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Authors
Mayeda, Elizabeth Rose
Whitmer, Rachel A
Yaffe, Kristine

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Diabetes and Cognition

Elizabeth Rose Mayeda, PhD, MPH [Postdoctoral Fellow],
Department of Epidemiology and Biostatistics, University of California, San Francisco, 185 Berry Street, Lobby 5, Suite 5700, San Francisco, CA 94107, Phone: 415-514-8018

Rachel A. Whitmer, PhD [Senior Research Scientist], and
Epidemiology, Etiology & Prevention, Kaiser Permanente Division of Research, 2000 Broadway, Oakland, CA 94612, Phone: 510-891-3400

Kristine Yaffe, MD [Vice Chair for Research, Scola Endowed Professor]
Departments of Psychiatry, Neurology, and Epidemiology and Biostatistics, University of California, San Francisco, San Francisco VA Medical Center, Box VAMC – 181, San Francisco, CA. 94143, Phone: 415-221-4810

Elizabeth Rose Mayeda: Elizabeth.Mayeda@ucsf.edu; Rachel A. Whitmer: Rachel.Whitmer@kp.org; Kristine Yaffe: Kristine.Yaffe@ucsf.edu

Synopsis

Dementia is a major cause of disability among older adults and is the fifth leading cause of death among older adults in the U.S. Evidence from epidemiologic studies suggest older adults with type 2 diabetes (T2D) are 50-100% more likely to develop dementia than those without T2D. However, studies examining the effect of T2D on cognitive decline have been less definitive, and it remains to be determined whether this association reflects a causal relationship between T2D and dementia pathogenesis. There are multiple proposed mechanisms through which T2D could cause cognitive decline and dementia, including the effects of insulin dysregulation and chronic hyperglycemia on both Alzheimer's disease and vascular pathology in the brain. Neuropathological and neuroimaging studies suggest that cerebral infarcts and brain atrophy are more common in older adults with T2D. Health care providers should be aware that older adults with T2D have an increased risk for development of dementia and should be attentive in looking for cognitive problems in older patients with T2D. More research is needed to elucidate the link between T2D and dementia and to identify strategies to maintain cognitive function among people with T2D.

Keywords

Type 2 diabetes; Cognition; Cognitive decline; Dementia; Aging; Epidemiology

Correspondence to: Elizabeth Rose Mayeda, Elizabeth.Mayeda@ucsf.edu.

Introduction

Type 2 diabetes (T2D) is highly prevalent among older adults, with more than a quarter of adults ≥65 in the U.S. affected by T2D.[1] As the population ages,[2] the prevalence of T2D increases,[3] and the life expectancy for people with T2D extends,[4] understanding the epidemiology of geriatric outcomes, including cognitive decline and dementia, among older adults with T2D is very important. Dementia is a major cause of disability among older adults and is the fifth leading cause of death for older adults in the U.S.[5] While current pharmacological treatments for dementia can moderately improve dementia symptoms, no currently available treatment can reverse the neuronal damage or affect disease progression.[6] Understanding the relationship between T2D and dementia could help identify possible strategies for prevention and treatment of dementia.

The goal of this review is to summarize the existing evidence evaluating the relationship between T2D and dementia. We will begin with an overview of dementia and a description of potential mechanisms linking T2D and dementia. Next, we will review evidence from longitudinal epidemiologic studies examining the relationship between T2D and incidence of dementia and cognitive decline, and we will also review evidence from autopsy and brain imaging studies. Finally, we will discuss risk factors for dementia among older adults with T2D.

Disease description

Overview of dementia

Dementia is a syndrome defined as a decline in at least two cognitive domains that is severe enough to interfere with daily activities.[7,8] Alzheimer's disease and vascular dementia are the two most common causes of dementia, and it is increasingly recognized that most older adults with dementia have both Alzheimer's disease and vascular pathologies.[9-12] In addition to studying dementia, examining rate of **cognitive decline** is important for understanding the effects of T2D on cognition among older adults.

Mild cognitive impairment (MCI) is a syndrome of modest cognitive decline that does not interfere with ability to perform activities of daily life that is considered to be a symptomatic pre-dementia state.[13] Not everyone with MCI will progress to dementia, but individuals with MCI develop dementia at higher rates and have higher mortality rates than people with normal cognition.[13,14]

Alzheimer's disease and vascular dementia

Alzheimer's disease and vascular dementia are thought to be the two most common causes of dementia.[6,15] **Alzheimer's disease** is characterized pathologically by neuritic plaques (extracellular deposits of beta-amyloid peptides), neurofibrillary tangles (intraneural fibrils of primarily hyperphysphorlylated tau protein), loss of synapses and neurons, and brain atrophy.[16] Beta-amyloid dysregulation, which leads to plaque formation, is thought to precede synaptic dysfunction and neuronal loss in Alzheimer's disease.[9,16] **Vascular dementia** (also called vascular cognitive impairment) is characterized by macrovascular and

microvascular cerebrovascular disease, including clinical stroke and subclinical vascular brain injury.[9]

Diagnosis of Alzheimer's disease and vascular dementia in clinical practice are based on objective cognitive assessments, such as neuropsychological testing and history-taking from the individual or an informant.[8] Brain autopsy studies have shown that most older people with dementia have both Alzheimer's disease and cerebrovascular pathology[9-12] and that Alzheimer's disease pathology and infarcts are commonly present in the brains of cognitively normal older adults.[10,11,17] These findings suggest that Alzheimer's disease pathology, cerebrovascular pathology, and cognitive reserve[18] interact in the development of dementia.[9] Since most people with dementia likely have mixed pathologies, this review will focus on studies of “all-cause” dementia, rather than clinically diagnosed Alzheimer's disease or vascular dementia.

Potential mechanisms

The interaction between Alzheimer's disease pathology, cerebrovascular pathology, and cognitive reserve[18] in development of dementia[9] and the complexity of metabolic dysregulation in T2D makes it difficult to identify the mechanisms linking T2D and dementia. The proposed mechanisms include the effects of hyperglycemia and insulin dysregulation (hyperinsulinemia and insulin resistance) on Alzheimer's disease pathology and macrovascular and microvascular pathology in the brain. Figure 1 illustrates the potential mechanisms linking T2D and dementia. It is beyond the scope of this article to cover all possible mechanisms, but this article will discuss commonly discussed mechanisms.

Pathophysiology of type 2 diabetes

T2D is a complex and heterogeneous metabolic disorder that typically begins with insulin resistance, which is linked with physical inactivity and obesity.[19] In insulin resistance, cells do not use insulin properly, and tissues need more insulin to help glucose enter cells, leading to hyperinsulinemia. Over time, the pancreas loses the ability to secrete enough insulin, and plasma glucose levels rise. It is well-established that long-term complications of T2D include microvascular and macrovascular disease throughout the body, including ischemic stroke in the brain.[20] The complexity and heterogeneity of the metabolic dysregulation in T2D and the many years over which it develops and could theoretically have neurologic effects presents a challenge in identifying the neurologic effects of T2D.

Chronic hyperglycemia

Glucose is the primary source of energy for the brain, but chronic hyperglycemia is known to cause damage to the **macrovasculature** and **microvasculature** throughout the body, including ischemic stroke, which can lead to dementia.[15] Retinopathy is a well-established microvascular T2D complication for which there is strong evidence of a causal link with chronic hyperglycemia.[20] Retinal and cerebral arterioles share morphological and physiological properties, so retinal microvascular damage is believed to be a marker of cerebral microvascular disease.[21,22] This is supported by evidence from epidemiologic

studies that have reported that retinopathy is associated with poorer cognitive function,[23] faster cognitive decline,[24] and higher incidence of dementia.[25] This supports the hypothesis that chronic hyperglycemia leads to microvascular cerebral damage that can impair cognitive function.

One of the mechanism through which chronic hyperglycemia damages microvascular tissue is by increasing reactive oxygen species, resulting in **oxidative stress**.[26] Oxidative damage has also been implicated in the accumulation of beta-amyloid and neurofibrillary tangles.[2728]

Advanced glycation end products (AGEs) are a mechanism through which chronic hyperglycemia contributes to the development of atherosclerosis.[15] AGEs are compounds formed by reactions between proteins, lipids, or nucleic acids and reducing sugars, such as glucose that accumulate during aging, but hyperglycemic environments facilitate the creation of AGEs.[29] In addition to contributing to vascular disease, AGEs are found in amyloid plaques and neurofibrillary tangles in people with Alzheimer's disease,[30] suggesting that AGEs contribute to Azlheimer's disease pathogenesis. The link between AGEs and dementia is further supported by the finding that circulating AGE levels are associated with greater cognitive decline in dementia-free older adults with and without T2D.[31]

Insulin dysregulation

In addition to addition to cerebral glucose utilization, insulin has multiple other functions in the brain that support neuronal function, including synaptogenesis, synaptic remodeling, and modulating neurotransmitter levels.[32] Insulin dysregulation includes pathways linked with hyperinsulinemia and functional insulin deficiency in the brain. Insulin dysregulation may impair beta-amyloid clearance in the brain and lead to plaque formation by regulating expression of and competing for insulin-degrading enzyme (IDE), which degrades beta-amyloid in addition to insulin.[33] Additional mechanisms through which insulin dysregulation may lead to Alzheimer's disease and cerebrovascular pathology include the effects of insulin resistance and hyperinsulinemia on cerebral glucose metabolism, hyperphosphorylation of tau, vascular dysfunction, lipid metabolism, oxidative stress, and inflammation.[32]

Inflammation

Inflammatory mechanisms have also been implicated in pathogenesis of Alzheimer's disease[28,34] and vascular dementia.[15] In epidemiologic studies, serum inflammatory markers have been linked with cognitive decline[35] and risk of dementia[36] in older adults. Inflammation has been implicated in development of T2D via contributing to insulin resistance,[37] and insulin dysregulation and chronic hyperglycemia may in turn also promote inflammation.[37]

Non-causal factors that may contribute to association between T2D and dementia

In addition to mechanisms reflecting a causal relationship between T2D and dementia, shared determinants of T2D and dementia may confound the association. Possible confounders include socioeconomic factors, such as educational and occupational

attainment, behavioral factors, such as diet and physical activity, and co-morbidities, such as obesity and hypertension. While many studies adjust for these factors, residual confounding may still be present. Reverse causation may also contribute to the observed association between T2D and dementia. Dementia pathology is thought to start to develop decades prior to manifestation of clinical symptoms,[9] which presents a challenge to establishing temporality, even in longitudinal studies.

Epidemiologic literature on T2D and risk of dementia

T2D and all-cause dementia

Table 1 summarizes results from longitudinal epidemiologic studies examining the relationship between T2D and risk of dementia. Estimates of the relative risk of dementia among people with T2D compared to those without T2D from longitudinal studies range from 1.2-2.8, although the confidence intervals from some studies include the null. The pooled risk estimate from a recent meta-analyses of nineteen longitudinal cohort studies published through 2010 suggested that older adults with T2D have approximately a 50% increased risk of dementia compared to those without T2D (RR: 1.51, 95% CI: 1.31-1.74).[38] More recent studies support an effect size that is at least this large, with risk estimates ranging from 1.6-2.4.[39-42]

Because pathogenesis of dementia is thought to begin many years prior to expression of clinical symptoms, examining the relationship between midlife T2D and late-life dementia is of great interest. Three longitudinal cohort studies have examined the relationship between midlife T2D and risk of dementia over a period of 14-35 years.[43-45] The association between T2D and incidence of dementia was strong in all three studies, which reported hazard ratio estimates ranging from 1.5-2.8.

T2D and Alzheimer's disease and vascular dementia

A number of studies have attempted to examine the relationship between T2D and Alzheimer's disease and vascular dementia, rather than “all-cause” dementia. Overall, there is a stronger association with vascular dementia than Alzheimer's disease in the literature. In a recent meta-analysis of sixteen studies examining Alzheimer's disease and ten studies examining vascular dementia, the pooled relative risk for T2D on vascular dementia is larger than the effect size for T2D on Alzheimer's disease (vascular dementia RR: 2.48, 95% CI: 2.08–2.96 vs. Alzheimer's disease RR:1.46, 95% CI: 1.20–1.77).[38] Additionally, the association between T2D and vascular dementia was relatively consistent across studies, and there was considerable variability in the association between T2D and Alzheimer's disease. However, the results of these results should be interpreted with caution, since most dementia cases are thought to be due to mixed Alzheimer's disease and vascular pathologies.[9-12]

T2D and cognitive decline

Cross sectional studies generally report modestly lower cognitive test scores among people with T2D compared to people without. A recent meta-analysis reported median effect sizes of 0.3-0.5 standard deviation units across cognitive domains.[46] Evidence relating T2D and cognitive decline is less consistent. Many studies report an association between T2D and

decline in one or more domains, but across studies, there is not a consistent association between T2D and decline in individual domains. One of the most frequently assessed domains in longitudinal studies examining T2D and cognitive change is processing speed; while multiple studies have reported an association between T2D and accelerated decline in processing speed,[47-51] several studies have not found an association.[52-54] T2D and change in memory over time has also been frequently assessed, and while several studies have found an association between T2D and change in memory over time,[49,52,55] some other studies have not.[48,50,56] Evidence is also mixed for change in executive functioning[49,51,56] and verbal fluency.[48,53,55] The inconsistency of results across studies a weak relationship between T2D and rate of cognitive change or may be due to the cognitive domains assessed, the specific neuropsychological tests used, how rate of cognitive decline was modeled, length of the study, or differences in characteristics of study populations.

Evidence from neuropathological and neuroimaging studies

Neuropathological and neuroimaging studies can help elucidate the mechanisms linking T2D and dementia. Most neuropathological studies have found more infarcts in the brains of people with T2D, but have not found evidence of greater burden of Alzheimer's disease pathology (beta-amyloid plaques and neurofibrillary tangles), with some studies reporting less Alzheimer's disease pathology in the brains of people with T2D.[57-61] However, in contrast to these findings, evidence from a recent neuropathological study reported a two-fold increased risk of autopsy-confirmed Alzheimer's disease among older adults with T2D compared to those without.[40]

Neuroimaging studies provide the opportunity to examine brain pathology in vivo, often in larger study samples that are less prone to selection-bias than autopsy studies. Structural MRI (magnetic resonance imaging) studies have consistently reported an association between T2D and cortical and subcortical cerebral atrophy among older adults.[56,62-67] It is important to note that cerebral atrophy is not a marker of a specific pathology and can represent neuronal loss from Alzheimer's disease or cerebrovascular disease.[68] Thus, while this evidence suggests an effect of T2D on neuronal loss, it does not indicate the specific disease process underlying this change. The association between T2D and cerebral infarcts in structural MRI studies is also relatively consistent across studies.[62-65,67] The association between T2D and white matter hyperintensities, a marker of microvascular cerebral damage, has been inconsistent,[62,64-67] but current structural MRI markers of microvascular disease in the brain may not represent the full spectrum microvascular damage to the brain that may be relevant for dementia.[69] A recent small study assessed beta-amyloid levels using carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) on positron emission tomography (PET) and found no difference in beta-amyloid deposition by glucose tolerance (dichotomized as high vs. low) or insulin resistance (dichotomized as high vs. low).[70]

Taken together, current evidence from neruopathological and neuroimaging studies suggest that T2D can lead to cerebrovascular damage and brain atrophy, but there is less evidence that T2D leads to Alzheimer's disease pathology. More research is needed to better understand the pathological effects of T2D on the brain.

Risk factors for dementia among people with T2D

Glycemic control is a central aspect of T2D care and is typically measured by glycosylate d hemoglobin (A1c) levels, a measure of the amount of glucose that binds to hemoglobin in red blood cells and represents average glycemic control over several months.[20] Among older adults with T2D, higher A1c levels are associated with lower cognitive function[47,55] and accelerated cognitive decline.[55] **Longer duration** of T2D and **higher A1c levels** have been shown to be associated with faster cognitive decline in middle-aged adults with T2D.[49,55] Higher average glucose levels have been shown to be associated with incidence of dementia, not only among older adults with T2D, but also among those without T2D.[71]

Severe hypoglycemic events may also contribute to development of dementia in older adults with T2D. Moderate hypoglycemia impairs cognitive function,[72] and severe hypoglycemia may cause neuronal damage.[72,73] Some epidemiologic studies support this hypothesis, as severe hypoglycemic episodes have also been associated with lower cognitive function, faster cognitive decline, and an increased risk of dementia among older adults with T2D.[74-76] However, the relationship between hypoglycemia and dementia may be bidirectional, with hypoglycemic events increasing risk of dementia and impaired cognitive function increasing the risk of hypoglycemic events.[75,76]

Depression and depressive symptoms have been linked with an increased risk of dementia in the general population.[77] Depression is more common among people with T2D than in the general population; it is estimated that nearly 20% of adults with T2D have depression.[78] [In this issue Park et. al., “Depression among older adults with diabetes mellitus,” provides a detailed discussion.] Two recent studies of members of two separate integrated health care delivery systems found that T2D patients with comorbid depression were twice as likely to develop dementia over five years compared to T2D patients without depression.[79,80] In the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) study, participants with depression experienced greater decline in psychomotor speed, verbal memory, and executive function (all domains assessed in this study) over 40 months.[81] Since depression is potentially modifiable, future research is needed to identify whether interventions to treat depression can also reduce cognitive decline in people with T2D.

A **10-year dementia risk score** has been developed and validated specifically for older adults with T2D based on two large longitudinal cohort studies.[82] This risk score is based on predictors assessable in a primary-care setting and encompasses T2D-specific characteristics. Out of 45 candidate predictors identified from the literature, age, education, microvascular disease, lower extremity complications, cerebrovascular disease, cardiovascular disease, acute metabolic events, and depression were most strongly predictive of dementia. Interestingly, the predictive value of end-organ complications that indicate prolonged exposure to hyperglycemia and cardiovascular risk factors was higher than the predictive value of duration of T2D and A1c levels.

Among people with T2D, some **racial/ethnic groups** may have a higher risk of dementia. Among older T2D patients, dementia incidence was 40-60% higher among African Americans and Native Americans compared to Asian Americans, and dementia incidence

was intermediate among non-Hispanic whites and Latinos, even after controlling for sociodemographic factors and clinical characteristics.[83]

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Key Points

- Older adults with type 2 diabetes are 50-100% more likely to develop dementia than those without diabetes.
- More research is needed to identify whether the observed association reflects a causal relationship between type 2 diabetes and dementia pathogenesis.
- The proposed link between type 2 diabetes and dementia includes mechanisms contributing to both Alzheimer's disease and vascular pathology.
- Infarcts and atrophy are more common in the brains of older adults with T2D.
- Among people with type 2 diabetes, those with longer duration of diabetes, poorer glycemic control, and more vascular complications are at the highest risk of developing dementia.

Summary

Consistent evidence exists that older adults with T2D are more likely to develop dementia than those without T2D. The literature on the effect of T2D on cognitive decline is less consistent. From a clinical perspective, it is important to know that people with T2D have an increased risk of dementia. However, understanding whether T2D has a causal effect on cognitive decline and dementia and if so, through what mechanisms is useful for identifying potential strategies to prevent or treat dementia. The biological plausibility of the multiple pathways through which T2D could lead to development of Alzheimer's disease and vascular pathology in the brain supports the hypothesis that the link is causal, although current evidence from neuropathologic and neuroimaging studies provide more evidence to support an effect of T2D on vascular pathology than Alzheimer's disease pathology.

Health care providers should be aware that older adults with T2D have an increased risk for development of dementia. Future research is needed to elucidate the pathways linking T2D and dementia, better understand risk factors for dementia in this high-risk population, and strategies to maintain cognitive function among people with T2D.

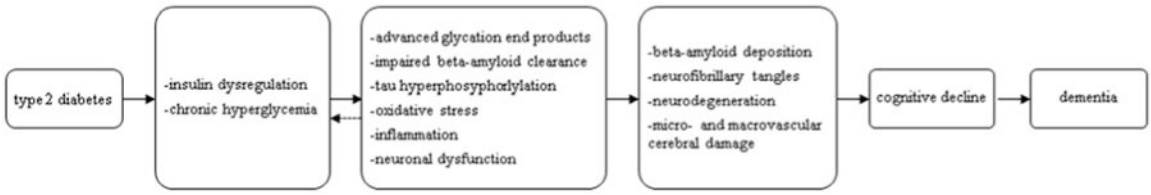

Figure 1. Figure illustrating potential causal links between type 2 diabetes and cognitive decline and dementia

Table 1

Type 2 diabetes and dementia risk among older adults

Publication	Cohort	Baseline age (years)	Follow up (years)	N			Diabetes	Dementia diagnosis	OR or HR (95% CI)
				Total	Diabetes	Dementia			
Brayne, 1998[84]	Population-based study in Cambridge, U.K.	75+	mean=2.4	376	17	36	Self-report	Multi-phase protocol	OR=2.6 (0.9-7.8)
Ott, 2002[85]	Rotterdam Study, The Netherlands	55+	6	6,370	692	126	Medication use, RBS, OGTT	Multi-phase protocol	HR=1.9 (1.3-2.8)
Peila, 2002[86]	Honolulu-Asia Aging Study, U.S.	mean=77	mean=2.9	2,574	900	~130	Self-report, medication use, FBS, OGTT	Multi-phase protocol	OR=1.5 (1.0-2.2)
MacKnight, 2002[87]	Canadian Study of Health and Aging, Canada	65+	5	5,574	503	467	Self-report, medical records, medication use, RBS	Multi-phase protocol	OR=1.3 (0.9-1.8)
Hassing, 2002[88]	Origins of Variance in the Oldest-Old Twin Study, Sweden	80+	6	702	108	187	Self-report, medical records	Multiphase protocol	HR=1.2 (0.8-1.7)
Schnaider Beeri, 2004[43]	Israeli Ischemic Heart Disease Study, Israel	mean=40-65	35	1,892	43	309	OGTT, medication use, physician-confirmed diagnosis	Multi-step protocol	OR=2.8 (1.4–5.7)
Whitmer, 2005[44]	Data from Kaiser Permanente Northern California, U.S.	40-44	mean=27	8,845	1,004	721	Self-report, FBS, RBS, medication use	Diagnosis in medical records	HR=1.5 (1.2-1.8)
Akomolafe, 2006[89]	Framingham Study, U.S.	mean=70	20	2,210	202	319	RBS, medication use	Multi-phase protocol	HR=1.2 (0.7-2.0)
Irie, 2008[90]	Cardiovascular Health Study, U.S.	65+	8	2,547	320	411	FBS, medication use	Multi-phase protocol	HR=1.4 (1.0-2.0)
Xu, 2009[91]	Kungsholmen Project, Sweden	75+	9	1,248	75	420	Diabetes inpatient registry, medication use, RBS	Multi-phase protocol	HR=1.4 (0.9-2.1)
Alonso, 2009[45]	Atherosclerosis Risk in Communities Study, U.S.	46-70	14	11,151	~1,445	203	FBS, RBS, self-report, medication use	Hospitalization discharge codes	HR=2.2 (1.6, 3.0)
Raffaitin, 2009[92]	Three-City Study, France	65+	4	7,087	~540	208	FBS, RBS, medication use	Multi-phase protocol	HR= 1.6 (1.1-2.4)
Ahtiluouto, 2010[60]	Vantaa 85+ Study, Finland	85+	10	588	131	106	Self-report, medical record, medication use	Multi-phase protocol	HR=2.1 (1.3-3.3)
Cheng, 2011[39]	Washington Heights-Inwood Columbia Aging Project, U.S.	65+	~9	1,488	253	161	Self-report, medication use	Multi-phase protocol	HR=1.7 (1.4-2.9)
Ohara, 2011[40]	Hisayama Study, Japan	60+	15	1,017	150	232	FBS, OGTT	Multi-phase protocol	HR=1.7 (1.2-2.5)
Kimm, 2011[41]	Data from National Health Insurance Corporation, Korea	40-95	14	Women: 358,060 Men: 490,445	Women: ~18,260 Men: ~33,350	Women: 1,755 Men: 1,497	FBS	Hospitalization discharge codes	Women: HR=1.6 (1.4-1.9) Men: R=1.6 1.3-1.8)
Mayeda, 2013[42]	Sacramento Area Latino Study on Aging, U.S.	60+	10	1,617	677	159	FBS, self-report, medication use	Multi-phase protocol; dementia/CIND	Untreated: R=1.9 1.2-3.1) Treated: HR=2.4 (1.7-3.4)

Abbreviations: FBS=fasting blood sugar, RBS=random blood glucose, OGTT=oral glucose tolerance test, HR=hazard ratio, OR=odds ratio, 95% CI = 95% confidence interval, CIND=cognitively impaired without dementia.