

Systematic Review

Type 2 Diabetes Mellitus as a Risk Factor for Alzheimer's Disease: Review and Meta-Analysis

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Abstract: Alzheimer's disease is the most common type of dementia, reaching 60–80% of case totals, and is one of the major global causes of the elderly population's decline in functionality concerning daily life activities. Epidemiological research has already indicated that, in addition to several others metabolic factors, diabetes mellitus type 2 is a risk factor of Alzheimer's disease. Many molecular pathways have been described, and at the same time, there are clues that suggest the connection between type 2 diabetes mellitus and Alzheimer's disease, through specific genes, autophagy, and even inflammatory pathways. A systematic review with meta-analysis was conducted, and its main goal was to reveal the multilevel connection between these diseases.

Keywords: type 2 diabetes mellitus; Alzheimer's disease; common mechanisms

1. Introduction

Alzheimer's disease is the most common type of dementia. In 2020, as many as 5.8 million Americans were living with AD, and this number is projected to nearly triple to 14 million people by 2060 [1]. Approximately 95% of AD patients are over 65 years old, and they form the late-onset group of the total AD population. The remaining 5%—familial AD (fAD)—consists of patients who manifest the disease in their thirties, forties or fifties and carry genetic mutations in three genes (as currently known): amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2). All three of these genes follow autosomal dominant inheritance, their mutations' penetrance is nearly 100%, and they are involved in the molecular processing of b-amyloid. APP is the responsible gene for the precursor protein of beta-amyloid encoding, whereas PS-1 and PS-2 code important components of the γ -secretase, a proteolytic enzyme required for the generation of b-amyloid from APP.

The etiology of late-onset AD is more complex and encompasses genetics, the strongest one being the epsilon four allele of the apolipoprotein E (ApoE4) gene, as well as other factors such as obesity, diabetes, depression and hypertension [2,3]. The APOE gene, on chromosome 19, encodes the brain's major cholesterol transporter and occurs in three allele variants: $\epsilon 2$ (less common frequency in the population), $\epsilon 3$ (most common) and $\epsilon 4$. Each

person has two alleles, and the presence of one or two $\epsilon 4$ alleles increases the risk of AD and reduces the average age of symptom onset. However, the $\epsilon 2$ allele is protective for AD. Major studies have emphasized APOE $\epsilon 4$ significance in cognitive impairment, with an autopsy study [4] that focused on the interactions of DM, the subsequent high risk of cerebral amyloid angiopathy (CAA) and the formation of neurofibrillary tangles and amyloid plaques [4,5].

In this context, earlier studies have focused on the incidence rate of diabetes in AD patients [6–8]. One such example, the Rotterdam study, a large prospective study published in 1999, revealed an increased relative risk of diabetics, especially for those on insulin treatment for AD [6]. In the same context, intranasal insulin has been previously indicated as a potential therapeutic agent for amnesic cognitive impairment [9–11].

Diabetes mellitus (DM) is a chronic metabolic disorder, whose prevalence increases in elderly people [12] and as a major midlife vascular risk factor, it has been studied regarding amyloid deposition in the human brain [13]. This neuropathologic approach is required mostly in the definition of AD, according to the new National Institute on Aging and Alzheimer's Association (NIA-AA) research framework (2018) [14], which impresses upon a biologically based definition, emphasizing the importance of biomarkers.

In order to confirm T2DM as a risk factor of AD, we conducted a quantitative meta-analysis of longitudinal studies, and we summarized the main common molecular mechanisms.

2. Materials and Methods

This study was based on the PRISMA statement (Figure 1). The electronic database of PubMed was searched from January 2008 to May 2021. The search terms were “type 2 diabetes mellitus” OR “diabetes” OR “vascular risk factor” OR “metabolic syndrome” AND “dementia” OR “Alzheimer disease” OR “p-tau” OR “b-amyloid”. There were 12,815 results, but by focusing on randomized controlled and clinical trials, as well as clinical and observational studies, there were 554 results. Initially, all the articles were screened according to their title and abstract, and some of them, which were not potentially relevant, were excluded (478). Additional relevant articles and reviews were retrieved for methodological issues and underlying mechanisms that were eligible for our qualitative synthesis (97).

Inclusion/Exclusion Criteria

For meta-analytic purposes, we included only human studies that contained mainly patients with diabetes mellitus. The studies reported data concerning odds ratios (OR), risk ratios (RR) or hazard ratios (HR), and dementia was defined according to the generally accepted criteria, mostly the NINCDS-ADRDA criteria. In respect to diabetes, there was variation in the parameters, which articles used in order to define it. More specifically, most of the medical history information, including DM, was based on national health insurance records, and some articles took for granted the presence of DM without a well-defined parameter. Nevertheless, there were studies that used the fasting plasma glucose (≥ 126 mg/dL) or the 75 g oral glucose tolerance test or the variations of fasting plasma glucose and glycated hemoglobin (HbA1c) represented by the coefficient of variation (CV). The duration of DM was also counted in one study, and a statistical significance was noticed over five years. Furthermore, studies with dementia subjects at baseline were also included. In addition, only papers published in English or translated into English were included. We excluded animal studies, case reports and reviews, for quantitative synthesis.

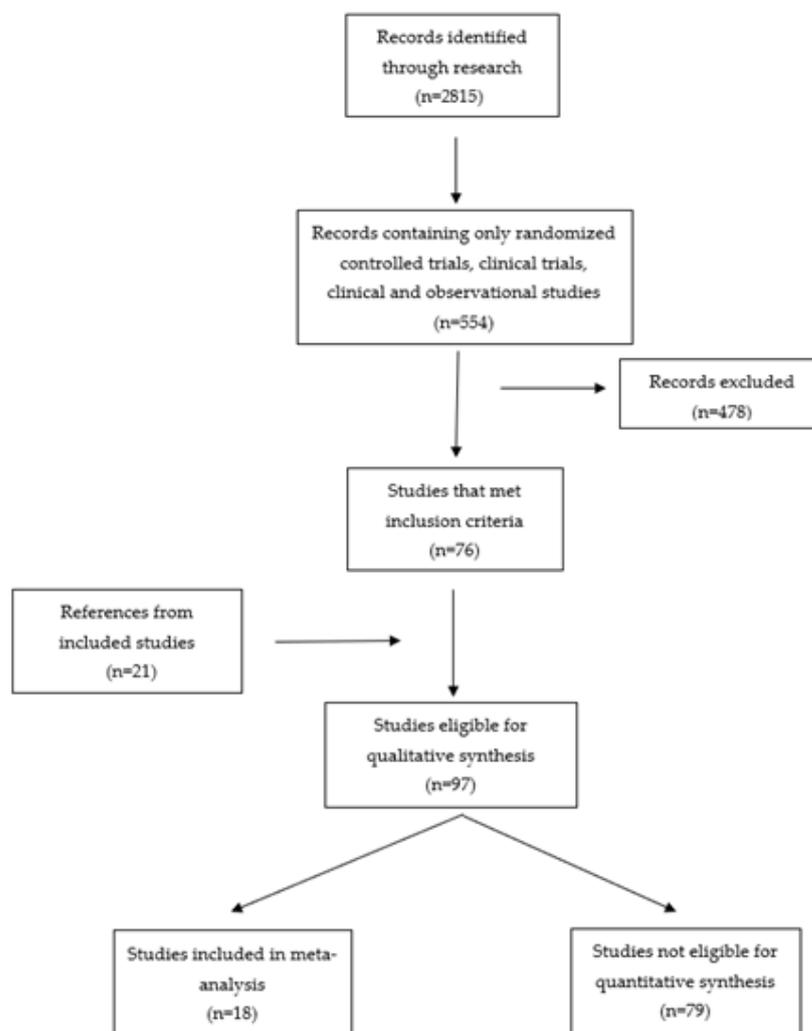


Figure 1. PRISMA flow diagram for the selection of included studies.

3. Statistical Analysis

The meta-analysis was performed following the random effects model with DerSimonian Laird method, as performed by the RevMan software. Although T^2 and X^2 were also reported, I^2 was the most important measure of heterogeneity (low < 25%, moderate 25–75%, high >75%). For publication bias, a funnel plot was created (Trim and Fill method), and Egger’s regression was performed using Meta-Essentials 1.5 (2020) [15]. Different meta-analyses were performed for publications reporting odds ratios, risk ratios or hazard ratios. Subgroup analyses were also performed.

4. Results

Meta-Analysis

Eighteen studies were included in the meta-analysis (Table 1) [16–33]. The meta-analysis was conducted separately regarding the measure of probability used; thus, there are three main groups (Figures 2–4).

Risk ratios were reported by five studies with a total of 6628 patients, showing significantly increased risk ratios for AD in patients with abnormal glucose metabolism ($p = 0.01$) and moderate heterogeneity as expressed by an I^2 of 74%. Egger’s test revealed no significant publication bias ($p = 0.797$). When removing the (statistically significant) Cache County study, the other studies showed significantly increased risk ratios for AD in patients with diabetes ($p = 0.008$), with no heterogeneity.

Table 1. Studies separated by different measures of probability.

	Study	Value (95% CI)	Number of Participants
RR	Becker et al. [17]	1.4 (0.7–3.1)	288
	Toro et al. [19]	1.18 (0.49–2.87)	381
	Cheng et al. [20]	1.5 (0.92–2.45)	1488
	Li et al. [23]	1.62 (1.00–2.62)	837
	Treiber et al. [33]	3.3 (2.5–4.3)	3634
OR	Tolppanen et al. [26]	1.25 (1.16–1.36)	28,093
	Giuseppe et al. [27]	0.98 (0.8–1.2)	6553
	Kadohara et al. [28]	1.31 (0.9–1.92)	1855
	Kim et al. [31]	1.77 (1.52–2.06)	84,144
HR	Irie et al. [16]	1.62 (0.98–2.67)	2547
	Raffaitin et al. [18]	1.15 (0.64–2.05)	7087
	Ohara et al. [21]	2.05 (1.18–3.57)	1017
	Kimm et al. [22]	1.6 (1.3–2.0)	848,505
	Wang et al. [24]	1.45 (1.38–1.52)	1,230,403
	Huang et al. [25]	1.76 (1.5–2.07)	142,744
	Yu et al. [30]	1.13 (1.11–1.15)	1,917,702
	Chung Li et al. [29]	1.32 (1.11–1.58)	16,706
	Longjian et al. [32]	1.22 (1.13–1.31)	63,117

Odds ratios were reported by four studies, with a total of 120,645 patients showing significantly increased odds ratio for AD in patients with abnormal glucose metabolism ($p = 0.03$), yet with high heterogeneity. Egger's test did not reveal significant publication bias ($p = 0.744$). Two of the studies were performed in the general populations and another two in subjects with early onset and/or familial AD. Only in the former was diabetes significantly associated with AD ($p = 0.02$), with high heterogeneity.

Hazard ratios were reported by nine studies, with a total of 4,229,828 patients showing significantly increased hazard ratios for AD in patients with abnormal glucose metabolism ($p = 0.0007$). High heterogeneity was observed with an I^2 of 97%. Egger's test revealed that publication bias was only marginally significant ($p = 0.053$). Subgroups with either diabetes or other definitions of abnormal glucose metabolism (glucose intolerance, fasting glucose levels) showed significant results, but heterogeneity was again moderate at best.

5. Discussion

5.1. Meta-Analyses

The present findings suggest that an abnormal glucose metabolism in general may be associated with an increased risk for developing Alzheimer's disease in the general population. Publication bias may not be significant. However, heterogeneities are generally moderate or high, probably as a result of different definitions of abnormal glucose metabolism, including diabetes, fasting plasma glucose levels, Hb1Ac levels and glucose intolerance as tested by the oral glucose tolerance test, commonly preferred for the characterization of prediabetes. Different study designs may also contribute to the heterogeneity, as was shown with the study (Treiber et al. [33]) of a subsample of the Cache County Study, which was cross-sectional with retrospective examination of vascular conditions in relation with probable or possible AD with neuropsychiatric symptoms. In addition, the effect of diabetes may not be significant in early-onset or familial AD, where specific genetic factors may be responsible.

5.2. The Role of Insulin Resistance, Hyperinsulinemia and Hyperglycemia in AD Pathology

As already mentioned, numerous lines of evidence indicate the etiological correlation between AD, DM, and diabetes mellitus types 2 in particular because of its higher prevalence. However, type 1 DM-related defects in cognition have been examined, especially from certain perspectives such as the frequency of diabetic ketoacidosis [34].

The cornerstone of the aforementioned correlation is hyperglycemia, insulin resistance and hyperinsulinemia, which are the main features of T2DM [35].

Insulin is an anabolic hormone that promotes glucose uptake, glycogenesis, lipogenesis and protein synthesis of skeletal muscle, and it is released from the pancreas. It is transported to the brain through a receptor-mediated process [36] and accomplishes its function through the tyrosine kinase receptor pathway. Insulin receptors are abundantly expressed in the hypothalamus, cortex, hippocampus and the olfactory bulb [37], and they exist in two isoforms (IR-A and IR-B), with IR-A as the one that is mainly located in the adult nervous system [38].

IR expression in the aforementioned sites indicates important roles in synaptic plasticity, memory and homeostatic regulation [39]. This latter function, most prominent in peripheral tissues, is carried out principally by GLUT4 and GLUT8 transporters, the known insulin responsive transporters [40] that eventually translocate to the plasma membrane. There are also other glucose transporters, including GLUT1 and GLUT3, that are independent of insulin levels, are expressed at the blood brain barrier (BBB) and are responsible for neuron glucose uptake from blood [40].

In a healthy state, insulin binds to the IR, it is auto-phosphorylated because its four subunits interact, and in turn, it activates insulin-receptor substrates. There are six identified protein substrates that constitute the IRS family, and IRS-1 and -2 are those that mediate downstream pathways in the brain. Thus, IRS initiates a signaling cascade through phosphatidylinositol-3-kinase (PI3K), which activates protein kinase B (PKB or AKT). The latter one phosphorylates glycogen synthase kinase 3beta (GSK-3 β), resulting in its inhibition [41]. When diabetes mellitus type 2 impacts insulin resistance, at first, the pancreas releases increased levels of insulin in order to compensate. However, chronically, insulin receptors at the BBB are downregulated, and the amount of insulin that enters the brain decreases [42]. This phenomenon is called brain insulin resistance and gives prominence to the key role of GSK-3 β in AD pathogenesis. In particular, GSK-3 β is hyperactive and can phosphorylate tau, which aggregates to form neurofibrillary tangles [43].

Studies reporting Risk Ratios for developing Alzheimer’s disease

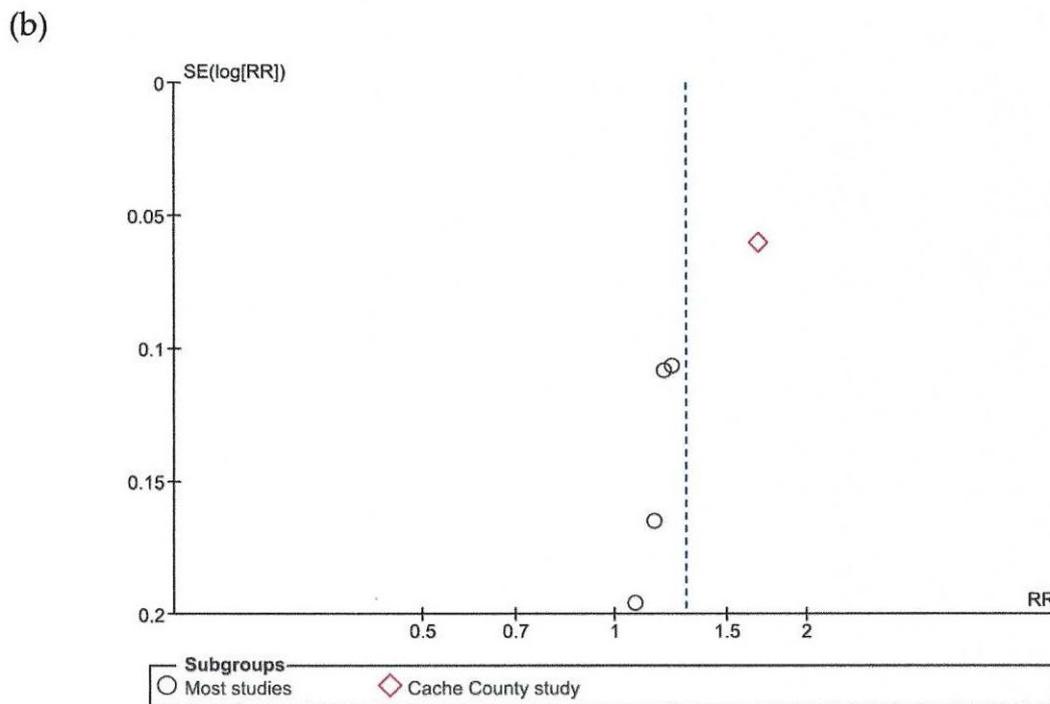
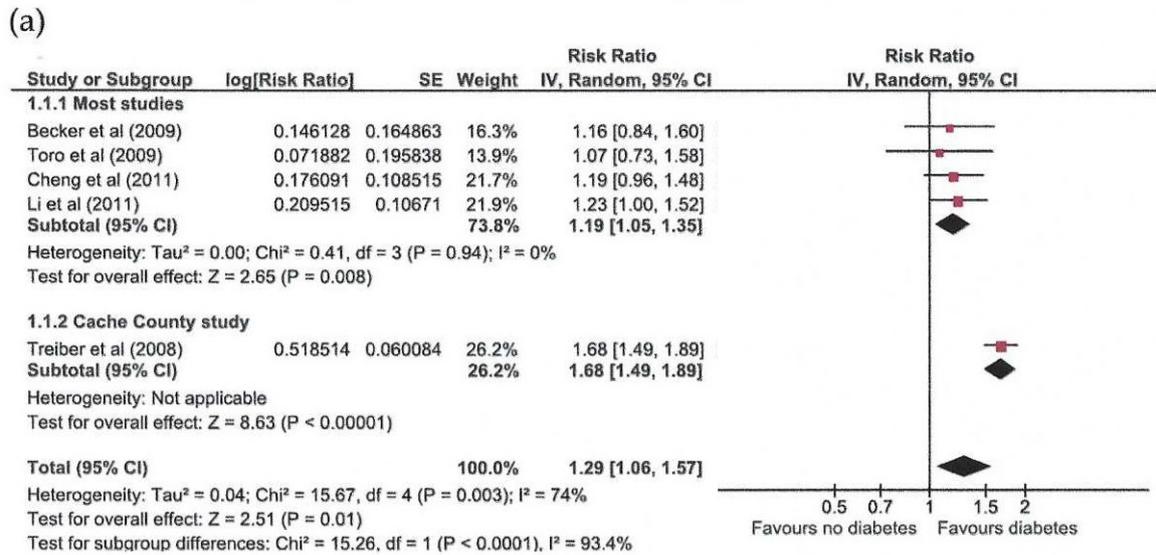


Figure 2. Meta-analysis (using the random effects model with the DerSimonian-Laird method) of studies reporting relative risks (RR) [17,19,20,23,33]. (a) Forest plot: effect sizes are represented as red squares with 95% confidence intervals. In the summary rows, the weighted average effect (or “combined” effect size) is represented as a diamond. (b) Funnel plot of the five studies included.

In light of the hallmarks of AD pathology, which are intracellular neurofibrillary tangles and extracellular Ab plaques, it is important to emphasize that hyperinsulinemia contributes to Ab toxicity as well. IDE is the metalloprotease insulin-degrading enzyme, responsible for the degradation of both Ab and insulin [44]. In T2DM, peripheral hyperinsulinemia causes Ab accumulation as a result of competition for IDE [45]. There is also evidence that brain insulin resistance may upregulate APP and b-secretase 1 (BACE 1) and increase, by extension, Ab formation [46].

At that point, the involvement of another crucial factor is necessary, as it can prevent the extent of the aforementioned processes. This factor is Glucagon-like peptide 1 (GLP-1), which is a product of post-translational processing on the proglucagon gene and is synthesized, including in the gastrointestinal tract, in the brainstem from the neurons of nucleus tractus solitarius, and it is transmitted to several cortical and subcortical areas, specifically to the hippocampus and cortical pyramidal neurons, of which those sites are abundant in GLP-1 receptors. GLP-1 mediates insulin secretion, decreases glucagon production and has protective properties on pancreatic β cells [47]. The regulation of peripheral insulin release prevents the development of hyperinsulinemia, which is associated with brain insulin resistance and reduced signaling. Thus, GLP-1 acts favorably on neuronal plasticity and prevents neurons from apoptosis [48,49].

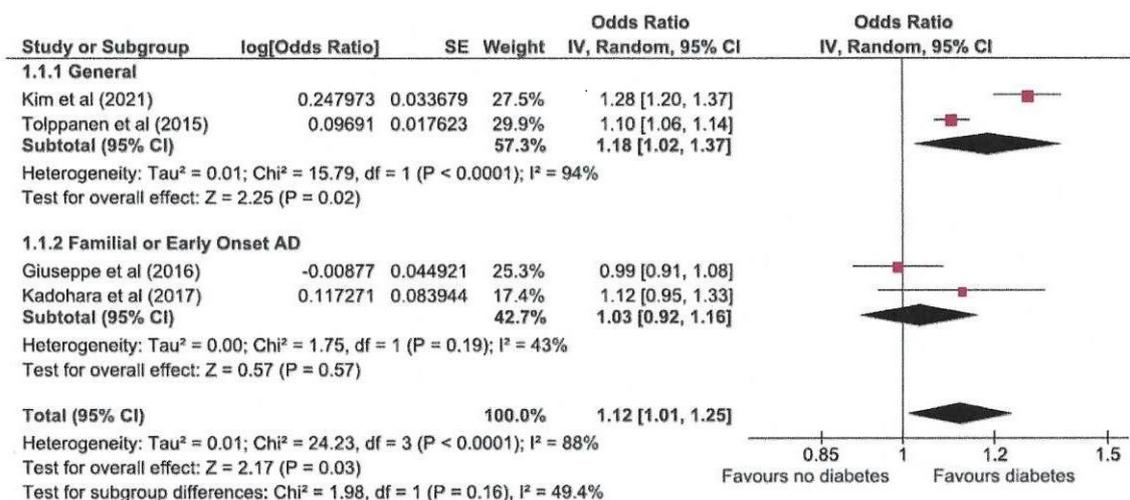
In addition, hyperglycemia plays a significant role in endothelial damage through the formation of advanced glycation end products (AGEs). These are glycated proteins and lipids formed by non-enzymatic glycosylation. The accumulation of AGEs provokes the subsequent increased expression of receptors of AGEs (RAGE) [50] which in turn stimulates inflammation, vascular injury [51] and oxidative stress. Mitochondrial dysfunction seems to be fundamental in AD pathogenesis [52]. Many research studies have focused on this theory and have included calcium imbalance in the common pathophysiological pathways of these two major diseases on a molecular level [53]. In terms of oxidative stress, a dysfunction in calcium homeostasis can activate abnormal calcium- and calmodulin-dependent protein kinases, with a final adverse effect in neuronal synapses [54].

5.3. The Role of Inflammatory Pathways

Inflammatory processes play a crucial role in the pathophysiological pathways linking AD and T2DM [55,56]. In T₂DM, as well as in insulin resistance, there is increased production of IL-6, IL-1 β , IL-18, tumor necrosis factor (TNF- α), alpha-1 antichymotrypsin and C-reactive protein [57–59]. The BBB in DM exhibits increased permeability [60] and is more susceptible to penetration from cytokines produced from the periphery, as it was noticed in a transgenic mouse model of AD [61]. Thus, the nervous tissue of AD patients may be more susceptible to peripheral inflammatory processes [62].

Studies reporting Odds Ratios for the presence of Alzheimer’s disease

(a)



(b)

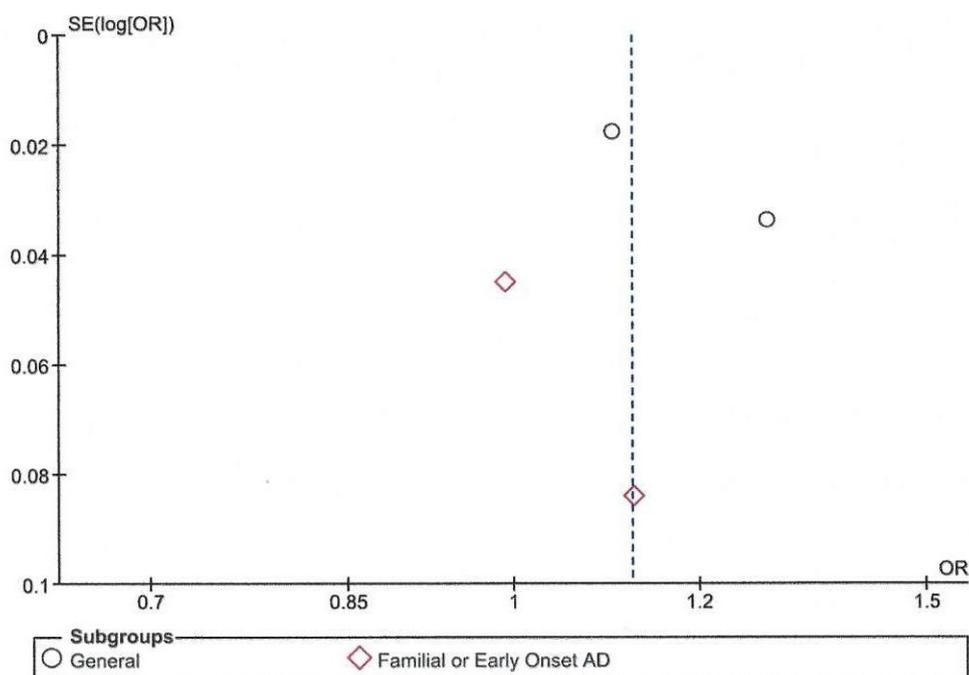


Figure 3. Meta-analysis (using the random effects model with the DerSimonian-Laird method) of studies reporting odds ratios (OR) [26–28,31]. (a) Forest plot: effect sizes are represented as red squares with 95% confidence intervals. In the summary rows, the weighted average effect (or “combined” effect size) is represented as a diamond. (b) Funnel plot of the four studies included.

Microglia express various receptors such as CD₁₄, CD₃₆, CD₄₇, a₆b₁ integrin, RAGE and Toll-like receptors which interact with Aβ oligomers [63]. In vitro findings indicate that the direction of microglia against Aβ can be regulated by the interaction of RAGE to Aβ [64]. Moreover, the connection of Aβ with CD₃₆ or TLR₄ can mobilize several inflammatory processes that augment neuronal destruction in specific areas of the brain in AD [63]. In T₂DM, insulin resistance produces AGEs due to oxidative stress, which leads to gluco-

toxicity and disruption of insulin signaling [65]. In various neurodegenerative diseases such as AD, these molecules interact with Toll-like receptors (TLRs) and RAGEs [65]. More specifically, in AD, interaction of RAGE with A β plays a crucial role in the pathophysiology of the disease.

The JNK (c-Jun N-terminal kinase) pathway is also important in insulin resistance and is a part of the signaling cascade of tumor necrosis factor α (TNF- α) [66]. This pathway is closely related to other stress kinases such as IKK (inhibitory κ B kinase) and PKR (double stranded RNA-dependent protein kinase) [67]. The IRS-1 protein is phosphorylated by the JNK and Ikba in the inhibitory serine 307 residue, resulting in a reduced effect of insulin attachment [68,69]. In AD patients, TNF- α , which is mainly produced by microglial cells, is augmented [70]. In this neurodegenerative disease, A β O (A β oligomers) aggregation results in the disposal of insulin receptors from the surface of cells [71–73]. The accumulation of A β in the brain causes the increased production of TNF- α from microglia, while A β oligomers trigger their receptors in neurons and stimulate stress kinases (JNK, PKR, IKK) additionally to TNF- α action [74–76]. IKK and PKR promote restriction of IRS-1 through A β oligomers in neurons of the hippocampus [74,76].

NF κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), which is provoked by a state of increased glucose and neuronal destruction, plays a significant role in the inflammatory process induced by diabetes [77,78]. Its activation causes the production of multiple inflammatory cytokines such as TNF- α and IL-6 [79] and can induce apoptosis. It has been suggested that, in streptozotocin-injected rats (a well-studied model mimicking DM), activation of NF κ B increases reactive oxygen species (ROS) in their hippocampus [68,80].

5.4. The Role of Autophagy

Autophagy is a degradative process that is used by cells to eliminate defective parts via a lysosome-dependent pathway [81]. Different forms of autophagy have been classified: macroautophagy, microautophagy, chaperone-mediated autophagy (CMA) and crinephagy [82]. One of the most common types of autophagy in neurons is macroautophagy, and it is severely impacted in AD patients [83,84]. Beclin 1 is a protein taking part in autophagy, and when it is expressed deficiently in neuronal cultures of transgenic mice, it can lead to increased production of A β and amyloid plaques [85]. Moreover, the absence of ATG7 (autophagy-related protein 7), another autophagy protein, in the forebrain of KO (knockout) mice, can lead to increased concentrations of phospho-tau in the neurons [86]. However, autophagic processes are also affected in T2DM patients' brain, since insulin resistance leads to increased generation of ROS, which impairs the ER (endoplasmic reticulum) and mitochondria, resulting in increased aggregation of misfolded proteins [87,88]. In order to investigate the connection between AD and DM as far as the autophagic processes are concerned, experimental models (OLEF rats) have been used [88]. In OLEF rats, increased concentrations of tau and phospho-tau were combined with the reduction of p62 protein, which is crucial for the autophagic degradation of tau [88]. In the brains of AD and T2DM mice models, a decrease in the levels of ATG7 and LC3-II (microtubule-associated proteins 1A/1B light chain 3B) has been observed, which may be important in autophagic pathways [89]. In conclusion, in T2DM, there is augmented oxidative stress that can cause dysfunction in autophagy, contributing to the gradual aggregation of proteins such as A β and tau, which can lead to the appearance of AD [35].

5.5. A β Oligomers and Amylin

The significance of A β oligomers in synaptic toxicity and their connection with brain insulin resistance has been described [90]. A β oligomers can bind to various receptors, such as RAGE and NMDA receptors, enhancing LTD (long term depression) at the synapses [91]. It is known that while LTP (long-term potentiation) promotes memory and is mediated by the GSK-3 β pathway [92], LTD contributes to the generation and progression of dementia [93].

Of note, recent studies have focused on another amyloidogenic molecule, namely amylin (islet amyloid polypeptide, IAPP), a pancreatic hormone that is oversecreted in insulin resistance [94] and can accumulate in brain tissue as well as in cerebral vessels [95]. This research provides an additional metabolic link between T2DM and AD since it indicates A β -amylin interaction and the presence of aggregated amylin in patients with both these diseases [96].

6. Concluding Remarks

Numerous studies have previously investigated the putative association between AD and other vascular risk factors, which could be modifiable, as in dyslipidemia [97], and is especially dependent upon insulin resistance [98]. The link with obesity through the excessive amount of free fatty acids (FFAs) and changes in the macrophages' phenotype within adipose tissue has also been indicated [99]. All these parameters pinpoint to the metabolic risk of AD and raise concepts about possible therapeutic implications. Considerable evidence highlights the potential benefit of antidiabetic drugs in AD [100], with many positive results indicated following the use of metformin, PPAR- γ and GLP-1 agonists.

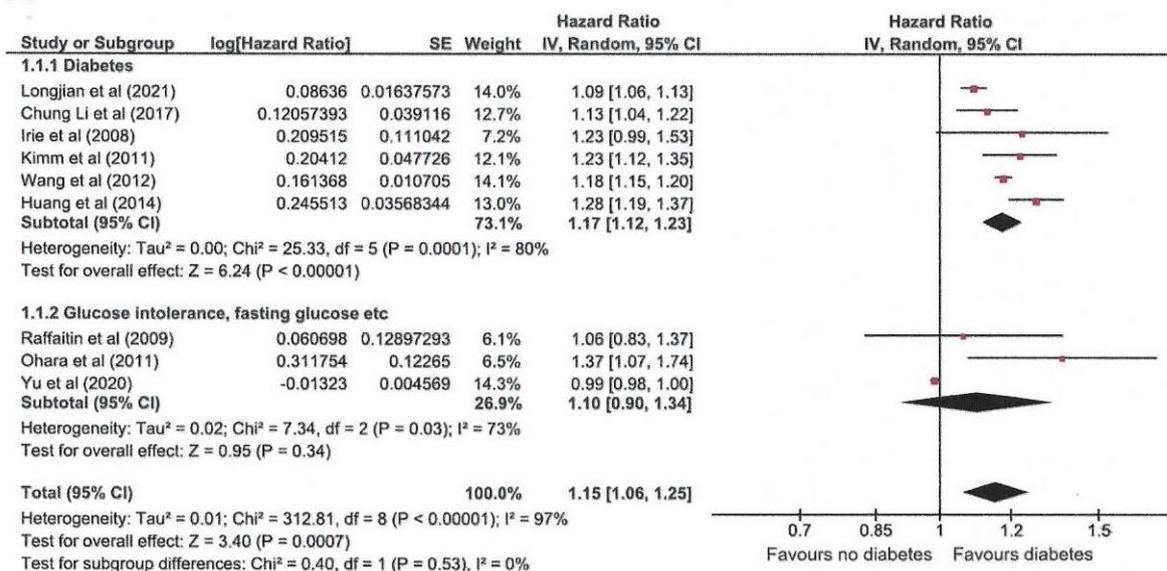
The hypoglycemic and neuroprotective properties of GLP-1 have led to the production of a variety of agonists. Many of those have been established in everyday practice as important anti-diabetic agents. In AD mouse models, these agents have shown the potential to suppress microglial activation and A β accumulation, thus delaying the disease course and ameliorating cognitive performance [101,102]. Liraglutide has been investigated in animal experimental models, as well as in randomized controlled trials, with promising results, showing increases in brain insulin signaling, and a possible effect on mental scale scores of patients with mild cognitive impairment [102–104]. Exenatide is another agent in the spotlight that has shown not only neuroprotective properties in AD transgenic mice [105,106], but also effects in mouse models of Parkinson's disease. Thus, mice treated with exendin-4 showed an increase in dopamine levels and in the density of neurons in the substantia nigra [107,108]. The GLP-1 analogue semaglutide may also protect from A β toxicity [109], and a clinical trial (EVOKE) has been launched to test its effect on early-onset AD.

An important observation concerns the impact of sex on AD incidence, indicated by previous studies on populations, such as postmenopausal women [32]. There is evidence that older women have an augmented incidence rate of AD dementia [110], and this phenomenon could be the result of an inflammatory imbalance, which is more prominent in females, especially in older ones due to the reduction of sex steroid hormones (e.g., progesterone and estrogen) [111]. Further, the hormonal dysregulation which is affected by nutritional lifestyle in this population is linked to insulin resistance, resulting in AD via this pathway as well [111].

Moreover, according to the included studies [19,23], the progression of mild cognitive impairment (MCI) in AD is of great interest, especially in patients with T2DM and MCI, because the early identification of these patients is the key for prevention of severe cognitive decline. Early remodeling of brain structural networks in these patients has been detected by diffusion tensor imaging (DTI) [112].

Studies reporting Hazard Ratios for developing Alzheimer’s disease

(a)



(b)

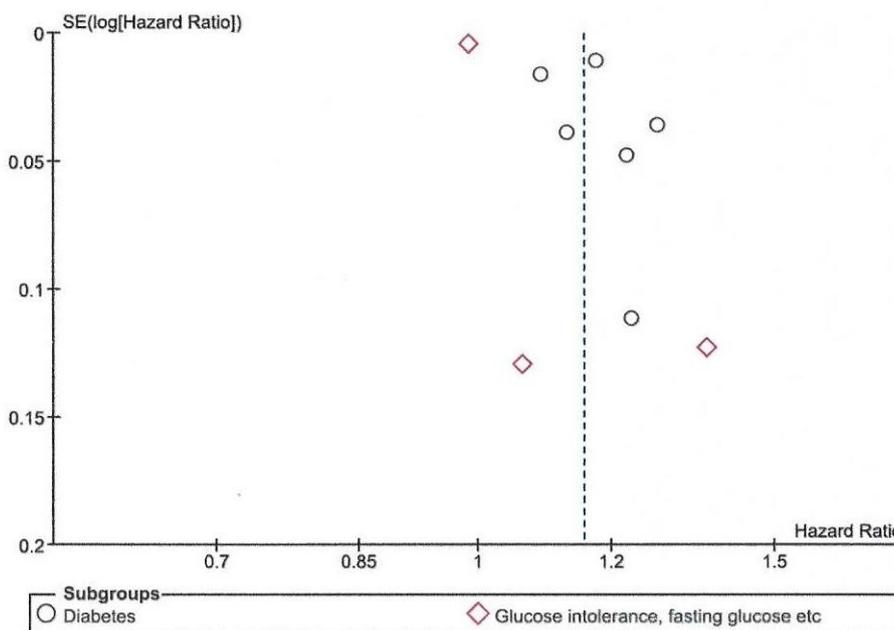


Figure 4. Meta-analysis (using the random effects model with the DerSimonian-Laird method) of studies reporting hazard ratios (HR) [16,18,21,22,24,25,29,30,32]. (a) Forest plot: effect sizes are represented as red squares with 95% confidence intervals. In the summary rows, the weighted average effect (or “combined” effect size) is represented as a diamond. (b) Funnel plot of the nine studies included.

The metabolic risk in AD is further supported by findings indicating defects in the insulin signaling pathway irrespective of diabetes [113]. This phenomenon suggests that brain insulin resistance in AD patients could be an adverse outcome of Ab aggregation independently of peripheral insulin resistance or diabetes [114]. Hence, a method to simulate brain insulin resistance in experimental animal models is important, and it has been proven that intracerebroventricular injection of streptozotocin in rats is a valid way to

mimic brain insulin resistance and, by extension, many aspects of sporadic AD [115,116]. As already mentioned, sporadic AD is complex because of its multifactorial heterogeneity. In particular, there are studies in rats that try to incorporate as many as possible etiological and risk factors, including the consequences of neuroinflammation, amyloid deposition, tau hyperphosphorylation and even changes of the hypothalamic–pituitary–adrenal (HPA) axis in cognitive impairment. An important AD-related vascular factor is also chronic cerebral hypoperfusion (CCH), provoked experimentally in rats via bilateral carotid artery stenosis, which has been referred to in these studies and indicates another major exacerbating factor in sporadic AD spectrum, interacting with amyloid toxicity and/or brain insulin resistance [116].

Generalization of the findings on DM as a risk factor for AD should also be confirmed by future studies on populations with a different prevalence of DM and different ethnic backgrounds, including the Mediterranean countries.

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References

1. Matthews, K.A.; Xu, W.; Gaglioti, A.H.; Holt, J.B.; Croft, J.B.; Mack, D.; McGuire, L.C. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥ 65 years. *Alzheimers Dement.* **2019**, *15*, 17–24. [[CrossRef](#)] [[PubMed](#)]
2. Bertram, L.; Tanzi, R.E. Genome-Wide Association Studies in Alzheimer's Disease. *Hum. Mol. Genet.* **2009**, *18*, 137–145. [[CrossRef](#)] [[PubMed](#)]
3. Li, J.; Tan, L.; Wang, H.; Tan, M.; Tan, L.; Xu, W.; Zhao, Q.; Wang, J.; Jiang, T.; Yu, J. Risk Factors for Predicting Progression from Mild Cognitive Impairment to Alzheimer's Disease: A Systematic Review and Meta-Analysis of Cohort Studies. *J. Neurol. Neurosurg. Psychiatry.* **2016**, *87*, 476–484. [[CrossRef](#)]
4. Gelber, R.P.; Launer, L.J.; White, L.R. The Honolulu-Asia Aging Study: Epidemiologic and neuropathologic research on cognitive impairment. *Curr. Alzheimer Res.* **2012**, *9*, 664–672. [[CrossRef](#)] [[PubMed](#)]
5. Jefferson, A.L.; Beiser, A.S.; Seshadri, S.; Wolf, P.A.; Au, R. APOE and Mild Cognitive Impairment: The Framingham Heart Study. *Age Ageing* **2015**, *44*, 307–311. [[CrossRef](#)] [[PubMed](#)]
6. Ott, A.; Stolk, R.P.; van Harskamp, F.; Pols, H.A.P.; Hofman, A.; Breteler, M.M.B. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **1999**, *53*, 1937. [[CrossRef](#)]
7. Leibson, C.L.; Rocca, W.A.; Hanson, V.A.; Cha, R.; Kokmen, E.; O'Brien, P.C.; Palumbo, P.J. Risk of Dementia among Persons with Diabetes Mellitus: A Population-Based Cohort Study. *Am. J. Epidemiol.* **1997**, *145*, 301–308. [[CrossRef](#)]
8. Yoshitake, T.; Kiyohara, Y.; Kato, I.; Ohmura, T.; Iwamoto, H.; Nakayama, K.; Ohmori, S.; Nomiyama, K.; Kawano, H.; Ueda, K.; et al. Incidence and Risk Factors of Vascular Dementia and Alzheimer's Disease in a Defined Elderly Japanese Population: The Hisayama Study. *Neurology* **1995**, *45*, 1161–1168. [[CrossRef](#)] [[PubMed](#)]
9. Craft, S.; Baker, L.; Montine, T.; Minoshima, S.; Watson, S.; Claxton, A.; Arbuckle, M.; Callaghan, M.; Tsai, E.; Plymate, S.; et al. Intranasal Insulin Therapy for Alzheimer Disease and Amnesic Mild Cognitive Impairment. *Arch. Neurol.* **2012**, *23*, 1–7. [[CrossRef](#)]
10. Shemesh, E.; Rudich, A.; Harman-Boehm, I.; Cukierman-Yaffe, T. Effect of Intranasal Insulin on Cognitive Function: A Systematic Review. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 366–376. [[CrossRef](#)] [[PubMed](#)]
11. Galindo-Mendez, B.; Trevino, J.A.; McGlinchey, R.; Fortier, C.; Lioutas, V.; Novak, P.; Mantzoros, C.; Ngo, L.; Novak, V. Memory Advancement by Intranasal Insulin in Type 2 Diabetes (MemAID) Randomized Controlled Clinical Trial: Design, Methods and Rationale. *Contemp. Clin. Trials.* **2020**, *89*, 105934. [[CrossRef](#)]

12. Rockwood, K.; Tan, M.-H.; Phillips, S.; McDowell, I. Prevalence of diabetes mellitus in elderly people in Canada: Report from the Canadian Study of Health and Aging. *Age Ageing* **1998**, *27*, 573–577. [[CrossRef](#)] [[PubMed](#)]
13. Gottesman, R.; Schneider, A.; Zhou, Y.; Coresh, J.; Green, E.; Gupta, N.; Knopman, D.; Mintz, A.; Rahmim, A.; Sharrett, R.; et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* **2017**, *176*, 139–148. [[CrossRef](#)]
14. Jack, C.R.; Bennett, D.A.; Blennow, K.; Carrillo, M.C.; Dunn, B.; Haeberlein, S.B.; Holtzman, D.M.; Jagust, W.; Jessen, F.; Karlawish, J.; et al. NIA-AA Research Framework: Toward a Biological Definition of Alzheimer’s Disease. *Alzheimer Dement.* **2018**, *14*, 535–562. [[CrossRef](#)]
15. Suurmond, R.; van Rhee, H.; Hak, T. Introduction, Comparison, and Validation of Meta-Essentials: A Free and Simple Tool for Meta-Analysis. *Res. Synth. Methods* **2017**, *8*, 537–553. [[CrossRef](#)] [[PubMed](#)]
16. Irie, F.; Fitzpatrick, A.L.; Lopez, O.L.; Kuller, L.H.; Peila, R.; Newman, A.B.; Launer, L.J. Enhanced Risk for Alzheimer Disease in Persons With Type 2 Diabetes and APOE E4. *Arch. Neurol.* **2008**, *65*, 89–94. [[CrossRef](#)]
17. Becker, J.T.; Chang, Y.F.; Lopez, O.L.; Dew, M.A.; Sweet, R.A.; Barnes, D.; Yaffe, K.; Young, J.; Kuller, L.; Reynolds, C.F. Depressed Mood Is Not a Risk Factor for Incident Dementia in a Community-Based Cohort. *Am. J. Geriatr. Psychiatry* **2009**, *17*, 653–663. [[CrossRef](#)] [[PubMed](#)]
18. Raffaitin, C.; Gin, H.; Empana, J.P.; Helmer, C.; Berr, C.; Tzourio, C.; Portet, F.; Dartigues, J.F.; Alperovitch, A.; Barberger-Gateau, P. Metabolic Syndrome and Risk for Incident Alzheimer’s Disease or Vascular Dementia. *Diabetes Care* **2009**, *32*, 169–174. [[CrossRef](#)] [[PubMed](#)]
19. Toro, P.; Schönknecht, P.; Schröder, J. Type II Diabetes in Mild Cognitive Impairment and Alzheimer’s Disease: Results from a Prospective Population-Based Study in Germany. *J. Alzheimer Dis.* **2009**, *16*, 687–691. [[CrossRef](#)] [[PubMed](#)]
20. Cheng, D.; Noble, J.; Tang, M.X.; Schupf, N.; Mayeux, R.; Luchsinger, J.A. Type 2 Diabetes and Late-Onset Alzheimer’s Disease. *Dement. Geriatr. Cogn. Disord.* **2011**, *31*, 424–430. [[CrossRef](#)] [[PubMed](#)]
21. Ohara, T.; Doi, Y.; Ninomiya, T.; Hirakawa, Y.; Hata, J.; Iwaki, T.; Kanba, S.; Kiyohara, Y. Glucose Tolerance Status and Risk of Dementia in the Community: The Hisayama Study. *Neurology* **2011**, *77*, 1126–1134. [[CrossRef](#)]
22. Kimm, H.; Lee, P.H.; Shin, Y.J.; Park, K.S.; Jo, J.; Lee, Y.; Kang, H.C.; Jee, S.H. Mid-Life and Late-Life Vascular Risk Factors and Dementia in Korean Men and Women. *Arch. Gerontol. Geriatr.* **2011**, *52*, 117–122. [[CrossRef](#)] [[PubMed](#)]
23. Li, J.; Wang, Y.J.; Zhang, M.; Xu, Z.Q.; Gao, C.Y.; Fang, C.Q.; Yan, J.C.; Zhou, H.D. Vascular Risk Factors Promote Conversion from Mild Cognitive Impairment to Alzheimer Disease. *Neurology* **2011**, *76*, 1485–1491. [[CrossRef](#)] [[PubMed](#)]
24. Wang, K.C.; Wong, L.C.; Tsai, M.T.; Liu, C.C.; Su, Y.H.; Li, C.Y. Risk of Alzheimer’s Disease in Relation to Diabetes: A Population-Based Cohort Study. *Neuroepidemiology* **2012**, *38*, 237–244. [[CrossRef](#)]
25. Huang, C.C.; Chung, C.M.; Leu, H.B.; Lin, L.Y.; Chiu, C.C.; Hsu, C.Y.; Chiang, C.H.; Huang, P.H.; Chen, T.J.; Lin, S.J.; et al. Diabetes Mellitus and the Risk of Alzheimer’s Disease: A Nationwide Population-Based Study. *PLoS ONE* **2014**, *9*, e87095. [[CrossRef](#)]
26. Tolppanen, A.M.; Lavikainen, P.; Solomon, A.; Kivipelto, M.; Uusitupa, M.; Soininen, H.; Hartikainen, S. History of Medically Treated Diabetes and Risk of Alzheimer Disease in a Nationwide Case-Control Study. *Diabetes Care* **2013**, *36*, 2015–2019. [[CrossRef](#)]
27. Tosto, G.; Bird, T.D.; Bennett, D.A.; Boeve, B.F.; Brickman, A.M.; Cruchaga, C.; Faber, K.; Foroud, T.M.; Farlow, M.; Goate, A.M.; et al. The Role of Cardiovascular Risk Factors and Stroke in Familial Alzheimer Disease. *JAMA Neurol.* **2016**, *73*, 1231–1237. [[CrossRef](#)] [[PubMed](#)]
28. Kadohara, K.; Sato, I.; Kawakami, K. Diabetes Mellitus and Risk of Early-Onset Alzheimer’s Disease: A Population-Based Case-Control Study. *Eur. J. Neurol.* **2017**, *24*, 944–949. [[CrossRef](#)] [[PubMed](#)]
29. Li, T.C.; Yang, C.P.; Tseng, S.T.; Li, C.I.; Liu, C.S.; Lin, W.Y.; Hwang, K.L.; Yang, S.Y.; Chiang, J.H.; Lin, C.C. Visit-to-Visit Variations in Fasting Plasma Glucose and HbA1c Associated with an Increased Risk of Alzheimer Disease: Taiwan Diabetes Study. *Diabetes Care* **2017**, *40*, 1210–1217. [[CrossRef](#)] [[PubMed](#)]
30. Yu, J.H.; Han, K.; Park, S.; Cho, H.; Lee, D.Y.; Kim, J.W.; Seo, J.A.; Kim, S.G.; Baik, S.H.; Park, Y.G.; et al. Incidence and Risk Factors for Dementia in Type 2 Diabetes Mellitus: A Nationwide Population-Based Study in Korea. *Diabetes Metab. J.* **2020**, *44*, 113–124. [[CrossRef](#)] [[PubMed](#)]
31. Kim, Y.J.; Kim, S.M.; Jeong, D.H.; Lee, S.K.; Ahn, M.E.; Ryu, O.H. Associations between Metabolic Syndrome and Type of Dementia: Analysis Based on the National Health Insurance Service Database of Gangwon Province in South Korea. *Diabetol. Metab. Syndr.* **2021**, *13*, 1–12. [[CrossRef](#)] [[PubMed](#)]
32. Liu, L.; Gracely, E.J.; Yin, X.; Eisen, H.J. Impact of Diabetes Mellitus and Cardiometabolic Syndrome on the Risk of Alzheimer’s Disease among Postmenopausal Women. *World J. Diabetes* **2021**, *12*, 69–83. [[CrossRef](#)]
33. Treiber, K.A.; Lyketsos, C.G.; Corcoran, C.; Steinberg, M.; Norton, M.; Green, R.C.; Rabins, P.; Stein, D.M.; Welsh-Bohmer, K.A.; Breitner, J.C.; et al. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer’s disease: The Cache County Study. *Int. Psychogeriatr.* **2008**, *20*, 538–553. [[CrossRef](#)] [[PubMed](#)]
34. Li, W.; Huang, E.; Gao, S. Type 1 Diabetes Mellitus and Cognitive Impairments: A Systematic Review. *J. Alzheimer Dis.* **2017**, *57*, 29–36. [[CrossRef](#)] [[PubMed](#)]
35. Chatterjee, S.; Mudher, A. Alzheimer’s Disease and Type 2 Diabetes: A Critical Assessment of the Shared Pathological Traits. *Front. Neurosci.* **2018**, *12*, 383. [[CrossRef](#)]
36. Banks, W.A.; Jaspan, J.B.; Huang, W.; Kastin, A.J. Transport of Insulin Across the Blood-Brain Barrier: Saturability at Euglycemic Doses of Insulin. *Peptides* **1997**, *18*, 1423–1429. [[CrossRef](#)]

37. Kim, B.; Feldman, E. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. *Exp. Mol. Med.* **2015**, *47*, e149. [[CrossRef](#)] [[PubMed](#)]
38. Ghasemi, R.; Dargahi, L.; Haeri, A.; Moosavi, M.; Mohamed, Z.; Ahmadiani, A. Brain Insulin Dysregulation: Implication for Neurological and Neuropsychiatric Disorders. *Mol. Neurobiol.* **2013**, *47*, 1045–1065. [[CrossRef](#)] [[PubMed](#)]
39. Plum, L.; Schubert, M.; Brüning, J.C. The role of insulin receptor signaling in the brain. *Trends Endocrinol. Metab.* **2005**, *16*, 59–65. [[CrossRef](#)] [[PubMed](#)]
40. Shah, K.K.; DeSilva, S.; Abbruscato, T.J. The Role of Glucose Transporters in Brain Disease: Diabetes and Alzheimer's Disease. *Int. J. Mol. Sci.* **2012**, *13*, 12629–12655. [[CrossRef](#)] [[PubMed](#)]
41. Avila, J.; León-Espinosa, G.; García, E.; García-Escudero, V.; Hernández, F.; DeFelipe, J. Tau Phosphorylation by GSK3 in Different Conditions. *Int. J. Alzheimer's Dis.* **2012**, *2012*, 1–7. [[CrossRef](#)]
42. Banks, W.A.; Owen, J.B.; Erickson, M.A. Insulin in the Brain: There and Back Again. *Pharmacol. Ther.* **2012**, *136*, 82–93. [[CrossRef](#)] [[PubMed](#)]
43. Avila, J.; Wandosell, F.; Hernández, F. Role of glycogen synthase kinase-3 in Alzheimer's disease pathogenesis and glycogen synthase kinase-3 inhibitors. *Expert Rev. Neurother.* **2010**, *10*, 703–710. [[CrossRef](#)] [[PubMed](#)]
44. Qiu, W.Q.; Folstein, M.F. Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: Review and hypothesis. *Neurobiol. Aging* **2006**, *27*, 190–198. [[CrossRef](#)]
45. Bosco, D.; Fava, A.; Plastino, M.; Montalcini, T.; Pujia, A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. *J. Cell. Mol. Med.* **2011**, *15*, 1807–1821. [[CrossRef](#)]
46. Devi, L.; Alldred, M.J.; Ginsberg, S.D.; Ohno, M. Mechanisms Underlying Insulin Deficiency-Induced Acceleration of β -Amyloidosis in a Mouse Model of Alzheimer's Disease. *PLoS ONE* **2012**, *7*, e32792. [[CrossRef](#)] [[PubMed](#)]
47. Calsolaro, V.; Edison, P. Novel GLP-1 (Glucagon-Like Peptide-1) Analogues and Insulin in the Treatment for Alzheimer's Disease and Other Neurodegenerative Diseases. *CNS Drugs* **2015**, *29*, 1023–1039. [[CrossRef](#)] [[PubMed](#)]
48. Holst, J.J. Glucagon-like Peptide 1 (GLP-1): An Intestinal Hormone, Signalling Nutritional Abundance, with an Unusual Therapeutic Potential. *Trends Endocrinol. Metab.* **1999**, *10*, 229–235. [[CrossRef](#)]
49. Duarte, A.I.; Candeias, E.; Correia, S.C.; Santos, R.X.; Carvalho, C.; Cardoso, S.; Plácido, A.; Santos, M.S.; Oliveira, C.R.; Moreira, P.I. Crosstalk between Diabetes and Brain: Glucagon-like Peptide-1 Mimetics as a Promising Therapy against Neurodegeneration. *Biochim. Et Biophys. Acta Mol. Basis Dis.* **2013**, *1832*, 527–541. [[CrossRef](#)] [[PubMed](#)]
50. Solito, E.; Sastre, M. Microglia Function in Alzheimer's Disease. *Front. Pharmacol.* **2012**, *3*, 14. [[CrossRef](#)] [[PubMed](#)]
51. Goldin, A.; Beckman, J.A.; Schmidt, A.M.; Creager, M.A. Advanced Glycation End Products: Sparking the Development of Diabetic Vascular Injury. *Circulation* **2006**, *114*, 597–605. [[CrossRef](#)]
52. Chaturvedi, R.K.; Beal, M.F. Author 's Accepted Manuscript Mitochondrial Diseases of the Brain. *Free. Radic. Biol. Med.* **2013**, *63*, 1–29. [[CrossRef](#)] [[PubMed](#)]
53. Nisar, O.; Pervez, H.; Mandalia, B.; Waqas, M.; Sra, H.K. Type 3 Diabetes Mellitus: A Link Between Alzheimer's Disease and Type 2 Diabetes Mellitus. *Cureus* **2020**, *12*, 10–13. [[CrossRef](#)] [[PubMed](#)]
54. Zhang, S.; Chai, R.; Yang, Y.-Y.; Guo, S.-Q.; Wang, S.; Guo, T.; Xu, S.-F.; Zhang, Y.-H.; Wang, Z.-Y.; Guo, C. Chronic diabetic states worsen Alzheimer neuropathology and cognitive deficits accompanying disruption of calcium signaling in leptin-deficient APP/PS1 mice. *Oncotarget* **2017**, *8*, 43617–43634. [[CrossRef](#)]
55. Gregor, M.F.; Hotamisligil, G.S. Inflammatory Mechanisms in Obesity. *Annu. Rev. Immunol.* **2011**, *29*, 415–445. [[CrossRef](#)] [[PubMed](#)]
56. Ferreira, S.T.; Clarke, J.R.; Bomfim, T.R.; Felice, F.G. de Inflammation, Defective Insulin Signaling, and Neuronal Dysfunction in Alzheimer's Disease. *JALZ* **2014**, *10*, S76–S83. [[CrossRef](#)]
57. Hak, A.E.; Pols, H.A.; Stehouwer, C.D.; Meijer, J.; Kiliaan, A.J.; Hofman, A.; Breteler, M.M.; Witteman, J.C. Markers of Inflammation and Cellular Adhesion Molecules in Relation to Insulin Resistance in Nondiabetic Elderly: The Rotterdam Study. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 4398–4405. [[CrossRef](#)]
58. Hotamisligil, G.S. Inflammatory pathways and insulin action. *Int. J. Obes.* **2003**, *27*, 53–55. [[CrossRef](#)] [[PubMed](#)]
59. Zietek, T.; Rath, E. Inflammation Meets Metabolic Disease: Gut Feeling Mediated by GLP-1. *Front. Immunol.* **2016**, *7*, 154. [[CrossRef](#)]
60. Acharya, N.K.; Levin, E.C.; Clifford, P.M.; Han, M.; Tourtellotte, R.; Chamberlain, D.; Pollaro, M.; Coretti, N.J.; Kosciuk, M.C.; Nagele, E.P.; et al. Diabetes and Hypercholesterolemia Increase Blood-Brain Barrier Permeability and Brain Amyloid Deposition: Beneficial Effects of the LpPLA2 Inhibitor Darapladib. *J. Alzheimer Dis.* **2013**, *35*, 179–198. [[CrossRef](#)] [[PubMed](#)]
61. Takeda, S.; Sato, N.; Ikimura, K.; Nishino, H.; Rakugi, H. Neurobiology of Aging Increased Blood e Brain Barrier Vulnerability to Systemic Inflammation in an Alzheimer Disease Mouse Model. *Neurobiol. Aging* **2013**, *34*, 2064–2070. [[CrossRef](#)]
62. De Felice, F.G.; Ferreira, S.T. Inflammation, Defective Insulin Signaling, and Mitochondrial Dysfunction as Common Molecular Denominators Connecting Type 2 Diabetes to Alzheimer Disease. *Diabetes* **2014**, *63*, 2262–2272. [[CrossRef](#)]
63. Doens, D.; Fernández, P.L. Microglia receptors and their implications in the response to amyloid β for Alzheimer's disease pathogenesis. *J. Neuroinflammation* **2014**, *11*, 48. [[CrossRef](#)] [[PubMed](#)]
64. Wyss-Coray, T.; Rogers, J. Inflammation in Alzheimer Disease—A Brief Review of the Basic Science and Clinical Literature. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006346. [[CrossRef](#)]

65. Özcan, U.; Cao, Q.; Yilmaz, E.; Lee, A.; Iwakoshi, N.N.; Özdelen, E.; Tuncman, G.; Görgün, C.; Glimcher, L.; Hotamisligil, G. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **2004**, *306*, 457–461. [[CrossRef](#)] [[PubMed](#)]
66. Hirosumi, J.; Tuncman, G.; Chang, L.; Görgün, C.Z.; Uysal, K.T.; Maeda, K.; Karin, M.; Hotamisligil, G.S. A Central Role for JNK in Obesity and Insulin Resistance. *Nature* **2002**, *420*, 333–336. [[CrossRef](#)] [[PubMed](#)]
67. Nakamura, T.; Furuhashi, M.; Li, P.; Cao, H.; Tuncman, G.; Sonenberg, N.; Gorgun, C.Z.; Hotamisligil, G.S. Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. *Cell* **2010**, *140*, 338–348. [[CrossRef](#)] [[PubMed](#)]
68. Jaeschke, A.; Czech, M.P.; Davis, R.J. An essential role of the JIP1 scaffold protein for JNK activation in adipose tissue. *Genes Dev.* **2004**, *18*, 1976–1980. [[CrossRef](#)] [[PubMed](#)]
69. Morel, C.; Standen, C.L.; Jung, D.Y.; Gray, S.; Ong, H.; Flavell, R.A.; Kim, J.K.; Davis, R.J. Requirement of JIP1-Mediated c-Jun N-Terminal Kinase Activation for Obesity-Induced Insulin Resistance. *Mol. Cell. Biol.* **2010**, *30*, 4616–4625. [[CrossRef](#)] [[PubMed](#)]
70. Grammas, P.; Ovase, R. Inflammatory Factors Are Elevated in Brain Microvessels in Alzheimer’s Disease. *Neurobiol. Aging* **2001**, *22*, 837–842. [[CrossRef](#)]
71. Zhao, W.; De Felice, F.G.; Fernandez, S.; Chen, H.; Lambert, M.P.; Quon, M.; Krafft, G.A.; Klein, W.L. Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J.* **2007**, *22*, 246–260. [[CrossRef](#)] [[PubMed](#)]
72. De Felice, F.G.; Wu, D.; Lambert, M.P.; Fernandez, S.J.; Velasco, P.T.; Lacor, P.N.; Bigio, E.H.; Jerecic, J.; Acton, P.J.; Paul, J. Alzheimer’s disease-type neuronal tau hyperphosphorylation induced by A beta oligomers. *Neurobiol. Aging* **2008**, *29*, 1334–1347. [[CrossRef](#)] [[PubMed](#)]
73. Lourenco, M.V.; Ferreira, S.T.; De Felice, F.G. Neuronal stress signaling and eIF2 α phosphorylation as molecular links between Alzheimer’s disease and diabetes. *Prog. Neurobiol.* **2015**, *129*, 37–57. [[CrossRef](#)] [[PubMed](#)]
74. Bomfim, T.R.; Forny-Germano, L.; Sathler, L.B.; Brito-Moreira, J.; Houzel, J.; Decker, H.; Silverman, M.A.; Kazi, H.; Melo, H.M.; Mcclean, P.L.; et al. An Anti-Diabetes Agent Protects the Mouse Brain from Defective Insulin Signaling Caused by Alzheimer’s Disease-Associated A β Oligomers. *J. Clin. Invest.* **2012**, *122*, 1339–1353. [[CrossRef](#)] [[PubMed](#)]
75. Ledo, J.H.; Azevedo, E.P.; Clarke, J.R.; Ribeiro, F.C.; Figueiredo, C.P.; Foguel, D.; de Felice, F.G.; Ferreira, S.T. Amyloid- β Oligomers Link Depressive-like Behavior and Cognitive Deficits in Mice. *Mol. Psychiatry* **2013**, *18*, 1053–1054. [[CrossRef](#)] [[PubMed](#)]
76. Lourenco, M.V.; Clarke, J.R.; Frozza, R.L.; Bomfim, T.R.; Batista, F.; Sathler, L.B.; Brito-moreira, J.; Amaral, O.B.; Silva, C.A.; Campello-Costa, P.; et al. TNF- α Mediates PKR-Dependent Memory Impairment and Brain IRS-1 Inhibition Induced by Alzheimer’s β -Amyloid Oligomers in Mice and Monkeys. *Cell. Metab.* **2013**, *18*, 831–843. [[CrossRef](#)] [[PubMed](#)]
77. Romeo, G.; Liu, W.-H.; Asnaghi, V.; Kern, T.S.; Lorenzi, M. Activation of Nuclear Factor- κ B Induced by Diabetes and High Glucose Regulates a Proapoptotic Program in Retinal Pericytes. *Diabetes* **2002**, *51*, 2241–2248. [[CrossRef](#)]
78. Wellen, K.E.; Hotamisligil, G.S. Inflammation, Stress, and Diabetes. *J. Clin. Invest.* **2005**, *115*, 1111–1119. [[CrossRef](#)]
79. Shoelson, S.E.; Lee, J.; Yuan, M. Inflammation and the IKK β /I κ B/NF- κ B axis in obesity- and diet-induced insulin resistance. *Int. J. Obes.* **2003**, *27*, 49–52. [[CrossRef](#)]
80. Locke, M.; Anderson, J. NF- κ B Activation in Organs from STZ-Treated Rats. *Appl. Physiol. Nutr. Metab.* **2011**, *36*, 121–127. [[CrossRef](#)] [[PubMed](#)]
81. Klionsky, D.J. Autophagy revisited: A conversation with Christian de Duve. *Autophagy* **2008**, *4*, 740–743. [[CrossRef](#)] [[PubMed](#)]
82. Csizmadia, T.; Juhász, G. *Crinophagy Mechanisms and Its Potential Role in Human Health and Disease*, 1st ed.; Elsevier Inc.: Amsterdam, The Netherlands, 2020.
83. Frake, R.; Ricketts, T.; Menzies, F.M.; Rubinsztein, D.C. Autophagy and neurodegeneration. *J. Clin. Investig.* **2015**, *125*, 65–74. [[CrossRef](#)] [[PubMed](#)]
84. Nixon, R.A. Autophagy, amyloidogenesis and Alzheimer disease. *J. Cell Sci.* **2007**, *120*, 4081–4091. [[CrossRef](#)] [[PubMed](#)]
85. Pickford, F.; Masliah, E.; Britschgi, M.; Lucin, K.; Narasimhan, R.; Jaeger, P.A.; Small, S.; Spencer, B.; Rockenstein, E.; Levine, B.; et al. The Autophagy-Related Protein Beclin 1 Shows Reduced Expression in Early Alzheimer Disease and Regulates Amyloid beta Accumulation in Mice. *J. Clin. Invest.* **2008**, *118*, 2190–2199.
86. Inoue, K.; Rispoli, J.; Kaphzan, H.; Klann, E.; Chen, E.I.; Kim, J.; Komatsu, M.; Abeliovich, A. Macroautophagy Deficiency Mediates Age-Dependent Neurodegeneration through a Phospho-Tau Pathway. *Mol. Neurodegener.* **2012**, *7*, 48. [[CrossRef](#)] [[PubMed](#)]
87. Quan, W.; Lim, Y.; Lee, M. Role of Autophagy in Diabetes and Endoplasmic Reticulum Stress of Pancreatic β -Cells. *Exp. Mol. Med.* **2012**, *44*, 81–88. [[CrossRef](#)] [[PubMed](#)]
88. Jung, H.; Soon, S.; Oh, J.; Kyeong, T.; Sik, C.; Ah, S. Increased Expression of Three-Repeat Isoforms of Tau Contributes to Tau Pathology in a Rat Model of Chronic Type 2 Diabetes. *Exp. Neurol.* **2011**, *228*, 232–241. [[CrossRef](#)]
89. Carvalho, C.; Santos, M.S.; Oliveira, C.R.; Moreira, P.I. Alzheimer’s Disease and Type 2 Diabetes-Related Alterations in Brain Mitochondria, Autophagy and Synaptic Markers. *Biochim. Biophys. Acta-Mol. Basis Dis.* **2015**, *1852*, 1665–1675. [[CrossRef](#)] [[PubMed](#)]
90. Zhao, W.; Townsend, M. Biochimica et Biophysica Acta Insulin Resistance and Amyloidogenesis as Common Molecular Foundation for Type 2 Diabetes and Alzheimer’s Disease. *BBA-Mol. Basis Dis.* **2009**, *1792*, 482–496. [[CrossRef](#)] [[PubMed](#)]

91. Batista, A.F.; Forny-Germano, L.; Clarke, J.R.; Lyra E Silva, N.M.; Brito-Moreira, J.; Boehnke, S.E.; Winterborn, A.; Coe, B.C.; Lablans, A.; Vital, J.F.; et al. The Diabetes Drug Liraglutide Reverses Cognitive Impairment in Mice and Attenuates Insulin Receptor and Synaptic Pathology in a Non-Human Primate Model of Alzheimer's Disease. *J. Pathol.* **2018**, *245*, 85–100. [[CrossRef](#)] [[PubMed](#)]
92. Bradley, C.A.; Peineau, S.; Taghibiglou, C.; Nicolas, C.S.; Whitcomb, D.J.; Bortolotto, Z.A.; Kaang, B.-K.; Cho, K.; Wang, Y.T.; Collingridge, G.L. A pivotal role of GSK-3 in synaptic plasticity. *Front. Mol. Neurosci.* **2012**, *5*, 13. [[CrossRef](#)]
93. Lourenco, M.V.; Frozza, R.L.; De Freitas, G.B.; Zhang, H.; Kincheski, G.C.; Ribeiro, F.C.; Gonçalves, R.A.; Clarke, J.R.; Beckman, D.; Staniszewski, A.; et al. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat. Med.* **2019**, *25*, 165–175. [[CrossRef](#)] [[PubMed](#)]
94. Lim, Y.; Rhein, V.; Baysang, G.; Meier, F.; Poljak, A.; Raftery, M.J.; Guilhaus, M.; Ittner, L.M.; Ekert, A.; Götz, J. Abeta and Human Amylin Share a Common Toxicity Pathway via Mitochondrial Dysfunction. *Proteomics* **2010**, *10*, 1621–1633. [[CrossRef](#)] [[PubMed](#)]
95. Srodulski, S.; Sharma, S.; Bachstetter, A.B.; Brelsfoard, J.M.; Pascual, C.; Xie, X.S.; Saatman, K.E.; Van Eldik, L.J.; Despa, F. Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin. *Mol. Neurodegener.* **2014**, *9*, 30. [[CrossRef](#)]
96. Jackson, K.; Barisone, G.A.; Diaz, E.; Jin, L.W.; DeCarli, C.; Despa, F. Amylin deposition in the brain: A second amyloid in Alzheimer disease? *Ann Neurol.* **2013**, *74*, 517–526. [[CrossRef](#)] [[PubMed](#)]
97. Reitz, C. Dyslipidemia and the Risk of Alzheimer's Disease. *Curr. Atheroscler. Rep.* **2013**, *15*, 307. [[CrossRef](#)] [[PubMed](#)]
98. Hong, S.; Han, K.; Park, C.-Y. The insulin resistance by triglyceride glucose index and risk for dementia: Population-based study. *Alzheimer's Res. Ther.* **2021**, *13*, 9. [[CrossRef](#)] [[PubMed](#)]
99. Hanson, A.J.; Rubinow, K.B. Optimizing Clinical Phenotyping to Better Delineate the Complex Relationship between Type 2 Diabetes and Alzheimer's Disease. *Clin. Transl. Sci.* **2021**, *14*, 1681–1688. [[CrossRef](#)] [[PubMed](#)]
100. Tumminia, A.; Vinciguerra, F.; Parisi, M.; Frittitta, L. Type 2 Diabetes Mellitus and Alzheimer's Disease: Role of Insulin Signalling and Therapeutic Implications. *Int. J. Mol. Sci.* **2018**, *19*, 3306. [[CrossRef](#)]
101. During, M.J.; Cao, L.; Zuzga, D.S.; Francis, J.S.; Fitzsimons, H.L.; Jiao, X.; Bland, R.J.; Klugmann, M.; Banks, W.A.; Drucker, D.J.; et al. Glucagon-like Peptide-1 Receptor Is Involved in Learning and Neuroprotection. *Nat. Med.* **2003**, *9*, 1173–1179. [[CrossRef](#)] [[PubMed](#)]
102. Mcclean, P.L.; Parthasarathy, V.; Faivre, E.; Holscher, C. The Diabetes Drug Liraglutide Prevents Degenerative Processes in a Mouse Model of Alzheimer's Disease. *J. Neurosci.* **2011**, *31*, 6587–6594. [[CrossRef](#)] [[PubMed](#)]
103. Talbot, K. Brain Insulin Resistance in Alzheimer's Disease and Its Potential Treatment with GLP-1 Analogs. *Neurodegener. Dis. Manag.* **2014**, *4*, 31–40. [[CrossRef](#)] [[PubMed](#)]
104. Femminella, G.D.; Frangou, E.; Love, S.B.; Busza, G.; Holmes, C.; Ritchie, C.; Lawrence, R.; Mcfarlane, B.; Tadros, G.; Ridha, B.H.; et al. Evaluating the Effects of the Novel GLP-1 Analogue Liraglutide in Alzheimer's Disease: Study Protocol for a Randomised Controlled Trial (ELAD Study). *Trials* **2019**, *20*, 191. [[CrossRef](#)] [[PubMed](#)]
105. Li, Y.; Duffy, K.B.; Ottinger, M.A.; Ray, B.; Bailey, J.A.; Holloway, H.W.; Tweedie, D.; Perry, T.; Mattson, M.P.; Kapogiannis, D.; et al. GLP-1 Receptor Stimulation Reduces Amyloid- β Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease. *J. Alzheimer's Dis.* **2010**, *19*, 1205–1219. [[CrossRef](#)]
106. Rachmany, L.; Tweedie, D.; Li, Y.; Rubovitch, V.; Holloway, H.W.; Miller, J.; Hoffer, B.J.; Greig, N.H.; Pick, C.G. Exendin-4 Induced Glucagon-like Peptide-1 Receptor Activation Reverses Behavioral Impairments of Mild Traumatic Brain Injury in Mice. *Age* **2013**, *35*, 1621–1636. [[CrossRef](#)] [[PubMed](#)]
107. Harkavyi, A.; Abuirmeileh, A.; Lever, R.; Kingsbury, A.E.; Biggs, C.S.; Whitton, P.S. Glucagon-like Peptide 1 Receptor Stimulation Reverses Key Deficits in Distinct Rodent Models of Parkinson's Disease. *J. Neuroinflammation* **2008**, *5*, 1–9. [[CrossRef](#)] [[PubMed](#)]
108. Li, Y.; Perry, T.A.; Kindy, M.S.; Harvey, B.K.; Tweedie, D.; Holloway, H.W.; Powers, K.; Shen, H.; Egan, J.M.; Sambamurti, K.; et al. GLP-1 Receptor Stimulation Preserves Primary Cortical and Dopaminergic Neurons in Cellular and Rodent Models of Stroke and Parkinsonism. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 1285–1290. [[CrossRef](#)] [[PubMed](#)]
109. Chang, Y.F.; Zhang, D.; Hu, W.M.; Liu, D.X.; Li, L. Semaglutide-Mediated Protection against A β Correlated with Enhancement of Autophagy and Inhibition of Apoptosis. *J. Clin. Neurosci.* **2020**, *81*, 234–239. [[CrossRef](#)] [[PubMed](#)]
110. Uddin, M.S.; Rahman, M.M.; Jakaria, M.; Rahman, M.S.; Hossain, M.S.; Islam, A.; Ahmed, M.; Mathew, B.; Omar, U.M.; Barreto, G.E.; et al. Estrogen Signaling in Alzheimer's Disease: Molecular Insights and Therapeutic Targets for Alzheimer's Dementia. *Mol. Neurobiol.* **2020**, *57*, 2654–2670. [[CrossRef](#)]
111. Ashraf, G.M.; Ebada, M.A.; Suhail, M.; Ali, A.; Uddin, M.S.; Bilgrami, A.L.; Perveen, A.; Husain, A.; Tarique, M.; Hafeez, A.; et al. Dissecting Sex-Related Cognition between Alzheimer's Disease and Diabetes: From Molecular Mechanisms to Potential Therapeutic Strategies. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 4572471. [[CrossRef](#)]
112. Li, C.; Zhang, J.; Qiu, M.; Liu, K.; Li, Y.; Zuo, Z. Alterations of Brain Structural Network Connectivity in Type 2 Diabetes Mellitus Patients With Mild Cognitive Impairment. *Front. Aging Neurosci.* **2021**, *12*, 534. [[CrossRef](#)] [[PubMed](#)]
113. Talbot, K.; Wang, H.-Y.; Kazi, H.; Han, L.-Y.; Bakshi, K.; Stucky, A.; Fuino, R.; Kawaguchi, K.; Samoyedny, A.; Wilson, R.; et al. Demonstrated Brain Insulin Resistance in Alzheimer's Disease Patients Is Associated with IGF-1 Resistance, IRS-1 Dysregulation, and Cognitive Decline. *J. Clin. Investig.* **2012**, *122*, 1316–1338. [[CrossRef](#)] [[PubMed](#)]

114. Yarchoan, M.; Toledo, J.B.; Lee, E.B.; Arvanitakis, Z.; Kazi, H.; Han, L.Y.; Louneva, N.; Lee, V.M.Y.; Kim, S.F.; Trojanowski, J.Q.; et al. Abnormal Serine Phosphorylation of Insulin Receptor Substrate 1 Is Associated with Tau Pathology in Alzheimer's Disease and Tauopathies. *Acta Neuropathol.* **2014**, *128*, 679–689. [[CrossRef](#)] [[PubMed](#)]
115. Lansdell, T.A.; Dorrance, A.M. Chronic cerebral hypoperfusion in male rats results in sustained HPA activation and hyperinsulinemia. *Am. J. Physiol. Endocrinol. Metab.* **2022**, *322*, E24–E33. [[CrossRef](#)] [[PubMed](#)]
116. Choi, B.R.; Seo, J.H.; Back, D.B.; Han, J.S.; Choi, D.H.; Kwon, K.J.; Shin, C.Y.; Lee, J.; Kim, H.Y. Effect of amyloid toxicity or chronic cerebral hypoperfusion on brain insulin resistance in a rat model with intracerebroventricular streptozotocin. *Brain Res. Bull.* **2020**, *158*, 40–50. [[CrossRef](#)] [[PubMed](#)]