receptor substrate-1 (IRS-1), a previously described biomarker of AD and brain atrophy (32, 33). IRS-1 has multiple phosphotypes, of which higher pS312-IRS-1 and lower pY-IRS-1 suggest insulin resistance (34). As part of the parent clinical trial involving participants without diabetes, 35 subjects with AD and 56 subjects with MCI were randomized to 20 or 40 IU of INI or placebo for 4 months. Neither dose of INI was associated with a change in total IRS-1. However, patients treated with 20 IU of INI showed positive correlations with certain phosphotypes (pS312-IRS-1 and pY-IRS-1), which were associated with worse cognitive performance on ADAS-Cog. Interestingly, in post hoc sensitivity analysis, this correlation was only observed among *APOEε4* non-carriers, whereas the 40 IU INI group was unaffected regardless of *APOEε4* status. Individuals with low genetic risk for AD who received low dose INI had insulin resistance compared to individuals who received a higher dose of INI. These results are challenging to interpret. One possible explanation is that small doses of INI could already be sufficient to induce insulin resistance and worsen cognition. Another possibility is that higher doses of INI may have little additional effect and that a plateau of insulin resistance is reached with no more effect on cognition, regardless of the *APOEε4* status. While there is indication of relation of insulin resistance based on phosphotypes with a measure of cognition, the small sample sizes, short study duration, and lack of additional cognitive testing are weaknesses.

In another trial, 27 sites recruited 289 persons without diabetes but with either MCI or AD (35). This double-blinded placebo-controlled trial examined the efficacy of daily 40 IU of INI for 12 months, followed by a 6-month open-label extension phase. The first intranasal device used by the first 49 participants was deemed unreliable midtrial. A second intranasal device was utilized by the other 240 participants, who were determined as the primary intention-to-treat population. ADAS-Cog was assessed at baseline and 3-month intervals while MRI, insulin, and biomarkers from cerebrospinal fluid (CSF; specifically Aβ42, Aβ40, total tau [t-tau], and tau p-181), were measured at baseline and 12 months. The insulin-treated group using the first device had improved ADAS-Cog scores at 6 months during the blinded phase (p=0.01) and at 15 and 18 months during the open-label phase (p=0.004 and p=0.02, respectively). Individuals using the second device showed no cognitive improvement. CSF biomarker changes were noted, despite no significant

differences in individual biomarkers only in those using the first device. Volume loss in the greater entorhinal cortex was found only in the insulin-treated group using the first device (p=0.003). Hippocampal volume loss was present only in those using the second device (p=0.03). Upon combining devices, the total group showed no changes for any outcome except entorhinal cortex volume loss at 12 months, but its impact on cognition is not yet known. The trial had moderate adherence rates with the first device, which had been used with good reliability in former studies by the same authors (36, 37). Despite showing significant results for those using the first device, the small sample reduced the power of the study. The second device had >90% adherence rates for insulin and placebo arms in blinded and open-label phases but had never been used in previous AD trials. Despite good adherence and a multisite trial, the use of two devices with different delivery mechanisms is a major limitation of this study. Cognitive improvement using the first device suggests that an intact insulin signaling cascade may play a role in cognition, but the consequence of volume loss on cognition is currently unknown and will need further examination. The study showed potential in the initial results before switching devices, and further study with the first device could provide stronger evidence of cognitive improvement with intranasal insulin.

To summarize, results of these medication studies were mixed. While it seems that either higher doses of INI may improve or have no effect on cognition, the results may be at least in part, because the methodology differed regarding measures of global cognitive function, optimal drug dosage, and form of medication administration. Larger studies, especially in a clinical trial setting, are needed to better understand the true effects of intranasal insulin on cognitive function, and several are underway.

Part C: Insulin and *in-vivo* markers of brain structure and function

Studies of structural and functional neuroimaging—Neuroimaging allows for the assessment of brain structure and function, including regional cerebral glucose metabolism by brain PET scanning. The following four MRI and PET studies explore how insulin levels or insulin resistance affect the structure, connectivity, or glucose metabolism in the brain.

Enlarged perivascular space (EPVS) are commonly found on MRI with aging, especially in the basal ganglia, and have been found to contribute to cognitive impairment and decline (38, 39). A cross-sectional study examined the correlation between insulin resistance and EPVS among 235 participants without diabetes or cognitive impairment, who were admitted to a hospital over four years (40). EPVSs in basal ganglia were counted by neuroradiologists, based on size and shape, and stratified by severity (mild vs moderate/severe). Insulin resistance (by HOMA-IR) was associated with an increased risk of moderate/severe EPVSs, after controlling for cardiovascular risk factors (OR=3.53; 95%CI:1.63–7.64). Excluding persons with diabetes, and no other structural MRI data or blood measurements of glucose or insulin, were limitations. Nonetheless, the findings imply that insulin resistance may be a contributing factor to structural changes in the brain among a healthy group of older persons.

In a longitudinal study of MCI (n=50) and cognitively-normal adults (n=60), data from clinical evaluations, neuropsychological testing, and functional MRI (fMRI) scans were

collected (41). Gene sequencing for exons involved in brain insulin resistance was performed. Cognitive testing evaluated general cognition (MMSE), episodic memory, visuospatial function, information processing speed, and executive function at both baseline and follow-up of maximum 35 months. Investigators performed genetic association analyses with single nucleotide polymorphisms to determine their cognitive relevance, and a brain network was subsequently constructed with various regions of interest. Multivariate linear regressions examined the relationship between network connectivity and cognitive decline. The MCI group had more regional deficits in connectivity on fMRI, as characterized by disconnections (presumed to be synaptic) in the cerebellum-frontal-temporal regions, compared to the cognitively-normal group. This suggests that certain genes of insulin resistance may lead to neuronal disconnections in the brain that further impair cognition. Some limitations include a large age range (54 to 80 years) and only two time points to measure cognitive change, but this novel study raises interesting avenues for future work.

Two PET studies examined cerebral glucose metabolism (CMglu) in 205 cognitively-normal adults without diabetes for the association between fasting blood insulin and HbA1c levels with Aβ positivity and neurodegeneration (42). In multiple linear regressions, decreased insulin levels were associated with increased Aβ positivity. Insulin was also positively associated with CMglu in AD-related brain regions, but not with cortical thickness. While HbA1c was not associated with Aβ, it was associated with neurodegeneration positivity rate in selective regions typically affected by AD. This study suggests that insulin levels may contribute to AD pathology, even among cognitively normal adults without diabetes. Further research into the associations among persons with cognitive impairment (MCI and dementia) and diabetes, and with longitudinal data, are needed.

The same research group examined basal insulin levels and resting-state CMglu in specific brain regions among 234 cognitively-normal adults without diabetes (43). After adjustments for *APOEε4*, glucose, cardiovascular risk factors, and demographics, there were positive associations between blood levels and CMglu in specific cerebral cortices and hippocampus, especially the right posterior hippocampus, parahippocampal region, and angular gyrus. There was correction for multiple comparisons and many covariates were considered, but it is unknown how the association between insulin and glucose metabolism would change in an active state or with comorbid conditions.

Overall, it appears that insulin resistance is associated with changes in brain structure and metabolism. More severe EPVS and decreased regional connections by fMRI may reveal underlying mechanisms for cognitive impairment induced by insulin resistance. Elevated blood or brain insulin indices also are associated with increased cerebral glucose metabolism in cerebral cortices and hippocampal regions, which may be involved in cognition as well. Some findings are regional, with increased blood insulin being associated with cerebral glucose metabolism in hippocampal regions specifically.

Other *in-vivo* studies—Insulin resistance reduces transport of insulin across the blood brain barrier, and greater CSF insulin levels reflect central (brain) insulin resistance (44). A study explored the association between CSF insulin levels with cognition and CSF AD biomarkers, amyloid-β and tau (45). Persons with subjective cognitive impairment (n=45),

MCI (n=44), or AD dementia (n=49) from memory clinics, completed neuropsychological tests for global cognition (MMSE) and memory. There was no association between CSF insulin and cognitive performance or CSF AD biomarkers in any group. However in stratified analyses, higher CSF insulin was associated with cognitive impairment, and with higher CSF tau (t-tau and p-tau) among women and in individuals without *APOEε4*. Limitations include the sample size, absence of fasting state prior to sample collection, and lack of blood samples. Despite these weaknesses, the study suggests that CSF insulin levels are affected by sex and *APOEε4*.

A study examined the association between insulin resistance and pancreatic β-cell function (HOMA-B) with cognitive performance and AD biomarkers, specifically CSF amyloid-β, tau, and hippocampal burden (46). A cohort of 1264 individuals were either cognitively-normal (n=905), with MCI (n=156), or with AD (n=203). In adjusted regression analyses, HOMA-IR increased in the AD group compared to the cognitively-normal group. HOMA-B was elevated only in the MCI group in post hoc analysis. Within the cognitively-normal group, HOMA-IR was inversely associated with verbal episodic memory, executive function, and global cognition, and there was a positive association with CSF t-tau and p-tau. HOMA-B was also weakly associated with executive function and global cognition in the cognitively-normal group and showed no changes in CSF biomarkers. After stratifying by sex, HOMA-IR and HOMA-B increased in MCI or AD groups in women only, in keeping with the prior study (45). The study had a large cohort and findings suggest increased insulin resistance may play a role in cognitive impairment and increased CSF tau levels in older adults.

Overall, these studies show that central insulin resistance as reflected by higher CSF insulin or HOMA-IR, is associated with worse cognitive performance and more AD pathology (elevated CSF total and p-tau levels). Among individuals with cognitive dysfunction, a study demonstrates insulin resistance is associated with lower global cognition in only women and those without *APOEε4* allele (45). Among cognitively-normal participants, insulin resistance was associated with worse global cognition as well as verbal episodic memory and executive function (46). Pancreatic function as measured by HOMA-B shows a weak association with cognition in the cognitively-normal group, but may play a role in women. These findings suggest that insulin resistance is involved in affecting cognition and elevating AD biomarkers.

Part D: Insulin-like Growth Factor-1 and Binding Proteins, and Cognition

Cross-sectional studies—Insulin-like growth factor-1 (IGF-1) is a hormone that mediates the effects of human growth hormone and is also neuroprotective by promoting neurogenesis and inhibiting apoptosis (47–49). Decreased levels of IGF-1 are associated with various neurodegenerative conditions (50, 51). As most IGF-1 bind to IGF-binding proteins (IGFBP), including IGFBP3 which contributes to tau phosphorylation, we examined studies on IGF and its binding proteins in association with cognition (52).

In a study (53) of patients with AD (70 with dementia; 11 with MCI), serum IGF-1, Aβ42, and Aβ40 were measured. Cognition was assessed with the MMSE and the Hasegawa's Dementia Scale-Revised (54). While results showed that IGF-1 decreases with increasing

age, there were positive correlations between IGF-1 with the MMSE and dementia scale, especially in recall, verbal fluency, and attention subscales. With findings from the regression analyses, these data suggest that IGF-1 may be implicated in some aspects of cognition. Interestingly, there was also a positive correlation between IGF-1 and the Aβ42/Aβ40 ratio. The meaning of this result and clinical significance are unclear at this time. Weaknesses of this study include the sample size, the basic statistical approach used, and lack of a control group.

Another study explored associations of IGF-1 with cognition in 203 Ashkenazi Jewish adults (mean age >95 years) (55). Women with low circulating IGF-1 levels had decreased odds of cognitive impairment compared to those with higher levels. Men showed no significant association. Limitations include generalizability, small sample size of men, and potential for reporting bias (self-reported medical history and cognitive impairment). It is possible that the "younger-old" group will show different findings compared to the "oldest-old" as studied here.

In a study of plasma IGFBP-2 and AD biomarkers (56) among 354 participants from the Alzheimer's Disease Neuroimaging Initiative (58 cognitively-normal; 197 with MCI; 99 with AD), high IGFBP-2 levels were associated with smaller hippocampal volumes in amyloid negative individuals (on CSF testing). This could suggest that IGFBP-2 may lead to neurodegeneration through pathways independent of AD neuropathology. Strengths include a large cohort with measurements of multiple AD biomarkers across modalities and biofluids, and cognitive performance. However, this is a well-educated and predominantly Caucasian sample, limiting generalizability.

Recent approaches to study complex conditions leverage mendelian randomization. In a study of select genes affecting circulating IGF concentrations, investigators examined nine IGF related single nucleotide polymorphisms within 984 subjects with AD and 10,304 controls from the Swedish Twin Registry (57). Results did not show that variation in IGF-1 affected AD risk.

Two (53, 55) of four cross-sectional studies show association between IGF-1 and brain function (cognition) or related measures (including AD biomarkers). In the other two studies, one demonstrates that genes affecting IGF concentrations may not be involved (57), while the other suggests IGFBP-2 may affect hippocampal volume through mechanisms apart from neuropathology with no significance with cognition (56). These studies show conflicting results, and much work needs to be done to disentangle the role of IGF-1 and IGFBPs in cognitive impairment.

Longitudinal studies—Baseline total serum IGF-1, IGFBP-3, and IGFBP-1 were measured in 840 cognitively-normal, Ashkenazi Jewish adults (58). Over a 7-year median follow-up, all-cause mortality, and composite incident morbidity, defined as onset of cardiovascular disease, diabetes, cancer, or multiple-domain cognitive impairment (MDCI), were assessed. A higher IGF-1/IGFBP-3 molar ratio (estimate of free circulating IGF-1) was associated with higher mortality risk. Higher IGF-1 levels were also associated with a greater risk for morbidity (HR=1.24; 95%CI:1.00–1.54) and incident MDCI outcome

specifically (HR=1.56; 95%CI:1.08–2.25). Other IGF-1 related proteins did not show associations. Analyzing persons with low prevalence of chronic diseases may be a strength because of fewer confounders. However, weaknesses include a single measure of IGF-1 to determine free circulating IGF-1 and no consideration of IGF-2, which can bind the same receptors as IGF-1.

A clinic-based study evaluated 342 participants with subjective complaints or MCI, determined by the Global Deterioration Scale, for baseline serum IGF-1 (59). At 4-year follow-up, cognition was reassessed and dementia status categorized. In Cox proportional-hazards regression analysis, IGF-1 levels did not show associations with dementia due to AD in those with cognitive impairment, though there were associations with vascular dementia. Further research is needed to collect repeated measurements of IGF-1. Change in IGF-1 or other proteins over time may be more important in predicting future cognitive impairment.

An analysis of data explored the association between IGF-1 and IGFBP3 with dementia in older men (60). Of 3967 men, 535 showed cognitive impairment on the MMSE. The remaining 3432 without cognitive impairment were followed for 9 years, with 571 developing dementia and 1230 dying without dementia. IGF-1 was not associated with incident dementia. However, men in the lowest quintile of IGFBP-3 had a 47% greater risk of incident dementia compared to the highest quintile. Strengths include the community setting and large sample. Some limitations are the absence of *APOEε4* data, and potential bias, as lower IGFBP-3 levels could be associated with other morbidities.

Thus, only one (58) of three recent longitudinal studies showed IGF-1 as being clearly related to risk of cognitive impairment, while there was some suggestion of a relation of IGF-1 and perhaps also IGFBP-3 to dementia. As a whole, there appears to be weak indication for a role of IGF-1 and related binding proteins in cognition.

Part E: Brain insulin signaling in human postmortem tissue

Examination of human postmortem tissue could further elucidate the association between different pathways in brain insulin signaling and cognitive function. Two recent studies examined how signaling may associate with antidiabetic medication and cognition, respectively.

A study measured insulin receptor signaling pathway (IRSP) and endothelial cell markers in the parahippocampal gyrus of postmortem human brain (61). Groups included controls (n=30; without AD and without diabetes), persons with AD (n=19), and persons with both AD and type 2 diabetes treated with insulin and/or oral medications, mostly sulfonylureas (n=34). There were more reductions in gene expression of endothelial cells and associated IRSP in AD compared to controls. In AD subjects treated for diabetes, there were fewer changes in endothelial cell and IRSP associated genes. Authors postulate that antidiabetics may normalize gene expression. However, whether gene expression is improved due to antidiabetics remains unclear, since there was no comparison with persons with both AD and diabetes but without exposure to antidiabetic agents. While more research is warranted, this study suggests a possible benefit of antidiabetic therapies on preserving gene expression.

A study from our group was among the retrieved articles. We measured, among 150 older subjects with or without diabetes, brain insulin signaling, including serine/threonine-protein kinase-1 (AKT1) and insulin receptor substrate-1 (IRS-1) by enzyme-linked immunosorbent assay (ELISA) and other methods (62). Subjects completed detailed neuropsychological tests grouped into five cognitive domains and global scores. Adjusted regressions showed that AKT1 phosphorylation was associated with lower scores on global cognition, as well as episodic memory and working memory, but IRS-1 phosphorylation showed no association. Secondary analyses showed AKT1 was also positively associated with AD pathology. Findings need replication and expansion, for example to assess blood glucose and insulin levels.

These two human postmortem studies suggest that brain IRSP and AKT may be involved in cognition, but much work remains.

DISCUSSION

This review included 26 studies that were identified by a literature search. Nine studies (16, 19, 20, 22–25, 28, 29) directly addressed the relation of insulin resistance with cognitive function. Taken as a whole, these nine studies provide data supporting an association between insulin resistance and poorer cognition, ranging from subtle cognitive changes to MCI and AD dementia. The other 17 studies addressed potential mechanisms of insulin and related measures on the brain: two intranasal insulin studies (32, 35), four on brain structure and metabolism (40–43), two on CSF biomarkers (45, 46), seven on various IGF proteins (53, 55–60), and two using postmortem human brain tissue (61, 62). These 17 studies cover different aspects of insulin and the brain and offer a range of insights. Results suggest that structural and metabolic changes in the brain, AD biomarkers, and brain IRSP and AKT insulin signaling pathways may each play a role in relating insulin to cognitive impairment.

Among the nine studies directly examining the relationship between insulin resistance with cognition, three (16, 19, 20) of four cross-sectional studies (22) showed associations between HOMA-IR and cognition; three (23, 28, 29) of five longitudinal studies showed relation to cognition while the other two showed significance only after subanalyses (24, 25). Most studies show that insulin resistance reduces cognitive performance on global cognition as well as specific measures on executive function, psychomotor speed, verbal fluency, and verbal episodic memory. These results suggest a broad effect of insulin on different cognitive systems.

In addition to examining cognition as an outcome, imaging studies examined the relation of insulin resistance to brain structure and pathology. Neuroimaging is useful for in-vivo studies to identify structural and functional changes in the brain over time, along with cognitive changes within the same individuals. Findings showed that insulin resistance is associated with enlarged perivascular spaces, increased regional deficits in synaptic connectivity, and increased insulin activity in the hippocampal region, seemingly more so in the right hemisphere. Structural neuroimaging, and potentially functional neuroimaging (while less practical), may shed insight into pathobiologic mechanisms linking insulin to brain dysfunction including cognition, and may also be used to study disease progression.

However, more molecular studies, including of insulin growth factors, binding proteins, and other molecules, are needed to better deconstruct the relation of diabetes, insulin resistance, and cognition, since results with current human data have been inconsistent. Postmortem studies have shown that IRSP and AKT pathways may be involved in brain insulin signaling and cognition, which could be further explored in the future.

Yet another avenue for research on insulin and the brain, is insulin delivered intranasally, which has been found to be safe and potentially beneficial for treating and preventing worsening cognition in AD. Of two clinical trials, one showed positive correlations with ADAS-Cog, while the other showed ADAS-Cog improvement only within a subset. However, many questions remain such as delivery mode and optimal dosage. Study with larger sample sizes, using different drugs and formulations, and with repeated outcome measures of cognitive performance, are underway to further expand this line of research. While most studies examine insulin resistance in the periphery, more studies examining brain insulin resistance specifically are needed. Whether the optimal metabolic targets for treating and preventing cognitive decline are peripheral or central (brain) remains unclear, and active research in ongoing for both (e.g., intranasal insulin, metformin, and other approved anti-diabetes medications).

Strengths of this review include the use of a robust, systematic search strategy to identify recent cross-sectional and longitudinal studies as well as clinical trials involving older persons with or without dementia or insulin resistance as measured by insulin levels or HOMA-IR. Other studies involving varying imaging modalities, biomarkers, and insulin growth factor serum levels were included to provide a broader understanding of insulin resistance and its structural and functional impact on the brain. Moreover, many studies examined the level of cognitive function as measured by a global score (e.g., using the MMSE), and/or by specific cognitive domains based on various individual neuropsychological tests or combination of tests, giving additional insights into underlying pathobiology.

Yet, there are many scientific gaps that remain in the field. First, mechanisms underlying insulin resistance, as well as cognitive impairment and AD, are complex conditions and still poorly understood. While the past decades brought many important scientific discoveries, our understanding of the complex interplay of biologic factors including genetic, and environmental factors including the exposome, remains incomplete. Second, while the links of peripheral insulin resistance and diabetes to cerebrovascular disease including stroke, and from cerebrovascular disease to cognitive impairment including dementia, are well established (e.g., vascular contributions to cognitive impairment and dementia [VCID]), a deeper understanding of this vascular pathway and elucidation of other pathways leading to dementia are urgently needed. Third, biomarkers for these conditions are limited, especially those that are practical for clinical practice. For example, HOMA-IR is not as useful longitudinally, and AD and VCID blood biomarkers are still not accepted as standard of care. Yet, the biomarker field for these common and disabling conditions is rapidly evolving, and promises to soon improve prediction, diagnosis, clinical course, and response to therapies. Fourth, there are currently limited resources of well-characterized and diverse persons for research, despite the knowledge that insulin resistance, diabetes,

and dementia are significantly more common in historically-marginalized populations (e.g., Blacks, Latinos). Specifically, we are not aware of any study of a large group of women and men from diverse racioethnic and other backgrounds and in mid-to-late life, with and without peripheral insulin resistance, diabetes and co-morbidities at baseline, who are well characterized clinically including for brain function (longitudinally-collected cognitive measures) and metabolic function (e.g., laboratory measures), as well as with other data (e.g., exposome, genome, transcriptome, etc.), and in whom blood and other biospecimens are available to characterize peripheral and central (brain) functions. Fifth, little is known about the relationship of peripheral to central insulin resistance (e.g., can brain insulin resistance occur in the absence of peripheral resistance, and if so then what triggers this?), and of these to brain structure and function including cognition and dementia. In fact, how to best define and measure brain insulin resistance remains unclear, particularly *in-vivo* in humans (63).

To be impactful on science and ultimately clinical care and public health (dementia prevention), future research needs to identify and characterize the biologic and environmental mechanisms involved in insulin resistance and cognitive impairment including AD, while evaluating for sex, racioethnic and exposome factors. In addition to experimental models of disease (e.g., animal and cell culture studies), studies should focus on humans, with an emphasis on large, diverse population-based and community-dwelling cohorts. At enrollment, participants would have a spectrum of metabolic dysfunction, from normoglycemia (controls) to insulin resistance and pre-diabetes, to diabetes. Prospective, longitudinal evaluations should include detailed phenotyping, with performance-based cognitive testing across domains, biospecimen collection (e.g., for novel blood biomarkers of insulin resistance, epigenetic markers of cognitive decline, microbiome analyses, etc.), neuroimaging (e.g., MRI), and evaluations of a range of medical (e.g., vascular) and environmental factors (e.g., social and behavioral). Sophisticated analytic approaches, such as with computational neuroscience, would be employed to analyze large and complex datasets, using bioinformatics and biostatistical modeling, as well as robust methods to minimize biases and errors. Results would rapidly be made publicly available, and data and remaining biospecimens would be available for sharing with qualified scientists to conduct additional research, following ethical and legal standards for resources sharing. While there is much work to be done in the space of insulin resistance, cognition and AD, the current state-of-the-science is well poised to support meaningful research with the long-term goal of decreasing and preventing cognitive impairment in aging.

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Conflicts of interest:

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REFERENCES

1. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64–74. Epub 2005/12/20. doi: 10.1016/s1474-4422(05)70284-2. [PubMed: 16361024]
2. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes care. 2016;39(2):300–7. [PubMed: 26681727]
3. Maggi S, Limongi F, Noale M, Romanato G, Tonin P, Rozzini R, et al. Diabetes as a risk factor for cognitive decline in older patients. Dementia and Geriatric Cognitive Disorders. 2009;27(1):24–33. [PubMed: 19088471]
4. Spauwen PJ, Köhler S, Verhey FR, Stehouwer CD, van Boxtel MP. Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. Diabetes care. 2013;36(6):1554–61. [PubMed: 23275366]
5. Wong RHX, Scholey A, Howe PRC. Assessing premorbid cognitive ability in adults with type 2 diabetes mellitus—a review with implications for future intervention studies. Current diabetes reports. 2014;14(11):1–12.
6. Zheng F, Yan L, Yang Z, Zhong B, Xie W. HbA(1c), diabetes and cognitive decline: the English Longitudinal Study of Ageing. Diabetologia. 2018;61(4):839–48. Epub 2018/01/26. doi: 10.1007/s00125-017-4541-7. [PubMed: 29368156]
7. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119. [PubMed: 34879977]
8. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care. 2000;23(1):57–63. Epub 2000/06/17. doi: 10.2337/diacare.23.1.57. [PubMed: 10857969]
9. Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R, et al. Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with type 2 diabetes. Diabetes Care. 2001;24(2):362–5. Epub 2001/02/24. doi: 10.2337/diacare.24.2.362. [PubMed: 11213893]
10. De Felice FG, Lourenco MV, Ferreira ST. How does brain insulin resistance develop in Alzheimer's disease? Alzheimer's & Dementia. 2014;10(1, Supplement):S26–S32. doi: 10.1016/j.jalz.2013.12.004.
11. Geroldi C, Frisoni GB, Paolisso G, Bandinelli S, Lamponi M, Abbatecola AM, et al. Insulin resistance in cognitive impairment: the InCHIANTI study. Arch Neurol. 2005;62(7):1067–72. Epub 2005/07/13. doi: 10.1001/archneur.62.7.1067. [PubMed: 16009759]
12. Rasgon NL, Kenna HA, Wroolie TE, Kelley R, Silverman D, Brooks J, et al. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol Aging. 2011;32(11):1942–8. Epub 2009/12/25. doi: 10.1016/j.neurobiolaging.2009.12.005. [PubMed: 20031276]
13. Rönnemaa E, Zethelius B, Sundelöf J, Sundström J, Degerman-Gunnarsson M, Berne C, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology. 2008;71(14):1065–71. Epub 2008/04/11. doi: 10.1212/01.wnl.0000310646.32212.3a. [PubMed: 18401020]
14. Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010;75(22):1982–7. Epub 2010/12/01. doi: 10.1212/WNL.0b013e3181ffe4f6. [PubMed: 21115952]
15. van Himbergen TM, Beiser AS, Ai M, Seshadri S, Otokozawa S, Au R, et al. Biomarkers for Insulin Resistance and Inflammation and the Risk for All-Cause Dementia and Alzheimer Disease: Results From the Framingham Heart Study. Archives of Neurology. 2012;69(5):594–600. doi: 10.1001/archneurol.2011.670. [PubMed: 22213409]

16. Sherzai AZ, Shaheen M, Jeffrey JY, Talbot K, Sherzai D. Insulin resistance and cognitive test performance in elderly adults: National Health and Nutrition Examination Survey (NHANES). Journal of the Neurological Sciences. 2018;388:97–102. [PubMed: 29627040]
17. Hoyer WJ, Stawski RS, Wasylyshyn C, Verhaeghen P. Adult age and digit symbol substitution performance: a meta-analysis. Psychol Aging. 2004;19(1):211–4. Epub 2004/04/07. doi: 10.1037/0882-7974.19.1.211. [PubMed: 15065945]
18. Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. Arch Neurol. 2008;65(1):89–93. Epub 2008/01/16. doi: 10.1001/archneurol.2007.29. [PubMed: 18195144]
19. Ma L, Li Y. Cognitive function and insulin resistance in elderly patients with type 2 diabetes. Neurological Research. 2017;39(3):259–63. [PubMed: 28107806]
20. Smith PJ, Mabe S, Sherwood A, Babyak MA, Doraiswamy PM, Welsh-Bohmer KA, et al. Association between insulin resistance, plasma leptin, and neurocognition in vascular cognitive impairment. Journal of Alzheimer's Disease. 2019;71(3):921–9.
21. Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet. 1997;349(9068):1793–6. Epub 1997/06/21. doi: 10.1016/s0140-6736(97)01007-6. [PubMed: 9269213]
22. Thankappan S, Sen S, Subramanian S, Sinha P, Purushottam M, Bharath S. Insulin resistance in patients with Alzheimer's dementia: A controlled study from India. Asian Journal of Psychiatry. 2018;38:33–4. [PubMed: 30391679]
23. Fava A, Colica C, Plastino M, Messina D, Cristiano D, Opipari C, et al. Cognitive impairment is correlated with insulin resistance degree: the "PA-NICO-study". Metabolic Brain Disease. 2017;32(3):799–810. [PubMed: 28229380]
24. Hooshmand B, Rusanen M, Ngandu T, Leiviskä J, Sindi S, von Arnim CA, et al. Serum insulin and cognitive performance in older adults: a longitudinal study. The American Journal of Medicine. 2019;132(3):367–73. [PubMed: 30502316]
25. Lee TH, Hurwitz EL, Cooney RV, Wu YY, Wang C-Y, Masaki K, et al. Late life insulin resistance and Alzheimer's disease and dementia: The Kuakini Honolulu heart program. Journal of the Neurological Sciences. 2019;403:133–8. [PubMed: 31284182]
26. Sarafidis PA, Lasaridis AN, Nilsson PM, Pikilidou MI, Stafilas PC, Kanaki A, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. J Hum Hypertens. 2007;21(9):709–16. Epub 2007/04/20. doi: 10.1038/sj.jhh.1002201. [PubMed: 17443211]
27. Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr. 1994;6(1):45–58; discussion 62. Epub 1994/01/01. doi: 10.1017/s1041610294001602. [PubMed: 8054493]
28. Kong SH, Park YJ, Lee JY, Cho NH, Moon MK. Insulin Resistance is Associated with Cognitive Decline Among Older Koreans with Normal Baseline Cognitive Function: A Prospective Community-Based Cohort Study. Sci Rep. 2018;8(1):650. Epub 2018/01/14. doi: 10.1038/s41598-017-18998-0. [PubMed: 29330465]
29. Neergaard JS, Dragsbæk K, Christiansen C, Nielsen HB, Brix S, Karsdal MA, et al. Metabolic Syndrome, Insulin Resistance, and Cognitive Dysfunction: Does Your Metabolic Profile Affect Your Brain? Diabetes. 2017;66(7):1957–63. Epub 2017/04/09. doi: 10.2337/db16-1444. [PubMed: 28389469]
30. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. Br J Psychiatry. 1973;123(575):467–70. Epub 1973/10/01. doi: 10.1192/bjp.123.4.467. [PubMed: 4748864]
31. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry. 1983;140(6):734–9. Epub 1983/06/01. doi: 10.1176/ajp.140.6.734. [PubMed: 6846631]

32. Mustapic M, Tran J, Craft S, Kapogiannis D. Extracellular vesicle biomarkers track cognitive changes following intranasal insulin in Alzheimer's disease. Journal of Alzheimer's Disease. 2019;69(2):489–98.
33. Mullins RJ, Mustapic M, Goetzl EJ, Kapogiannis DExosomal biomarkers of brain insulin resistance associated with regional atrophy in Alzheimer's disease. Hum Brain Mapp. 2017;38(4):1933–40. Epub 2017/01/21. doi: 10.1002/hbm.23494. [PubMed: 28105773]
34. Kapogiannis D, Boxer A, Schwartz JB, Abner EL, Biragyn A, Masharani U, et al. Dysfunctionally phosphorylated type 1 insulin receptor substrate in neural-derived blood exosomes of preclinical Alzheimer's disease. Faseb j. 2015;29(2):589–96. Epub 2014/10/25. doi: 10.1096/fj.14-262048. [PubMed: 25342129]
35. Craft S, Raman R, Chow TW, Rafii MS, Sun C-K, Rissman RA, et al. Safety, efficacy, and feasibility of intranasal insulin for the treatment of mild cognitive impairment and Alzheimer disease dementia: a randomized clinical trial. JAMA neurology. 2020;77(9):1099–109. [PubMed: 32568367]
36. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012;69(1):29–38. Epub 2011/09/14. doi: 10.1001/archneurol.2011.233. [PubMed: 21911655]
37. Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, Trittschuh EH, et al. Effects of Regular and Long-Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. J Alzheimers Dis. 2017;57(4):1325–34. Epub 2017/04/05. doi: 10.3233/jad-161256. [PubMed: 28372335]
38. MacLullich A, Wardlaw J, Ferguson K, Starr J, Seckl J, Deary I. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. Journal of Neurology, Neurosurgery & Psychiatry. 2004;75(11):1519–23. [PubMed: 15489380]
39. Wardlaw JM. Blood-brain barrier and cerebral small vessel disease. J Neurol Sci. 2010;299(1–2):66–71. Epub 2010/09/21. doi: 10.1016/j.jns.2010.08.042. [PubMed: 20850797]
40. Wu D, Yang X, Zhong P, Ye X, Li C, Liu X. Insulin resistance is independently associated with enlarged perivascular space in the basal ganglia in nondiabetic healthy elderly population. American Journal of Alzheimer's Disease & Other Dementias®. 2020;35:1533317520912126.
41. Su F, Shu H, Ye Q, Wang Z, Xie C, Yuan B, et al. Brain insulin resistance deteriorates cognition by altering the topological features of brain networks. NeuroImage: Clinical. 2017;13:280–7.
42. Byun MS, Kim HJ, Yi D, Choi HJ, Baek H, Lee JH, et al. Differential effects of blood insulin and HbA1c on cerebral amyloid burden and neurodegeneration in nondiabetic cognitively normal older adults. Neurobiology of aging. 2017;59:15–21. [PubMed: 28780367]
43. Byun MS, Kim HJ, Yi D, Choi HJ, Baek H, Lee JH, et al. Region-specific association between basal blood insulin and cerebral glucose metabolism in older adults. NeuroImage: Clinical. 2019;22:101765.
44. Kern W, Benedict C, Schultes B, Plohr F, Moser A, Born J, et al. Low cerebrospinal fluid insulin levels in obese humans. Diabetologia. 2006;49(11):2790–2. doi: 10.1007/s00125-006-0409-y. [PubMed: 16951936]
45. Geijselaers SL, Aalten P, Ramakers IH, De Deyn PP, Heijboer AC, Koek HL, et al. Association of cerebrospinal fluid (CSF) insulin with cognitive performance and CSF biomarkers of Alzheimer's disease. Journal of Alzheimer's Disease. 2018;61(1):309–20.
46. Laws SM, Gaskin S, Woodfield A, Srikanth V, Bruce D, Fraser PE, et al. Insulin resistance is associated with reductions in specific cognitive domains and increases in CSF tau in cognitively normal adults. Scientific reports. 2017;7(1):1–11. [PubMed: 28127051]
47. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci. 2001;21(15):5678–84. Epub 2001/07/24. doi: 10.1523/jneurosci.21-15-05678.2001. [PubMed: 11466439]
48. Clemmons DR. Clinical utility of measurements of insulin-like growth factor 1. Nat Clin Pract Endocrinol Metab. 2006;2(8):436–46. Epub 2006/08/26. doi: 10.1038/ncpendmet0244. [PubMed: 16932333]

49. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci. 2001;21(5):1628–34. Epub 2001/02/27. doi: 10.1523/jneurosci.21-05-01628.2001. [PubMed: 11222653]
50. Busiguina S, Fernandez AM, Barrios V, Clark R, Tolbert DL, Berciano J, et al. Neurodegeneration is associated to changes in serum insulin-like growth factors. Neurobiol Dis. 2000;7(6 Pt B):657–65. Epub 2000/12/15. doi: 10.1006/nbdi.2000.0311.
51. Trejo JL, Carro E, Garcia-Galloway E, Torres-Aleman I. Role of insulin-like growth factor I signaling in neurodegenerative diseases. J Mol Med (Berl). 2004;82(3):156–62. Epub 2003/12/03. doi: 10.1007/s00109-003-0499-7. [PubMed: 14647921]
52. Watanabe K, Uemura K, Asada M, Maesako M, Akiyama H, Shimohama S, et al. The participation of insulin-like growth factor-binding protein 3 released by astrocytes in the pathology of Alzheimer's disease. Mol Brain. 2015;8(1):82. Epub 2015/12/08. doi: 10.1186/s13041-015-0174-2. [PubMed: 26637371]
53. Kimoto A, Kasanuki K, Kumagai R, Shibata N, Ichimiya Y, Arai H. Serum insulin-like growth factor-I and amyloid beta protein in Alzheimer's disease: relationship with cognitive function. Psychogeriatrics. 2016;16(4):247–54. [PubMed: 26439951]
54. Jeong JW, Kim KW, Lee DY, Lee SB, Park JH, Choi EA, et al. A normative study of the Revised Hasegawa Dementia Scale: comparison of demographic influences between the Revised Hasegawa Dementia Scale and the Mini-Mental Status Examination. Dement Geriatr Cogn Disord. 2007;24(4):288–93. Epub 2007/08/25. doi: 10.1159/000107592. [PubMed: 17717415]
55. Perice L, Barzilai N, Verghese J, Weiss EF, Holtzer R, Cohen P, et al. Lower circulating insulin-like growth factor-I is associated with better cognition in females with exceptional longevity without compromise to muscle mass and function. Aging (Albany NY). 2016;8(10):2414. [PubMed: 27744417]
56. Lane EM, Hohman TJ, Jefferson AL. Insulin-like growth factor binding protein-2 interactions with Alzheimer's disease biomarkers. Brain imaging and behavior. 2017;11(6):1779–86. [PubMed: 27817134]
57. Williams DM, Karlsson IK, Pedersen NL, Hägg S. Circulating insulin-like growth factors and Alzheimer disease: A mendelian randomization study. Neurology. 2018;90(4):e291–e7. [PubMed: 29282328]
58. Zhang WB, Aleksic S, Gao T, Weiss EF, Demetriou E, Verghese J, et al. Insulin-like Growth Factor-1 and IGF Binding Proteins Predict All-Cause Mortality and Morbidity in Older Adults. Cells. 2020;9(6). Epub 2020/06/05. doi: 10.3390/cells9061368. [PubMed: 33375150]
59. Quinlan P, Horvath A, Nordlund A, Wallin A, Svensson J. Low serum insulin-like growth factor-I (IGF-I) level is associated with increased risk of vascular dementia. Psychoneuroendocrinology. 2017;86:169–75. [PubMed: 28963885]
60. Almeida OP, Hankey GJ, Yeap BB, Paul Chubb SA, Gollege J, Flicker L. Risk of prevalent and incident dementia associated with insulin-like growth factor and insulin-like growth factor-binding protein 3. Mol Psychiatry. 2018;23(8):1825–9. Epub 2017/11/21. doi: 10.1038/mp.2017.152. [PubMed: 29155799]
61. Katsel P, Roussos P, Beeri M, Gama-Sosa M, Gandy S, Khan S, et al. Parahippocampal gyrus expression of endothelial and insulin receptor signaling pathway genes is modulated by Alzheimer's disease and normalized by treatment with anti-diabetic agents. PLoS One. 2018;13(11):e0206547. [PubMed: 30383799]
62. Arvanitakis Z, Wang HY, Capuano AW, Khan A, Taïb B, Anokye-Danso F, et al. Brain Insulin Signaling, Alzheimer Disease Pathology, and Cognitive Function. Ann Neurol. 2020;88(3):513–25. Epub 2020/06/20. doi: 10.1002/ana.25826. [PubMed: 32557841]
63. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol. 2018;14(3):168–81. Epub 2018/01/30. doi: 10.1038/nrneurol.2017.185. [PubMed: 29377010]

STUDY IMPORTANCE

What reviews have already been published on this subject?

- While there are prior publications on insulin resistance and cognition or Alzheimer's disease (AD), many used animal models of disease or other experimental non-human designs.
- There are few reviews using a structured search of the literature to specifically examine the recent data relating insulin and cognition, with a focus on older persons.

What are the new findings in your manuscript?

- Most cross-sectional and longitudinal clinical studies show an association between insulin resistance, often defined by HOMA-IR, and cognition in older persons. But often, only a single or global cognitive test is used, and there is little information on which specific cognitive domains are implicated.
- Several studies used imaging and other tools to study insulin and cognition. While results are mixed, changes on brain imaging such as in cerebral glucose metabolism in hippocampal regions, appear to be associated with cognitive impairment. Further, brain insulin receptor signaling may be involved in cognition.
- Many gaps remain in knowledge about insulin resistance, cognition, and AD.

How might your results change the direction of research or the focus of clinical practice?

- Insulin resistance and cognition manifest uniquely in humans compared to animals or other experimental setting.
- Further human research relating insulin to cognition at various levels from molecular, genetic, and other biologic pathways, to environmental, exposome, and other factors, are needed.
- Because insulin metabolism is potentially modifiable, such research has potential to inform future clinical practice.
- Future research will include studies with large and diverse populations, with detailed clinical and laboratory phenotyping, who are prospectively followed longitudinally including with detailed cognitive function data

Table 1

Cross-sectional studies of the association of insulin resistance and cognition

Author, year	Sample size (total), source of subjects	Baseline mean age (SD), women:men	Study groups	Key variables	Covariates	Results
Ma & Yun, 2017	212 patients from Xuanwu Hospital in China	71 (9.73), 76:136	All individuals with T2D. of which: 100 individuals with cognitive impairment; 112 with normal cognition.	HOMA-IR; MMSE	Age, gender, education, BMI, total cholesterol, triglyceride, LDL, creatinine, fasting plasma glucose, fasting insulin	Among participants with T2D, fasting plasma insulin, HOMA-IR, and education level were associated with lower MMSE score.
Sherzai et al., 2018	1028 National Health and Nutrition Examination Survey (1999–2000, 2001–2002)	70 (0.28), 520: 508	1028 individuals with normal cognition ≥ 60 years old.	HOMA-IR; Digital Symbol Substitution (DSS)	Age, gender, race, education, BMI, SBP, DBP, total cholesterol, LDL, HDL, triglyceride, physical activity, DM, stroke, congestive heart failure	Higher HOMA-IR was associated with lower cognitive test performance on the DSS.
Smith et al., 2019	160, ENLIGHTEN trial of vascular Cognitive Impairment, No Dementia	65 (6.8) 106:54	160 sedentary adults with vascular cognitive impairment, no dementia.	HOMA-IR, plasma leptin, IGF-1; battery assessing executive function, verbal memory, and visual memory	Age, gender, BMI, total cholesterol, LDL, HDL, VLDL, CRP, DM, *APOEε4* status	Higher HOMA-IR and leptin were associated with lower executive function, but not verbal memory or visual memory.
Thankappan et al., 2018	80, National Institute of Mental Health and Neurosciences in Bengaluru, India	67 (1.32), 48:32	40 patients with AD; 40 with normal cognition. None taking insulin.	Serum insulin; Hindi mental status examination, everyday abilities scale for India, Clinical Dementia rating	Age, gender, BMI, DM, *APOEε4* status	There was no significant difference in insulin resistance between individuals with or without AD.

BMI body mass index, *AD* Alzheimer's disease, *APOE* apolipoprotein, *BMI* body mass index, *CRP* C-reactive protein, *DM* diabetes, *HDL* high density lipoprotein, *HOMA-IR* homeostatic model assessment for insulin resistance, *IGF*-1 insulin growth factor-1, *LDL* low density lipoprotein, *MMSE* mini-mental state exam, *SBP* systolic blood pressure, *VLDL* very low-density lipoprotein, *T2D* type 2 diabetes

Table 2

Longitudinal studies of the relation of insulin resistance and cognition

Author, year	Sample size (total), source of subjects, follow-up duration (SD)	Baseline mean age (SD), women: men	Study groups	Key variables	Covariates	Results
Fava et al., 2017	477; prospective case control study in Southern Italy; 7 years	66 (11.6) 245:232	335 with DM, 142 without DM. All with normal cognition.	Predictor: HOMA-IR Outcome: annual MMSE, ADAS-Cog	Model 1: sex, education, *APOEε4* status, HOMA-IR Model 2: +BMI, blood profile, triglycerides, HbA1c, heart disease Model 3: +depression	Participants with the highest HOMA-IR had lower scores on MMSE (p=0.001) and ADAS-Cog (p=0.001) compared to baseline, with consistent results across analytic models.
Neergaard et al., 2017	1759; Prospective Epidemiological Risk Factor (PERF) study in Denmark, up to 15 years	68 (unreported), 1759:0	1759 women with or without cognitive dysfunction.	Predictor: HOMA-IR, fasting plasma glucose Outcome: Short blessed test, category fluency test	Age, education, smoking, alcohol consumption, physical activity, hormone replacement therapy	Women with increased MetS risk factors showed an increased odds of poorer verbal fluency compared to those without risk factors (OR=3.09; 95%CI:1.09–8.69). Those with high HOMA-IR also had higher odds of poorer performance on verbal fluency (OR=1.47; 95%CI:1.09–1.99).
Kong et al., 2018	442; Ansung cohort study in Korea, 5.9 (0.1) years	69 (2.9), 220: 222	442 individuals > 65 years old with normal cognition.	Predictor: HOMA-IR, HbA1c, fasting insulin, total cholesterol, HDL, LDL, triglycerides Outcome: MMSE, early dementia screening	Model 1: age, sex, baseline MMSE, education, baseline GDS-K. Model 2: +smoking, DM, HTN, BMI Model 3: + *APOEε4*status	Increases in HOMA-IR was related to fasting insulin levels (p=0.001), and reduction in MMSE (p=0.004) with consistent results across analytic models.
Lee et al., 2019	1544, Honolulu-Asia Aging Study, 3 years	80 (3.8), 0:100	1544 without dementia or T2D.	Predictor: HOMA-IR, McAuley index, combined McAuley and HOMA index Outcome: incident dementia	Model 1: age, BMI, alcohol, change in cholesterol,smoking Model 2: +HTN Model 3: model 2 but replaced HTN with WC	Using only the McAuley index, insulin resistance was related to decreased odds of AD and dementia (OR=0.61; 95% CI: 0.39–0.94) with consistent results across analytic models. HOMA-IR or combined indices did not show significance.
Hooshmand et al., 2018	269; Cardiovascular Risk Factors, Aging, and Dementia study, 7.4 (0.3) years	71 (3.6), 165:104	269 without dementia.	Predictor: HOMA-IR, serum insulin levels Outcome: MMSE, measures of episodic memory, executive function, verbal expression, psychomotor speed	Model 1: age, sex, education, follow-up duration, cognitive measures Model 2: +mean baseline SBP and DBP, BMI, stroke, DM, smoking, *APOEε4*status, CRP	Excluding participants with incident dementia, higher baseline HOMA-IR are related to worse global cognition (β=−0.50, p=0.04) and psychomotor speed (β=−0.06, p =0.04), consistent in both models. Raised serum insulin levels are also associated with poorer global cognition (β=−0.054, p=0.04), but only in Model 2.

AD Alzheimer's disease, *ADAS-Cog* Alzheimer's disease's assessment scale-cognitive subscale, *APOE* apolipoprotein, *BMI* body mass index, *CRP* C-reactive protein, *DBP* diastolic blood pressure, *DM* diabetes, *GDS-K* Korean Geriatric Depression Scale, *HDL* high density lipoprotein, *HOMA-IR* homeostatic model assessment for insulin resistance, *HTN* hypertension, *LDL* low-density lipoprotein, *MetS* Metabolic syndrome, *MMSE* mini-mental state exam, *SBP* systolic blood pressure, *T2D* type 2 diabetes, *WC* waist circumference.

Table 3

Clinical trials involving diabetes medications

Author, year	Sample size (total), source of subjects	Baseline mean age (SD), women:men	Study groups	Key variables	Covariates	Results
Craft et al., 2020	289; 49 used first INI device, 240 used second INI device All from 27 sites of the Alzheimer's Therapeutic Research institute	First device: 71 (7.1), 117:123 Second device: 70.9 (7.1), 134: 155	First device: 24 INI 25 placebo Second device: 121 INI 119 placebo All subjects without DM.	Intervention: 40 IU of INI or placebo daily for 12 months using two different INI devices Outcome: ADAS-Cog, MRI, CSF biomarkers, entorhinal cortex volume	Age, sex, study site, MMSE, *APOEε4* status	Subjects using the first INI device showed improved ADAS-Cog performance upon 6, 15, and 18 months of use (p=0.01, p=0.004, p=0.02, respectively). They also showed decreased volume loss in the entorhinal cortex volume (p=0.03) but no changes in hippocampal volume. Individuals using the second INI device showed only decreased reductions in hippocampal volume (p=0.03).
Mustapic et al., 2020	91, Study of Nasal Insulin in the Fight against Forgetfulness	72.0 (8.3) 56:35	35 subjects with AD, 56 subjects with mild cognitive impairment	Intervention: 20 or 40 IU INI daily for 4 months Outcome: MMSE and ADAS-Cog, insulin receptor substrate-1	None	Within the group who received 20 IU of INI, extracellular vesicle biomarkers (pY-IRS-1 and pS312-IRS-1) showed positive correlations with only ADAS-Cog. The 40 IU INI group showed no significant findings.

AD Alzheimer's disease, *ADAS-Cog* Alzheimer's disease's assessment scale-cognitive subscale, *APOE* apolipoprotein, *CSF* cerebrospinal fluid *DM* diabetes, *INI* Intranasal insulin, *MMSE* mini-mental state exam, *MRI* magnetic resonance imaging