HHS Public Access

Author manuscript

Trends Mol Med. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Trends Mol Med. 2023 December ; 29(12): 1029–1044. doi:10.1016/j.molmed.2023.09.005.

Diabetes: a tipping point in neurodegenerative diseases

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Abstract

Diabetes is associated with an increased risk and progression of Alzheimer's (AD) and Parkinson's (PD) diseases. Conversely, diabetes may confer neuroprotection against amyotrophic lateral sclerosis (ALS). It has been posited that perturbations in glucose and insulin regulation, cholesterol metabolism, and mitochondrial bioenergetics defects may underlie the molecular underpinnings of diabetes effects on the brain. Nevertheless, the precise molecular mechanisms remain elusive. Here, we discuss the evidence from molecular, epidemiological, and clinical studies investigating the impact of diabetes on neurodegeneration and highlight shared dysregulated pathways between these complex comorbidities. We also discuss promising antidiabetic drugs, molecular diagnostics currently in clinical trials, and outstanding questions and challenges for future pursuit.

Keywords

Alzheimer's disease; amyotrophic lateral sclerosis; diabetes; insulin resistance; Parkinson's disease

Diabetes: a metabolic disease with devastating effects on brain health.

Diabetes is a chronic metabolic disease characterized by the incapacity of the pancreas to produce enough insulin and the inability of the body to efficiently use the insulin it

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Declaration of interests

J.A.S is the founder of NeuroHub Analytics LLC. J.A.P. will test biomarkers in the LixiPark study RC31/16-8912 (NCT03439943)vii. J.A.P. and J.A.S. are the inventors on United States Patent US 9,970,056 B2, Methods and Kits for Diagnosing, Prognosing and Monitoring Parkinson's Disease. M.K, M.L, and D.V declares no competing interests.

Resources

[xvi] https://clinicaltrials.gov/study/NCT01041989

produces, known as insulin resistance. These perturbations lead to **hyperglycemia** (See Glossary), which could deteriorate various organ systems, particularly the nerves and blood vessels, leading to blindness, peripheral neuropathy, peripheral vascular disease, kidney disease, cardiovascular disease, and cognitive impairment. According to the World Health Organization (WHO), approximately 422 million people worldwide have diabetes, causing nearly 1.5 million deaths yearly[i]. Different forms of diabetes exist, including **type 2 diabetes mellitus** (T2DM), accounting for more than 90% of the cases occurring primarily in adults, and **type 1 diabetes** (T1D), commonly present in children and adolescents.

Mounting evidence from epidemiological studies indicate that T2DM has a detrimental impact on brain structure and function and contributes to different degrees of cognitive deterioration, ranging from subtle cognitive decline to overt dementia [1,2]. Moreover, insulin resistance and T2DM have been associated with smaller brain volumes and poorer cognitive functions in subjects free of cerebrovascular disease and dementia [3]. A meta-analysis indicated that T2DM is associated with greater brain atrophy over time and suggested that these changes may start early in adulthood and correlate with disease duration [4]. Brain atrophy due to T2DM has been primarily observed in the ventral striatum, cerebellum, putamen, caudate, and pre-motor cortex, brain areas commonly affected in neurodegenerative diseases [5].

A growing number of studies indicate that T2DM is involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (Box 1). Specifically, T2DM is associated with an increased risk of AD and PD [6–11]. Intriguingly, a neuroprotective role of T2DM has been reported in ALS [12–15]. The question arises; why is T2DM a precursor to AD and PD but protective against ALS? There is no clear answer, but it may be found in how genetics and environmental factors influence how the body processes metabolic precursors used in cellular bioenergetics pathways [16–18] (Figure 1, Key Figure). In the following sections, we will discuss the studies investigating the impact of T2DM on brain health and its pathogenic role in neurodegenerative diseases as well as the neuroprotective potential of antidiabetic drugs currently being tested in clinical trials of neurodegenerative diseases.

Diabetes and Alzheimer's disease dementia

Evidence from epidemiological studies suggest that T2DM increases the risk of AD in several populations globally (Table 1). An earlier systematic review reported a higher incidence of any dementia type, including AD and **vascular dementia**, among patients with T2DM [19]. Vascular complications and impaired glucose, insulin, and amyloid metabolism were suggested to underlie the link between both diseases. Larger, multicenter meta-analyses have obtained similar findings indicating that T2DM increases the risk of cognitive impairment, AD, and other dementias [2,20]. Further, T2DM had an additional 35% increased risk of dementia in individuals carrying mutations in *APOE4*, the strongest genetic risk factor in AD [21].

[i] https://www.who.int/health-topics/diabetes#tab=tab_1

In contrast, several studies have reported conflicting results. For example, T2DM increased the risk of vascular dementia but not AD in several populations [22,23]. Another cross-sectional study indicated that T2DM was not associated with AD neuropathology, including neuritic plaques and intraneuronal neurofibrillary tangles (NFTs) [24]. Additionally, the Framingham Study showed that T2DM did not increase the risk of incident dementia [25].

Several factors may explain these discrepancies. For instance, these studies did not analyze the age of T2DM onset, duration of T2DM, and other comorbidities. Age of onset, for example, is an important consideration since longitudinal studies have reported that T2DM diagnosed in midlife was associated with a 19% greater cognitive decline in a 20-year follow-up period [26] and that younger age of T2DM onset was associated with a higher risk of developing dementia [27,28]. Likewise, the duration of T2DM is associated with an increased incidence of dementia [29,30]. Notably, individuals in the Framingham Study were predominantly white, and non-fasting glucose levels, instead of fasting, were used to define diabetes [25]. Thus, the cohort used was not representative of the general population, and subjects with impaired glucose tolerance may have been misclassified as non-diabetic.

The impact of other comorbidities and their temporal association with T2DM and dementia are not clearly explained in most epidemiological studies. Patients with T2DM commonly present with hyperlipidemia and hypertension, a cluster of conditions collectively known as the '**metabolic syndrome**,' also implicated in neurodegeneration. Indeed, a study cohort indicated that T2DM, metabolic syndrome, and obesity were associated with an increased risk of mild cognitive impairment (MCI) progression to dementia [31]. Therefore, a thorough analysis of other comorbidities frequently associated with T2DM will be critical in determining metabolic risk factors in neurodegenerative diseases.

Diabetes and Parkinson's disease

Like AD, most **prospective studies** have reported an increased risk of PD among T2DM patients in several populations (Table 2). For example, an increased risk of PD was observed in Finnish men and women with T2DM during an 18-year follow-up period [32]. Similarly, patients with T2DM for more than ten years showed a 40% increased risk of PD in a prospective study in the United States [33]. Similar associations between PD and T2DM have been observed in other populations worldwide [6–10]. These results have been reinforced by a meta-analysis comprising seven population-based cohorts that found a 38% increased risk of PD among T2DM patients [34].

Conversely, **case-control studies** investigating the T2DM-PD linkage have shown conflicting results (Table 2). One study found a positive association between T2DM and PD [6], and another study indicated an increased risk of PD only among those subjects with a long duration of T2DM [35]. Other groups have reported a decreased risk of PD among T2DM patients [36,37] or no significant association [38,39]. In addition, a meta-analysis of 14 case-control studies observed an inverse association between T2DM and PD [40].

A closer inspection of the case-control studies revealed smaller sample sizes and retrospective exposure assessments. Additionally, some studies relied on self-report

diagnoses for T2DM. Another consideration is that the distinction between T1D and T2DM was not documented in all the studies. Case-control studies used prevalent PD cases, and the exposure time is sometimes insufficient or not specified. Notwithstanding, most of the more extensive prospective studies, less prone to recall and selection biases, support a positive association between T2DM and PD.

Recently, findings from larger cohort studies indicate that prediabetes and T2DM were associated with a higher risk of PD [41–43]. Interestingly, analysis stratified by sex showed that prediabetes was a risk factor for subsequent PD only in women, and women with T2DM had a higher risk of PD than men [41]. Supporting these findings, recent extensive prospective studies reported that women with T2DM have a higher risk of subsequent PD than men [9,44,45]. This is interesting since most epidemiological studies indicate a higher risk of PD in men [46]. Sex-specific hormonal differences may explain this discrepancy. For instance, estrogen has been suggested to be neuroprotective [47]; thus, its deficiency during menopause and a concurrent T2DM disease process may confer a higher risk of PD in women than men.

Several investigations have explored the impact of T2DM on PD progression and cognitive decline [48–50]. Patients with T2DM who developed PD had greater Unified Parkinson's Disease Rating Scale (UPDRS) and Hoenh Yahr scores, standard motor scales useful for assessing disease progression [51]. PD patients with comorbid T2DM displayed more severe motor and non-motor symptoms, including worsening gait impairment, cognitive decline, and depression [52]. An important consideration raised in a study [52] is that PD patients with comorbid T2DM were older, had a later disease onset, and had a higher BMI than the PD group. Several studies have reported that T2DM patients with longer disease duration are more likely to develop PD [44,53], which may explain the later PD onset. Moreover, the duration of T2DM increases mortality in PD patients who develop T2DM before PD onset [54]. Additionally, the sample size of PD with comorbid T2DM analyzed in these studies was relatively small, and diagnosis mainly relied on self-report and medication data. Finally, and perhaps more challenging to assess, is the impact of other comorbidities associated with T2DM, as these may also affect PD risk and progression.

Interestingly, an increased risk of PD has been reported in patients with complicated T2DM and younger individuals with T2DM [41,44]. It has been suggested that younger individuals with T2DM may have a greater genetic liability to PD than older individuals, which may be explained by a greater number of shared genetic factors associated with PD and T2DM [41,44]. More studies are needed to clarify the genetic interactions with age in PD and T2DM. Nevertheless, the impact of T2DM on worsening symptoms, disease progression, and increased mortality indicates that T2DM could trigger a more aggressive PD phenotype. It remains unclear whether the effects of T2DM on PD are strictly causal or if there is a synergistic effect of T2DM on PD risk and progression. Because age, age of onset of PD, duration of T2DM, and comorbidities have been shown to influence PD risk and progression, further evaluation in larger, well-characterized, and phenotyped T2DM cohorts will be critical to dissect the linkage between both diseases.

Diabetes and amyotrophic lateral sclerosis

Intriguingly, epidemiological studies suggest a neuroprotective role of T2DM in ALS. A case-control study determined that premorbid T2DM was associated with reduced risk and 4-years later onset of ALS [55]. Another case-control study showed a protective role of T2DM in ALS [56], while other studies did not find a significant association [57,58]. Nevertheless, increasing evidence from case-control and cohort studies from different countries has observed a protective role of T2DM in ALS [12–15] (Table 3).

In contrast, some studies have found a positive association between T2DM and ALS. A retrospective cohort study in Taiwan reported a greater risk of ALS among patients with diabetes [59]. Notably, this study did not distinguish between T1D and T2DM, which may have affected the results. A prospective cohort in China found that higher blood levels of glycated hemoglobin (HbA1c), a surrogate marker of T2DM, were associated with increased mortality in ALS [60]. However, a larger prospective cohort in Sweden reported that high glucose levels (≥6.1 mmol/L) were associated with a lower incidence of ALS [15].

Other intriguing findings are related to the interaction between T2DM and the age of onset of ALS. Two European case-control studies showed that T2DM is protective against ALS only in subjects aged 70 or older but increases the risk in younger individuals (<65 years) [14,61]. These age-specific findings are consistent with those reported in two Asian population-based studies [62,63] and a case-control study in the USA [55].

In this regard, aging is associated with a slower metabolism, decreased insulin sensitivity, muscle loss, and weight gain [64]. Metabolic abnormalities, including hyperlipidemia and increased body mass index (BMI), frequently reported in T2DM patients, are considered protective factors in ALS patients [65–67]. Furthermore, hypermetabolism occurs in more than half of ALS patients [68] and is associated with faster functional decline and greater mortality [69]. Although speculative, T2DM may paradoxically confer neuroprotection against ALS by supplying a surplus of glucose and lipids critical for maintaining key cellular and metabolic functions of the motor neuron and respiratory system in older individuals with an ongoing motor neuron degenerative process or increased susceptibility to ALS. Younger individuals, however, are presumably more likely to exhibit a faster metabolism with greater energetic demand, more consistent with the hypermetabolic phenotype observed in ALS patients.

Since metabolic abnormalities and energetic defects have been observed in ALS patients, high-caloric diets have been explored for increasing survival. Preclinical models have reported that a high-caloric diet, either high in fats or carbohydrates, mitigates the energy deficits in motor neurons and improves prognosis in ALS [70], but results from clinical trials have proven futile [71].

Defective insulin signaling, glucose metabolism and cellular bioenergetics in neurodegeneration.

Impaired insulin signaling, glucose metabolism, and defective cellular bioenergetics may underlie the association between T2DM and neurodegeneration. Insulin, a polypeptide hormone secreted in the bloodstream by pancreatic β cells, plays a central role in glucose homeostasis and is critical in neuronal development, survival, and proliferation [72]. How insulin interacts with the blood-brain barrier (BBB) and regulates brain function is the subject of extensive investigation.

Insulin receptors (IRs) are widely expressed in different brain regions, including the hypothalamus, hippocampus, cerebral cortex, striatum, cerebellum, choroid plexus, and olfactory bulb [73,74]. Decreased expression of IRs has been reported in postmortem brain studies of AD and PD patients. For example, there is reduced expression of IR, IR substrates (IRS1, IRS2), insulin-like growth factor 1 (IGF-1), and its receptor (IGF1R) in the brain of AD patients [75,76]. Additionally, there is decreased expression of downstream insulin signaling factors, phosphatidylinositol 3-kinase (PI3K), and activated Akt/PKB in AD [75]. Furthermore, there is increased expression of brain insulin resistance markers, IRS-phosphorylated at serine 616 (IRS-1 pS^{616}) and IRS-1 $pS^{636/639}$, in the hippocampus and cerebellar cortex of AD patients without T2DM [77]. Brain insulin resistance markers correlated positively with oligomeric Aβ plaques and negatively with episodic and working memory [77]. Impaired insulin signaling is implicated in the accumulation of neurotoxic Aβ and hyperphosphorylated tau via decreased PI3K-AKT signaling and increased activation of glycogen synthase kinase 3β (GSK3β) [78].

Similar patterns of brain insulin resistance are documented in PD. For example, there is decreased expression of IR mRNA and increased expression of IRS-1pS^{312} in nigral dopaminergic neurons in PD patients and in a rodent model of A53Tmutated *SNCA* [79,80]. Insulin resistance biomarkers correlated with decreased brain volume in the prefrontal cortex and medial temporal regions in AD and increased in PD patients' parietal region [81].

Peripheral insulin resistance and impaired glucose metabolism have been reported in several PD studies [82–85]. Though insulin resistance is thought to be underdiagnosed in PD patients [82], it remains unclear whether it is more prevalent in PD than in the general population. Noteworthy, impaired insulin signaling, mitochondrial dysfunction, and inflammation are intimately related processes implicated in neurodegeneration. Insulin resistance promotes lipolysis, producing cytotoxic ceramides that activate proinflammatory molecules, contributing to oxidative stress, mitochondrial dysfunction, apoptosis, DNA damage, and endoplasmic reticulum stress, ultimately leading to neurodegeneration [11].

Recently, a preclinical study demonstrated that human and murine cerebral IRs were concentrated in microvessels rather than the brain parenchyma [86]. Interestingly, the concentration of IRs was lower in microvessels in the parietal cortex of AD subjects and correlated positively with cognitive scores and negatively with Aβ plaques. Surprisingly, activation of IRs was restricted to microvessels. This study indicated for the first time that defective IR signaling at the BBB contributes to brain insulin resistance in AD.

Tight glucose control is essential for maintaining cellular metabolic processes and vital organ functions, including the brain, which relies upon glucose as its primary energy source. Contrary to AD and PD, hyperglycemia has been paradoxically associated with a lower incidence of ALS [15]. Defective glucose metabolism has been reported in mutant SOD1 mouse models and ALS patients [87,88]. Pre-clinical models in *Caenorhabditis elegans* and *Drosophila* models showed that increasing glucose availability reduces protein misfolding, improves locomotor function, and increases lifespan [89,90]. Strikingly, overexpression of phosphofructokinase (*PFK*), the rate-limiting enzyme in glycolysis, rescued motor deficits induced by TDP43 proteinopathy [90]. Similarly, targeting phosphoglycerate kinase 1 (PGK1), the first glycolytic enzyme to produce ATP in glycolysis, with terazosin, a commonly prescribed drug for benign prostatic hyperplasia and hypertension, improved motor function and increased motor neuron number *in vitro* and *in vivo* models of ALS [17]. Likewise, terazosin stimulation of glycolysis through PGK1 activation increased brain ATP and dopamine levels and improved motor function in toxin-induced and genetic models of PD [18]. Furthermore, terazosin use was associated with slower disease progression and a lower frequency of PD diagnoses. These findings suggest that targeting bioenergetics pathways through modulation of glycolysis and mitochondrial respiration is a promising therapeutic target in ALS and PD [91].

Shared genetic links between diabetes and neurodegenerative diseases

Several studies have uncovered shared genetic factors between T2DM and neurodegeneration. For example, PD-related genes, *PINK1* and *PARKIN*, are involved in mitochondrial dysfunction, glucose homeostasis, glycolysis, and autophagy, processes implicated in both PD and T2DM [92–94]. In addition, PARK7, also known as DJ-1, an enzyme mutated in autosomal recessive PD, prevents cellular damage by destroying the glycolytic enzyme 1,3-biphosphoglycerate involved in carbohydrate metabolism [95]. Additionally, DJ-1 preserves mitochondrial integrity via the modulation of reactive oxygen species and plays a role in glucose homeostasis in T2DM [96,97]. Another genetic link between PD and T2DM is the downregulation of insulin secretion resulting from the interaction between SNCA and the K_{ATP} channels in pancreatic β cells [98]. Similarly, loss of TDP43 linked to sporadic and familial ALS inhibited early-phase insulin secretion by pancreatic β cells through downregulating Cav1.2 calcium channels [99]. Additionally, nuclear depletion of TDP43 in the pancreatic islets mediated the impaired insulin secretion and glucose intolerance observed in early-stage ALS patients [99]. Thus, key genes and proteins linked to pathogenesis in PD and ALS are linked to mechanisms associated with T2DM.

T2DM partly accelerates cognitive decline in AD through interactions with *APOE* [100,101]. Specifically, T2DM contributed to cognitive decline in *APOE3* and *APOE2* but not *APOE4* carriers {Shinohara, 2020 #175}. Interestingly, T2DM was associated with increased infarcts or lacunes in *APOE3* carriers. In contrast, the carrying of *APOE4* was associated with lower cognition in T2DM and T2DM-MCI subjects {Zhen, 2018 #176}. Given the functional role of APOE in dyslipidemia and atherosclerosis [101], it is plausible to speculate that T2DM may trigger neurodegeneration in AD through atherosclerosis-induced vascular impairments. Transcriptomic analysis identified shared

molecular networks enriched in PI3K-AKT signaling and atherosclerosis in the blood of AD patients [102]. Collectively, these studies suggest that shared genetic links between T2DM and neurodegenerative diseases are predominantly involved in regulating glucose, insulin, and cholesterol, thereby highlighting the impact of metabolic abnormalities in neurodegeneration.

Despite this progress, finding a causal relationship between T2DM and neurodegenerative diseases has been challenging. In the context of AD, genetic correlation analyses using linkage disequilibrium regression and polygenic risk scores did not find convincing evidence for shared genetic susceptibility [103]. **Mendelian randomization** (MR) studies have identified causal associations in PD and ALS. For example, an MR study found single nucleotide polymorphisms (SNPs) with a significant causal effect of T2DM on PD risk and PD progression [50]. Likewise, an MR approach using large-scale GWAS identified SNPs supporting a neuroprotective role for T2DM in ALS in a European population [104]. Another MR study reported a negative correlation between genetic variants shared between T2DM and ALS, resulting in approximately 5% reduced risk of ALS [105].

Repurposing T2DM drugs for neurodegenerative diseases

One promising area of research is the investigation of antidiabetic drugs for the treatment of neurodegenerative diseases. Targeting the insulin signaling pathway with commonly prescribed antidiabetic drugs has elicited neuroprotective effects in preclinical studies and clinical trials. A longitudinal study of 5,528 veterans with T2DM showed that metformin therapy for more than four years decreased the risk of AD and PD [106]. Another study showed that metformin alone reduced the risk of PD by 60% in T2DM patients [8]. Although some epidemiological studies have found adverse effects of metformin, including cognitive impairment and increased risk of AD and PD [107–109], clinical trials have yielded encouraging results. Metformin intake for eight months was associated with improved executive function, learning, and memory in non-diabetic individuals with MCI and dementia in a phase 2 randomized clinical trial (RCT) (NCT01965756)[iii] [110]. Similarly, metformin administration for one year improved total memory recall in overweight amnestic MCI subjects in a phase 2 RCT (NCT00620191)[iv] [111]. Metformin's neuroprotective effects are mediated via the modulation of AMP-activated protein kinase (AMPK) activity in regulating several key cellular processes such as autophagy, cell growth, and mitochondrial function [112–114] and inhibition of microglial activation and inflammation [115].

Several investigations have explored the therapeutic potential of intranasal insulin in MCI and AD patients with mixed findings. A small phase 2 double-blind RCT (NCT01595646)[v] showed that intranasal delivery of regular insulin but not long-acting insulin improved memory, preserved MRI brain volume, and reduced CSF tau-P181/Aβ42 ratio after four months in MCI and AD patients compared to placebo [116]. In contrast, treatment with long-acting insulin resulted in memory improvement in APOE4 carriers and worsening in

[iii] https://clinicaltrials.gov/study/NCT01965756
[iv] https://clinicaltrials.gov/study/NCT00620191
[v] https://clinicaltrials.gov/study/NCT01595646

non-carriers [117]. Another study showed that insulin treatment was dose dependent and may vary by sex and APOE status [118]. Interestingly, only APOE4 negative men showed improved cognition, whereas APOE4 negative women displayed the poorest cognitive outcome. These studies highlight the importance of personalized medicine strategies in treating neurodegenerative diseases.

Glucagon-like peptide 1 (GLP1) agonists such as exenatide and lixisenatide are reported to confer neuroprotection. This class of drugs binds to and stimulates GLP-1 receptors in the pancreas, enhancing insulin release and suppressing glucagon release, thus mediating glucose control, and delaying gastric emptying. A phase 2 double-blind RCT showed that PD patients receiving exenatide displayed improved motor symptoms compared to the placebo group at the 60-week time-point [119]. The Exenatide-PD3 study (NCT04232969)[vi], a multicenter phase 3 clinical trial, is underway and will determine if previous findings are maintained in a larger cohort over two years [120]. Furthermore, liraglutide and lixisenatide, both GLP1 mimetics, have elicited neuroprotection in animal models of PD [121]. These drugs can cross the blood-brain barrier, enhance neurogenesis in the hippocampus, and increase Brain-derived neurotrophic factor (BDNF) expression, thereby promoting neuroprotection in AD and PD [122,123]. The ELAD study (NCT01843075)[vii] and the LixiPark study (NCT03439943)[viii] are phase 2 double-blind and placebo-controlled trials evaluating the efficacy of liraglutide in AD [124] and lixisenatide in PD patients, respectively. These trials also incorporate several biomarkers as surrogate endpoints in the drug development process (Box 2).

Concluding remarks

T2DM poses a significant threat to brain health, and its detrimental effects on cognitive deterioration and neurodegeneration are well documented. Although the precise mechanisms by which T2DM mediates neurodegeneration in AD, PD, or neuroprotection in ALS remain elusive, impaired insulin signaling, glucose metabolism, and defective bioenergetics are linked to the neurodegenerative process (Outstanding Questions). Given the multifactorial nature of T2DM and neurodegenerative diseases, a single shared genetic cause or dysregulated pathway is unlikely to explain this complex comorbidity. The impact of T2DM on neurodegeneration should be analyzed in a much broader context of metabolic abnormalities, including but not limited to glucose, insulin, cholesterol, obesity, and other comorbid conditions clustered within the metabolic syndrome. Pharmacological interventions used in T2DM and drugs that modulate glycolysis, have shown significant progress and provide an amenable alternative for preventing or alleviating cognitive decline and neurodegeneration. GLP-1 mimetics have shown neuroprotective potential in clinical trials. Larger prospective clinical trials testing these drugs in pre-diabetics and at-risk patients will be crucial for advancing treatments. In the absence of disease-modifying therapies, lifestyle modifications, including physical activity and diet, may also help mitigate cognitive impairment and neurodegeneration [125–128](Clinician’s Corner). Multidomain

[vi] https://clinicaltrials.gov/study/NCT04232969
[vii] https://clinicaltrials.gov/study/NCT01843075
[viii] https://clinicaltrials.gov/study/NCT03439943

clinical trials evaluating the efficacy of multimodal approaches, including diet, physical activity, cognitive training, and mindfulness, are expected to reduce comorbidities such as T2DM, obesity, depression, and cardiovascular disease and thus be more promising in preventing neurodegeneration.

Clinician's Corner

Recent phase 3 randomized clinical trials (RCTs) using anti-Aβ monoclonal antibodies have shown promise in slowing cognitive decline in early-stage AD, but their efficacy and safety are currently debated (NCT03887455)[ix], (NCT04437511)[x]. Further, current treatments for PD, ALS, and other neurodegenerative diseases provide symptomatic relief, but disease-modifying drugs are lacking. Although common drugs prescribed for the treatment of diabetes have been reported to elicit neuroprotective effects in preclinical models and clinical trials, there are still many challenges to overcome.

WHO declared physical inactivity as the fourth cause of mortality globally. More than 500 million people will develop obesity, T2DM, and cardiovascular disease resulting from a sedentary lifestyle[xi]. To this end, non-pharmacological interventions, including diet, physical activity, cognitive therapy, sleep hygiene, and mindfulness, could be adjunct treatments for neurodegenerative diseases. Engaging in daily physical activity has been shown to provide numerous benefits for brain health, including improved cognition, memory, and motor symptoms in several RCTs of neurodegenerative diseases (NCT01506479)[xii] (NCT02000583)[xiii].

Similarly, healthy eating habits such as those adopted by the Mediterranean diet, Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), and the Dietary Approaches to Stop Hypertension (DASH), rich in leafy green vegetables, fruits, fish, nuts and olive oil may prevent or slow cognitive decline as demonstrated in an open-label RCT (NCT03020186)[xiv].

Cognitive training and mindfulness meditation have been shown to reduce depression and improve sleep and cognition. A RCT demonstrated the positive effects of mindfulness training in improving cognitive performance and strengthening connectivity in brain regions vulnerable to aging (NCT02628548)[xv].

Given the multifactorial nature of neurodegenerative diseases, it has become evident that a single pharmacological intervention may fall short in preventing neurodegeneration. Multidomain clinical trials evaluating several lifestyle modifications, including diet and physical activity, are expected to determine whether multimodal approaches are more efficient in preventing neurodegeneration as shown in the Finnish Geriatric Intervention

[ix] https://clinicaltrials.gov/study/NCT03887455
[x] https://clinicaltrials.gov/study/NCT04437511
[xi] https://www.who.int/publications/i/item/9789240059153
[xii] https://clinicaltrials.gov/study/NCT01506479
[xiii] https://clinicaltrials.gov/study/NCT02000583
[xiv] https://clinicaltrials.gov/study/NCT03020186
[xv] https://clinicaltrials.gov/study/NCT02628548

Study to Prevent Cognitive Impairment and Disability (NCT01041989; RCT, active, not recruiting)[xv].

Acknowledgments

J.A.S is the founder of NeuroHub Analytics LLC. M.K, M.L, and D.V, perform independent research at NeuroHub Analytics LLC. J.A.P is a Professor in the Center for Neurodegenerative Diseases and Therapeutics at Rosalind Franklin University of Medicine and Science and Discipline Chair of Cellular and Molecular Pharmacology at the Chicago Medical School. J.A.P is funded by the National Institute on Aging (NIA) grant number R01AG062176, The Cure Parkinson's Trust, and Rosalind Franklin University of Medicine and Science. This work is dedicated to all the people affected by neurodegenerative diseases and to their caregivers.

Glossary

Case-control study
a study that compares groups of people with the disease (cases) and those who do not have the disease (control).

Hyperglycemia
blood glucose level that is greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 hours postprandial.

Mendelian randomization
utilizes variations of genes of known function associated with an exposure of interest to determine the causal effects between the exposure and a disease outcome.

Metabolic syndrome
describes a cluster of conditions that increase cardiovascular, stroke and diabetes risk. The main components of metabolic syndrome include obesity, high blood pressure, high blood triglycerides, low levels of HDL, and insulin resistance.

Prospective study
a type of longitudinal study where subjects are observed over a time period and gathers information about the development of outcomes.

Type 1 diabetes
an autoimmune condition where the pancreas cannot produce insulin due to the destruction of the beta cells, leading to hyperglycemia.

Type 2 diabetes mellitus
a condition where there are high blood glucose levels due to insulin resistance. Normally, our body breaks down glucose and stores it as energy in cells with the help of insulin. However, in type 2 diabetes, the cells do not respond to the insulin and do not take in glucose, leading to hyperglycemia.

Vascular dementia
a stepwise decline in executive dysfunction due to conditions that block or reduce blood flow to the brain. It is caused by cerebrovascular disease such as diabetes or impaired cerebral blood flow, such as strokes/embolisms.

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Box 1.

Neurodegenerative diseases linked to diabetes.

AD, PD, and ALS are sporadic neurodegenerative diseases in which the interplay of genetic and environmental factors contributes to disease pathogenesis. AD is the most common cause of dementia, and it is characterized by a gradual decline in memory and behavior, known as mild cognitive impairment (MCI), that over time progresses to frank dementia. Pathological features of AD include the accumulation and clumping of extracellular amyloid β plaques (Aβ) and intraneuronal neurofibrillary tangles (NFTs) [129]. With age being the greatest risk factor, most people with AD are 65 and older. A smaller number of cases present as early-onset familial AD, caused by mutations in amyloid precursor protein (*APP*) and presenilin 1 and 2 (*PSEN1*, *PSEN2*) [130]. Genome-wide association studies (GWAS) have unveiled more than 56 common genetic loci associated with AD risk [131].

PD affects nearly 8.5 million people worldwide[ii]. It is categorized as a movement disorder with tremors, postural instability, rigidity, and bradykinesia. Dopaminergic cell dysfunction and cell death in the substantia nigra underlies the observed motor dysfunction in PD patients. Accumulation of misfolded α-synuclein (SNCA) in Lewy bodies is a pathological hallmark of PD. Like AD, most cases are sporadic but highly penetrant mutations in *SNCA*, leucine-rich repeat kinase 2 (*LRRK2*), vacuolar sorting protein 35 (*VPS35*), parkin RBR E3 ubiquitin-protein ligase (*PRKN*), PTEN induced kinase 1(*PINK1*), parkinsonism associated deglycase (*PARK7*), and glucosylceramidase beta (*GBA*) have been linked to familial PD [129]. GWAS has identified a total of 90 risk loci associated with PD risk [132].

ALS is characterized by the progressive degeneration of brain and spinal cord motor neurons. Typical cases of ALS present with simultaneous upper and lower motor neuron symptoms at disease onset but varying phenotypes with either predominance of upper or lower motor neuron symptoms may also exist [133]. Genetic forms account for approximately 10% of the cases, presenting with autosomal dominant mutations in genes encoding Cu/Zn superoxide dismutase (*SOD1*), TAR-DNA binding protein 43 (*TDP-43*), *C9ORF72*, fused in sarcoma (*FUS*) and less frequently in optineurin (*OPN*), valosin-containing protein (*VCP*) and ubiquilin 2 (*UBQLN2*) [134]. Unfortunately, patients commonly die from paralysis of respiratory muscles within 2–5 years of disease onset [133].

[ii] https://www.who.int/news-room/fact-sheets/detail/parkinson-disease

Box 2.

Biofluid biomarkers as surrogate endpoints in clinical studies testing antidiabetic drugs.

Finding useful biomarkers for early diagnosis and therapeutic development in neurodegenerative diseases remains an unmet goal. Several biomarkers are being evaluated as surrogate endpoints in clinical trials of antidiabetic drugs in PD. For instance, treatment with exenatide showed increased levels of phosphorylated IRS-1^{Tyr}, IRS-1^{S616}, IRS-1^{S312}, total Akt, Akt ^{S473}, and p-mTOR^{S2448} indicating the activation of the insulin, Akt, and mTOR signaling pathways in exosomes extracted from peripheral blood of PD patients enrolled in the Exenatide-PD trial [135]. Likewise, the LixiPark trial is evaluating the expression levels of *HNF4A* and *PTBP1* mRNAs, previously identified as potential biomarkers of PD [85,136,137], in early-stage PD patients treated with lixisenatide. If successful, these biomarkers may be used as objective measures of target engagement, monitor disease progression, and therapeutic effects of drugs in clinical trials.

Other shared biomarkers between neurodegenerative diseases and T2DM may be used for therapeutic development. For example, higher levels of HbA1c were associated with cognitive decline and executive functions in patients with T2DM [138] and nondiabetic subjects [139]. Lower serum TREM2 and increased levels of phosphorylated tau, linked to AD pathogenesis [129], were reported in T2DM patients compared to healthy controls [140]. Further, increased serum levels of neurofilament light chain (Nfl), a marker of axonal degeneration, were associated with worsening cognitive functions in T2DM [141]. T2DM patients exhibited lower striatal dopamine transporter binding and higher cerebrospinal fluid levels of tau and SNCA compared to healthy controls [48]. Additionally, plasma progranulin (PRGN) concentrations are increased in T2DM and correlated with insulin resistance [142]. *PRGN* deficiency and lysosomal dysfunction are shared features in AD, PD, ALS, and frontotemporal dementia [143]. Furthermore, overexpression of PRGN reversed motor neuron defects in TDP43 and FUS mutant zebrafish models [144]. Finally, GLP-1 agonists have been shown to impact the expression of BAX and BCL2, critical factors involved in apoptosis and mitochondrial function [121]. Evaluation of these biomarkers in pre-diabetic and T2DM patients may inform us about cognitive deterioration and impending neurodegeneration.

Outstanding Questions

Hyperglycemia, prediabetes, insulin resistance, and T2DM have been shown to increase the risk of AD and PD. In parallel, the same conditions are accompanied by significant inflammation. Is the impairment in glucose metabolism and insulin signaling or is the inflammation resulting from these processes the main trigger of neurodegeneration?

Targeting the insulin signaling pathway with antidiabetic drugs such as metformin and GLP-1 mimetics and glycolytic pathways has shown promise in preclinical models and clinical studies in neurodegenerative diseases. Will the repurposing of currently approved drugs such as exenatide, lixisenatide and terazosin, be useful prophylaxis treatments in individuals at risk of neurodegeneration?

In the absence of disease-modifying agents for neurodegenerative diseases will implementation of lifestyle modifications such as high calorie diets in early-stage ALS patients, and Mediterranean diet in those at risk for AD and PD, be useful preventative strategies?

Highlights

Epidemiological studies indicate that diabetes increases the risk of Alzheimer's (AD) and Parkinson's (PD) diseases. Conversely, diabetes may confer neuroprotection against amyotrophic lateral sclerosis (ALS) in elderly individuals.

Molecular studies have shown that targeting insulin signaling using commonly prescribed antidiabetic drugs and stimulating enzymes in the glycolysis pathway elicits neuroprotection in AD, PD, and ALS.

Ongoing clinical trials testing antidiabetic drugs have shown promise in improving cognitive decline and motor function deterioration in patients with AD and PD.

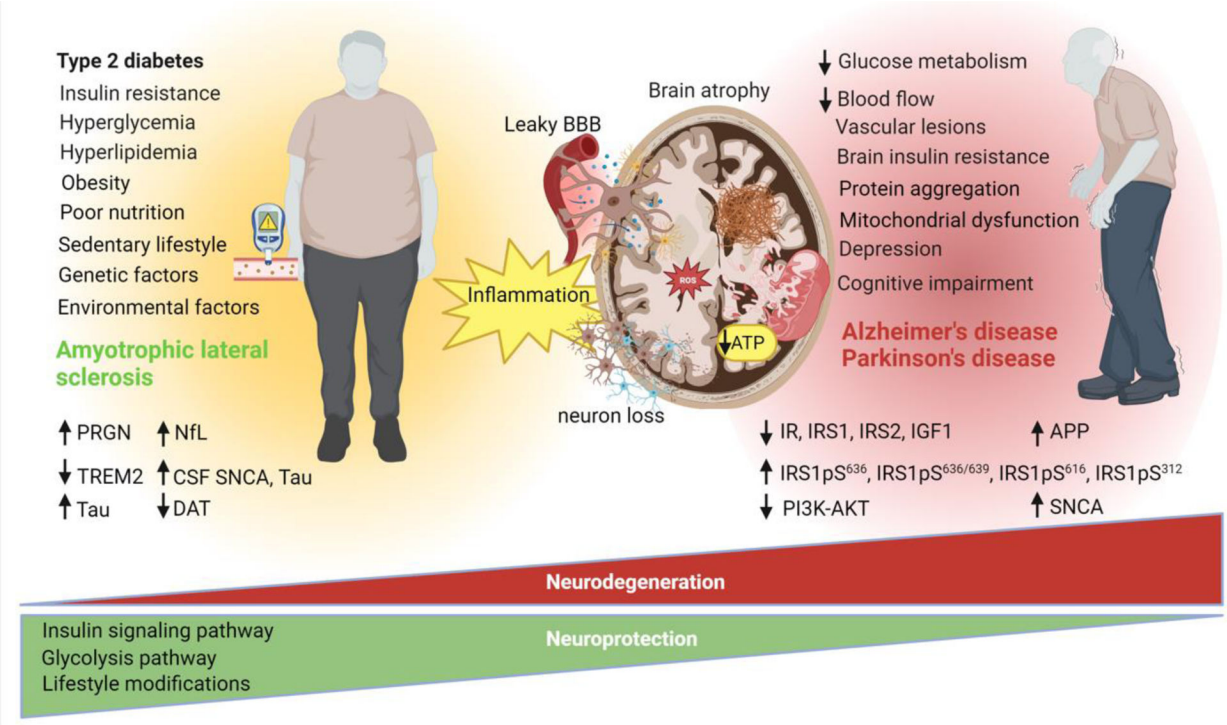

Figure 1 (Key Figure). Diabetes: a tipping point in neurodegeneration.

T2DM has many detrimental effects on brain structure and function. T2DM is associated with smaller brain volumes, brain atrophy, decreased blood flow, vascular lesions, disruption of the blood brain barrier, mitochondrial dysfunction, brain insulin resistance, depression, and cognitive impairment. Increasing evidence indicates that T2DM is a risk factor for AD and PD. Metabolic abnormalities associated with T2DM and the metabolic syndrome including insulin resistance, hyperglycemia, hyperlipidemia, and inflammation are implicated in the pathogenesis of neurodegenerative diseases. Intriguingly, these same metabolic abnormalities including T2DM, hyperglycemia, and hyperlipidemia are associated with a decreased risk of ALS in elderly individuals. Emerging research suggests that perturbations in glucose metabolism, insulin signaling, and bioenergetics defects could underlie the relationship between T2DM and neurodegenerative diseases. Several biomarkers, including progranulin (PRGN), triggering receptor on myeloid cells 2 (TREM2), tau, neurofilament light chain (NfL), cerebrospinal fluid (CSF) α-synuclein (SNCA), CSF tau, dopamine binding transporter (DAT), insulin signaling proteins (IR, IRS1, IRS2, IGF1, IRS1pS^{616}, IRS-1 pS$^{636/639}$, IRS1pS^{312}, PI3K-AKT) are implicated in T2DM and neurodegeneration and may be useful for therapeutic development. Targeting the insulin pathway with antidiabetic drugs and the glycolysis pathway have elicited neuroprotection in several studies. To date, no disease modifying therapy is available for AD, PD, and ALS. Lifestyle modifications including diet and physical activity may help mitigate symptoms and possibly confer neuroprotection. This figure was created using BioRender (https://biorender.com/).

Table 1.

Epidemiological studies investigating the association between diabetes and Alzheimer's disease dementia.

Study, year	Country	Study design	Sample size	Statistics	Main outcome	Refs.
Cheng et al., 2012.	Multiple	Meta-analysis	N: 44,714 T2DM: 6,184 HC: 38,530	RR:1.46 [1.20–1.77]	T2DM increases the risk for AD and related dementias.	[20]
Chatterjee et., al 2016.	Multiple	Meta-analysis	N: 2,310,330 T2DM: 70,575 Dementia: 102,174	Women RR: 1.62 [1.45–1.80] Men RR: 1.58 [1.38–1.81]	T2DM is associated with a 60% increased risk of dementia in both sexes.	[145]
Ng et al., 2016.	Singapore	Prospective cohort	N:1519 MetS: 340 T2DM: 120	HR: 2.47 [1.92–4.19]	T2DM was associated with an increased risk of MCI progression to dementia.	[31]
Kivimaki et al., 2019.	Multiple	Meta-analysis	N: 404,840 T2DM: 2,196 Dementia: 94,739	Follow-up <10 years HR:1.61 [0.82–3.17] Follow-up > 10 years HR: 1.55 [0.95–2.53]	T2DM is associated with an increased risk of dementia. Excess dementia risk was observed among physically inactive subjects with cardiometabolic disease.	[146]
Xue et al., 2019.	Multiple	Meta-analysis	N: 9,359,005	Prediabetes and the risk of: Dementia RR: 1.18 [1.02–1.36] AD 1.36 [1.09–1.70] T2DM and risk of: MCI 1.49 [1.26–1.77] AD 1.43 [1.25–1.62]	Prediabetes and T2DM were associated with an increased risk of MCI, dementia, and AD. Elevated FPG, HbA1c levels, and hypoglycemia were associated with an increased risk of dementia.	[2]
Li et al., 2020.	Multiple	Meta-analysis	N: 16,200	RR: 1.35 [1.13–1.63]	T2DM conferred a 35 % increased risk of dementia, AD, and vascular dementia. An additional 35% increased risk for those with APOEε4.	[21]
Barbiellini et al., 2021.	United Kingdom	Prospective	N: 10,095 T2DM: 1,710 Dementia: 639	T2DM onset (HR): >10 yrs, 2.12 [1.50–3.00] 6–10 yrs, 1.49 [0.05–2.32], < 5 yrs 1.11[0.70–1.76]	Younger age at the onset of diabetes increases the risk of dementia.	[27]
Zhang et al., 2017.	Multiple	Meta-analysis	N: 1,746,777	RR: 1.52 [1.42–1.63]	T2DM is associated with a higher incidence of AD.	[147]
Rawlings et al., 2014.	USA	Prospective cohort	N: 13,351 T2DM: 1,779	Adjusted Z score −0.15 [−0.22–0.08]	T2DM was associated with a 19% greater cognitive decline in a 20-year follow-up.	[26]
Zheng et al., 2018.	United Kingdom	Prospective cohort	N: 5,189 HC: 3553 Prediabetes: 1190 T2DM: 446	Z-score SD/year, 95% CI: global cognitive −0.0009 [−0.0014, −0.0003], memory −0.0005 [−0.0009, −0.0001]	A 1 mmol/mol increment in HbA1c was associated with an increased decline in cognitive scores, memory, and executive functions.	[138]

HC: healthy controls; HR: hazard ratio; FPG: fasting plasma glucose; RR: risk ratio; MetS: metabolic syndrome; N: number of participants

Table 2.

Epidemiological studies investigating the association between diabetes and Parkinson's disease.

Study	Country	Study design	Sample size	Statistics	Main outcome	Refs.
Xue et al., 2010.	USA	Prospective cohort	N: 288,662 Diabetes: 21,611 Non-diabetic: 267,051 PD: 1565	OR:1.41 [1.20–1.66]	T2DM increased the risk of PD by 40%.	[33]
Palacios et al., 2011.	USA	Prospective cohort	N: 147,096 PD: 656	RR: 0.88 [0.62–1.25]	A diagnosis of T2DM at baseline was not associated with PD risk.	[148]
Schernhammer et al., 2011.	Denmark	Prospective cohort	N: 11,582 PD: 1,931	OR: 1.36 [1.08–1.71]	T2DM was associated with a 36% increased risk of PD.	[6]
Savica et al., 2012.	USA	Case-control	N:392 PD:196	OR: 0.77 [0.37–1.57]	T2DM, or the use of antidiabetic drugs, was not associated with the risk of PD.	[38]
Sun et al., 2012.	China	Retrospective, case-control	N: 1,075,604 T2DM: 603,416	HR: Men 21–40 years, 2.10 [1.01–4.42]; women 41–60 yrs, 2.05 [1.82–2.30]; older women >60 yrs, 1.65 [1.58–1.73]	T2DM was associated with an increased risk of PD.	[7]
Skeie et al., 2013.	Norway	Case-control	N: 387 PD: 212	OR: 1.94 [0.82–4.57]	T2DM is not associated with PD.	[39]
Lu et al., 2014.	Multiple	Meta-analysis	N:105974 PD: 21,395	OR: 0.75 [0.58–0.98]	T2DM is associated with a decreased risk of PD.	[40]
De Pablo Fernandez et al., 2018.	United Kingdom	Prospective cohort	N: 6,173,208 T2DM: 2,017,115	HR: 1.32 [1.29–1.35]	T2DM increases the risk of PD. A greater increase is observed in those with complicated T2DM.	[44]
Yang et al., 2017.	Taiwan	Case-control	N: 145,176 T2DM: 36,294	HR: 1.19 [1.08–1.32]	The incidence of PD was 1.36 higher in T2DM than in non-diabetic controls.	[9]
Wahlqvist et al., 2012.	Taiwan	Case-control	N: 800,000 T2DM: 64,166	HR: 0.78 [0.61–1.01]	Metformin-sulfonylurea reduced the risk of PD.	[8]
Liu et al., 2021.	Multiple	Meta-analysis	N: 3,845,660 PD:26,654 T2DM: 3,819,006	Cohort RR: 1.29 [1.15–1.45] Case-controls OR: 0.74, [0.51–1.09]	T2DM is associated with an increased risk of PD in cohorts but not in case-control studies.	[149]
Sanchez-Gomez et al., 2021.	Spain	Retrospective cohort	N: 2,556,928 T2DM: 281,153 Pre-diabetes: 26,379	T2DM HR: 1.19 [1.13–1.15] Prediabetes HR: 1.07 [1.00–1.14]	T2DM and prediabetes were associated with a higher risk of PD. Both prediabetes and T2DM increase the odds of PD, predominantly in women.	[41]
Deischinger et al., 2021.	Austria	Cross-sectional	N: 2,173,441 PD: 235,268	Men-T2DM OR: 1.46 [1.38–1.54] Women-T2DM OR:1.71 [1.11–1.30]	Men with T2DM had an increased risk of PD than non-diabetes men. Women with T2DM showed a greater risk of PD than men with T2DM.	[45]
Jacobs et al., 2020.	United Kingdom	Case-control	N: 501,780 PD: 1,276	OR: 1.27 [1.03–1.57]	T2DM is associated with an increased risk of PD.	[10]
Cereda et al., 2012.	Italy	Case-control	N: 961 PD: 783 T2DM: 89	UPDRS motor, 22.3 ±9.0 vs. 19.3 ± 7.9; Hoehn and Yahr staging, p=0.009	The onset of T2DM before the onset of PD was associated with higher UPDRS motor scores and	[51]

Study	Country	Study design	Sample size	Statistics	Main outcome	Refs.
					higher Hoehn and Yahr staging.	
De Pablo Fernandez et al., 2017.	Spain	Case-control	N: 4,998 PD: 79	PD and T2DM OR: 1.89 [0.90–3.98] Long-T2DM duration OR: 3.27 [1.21–8.85]	No association between PD and T2DM. A positive association in those with long T2DM duration.	[35]
Pagano et al., 2018.	USA	Case-control	N: 53 PD-T2DM: 25 T2DM: 14 HC:14	Motor progression HR: 4.52 [1.46–13.92] Cognitive decline HR: 9.31 [1.16–74.51]	T2DM was associated with faster motor progression and cognitive decline.	[44]
Chohan et al., 2021.	Multiple	Meta-analysis	T2DM specific meta-analysis Total: ~10 million Any diabetes meta-analysis Total: ~1.3 million	PD, OR 1.21 [1.07–1.36] motor symptoms, SMD 0.55 [0.39–0.72], causal effect, OR 1.08 [1.02–1.14]	T2DM was associated with an increased risk of PD and faster progression of motor symptoms. A causal effect of T2DM on PD risk.	[50]
Athauda et al., 2022.	United Kingdom	Case-control	N: 1,930 PD-T2DM: 167 PD:1,763	UPDRS-III, 25.8 [0.9] vs. 22.5 [0.3]; non-motor symptoms scale, 38.4 [2.5] vs. 31.8 [0.7]	T2DM patients had more severe motor symptoms assessed by UPDRS-III and non-motor symptoms scales.	[52]
Pezzoli et al., 2022.	Italy	Retrospective and prospective study	N: 9,862 PD: 8,380 PD-T2DM: 673	HR: 1.64 [1.33–2.02]	Occurrence of T2DM before PD onset was associated with a worse prognosis.	[54]
Zhong et al., 2023.	Multiple	Systematic review and meta-analysis	Total: 12,505,077 PD: 306,513	Risk of PD OR/RR: 1.23 [1.12–1.35] Motor progression RR: 1.85 [1.47–2.34] Cognitive decline OR/RR: 1.92 [1.45–2.55]	T2DM is associated with a higher risk of PD, motor progression, and cognitive decline.	[49]

HR: hazard ratio; FPG: fasting plasma glucose; OR: odds ratio; RR: risk ratio; N: number of participants; SMD: standardized mean difference

Table 3.

Epidemiological studies investigating the association between diabetes and ALS.

Study	Country	Study design	Sample size	Statistics	Main outcome	Refs.
Jawaid et al., 2010.	USA	Case-control	N: 2,371	ALS-T2DM: years vs. controls 56.3 years, p< 0.05	T2DM was associated with a 4-year later onset of ALS and motor symptoms.	[55]
Zhang et al., 2019.	China	Cohort	N:1,331 ALS-DM: 100 ALS: 1,231	Mean age (SD) ALS-T2DM: 57 (9.6) ALS: 52.6 (10.3)	ALS-T2DM patients showed a 4.4-year delay in disease onset compared to ALS patients without T2DM.	[62]
Mitchell et al., 2015.	USA	Case-control	N: 8,849 ALS: 1,288 Controls: 7,561	OR: 0.47 [0.38–0.58]	T2DM was associated with a decreased risk of ALS.	[56]
Hollinger et al., 2016.	USA	Case-control	N: 1,439 ALS-DM: 129 ALS: 1,310	OR: 0.79 [0.526–1.121]	No association between diabetes and ALS.	[58]
D'Ovidio et al., 2018.	Italy	Prospective cohort	N=727,977	HR: 0.30 [0.19–0.45]	T2DM decreases the risk of ALS.	[12]
Tsai et al., 2018.	Taiwan	Case-control	ALS:705 Controls: 14,100	OR: 0.7 (p<0.05)	T2DM was associated with a lower risk of ALS.	[13]
Mariosa et al., 2015.	Sweden	Case-control	ALS: 5,108 Controls: 25,540	OR: 0.66 [0.53–0.81]	T2DM decreases the risk of ALS mostly among subjects older >70.	[61]
Tsai et al., 2019.	Taiwan	Retrospective cohort	T2DM: 2,135,427	T2DM onset ≥55 years HR: 0.72 [0.55–0.95] Unstratified analysis HR: 0.87 [0.7–1.07]	T2DM was negatively associated with ALS only in subjects >55 years at T2DM diagnosis but not in the unstratified analysis.	[63]
Sun et al., 2015.	Taiwan	Retrospective cohort	Diabetes: 615,492 controls: 614,835	HR: 1.35 [1.10–1.67]	Diabetes increases the risk of ALS, especially in men. There is no distinction between T1D and T2DM.	[59]
Kioumourtzoglou et al., 2015.	Denmark	Case-control	ALS: 3,650 Controls:365,000	T2DM OR: 0.61 [0.46–0.80]	T2DM but not T1D is protective against ALS.	[14]
Zhang et al., 2022	European and East Asian	Meta-analysis	ALS:1234 Controls: 2850	OR: 0.83 [0.700.992]	T2DM was associated with lower odds of ALS in European and East Asian populations.	[150]
Mariosa et al., 2017.	Sweden	Prospective cohort	N: 636,132	HR: 0.62 [0.42–0.93]	High glucose level (>6.1 mmol/L) was associated with a lower incidence of ALS.	[15]
Mariosa et al., 2020.	Sweden	Case-control	ALS:2475 Controls: 12,375	OR: 0.76 [0.65–0.90]	ALS patients were less likely to be prescribed antidiabetic medications than controls.	[151]
Paganoni et al., 2015.	USA	Retrospective cohort	N: 1,322 ALS-T2DM: 71 ALS: 1,251	Log-rank test, p=0.98	No association between T2DM and ALS prognosis.	[57]
Wei et al., 2017.	China	Prospective cohort	ALS:450	HbA1c, 5.76.4%, HR:1.4 [1.02–1.99]; HbA1c >6.5, HR: 2.06 [1.07–3.96]	Higher blood HbA1c levels were associated with increased mortality in ALS.	[60]

HC: healthy controls; HR: hazard ratio; FPG: fasting plasma glucose; OR: odds ratio; PD: RR: risk ratio; N: number of participants; SMD: standardized mean difference; SD: standard deviation