A confluence of factors related to dietary changes, sedentary lifestyle, and an aging population in Western cultures has led to a rapid rise in the incidence of type 2 diabetes, a disease that carries enormous burden in terms of health and economic outcomes. Increasingly, type 2 diabetes is recognized as a major contributor to cognitive decline and dementia in older adults. As both type 2 diabetes and dementia reach epidemic proportions in the United States, the need to identify methods of prevention and treatment grows increasingly important.

Recently, there has been an emphasis on precision medicine, a model of focused identification and treatment of disease based on individual risk, as it applies to dementia. Even more compelling than precision medicine, a
sion medicine is the aspirational goal of precision health, through which graded surveillance based on risk discloses preclinical pathophysiological processes that motivate interventions that preserve health and prevent clinical expression of disease. The ability to identify an at-risk population, to detect pathological changes early in the disease process, and to select from a variety of potential targeted treatments make type 2 diabetes an ideal focus for a precision health approach to reducing the impact of dementia.

Type 2 Diabetes and Cognition in Older Adults
Type 2 diabetes is a robust predictor of cognitive impairment and decline in older adults. Multiple population-based studies have reported an association between type 2 diabetes and cognitive impairment (1–4), and older adults with type 2 diabetes experience global cognitive decline at a rate that is double those without type 2 diabetes over a 5-year period (5). General cognitive slowing, thought to be a marker for accelerated brain aging and dementia risk, is related to type 2 diabetes in middle-aged and older adults (6,7), and interactions between type 2 diabetes and genetic risk predict more rapid decline in cognitive speed (8). With regard to specific cognitive domains, associations between type 2 diabetes or even prediabetic levels of insulin resistance are most commonly reported with both episodic memory and decreased executive function, including verbal fluency, working memory, processing speed, cognitive flexibility, and cognitive control (7). Executive function, which may be most predictive of functional performance, also declines more rapidly among older women with type 2 diabetes (9). Conversely, remaining free from diabetes has been associated with preserved cognitive function in women >80 years of age (10).

Several mechanisms may underlie these associations, including peripheral metabolic derangements from insulin resistance or type 2 diabetes that indirectly damage the brain, vascular brain injury from the vasculopathic consequences of insulin resistance and type 2 diabetes, disruption of the ability of insulin to perform its normal actions in the brain in patients with type 2 diabetes, or some combination of these.

Insulin in the Brain
Sensitivity of target cells in the periphery and in the central nervous system (CNS) to insulin, a peptide hormone secreted by pancreatic β-cells, is suppressed in type 2 diabetes. First recognized as a principle regulator of peripheral glucose, insulin also has been identified as a key factor in memory and other cognitive processes. Insulin is readily transported into the CNS across the blood-brain barrier via a saturable, receptor-mediated process, which likely accounts for the majority of available insulin in the brain (11). Additionally, recent evidence suggests that insulin is also produced in the brain, a process that is potentially regulated by the Wnt/β-catenin/NeuroD1 pathway in the hypothalamus (12), although this has yet to be verified in human studies. Regardless of source, the CNS is rich with insulin receptors, most prominently in areas important for learning and memory, including the hippocampus, amygdala, parahippocampal gyrus, thalamus, and caudate-putamen (13).

Role of Insulin in Learning and Memory
The salutary effects of acute insulin administration on cognition are well documented. In rats, acute intracerebroventricular insulin administration improves memory on a passive-avoidance task and enhances spatial memory via potentially age-dependent inflammatory reduction processes (14,15). In humans, acute intravenous and intranasal insulin administration (while maintaining euglycemia) consistently improves declarative memory performance (16). Learning also appears to influence insulin receptor expression and function in the dentate gyrus and CA1 area of the hippocampus (17). Together, these studies support insulin as an important factor in normal memory functioning. Potential mechanisms for the influence of insulin on memory include regional effects of insulin on cerebral glucose metabolism, influence on components of the long-term potentiation cascade, and modulation of acetylcholine and norepinephrine, neurotransmitters that are known to influence cognitive function.

Chronic Effects of Hyperinsulinemia on Cognition
Despite the beneficial effects of acute hyperinsulinemia in the CNS, prolonged elevated levels of circulating insulin may exert an opposing influence on cognition. Sustained peripheral hyperinsulinemia reduces insulin transport into the brain (18). Prolonged insulin resistance, a syndrome characterized by high peripheral insulin and diminished insulin-mediated glucose clearance, underlies the development of type 2 diabetes. Among people with type 2 diabetes, reductions in brain volume (most prominently in the frontal and temporal lobes) and corresponding impairments in cognition are found in comparison to nondiabetic control subjects (19,20). Even in the absence of hyperglycemia, declarative memory impairment has been observed in individuals with chronic hyperinsulinemia (21), consistent with a deleterious role of insulin resistance on cognitive function. Subtle cognitive changes that can accompany early stages of insulin resistance due to aging, type 2 diabetes, and other factors may eventually develop into clinically significant cognitive impairment, including dementia (Figure 1).

Toward a Precision Medicine Model for Dementia: Type 2 Diabetes as a Target Risk Factor
Precision health uses emerging knowledge about specific diseases to identi-
fy optimal and targeted interventions based on individually determined risk factors. To effectively adapt the concept of precision health to cognitive impairment and dementia in older adults, it is imperative to first identify groups of differing risk.

Dementia develops as a result of a complex interplay of clinical and biological factors and is beset by multiple underlying pathological features. People with type 2 diabetes represent an important risk group for cognitive impairment and dementia caused by both Alzheimer’s disease dementia and vascular dementia, are most strongly associated with type 2 diabetes.

**Type 2 Diabetes and Alzheimer’s Disease Dementia**

The importance of the connection between type 2 diabetes and Alzheimer’s disease dementia is perhaps best captured by the term “type 3 diabetes,” coined to describe a portion of patients who develop Alzheimer’s disease dementia presumably as a result of diabetes-related injury and degeneration (25). Meta-analytic data demonstrate a 56% increased risk for Alzheimer’s disease dementia among individuals with type 2 diabetes (22). Among the studies included in the meta-analysis was the prospective, community-based Rotterdam study, which found that type 2 diabetes significantly increased the risk of Alzheimer’s disease dementia, with greater risk apparent in people who were treated with insulin (and therefore likely to be in the more severe stages of the disease) at baseline (26).

A type 2 diabetes diagnosis appears to raise the risk for Alzheimer’s disease dementia independently (although likely with additive effects) from vascular or other dementias or from *APOE* E4 gene status (26,27). Among patients already diagnosed with Alzheimer’s disease dementia, an increased prevalence of type 2 diabetes (35 vs. 18% in nondemented control subjects) and impaired glucose tolerance (46 vs. 24%) was reported (28).

Despite strong results from observational studies, recent explorations into genome-wide associations for type 2 diabetes susceptibility loci, as well as Mendelian randomization (MR) studies that combine genetic factors for type 2 diabetes, have failed to find an association with Alzheimer’s disease dementia (29,30). However, in a follow-up MR study that examined single nucleotide polymorphisms independently according to their specific biological mechanism, Alzheimer’s disease dementia risk correlated negatively with insulin sensitivity only (31), a finding that is not surprising given the wealth of literature that connects insulin dysfunction with Alzheimer’s disease dementia-specific neuropathological changes. In addition, a recent examination of genome-wide association study data found significant overlap between single-nucleotide polymorphisms (SNPs) associated with type 2 diabetes and Alzheimer’s disease, providing initial evidence that the two diseases may indeed share genetic risk. Among the shared type 2 diabetes and Alzheimer’s risk–associated SNPs, those responsible for immune regulation, cell signaling, and long-term potentiation were strongly represented (32). Further investigation into the shared genetic risk profile between type 2 diabetes and Alzheimer’s disease may lead to targeted and more effective prevention and intervention approaches.
There are several potential mechanisms by which type 2 diabetes may induce the neuropathological changes of Alzheimer’s disease. Chronic peripheral hyperinsulinemia caused by insulin resistance in type 2 diabetes ultimately lowers brain insulin levels and results in desensitization of neuronal insulin receptors, which may in turn lead to decreased clearance of beta amyloid (Aβ) peptide (33) and increased hyperphosphorylation of τ protein, which forms neurofibrillary tangles (34). In vivo, insulin modulates Aβ levels and promotes release of intracellular Aβ; thus, reduced sensitivity to insulin in the brain may reduce clearance of Aβ to extracellular compartments (33). Furthermore, soluble Aβ binds to the insulin receptor and disrupts its signaling capacity as well as long-term potentiation induction, which forms the basis for learning and memory, an effect that is prevented by insulin pretreatment (35,36). Insulin also inhibits phosphorylation of τ protein, possibly through its regulation of glycogen synthase kinase 3β, a downstream target in the insulin signaling pathway (37). In a conditional knockout mouse model in which the insulin receptor gene was inactivated in the CNS, phosphorylation of τ and the presence of tangle pathology was significantly increased (38,39). Type 2 diabetes also causes apoptosis in the hippocampus via a number of other dementia-associated processes that are independent of Aβ and τ, including increased oxidative stress, reduction of caspases, disturbed expression of apoptosis-regulator genes, and defective mitochondrial function (40). Recently, a nontransgenic animal model for Alzheimer’s disease dementia was developed that relies on prolonged insulin resistance in the brain (41). In this model, rats are injected with intracerebroventricular streptozotocin to induce insulin resistance and subsequently demonstrate multiple and progressive Alzheimer’s disease dementia–like changes in the brain, including accumulation of the Aβ peptide and hyperphosphorylated τ, the predominant features in Alzheimer’s disease dementia neuropathology, as well as associated structural and cognitive changes. Despite evidence from in vitro and animal studies that insulin resistance modulates the predominant pathological features of Alzheimer’s disease dementia, along with the consistently reported increased risk for Alzheimer’s disease dementia associated with type 2 diabetes, recent imaging studies have produced somewhat conflicting results. For example, among nondemented participants in the Mayo Clinic Study of Aging (42), type 2 diabetes and elevated A1C levels were associated with brain hypometabolism in Alzheimer’s disease dementia–specific brain regions; however, these factors did not correlate with significant amyloid accumulations (42). Similarly, among participants enrolled in the Alzheimer’s Disease Neuroimaging Initiative, type 2 diabetes was associated with lower bilateral frontal and parietal cortical thickness, but not with cerebrospinal fluid (CSF) Aβ42 levels or with amyloid accumulations by neuroimaging (43). Conversely, total and phosphorylated CSF τ proteins were negatively associated with type 2 diabetes. These findings may support a pathway to Alzheimer’s disease dementia that is less dependent on Aβ in people with type 2 diabetes. Future studies that incorporate human τ imaging will help to clarify whether the typical course of Alzheimer’s pathology is altered in the insulin-resistant brain.

**Type 2 Diabetes and Vascular Dementia**

Vascular disease represents a principle factor in accelerated brain aging, and vascular brain injury is an important contributor to cognitive dysfunction in older adults (44). Type 2 diabetes is a known risk factor for cardiovascular and cerebrovascular disease and may increase susceptibility to large and small caliber vessel–mediated injury to the brain, including hypoxic events, ischemia, and blood-brain barrier leakage. Dysfunction of vascular endothelial cells secondary to insulin resistance and inflammation is a characteristic consequence of type 2 diabetes, and disruption of white matter networks is seen on neuroimaging in patients with type 2 diabetes (45–47). Furthermore, white matter dysfunction is associated with poorer cognitive performance in patients with type 2 diabetes (46–48).

Type 2 diabetes is frequently reported to be more strongly correlated with vascular dementia than with other types, including Alzheimer’s disease dementia. Indeed, a recent meta-analysis of prospective studies that examined the risk of dementia in patients with type 2 diabetes reported a pooled relative risk of 2.27 for vascular dementia (22). Interestingly, new evidence suggests the increased risk for vascular dementia may be especially prominent in women; women with type 2 diabetes had a 19% greater chance of vascular dementia than men (49). In addition, those with longer duration and earlier age of onset of type 2 diabetes were more likely to develop vascular dementia.

Vascular burden in dementia is substantial but often co-occurs with other pathology (50). It is important to note that vascular risk factors may interact synergistically to amplify the effects of the Alzheimer’s disease cascade. For example, vascular dysfunction may be associated with progression of both amyloid and τ pathology (51). In patients already diagnosed with Alzheimer’s disease dementia and mild cognitive impairment, both cognitive and affective dysfunction were increased among those with insulin resistance (52,53), and treating vascular risk factors helped to slow cognitive decline (54). The strong association between type 2 diabetes and vascular contributions to dementia should be carefully considered when implementing treatment and prevention measures.
Precision Health: Early Detection
To effectively target and treat dementia associated with type 2 diabetes, such treatment would be most effective when implemented as early as possible, preferably during a latent or prodromal phase when the neuropathological changes are not yet significant enough to result in significant overt clinical symptoms (55). Importantly, both type 2 diabetes and dementia are associated with prolonged prodromal phases, and although symptoms may not be overt, current advances permit early identification of both syndromes.

It is now established that the pathophysiological processes underlying dementia may begin years or even decades before clinical manifestation of symptoms (56,57). Similarly, the insulin resistance syndrome is associated with a silent phase before the onset of frank diabetes, during which the pancreas is able to compensate by producing adequate levels of insulin to lower peripheral glucose levels. Midlife is thus frequently identified as a potentially crucial period of intervention. Impaired glucose tolerance and other cardiovascular risk factors during midlife may be particularly associated with impaired cognition and, later, dementia risk (58). Thus, this period may be an important point for widespread intervention in pursuit of precision health for the aging brain. For example, a recent study of late-middle-aged participants demonstrated a positive association between elevated insulin resistance and amyloid deposition (59). Thus, developing wide-scale prevention and treatment methods early in the course of insulin resistance may lead to substantial reductions in the burden of both type 2 diabetes and dementia in later years.

Precision Health: Approaches to Intervention
The precision medicine model assumes that innovative treatments will target specific risk factors based on individuals’ disease risk. Currently, approved pharmacological treatments for Alzheimer’s disease are prescribed comprehensively, regardless of specific disease risk and despite known limited effectiveness. Given the impact of type 2 diabetes on risk for both vascular and Alzheimer’s diseases, interventions that target insulin resistance may have significant potential to affect the clinical symptomatology associated with Alzheimer’s disease dementia.

Diet
A typical Western diet consists of high levels of saturated fats and simple carbohydrates, a pattern of consumption that substantially raises the risk of insulin resistance and type 2 diabetes and related cognitive impairment. Conversely, improving the dietary profile may produce protective effects on cognitive functioning and Alzheimer’s disease dementia risk (60). In animals, diets high in either saturated fat or sucrose modify processing of the amyloid precursor protein, elevate Aβ-related cerebrovascular disturbance, and reduce brain insulin signaling and expression of insulin-degrading enzyme (61,62). Evidence from population-based studies generally supports that an improved dietary profile, in particular, a Mediterranean diet, leads to a reduced risk of age-related cognitive decline and dementia (63). In an intervention trial (64) aimed at examining the effects of diet on cognitive function and CSF biomarkers in older adults with and without cognitive impairment, subjects were assigned to a 4-week isocaloric diet that consisted of either high saturated fat/high simple carbohydrates (HIGH; a pattern associated with type 2 diabetes and insulin resistance) or low saturated fat/low simple carbohydrates (LOW). In this study, diet intervention influenced insulin sensitivity, Alzheimer’s disease dementia biomarker profile, level of oxidative stress, and cognition. The confluence of population-based evidence, animal models, and initial intervention trials suggests that increasing insulin sensitivity via dietary modification may play a key role in overall dementia risk reduction.

Physical Exercise
An increasingly sedentary lifestyle present in Western cultures is likely also a key factor in the rise in type 2 diabetes in recent years. Aerobic exercise, which is known to be an effective treatment for diabetes and related conditions, also has potent salutary effects in the brain. Increased physical activity is consistently linked with improved learning and memory, both in humans and in animal models (65). The benefits of exercise on cognitive function have been demonstrated in healthy older adults and in adults with cognitive impairment, and exercise appears to have positive implications for the reduction of dementia risk (66–69). The favorable effects of exercise likely are exerted through multiple pathways known to be influenced by insulin, including improved cardiovascular and cerebrovascular function, anti-inflammatory processes, and enhanced insulin-dependent energy metabolism. Thus, aerobic exercise has the potential to modify multiple processes compromised in pathological brain aging.

Regular exercise during midlife, when many pathological disease processes likely begin, has been linked to reduced dementia risk and improved cognitive profile in older adults (70,71). Among older adults, those who exercised for at least 30 minutes per day, 5 days per week, for at least 10 years demonstrated lower brain Aβ deposition (using Pittsburgh compound B on positive emission tomography [PET] scan) (72). Given its multiple beneficial effects in the brain, regular physical exercise is recommended to help reduce the negative cognitive effects of type 2 diabetes.

Intranasal Insulin
Augmenting insulin in the CNS via intranasal insulin administration is one promising and innovative ap-
approach currently under investigation. Animal models and human studies support that insulin may be transported effectively into the CNS via intranasal administration without substantially affecting peripheral insulin levels (73–75). Initial studies examining younger adult participants found that acute intranasal administration improved both verbal memory and mood (76). Subsequently, intranasal insulin was found to improve verbal memory acutely in nondiabetic subjects with Alzheimer’s disease dementia or amnestic mild cognitive impairment (MCI) without affecting plasma insulin or glucose (77,78). Research into the chronic effects of regular and long-acting formulations demonstrated improved general cognitive abilities, declarative memory, and aspects of executive function, including verbal and nonverbal working memory and selective attention, among healthy control subjects and participants with MCI and early Alzheimer’s disease (79–81). In addition, changes in CSF Aβ42 and τ/Aβ42 ratios over the course of treatment were associated with cognitive and functional changes for insulin-treated participants. On fluorodeoxyglucose PET imaging, the intranasal insulin-treated group showed reduced progression of hypometabolism in the bilateral frontal, right temporal, bilateral occipital, and right precuneus/cuneus regions over a 4-month treatment period (80). Cumulative results to date thus support intranasal insulin administration as a potentially effective intervention in older adults with cognitive impairment or type 2 diabetes. A phase 3 clinical trial is underway to examine the effectiveness of intranasal insulin in people with early cognitive changes associated with Alzheimer’s disease.

**Type 2 Diabetes Treatments**

Although early treatment of type 2 diabetes may reduce the risk for complications, including cognitive decline, there may be differential effects in the brain related to the type of pharmacological intervention employed. Metformin, the typical first-line therapy for treatment of type 2 diabetes, has been both lauded for potential cognition-enhancing effects (82,83) and identified as a potential risk factor in increased cognitive impairment (84) among patients with type 2 diabetes. However, the association between metformin and cognition is murky because of multiple factors, including the fact that those taking metformin for many years may be at higher risk for cognitive impairment as a function of the disease process rather than the medication per se. Conversely, treated versus untreated type 2 diabetes may confer a differing risk for cognitive decline due to vascular injury versus amyloid deposition (85). A recent meta-analysis found no significant effect of treatment type across multiple cognitive domains among older adults with type 2 diabetes, although there appeared to be protective effects on verbal learning, working memory, and executive function for those who only used metformin (86).

 Peroxisome proliferator–activated receptor-γ (PPAR-γ) agonists, which act specifically to reduce insulin resistance, may help to normalize Aβ levels in the brain and to improve associated behavioral symptoms. Ongoing in vitro and animal studies show beneficial effects of these agents via reduced inflammation, enhanced clearance of Aβ, reductions in hyperphosphorylation of τ, and improved synaptic plasticity (Figure 2) (87–89).

 However, clinical trials using these medications have been less convincing. Although early pilot studies suggested improved cognition, a more favorable plasma Aβ40/42 ratio, and enhanced regional cerebral blood flow in patients with MCI or early Alzheimer’s disease (90), subsequent phase 3 clinical trials using rosiglitazone failed to show cognitive improvement in patients with mild to moderate Alzheimer’s disease dementia (91,92). Pioglitazone has produced similarly mixed results. Treatment with pioglitazone in patients with both type 2 diabetes and Alzheimer’s disease dementia produced improvement in general cognitive status and declarative verbal memory, as well as improved regional cerebral blood flow in the parietal lobe, after 6 months of treatment (93,94). However, another trial that was designed primarily to assess the safety of pioglitazone in nondiabetic patients with Alzheimer’s disease dementia failed to show any improvements on secondary cognitive and functional outcome measures (95).

 Interestingly, a recent in vitro model suggested that a subclinical dose of rosiglitazone may produce more beneficial effects on Aβ clearance than higher doses (96). Thus, follow-up studies that use lower doses may be illuminating. Furthermore, the larger trials above included patients with clinically diagnosed Alzheimer’s disease dementia; it is possible that treating insulin resistance before the onset of clinically significant dementia (e.g., MCI) may produce more favorable cognitive results.

**Practical Treatment Considerations**

Given the relationship between type 2 diabetes and subsequent clinical effects on vascular or Alzheimer’s pathology, it is reasonable to provide guidelines to patients at multiple levels of intervention. Primary prevention of type 2 diabetes and other metabolic and vascular diseases may ultimately be crucial to curtailing the rapid increase in the cognitive disorders of aging. Thus, instituting dietary and exercise guidelines at midlife or before, particularly among those most at risk for cardiovascular disease or diabetes, is particularly important. Once diabetes has been diagnosed, targeted secondary prevention methods designed to reduce or even reverse the impact of the disease early on, including diet, exercise, and any necessary medical treatments, should...
be considered. In particular, those at risk for cognitive decline, including patients with a family history of dementia, additional vascular risk factors, or a diagnosis of MCI, may be best targeted for education and intervention. Referral for detailed cognitive assessment and intervention should be considered for those who express concerns about changes in cognition. Baseline cognitive assessment may be useful for older adults diagnosed with diabetes to identify those at high cognitive risk (e.g., MCI) and to adequately track subsequent cognitive changes over time. Finally, for those who have already developed clinically significant cognitive symptoms, treatments now in development such as those described above may eventually represent viable options for tertiary prevention.

Summary
With an aging population and concurrent rise in chronic health conditions, there has come a rapid escalation in the incidence of both type 2 diabetes and dementia. The risk for cognitive impairment and dementia is increased among those with type 2 diabetes, and insulin resistance represents a potential mechanism by which both Alzheimer’s and vascular disease can develop. Fortunately, type 2 diabetes is amenable to intervention, and promising therapeutic interventions are under investigation. The abilities to establish risk among specific populations, identify and perhaps prevent progression of the disease early in its process, and institute targeted interventions help to establish type 2 diabetes as an ideal candidate for a precision health approach in dementia.

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Duality of Interest
No potential conflicts of interest relevant to this article were reported.

References

**FIGURE 2.** Targets of thiazolidinedione (TZD) drugs in Alzheimer’s disease. TZDs can bind to PPAR-γ receptors and other pathways that regulate energy metabolism in cellular and animal models of Alzheimer’s disease. In cognition and behavioral tests, these drugs increase the memory performance of the animals and also decrease Ab deposits, accelerating amyloid plaque clearance. At more cellular levels, TZDs promote neuronal survival, differentiation, and synaptic plasticity and also increase phagocytosis and reduce neuroinflammation in both astrocytes and microglia. In the mitochondria, TZDs induce biogenesis and enhance the mitochondrial function observed by a rise in respiratory complex activities and decrease in oxidative stress. Finally, TZDs are capable of reducing τ phosphorylation through the inhibition of different kinase activities and the later formation of the neurofibrillary tangles presented in Alzheimer’s disease. Reprinted from Pérez MJ, Quintanilla RA. Therapeutic actions of the thiazolidinediones in Alzheimer’s disease. PPAR Res 2015;2015:957248. This is an open-access article distributed under the Creative Commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.


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