Risk of Dementia in Seniors With Newly Diagnosed Diabetes: A Population-Based Study

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OBJECTIVE

To study whether diabetes onset in late life is a risk factor for dementia.

RESEARCH DESIGN AND METHODS

We conducted a population-based matched cohort study using provincial health data from Ontario, Canada. Seniors with (*n* = 225,045) and without newly diagnosed diabetes (*n* = 668,070) between April 1995 and March 2007 were followed until March 2012 for a new diagnosis of dementia. Cox proportional hazards modeling was used to compare the risk of dementia between groups after adjusting for baseline cardiovascular disease, chronic kidney disease (CKD), hypertension, and other risk factors.

RESULTS

Over this period, we observed 169,114 new cases of dementia. Individuals with diabetes had a modestly higher incidence of dementia (2.68 vs. 2.62 per 100 person-years) than those without diabetes. In the fully adjusted Cox model, the risk of dementia was 16% higher among our subgroup with diabetes (hazard ratio [HR] 1.16 [95% CI 1.15–1.18]). Adjusted HRs for dementia were 1.20 (95% CI 1.17–1.22) and 1.14 (95% CI 1.12–1.16) among men and women, respectively. Among seniors with diabetes, the risk of dementia was greatest in those with prior cerebrovascular disease (HR 2.03; 95% CI 1.88–2.19), peripheral vascular disease (HR 1.47; 95% CI 1.19–1.82), and CKD (HR 1.44; 95% CI 1.38–1.51), and those with one or more hospital visits for hypoglycemia (HR 1.73; 95% CI 1.62–1.84).

CONCLUSIONS

In this population-based study, newly diagnosed diabetes was associated with a 16% increase in the risk of dementia among seniors. Preexisting vascular disease and severe hypoglycemia were the greatest risk factors for dementia in seniors with diabetes.

The incidence and prevalence of diabetes have increased substantially in recent years (1). Diabetes is a risk factor for blindness, kidney failure, coronary artery disease (CAD), stroke, and some cancers. However, medical advances over the past two decades have led to reductions in cardiovascular risk, resulting in longer life expectancy (2). This has led to the emergence of geriatric complications in elderly people with diabetes, including Alzheimer disease and related dementias. With the aging of the world's population, both diabetes and dementia are expected to become global epidemics. Currently, ~44 million people have dementia, and this number is expected to reach 135 million by the year 2050 (3).

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A slide set summarizing this article is available online.

There is a growing body of evidence supporting an association between diabetes and dementia (4–11). Since the two entities appear to share antecedent cardiometabolic risk factors, dementia may be yet another vascular complication of diabetes. Cardiovascular risk factors in midlife such as hypertension (HTN), dyslipidemia, and obesity have been implicated in the risk of dementia in later life, although few studies have had sufficient follow-up to draw firm conclusions (4,7,9). The demonstration of selective central nervous system abnormalities in insulin signaling have led to the notion that Alzheimer disease represents "type 3" diabetes (12–14). In animal models, insulin resistance at the level of the brain leads to tau hyperphosphorylation and β-amyloid accumulation, both of which may promote the development of Alzheimer disease (15). Moreover, insulin may have direct effects on cortical function. Hyperglycemia, itself, may exert direct effects through advanced glycation end products, oxidative stress, inflammation, and microvascular alterations such as capillary basement membrane thickening, similar to abnormalities seen in the kidney and retina (13,14).

Epidemiological evidence also supports a direct link between diabetes and dementia (5–11). A meta-analysis published in 2011, based on 19 longitudinal studies, found a nearly 1.5-fold higher incidence of Alzheimer disease and a 2.5 times higher likelihood of vascular dementia in those with preexisting diabetes (5). However, eligible studies had heterogeneous results and differed substantially with respect to their definitions of exposure and outcome events. Moreover, many studies were limited by relatively small sample sizes, insufficient numbers of outcome events, and lack of data on diabetes duration or vascular risk factors.

It is still unknown whether the onset of diabetes in late life can accelerate cognitive decline. The primary aim of our study was to examine whether incident diabetes is a risk factor for dementia in elderly individuals. We hypothesized that exposure to even short-term hyperglycemia in late life can trigger or accelerate cognitive decline and therefore that incident diabetes is a risk factor for dementia after accounting for differences in cardiovascular disease and other common risk factors. Our secondary aim was to identify factors that predict a higher risk of dementia in elderly patients with diabetes, as an aid to individualized risk assessment and prevention.

RESEARCH DESIGN AND METHODS

Setting and Data Sources

We conducted a population-based matched cohort study to assess the association between new-onset diabetes and dementia using provincial health administrative databases from Ontario, Canada. Virtually all of Ontario's 13.5 million residents receive coverage for health services under the province's publicly funded universal health care system. The Registered Persons Database contains information on demographics, location of residence, and vital status of all individuals registered under the province's health plan (i.e., all Ontario residents, including new immigrants ≥3 months since arrival). Records can be linked anonymously across databases in order to track each individual's health care utilization and health outcomes over time. This study was approved by the Institute for Clinical Evaluative Sciences and the institutional review board of Sunnybrook Health Sciences Centre in Toronto.

Study Population and Eligibility

Our study cohort consisted of Ontario seniors with newly diagnosed (incident) diabetes and a matched comparison cohort without diabetes, who were 66–105 years of age between 1 April 1995 and 31 March 2007. Individuals who had a new record in the Ontario Diabetes Database (ODD) during this window served as our exposure group. The ODD is a validated administrative data-derived registry that has a sensitivity and specificity of 86 and 97% (respectively) for identifying individuals with physician-diagnosed diabetes (16). Only individuals with health care coverage for a minimum of 3 years were included to ensure that new entries into the ODD were truly incident cases. We then identified three matches without diabetes with the same age, sex, and region of residence for every person with newly diagnosed diabetes in our cohort, using their entry date into the ODD as the baseline (index) date for both groups. We excluded individuals living in long-term care facilities (given the high prevalence of dementia in this setting) and those with evidence of physician-diagnosed dementia at baseline, based on physician billing claims and hospitalizations.

Outcome Definitions

Individuals were followed until 31 March 2012 for a new diagnosis of dementia, our primary outcome. This was defined based on one or more hospitalization records or two outpatient physician billing claims (within 6 months) listing a relevant ICD-9 code (prior to 1 April 2002: 290.x [except 290.8 or 290.9, indicating senile psychosis], 331.0, 331.2, or 797) or ICD-10 code (1 April 2002 onwards: F00, F01, F02.3, F03, F05.1, F09, G30, G31.1, or R54) (17–20). This algorithm was validated in a population of ~2,000 participants enrolled in the Canadian Study of Health and Aging and found to have positive and negative predictive values of 73 and 94%, respectively, using results from extensive cognitive testing as the gold standard (18).

Baseline Variables

We collected data on baseline covariates including age, sex, income, HTN, and history of CAD, cerebrovascular disease (CVD), peripheral vascular disease (PVD), and chronic kidney disease (CKD) in the 36 months prior to the index date, using previously defined diagnostic algorithms (21–24) (Supplementary Table 1). HTN was defined using an algorithm based on hospitalization and physicians' claims data, similar to that of diabetes, which has a positive and negative predictive value of 87 and 88%, respectively (21). Prior CAD included hospitalizations for acute myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass surgery. Our definition of CVD included hospitalization for stroke, transient ischemic attack, or carotid endarterectomy. We identified patients undergoing lower extremity arterial bypass surgery or percutaneous transluminal angioplasty as having PVD. Information on individual-level income was not available in our data sources; hence the median household income level of each individual's neighborhood of residence, derived from the nearest Canadian census year (1996, 2001, or 2006) was attributed to them using their postal code.

Among individuals with diabetes, we also captured information on ethnicity using a validated algorithm that uses surnames to identify those of South

Asian or Chinese heritage, and on immigration status using Canadian Citizenship and Immigration data (25,26). We also captured information on the use of statins and antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers [CCBs]) and antidiabetic treatment (metformin, sulphonylureas, or insulin) from the Ontario Drug Benefit Database, which contains records for all prescriptions filled by Ontario seniors. Last, we included information about hospital admissions and emergency department (ED) visits for hypoglycemia.

Statistical Analysis

Primary Analysis

We conducted a time-to-event analysis using Cox proportional hazards modeling to study the relationship between newly diagnosed diabetes and incident dementia, stratifying by matched clusters of exposed and unexposed individuals. Models were adjusted for baseline income and each of the comorbidities defined above, including HTN, CKD, and vascular disease of various etiologies. We used cause-specific hazard functions to account for the competing risk of death, rather than Fine-Gray regression models (27). Cumulative incidence functions (CIFs), which also account for death as a competing risk, were used to estimate the probability of the occurrence of dementia. As a comparison, CIF curves were also generated for the incidence of death from any cause, and dementia or death from any cause. All analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

Sensitivity Analyses

Because unrecognized dementia may be unmasked by the complexity of diabetes management (i.e., the need for lifestyle changes, regular medication administration, and glucose monitoring), we conducted a sensitivity analysis to examine whether detection bias could explain an elevated risk of dementia among patients with incident diabetes. To do so, we allowed the effect of diabetes status to vary between earlier (<180 days) and later (>180 days) periods of follow-up among the entire sample. Similar analyses were conducted using earlier time thresholds of 30, 60, and 90 days.

We further examined whether the proportional hazards assumption held by running an additional model in the overall sample that included an interaction term for diabetes and time. Again, we hypothesized that if detection bias were a major driver of the relationship between diabetes and dementia, then the effect of incident diabetes would lessen over time.

Secondary Analysis

Cox proportional hazards modeling was used to identify risk factors for dementia among individuals with diabetes. Covariates included age, sex, income, ethnicity, recent immigration (<10 years since landing), baseline CAD, CVD, PVD, HTN, or CKD, and hospitalizations or ED visits for hypoglycemia during follow-up (as a time-varying covariate). Because the latter could not be ascertained reliably from our databases prior to 1 April 2002, we restricted this analysis to members of the cohort with diabetes entering the ODD on or after this date (n = 110,816). We also looked at the effect of various medication classes. First, we examined the cumulative duration (number of days received) of each class of medication between diagnosis and the end of follow-up, based on the number of prescriptions dispensed and the number of days supplied per prescription (adding 50% to the number of days dispensed for the last prescription observed). For insulin use, we counted the total number of prescriptions from the index date until date of censoring. Second, we treated medication exposure as a time-varying covariate, allowing the use of each class of drug to change over time and denoting whether each individual was currently exposed (yes/no) on a given day of follow-up. Because of the size of our data, this analysis could not be performed on the entire sample but was conducted on a 5% random subset (11,252).

RESULTS

Patient Characteristics

We identified 225,045 seniors with newly diagnosed diabetes who were matched to 668,070 individuals without diabetes (from a pool of 1,016,256 potentially eligible matches). Their baseline characteristics are shown in Table 1. The median age of our cohort was 73 years (interquartile range 69–78).

Table 1—Baseline characteristics of study cohort with newly diagnosed diabetes and matched comparison group without diabetes

Characteristic	Newly diagnosed diabetes, n = 225,045	No diabetes, n = 668,070	Total, n = 893,115
Age (years), median (IQR)	73 (69–78)	73 (69–78)	73 (69–78)
Women	114,203 (50.8)	341,557 (51.1)	455,760 (51.0)
Income quintile (Q)			
Q1 (lowest)	49,527 (22.0)	128,826 (19.3)	178,353 (20.0)
Q2	50,732 (22.5)	141,088 (21.1)	191,820 (21.5)
Q3	44,811 (19.9)	132,641 (19.9)	177,452 (19.9)
Q4	40,658 (18.1)	126,697 (19.0)	167,355 (18.7)
Q5 (highest)	38,723 (17.2)	137,243 (20.5)	175,966 (19.7)
CAD	13,181 (5.9)	18,410 (2.8)	31,591 (3.5)
CVD	6,652 (3.0)	9,147 (1.4)	15,799 (1.8)
PVD	1,189 (0.5)	1,981 (0.3)	3,170 (0.4)
HTN	158,151 (70.3)	371,313 (55.6)	529,464 (59.3)
CKD	25,863 (11.5)	47,516 (7.1)	73,379 (8.2)

Data are n (%) unless indicated otherwise. IQR, interquartile range.

Individuals with diabetes had a higher prevalence of HTN, vascular disease, and CKD at baseline relative to those in the comparison group.

Primary Analysis

The average duration of follow-up was 7.2 years, during which 169,114 individuals were diagnosed with dementia. Individuals with diabetes experienced a modestly higher incidence of dementia compared with those without diabetes (2.68 vs. 2.62 per 100 person-years) (Table 2). Based on the Cox model, diabetes was associated with a 19% increased risk of dementia (unadjusted hazard ratio [HR] 1.19; 95% CI 1.18–1.21). The HR remained similar in magnitude after adjusting for baseline covariates, including HTN, CAD, CVD, PVD, and CKD (adjusted HR 1.16; 95% CI 1.15–1.18). Both men (HR 1.20; 95% CI 1.17–1.22]) and women (HR 1.14; 95% CI 1.12–1.16) with diabetes experienced elevated risks of dementia compared with their counterparts without diabetes.

Sensitivity Analysis

The CIF curve (Fig. 1) showed a very early separation in dementia risk between those with and without diabetes, occurring in the first 6 months. The risk associated with diabetes remained unchanged from very early (<180 days) to later time periods (>180 days) ($P > 0.5$ for differences in HR between the very early and later periods), and the results were similar when even earlier time thresholds were used (30, 60, or 90 days). However, only a small percentage of outcome events occurred in the first 6 months of follow-up (2.8%). When testing the proportional hazards assumption, we did detect a significant interaction between diabetes status and time. The HR associated with diabetes status was 1.19 (95% CI 1.16–1.22), and this effect increased by about 1% per year (HR for diabetes × year interaction: 1.009; 95% CI: 1.004–1.014). Thus, after 10 years of duration, diabetes was associated with a nearly 30% higher incidence of dementia. At any time point, the likelihood of death greatly outweighed the likelihood of dementia (Fig. 1). In this older population, the likelihood of dementia or death from any cause approached 50% within 10 years of diabetes diagnosis.

Predictors of Dementia Among Those With Diabetes

Factors associated with an increased risk of dementia among individuals with diabetes are shown in Fig. 2. Dementia risk increased by 12% per year with advancing age. Individuals living in the lowest income areas were 16% more likely compared with those in the wealthiest area (adjusted HR 1.17; 95% CI 1.12–1.24). Prior vascular disease and CKD were associated with significantly increased risks of dementia; however, the strongest predictor was previous CVD, associated with a doubling in risk (adjusted HR 2.03; 95% CI 1.88–2.19). Hospitalization and ED visits for hypoglycemia were also significant predictors of dementia (adjusted HR 1.73; 95% CI 1.62–1.84 for one or more vs. zero episodes). Factors associated with a lower risk of dementia included recent immigration (adjusted HR 0.63; 95% CI 0.55–0.72) and both South Asian and Chinese ethnicity (adjusted HRs 0.68; 95% CI 0.59–0.78 and 0.82; 95% CI 0.74–0.90, respectively, compared with other ethnic groups). Paradoxically, HTN also appeared to be mildly protective against the development of dementia (HR 0.95; 95% CI 0.91–0.99).

We examined the impact of various classes of medications on dementia risk (glucose-, blood pressure–, and cholesterol-lowering agents) in individuals with diabetes. When we modeled the impact of cumulative medication use, all drug classes were associated with a significantly lower risk of dementia, with adjusted HRs ranging from 0.90 to 0.95 per 180 days of use ($P < 0.0001$ for each). In models that treated medication use as time-varying exposures, the risk of dementia was significantly lower only with current statin (HR 0.78; 95% CI 0.71–0.86) and CCB (HR 0.80; 95% CI 0.73–0.89) use, whereas insulin use was associated with a substantially higher risk (HR 1.74; 95% CI 1.37–2.21). In these models, HTN was no longer associated with dementia (HR 0.99; 95% CI 0.89–1.09).

CONCLUSIONS

Our study found a significantly higher risk of dementia among seniors with newly diagnosed diabetes. This is of serious concern given the aging population, increasing prevalence of diabetes, and the limited effective treatment currently available for dementia. This increased risk was independent of preexisting CAD or CVD, HTN, and CKD, conditions thought to mediate the association between diabetes and dementia.

Our results are supported by prior meta-analyses of largely smaller observational

Table 2—Risk of dementia among seniors with newly diagnosed diabetes and matched comparison group without diabetes†

Group	*n*	Number of new dementia cases	Total person-years of follow-up	Incidence rate of dementia per 100 person-years*	Unadjusted HR (95% CI)	Fully adjusted HR‡ (95% CI)
Men and women						
No diabetes	668,070	126,085	4,811,236	2.62	1.00	1.00
Diabetes	225,045	43,029	1,602,844	2.68	1.19 (1.18–1.21)	1.16 (1.15–1.18)
Men						
No diabetes	326,513	53,819	2,283,649	2.36	1.00	1.00
Diabetes	110,842	18,865	769,158	2.45	1.23 (1.20–1.25)	1.20 (1.17–1.22)
Women						
No diabetes	341,557	72,266	2,527,587	2.86	1.00	1.00
Diabetes	114,203	24,164	833,685	2.90	1.17 (1.15–1.19)	1.14 (1.12–1.16)

†Groups with and without diabetes matched by age, sex, and region of residence. *Event rates are number of new dementia cases per 100 person-years. ‡Adjusted for CAD, CVD, or PVD hospitalizations and procedures ≤36 months prior to baseline entry, as well as HTN, CKD, and neighborhood socioeconomic status at baseline entry.

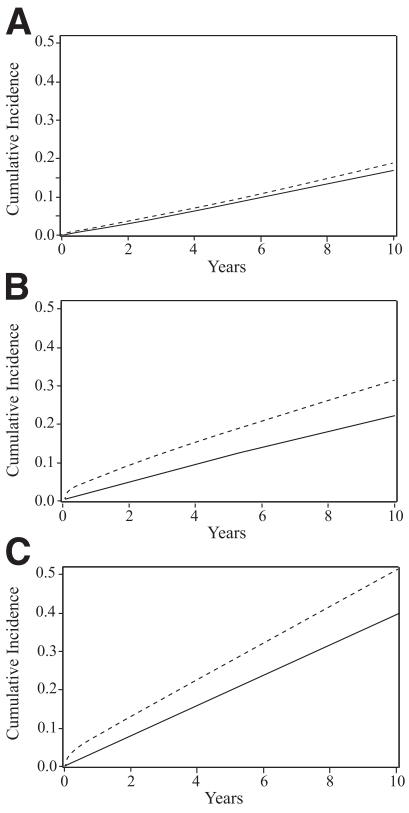

Figure 1—Cumulative incidence of dementia, death from any cause, and dementia or death from any cause among the study population with and without diabetes. *A*: Cumulative incidence of dementia. *B*: Cumulative incidence of death from any cause. *C*: Cumulative incidence of dementia or death from any cause. Group with diabetes, dotted line; group without diabetes, solid line.

and cohort studies that reported a 1.5- and 2.5-fold higher risk of Alzheimer disease and vascular dementia (respectively) in patients with established diabetes (5–8). There was considerable heterogeneity across studies with respect to exposure and outcome ascertainment, and many failed to account for preexisting vascular disease. Our risk estimates may have been lower than in these latter studies because our population was earlier in their course of diabetes. However, it is also possible that a survival effect led to lower event rates in our diabetes population than expected, since we limited our analysis to seniors. Individuals who develop diabetes at an older age may be relatively healthier in comparison with their counterparts without diabetes than those who develop diabetes in midlife. Conversely, selection bias may have resulted in healthier control subjects without diabetes in cohort studies, and therefore higher observed effect sizes. One other population-based study conducted using the Taiwan National Health Database found a 76% higher HR for Alzheimer disease in those with incident diabetes; however, participants were from a broad age-group (11). To the best of our knowledge, ours is the first large, population-wide study to report an association between diabetes and dementia among elderly people with newly diagnosed diabetes, and the first of its kind in North America. The large sample size afforded us sufficient statistical power to study this association and to identify subsets of the elderly population with diabetes that are most vulnerable to developing dementia. We were also able to test for the role of detection bias as a potential mediator in the association between diabetes and dementia and accounted for the large competing risk of death in this population. This adds further credence to our findings and those of others demonstrating a clear link between these two entities.

Our results are congruent with existing data that vascular risk factors and CKD aggravate the risk of dementia (13,28,29). In our study, CVD was associated with a twofold increase in the risk of dementia, underscoring the importance of stroke prevention. There is some evidence supporting a role for vascular dysfunction and cerebral hypoperfusion in the pathophysiology of Alzheimer disease (30), and for stroke prevention as a means of preventing further cognitive decline (31). In addition, our findings demonstrated a harmful effect of severe hypoglycemia in seniors, a factor that may underlie the link we observed between insulin use and dementia in this population. In the ACCORD-MIND trial, tight glycemic control was associated with a lower likelihood of cerebral atrophy but had no effect on cognition (32). Some have theorized that potential benefits may have been partly negated by a greater exposure to severe hypoglycemia in the intensively treated group. On the contrary, patients with cognitive dysfunction may be more susceptible to hypoglycemia, leading to a bidirectional relationship between severe hypoglycemia and dementia (33,34). Another important observation was that the association between diabetes and dementia risk increased over time, possibly because of cumulative exposure to microvascular insults, hypoglycemia, and other diabetes-related effects. However, mortality rates

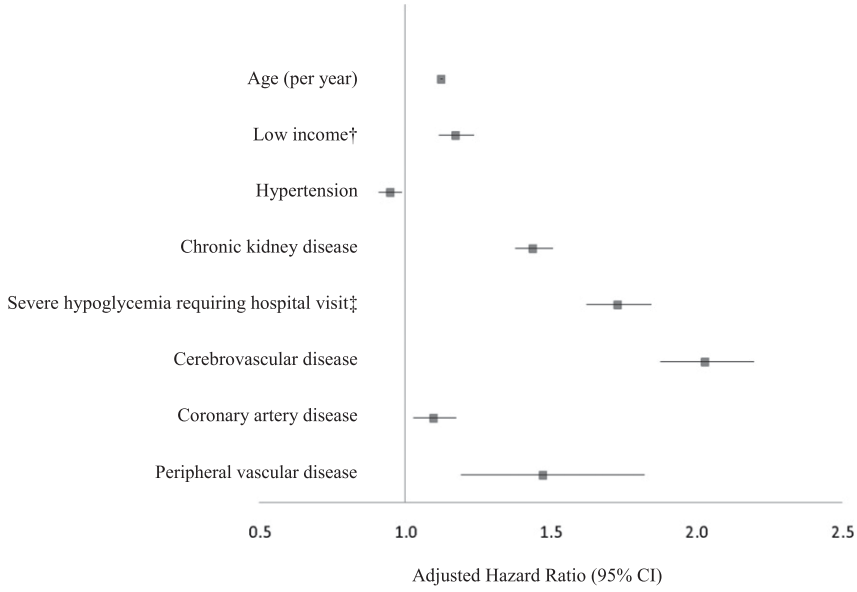

Figure 2—Risk factors for dementia in seniors with newly diagnosed diabetes (n = 110,816). Cohort was restricted to individuals with diabetes entering the ODD 1 April 2002 through 31 March 2007. †Lowest vs. highest income quintile based on median household income level of neighborhood of residence; ‡one or more hospitalizations or ED visits during follow-up, treated as time-varying covariate. Model includes all of the above covariates, as well as sex, ethnicity, and immigration status.

remain high among seniors with diabetes; thus, those who survive longer will also have more opportunity to develop dementia, whereas those who succumb earlier will not. Thus, if recent gains in life expectancy continue to occur among patients with diabetes, the burden of dementia in this population may paradoxically rise despite overall improvements in care.

We found that certain factors appeared to be protective with respect to the risk of dementia. Fewer South Asians developed dementia despite being thought to have a higher risk of cardiovascular complications. Varied cultural and genetic factors may contribute to the differential susceptibility to dementia across racial groups; however, the "healthy immigrant effect" caused by health screening during immigration, immigrant self-selection, and the return of recent immigrants with poor health to their native countries may also play a role (26,35). In contrast, low income was a risk factor for dementia, as it is for other diabetes-related outcomes (36,37). Impaired health literacy, poorer self-management, and adverse health behaviors, such as smoking, have been linked to low income and could explain this association. From epidemiologic data, smoking appears to be a risk factor for both diabetes and dementia (38–40); however, levels of current smoking are comparable between the populations with and without diabetes and fall significantly over age 65 years (23,41). Whether prior smoking predicts dementia (or significantly differed across groups) is unclear.

In our study, many commonly used vascular and antidiabetic medications showed no association with the risk of dementia, with the exception of statins and CCBs. Although such treatments have been postulated to be protective against dementia, numerous trials have failed to identify any beneficial role of glucose-, blood pressure–, or lipid-lowering agents on cognitive decline (31,32,42–45), as suggested by previous observational data (11,46,47). The latter may be vulnerable to numerous biases, including the healthy user effect, since patients with cognitive decline may be less willing to take multiple therapies or less likely to be prescribed them. Although this phenomenon may explain the nonspecific reduction in dementia risk we observed in association with any drug class, analyses using time-varying drug exposures were designed to minimize such effects. Last, we found a paradoxically lower risk of dementia in patients with established HTN based on diagnostic codes from hospitalization records and physicians' service claims. However, individuals who were captured as having HTN may have had greater exposure to protective therapies (CCBs and statins), since this effect became neutral once medication use was accounted for in our analysis. Physicians who recognize and submit claims for HTN management may also treat blood pressure to lower targets; however, our databases lacked information on actual blood pressure levels and therefore we were unable to separate out the effects of blood pressure itself from its treatment.

Our study has many strengths, including a large sample size and well-validated diagnostic algorithms to define diabetes, dementia, and other relevant covariates. Furthermore, our population-based design reduces selection bias and makes the results more generalizable. However, there are certain limitations that merit discussion, including ambiguity about the time of onset of dementia. Although we had excluded previous dementia as comprehensively as we could, some patients might have had some degree of cognitive decline at baseline. Thus we are unable to comment on whether newly diagnosed diabetes led to the development of dementia or accelerated its progression. Detection bias may have contributed to dementia in our population with diabetes; however, only a very small proportion of events occurred within a short time window of diabetes diagnosis. Furthermore, the effect of diabetes grew over time rather than lessened. However, we cannot entirely rule out an element of reverse causation whereby individuals with early cognitive decline experienced a change in diet or activity pattern leading to a greater likelihood of gaining weight and developing diabetes. Further, we could not examine the impact of diabetes on different subtypes of dementia separately, as the databases we used do not adequately discriminate between them. Primary care physicians in Ontario may be more likely to list a diagnosis of diabetes than dementia on a billing claim for individuals with both conditions, since incentive fees, linked to monetary compensation, are provided for diabetes management. Therefore, we may have undercaptured cases of dementia in the population with diabetes. Last, we have not accounted for confounders such as abdominal obesity or other correlates of insulin resistance, HbA_{1c} levels, vascular risk factors (e.g., blood pressure, serum lipids, or smoking), or genetic factors such as APOE4 mutations, since administrative databases lack information about these.

Our results suggest that newly diagnosed diabetes is an important risk factor for the diagnosis of dementia in older adults. Severe hypoglycemia, stroke, and other vascular diseases may represent modifiable risk factors for dementia. Clinical trials suggest that current therapeutic measures to control hyperglycemia, blood pressure, and dyslipidemia are unable to prevent the onset of dementia in older adults with diabetes. More research is needed to identify strategies that can effectively ward off dementia in this growing segment of the population.

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manuscript. J.W. researched data, contributed to the discussion, and edited the manuscript. G.L.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007;369:750–756
2. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia 2013;56:2601–2608
3. Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050. Alzheimer's Disease International (ADI), London, December 2013. Available from http://www.alz.co.uk/research/GlobalImpactDementia2013.pdf. Accessed 31 August 2014
4. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch Neurol 2011;68:1185–1190
5. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012;42:484–491
6. Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PLoS One 2009;4:e4144
7. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74
8. Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev 2013;35:152–160
9. Kimm H, Lee PH, Shin YJ, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. Arch Gerontol Geriatr 2011;52:e117–e122
10. Wang KC, Woung LC, Tsai MT, Liu CC, Su YH, Li CY. Risk of Alzheimer's disease in relation to diabetes: a population-based cohort study. Neuroepidemiology 2012;38:237–244
11. Huang CC, Chung CM, Leu HB, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. PLoS One 2014;9:e87095
12. Pilcher H. Alzheimer's disease could be "type 3 diabetes". Lancet Neurol 2006;5:388–389
13. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol 2011;7:108–114
14. Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology 2010;75:1982–1987
15. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 2012;122:1316–1338
16. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care 2002;25:512–516
17. St Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 2012;79:1049–1055
18. Gill SS, Camacho X, Poss JW. Community-dwelling older adults with dementia: tracking encounters with the health system. In *Health System Use by Frail Ontario Seniors: An In-Depth Examination of Four Vulnerable Cohorts*. Bronskill SE, Camacho X, Gruneir A, Ho MM, Eds. Toronto, ON, Institute for Clinical Evaluative Sciences, 2011
19. Al-Omran M, Mamdani MM, Lindsay TF, Melo M, Juurlink DN, Verma S; Systematic Assessment of Vascular Risk Investigators. Suboptimal use of statin therapy in elderly patients with atherosclerosis: a population-based study. J Vasc Surg 2008;48:607–612
20. Seitz DP, Gill SS, Bell CM, et al. Postoperative medical complications associated with anesthesia in older adults with dementia. J Am Geriatr Soc 2014;62:2102–2109
21. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med 2007;1:e18–e26
22. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29–36
23. Booth GL, Lipscombe LL, Degani N, et al. Diabetes. In *Project for an Ontario Women's Health Evidence-Based Report*. Vol. 2. Bierman AS, editor. Toronto, St. Michael's Hospital and the Institute for Clinical Evaluative Sciences, 2010
24. Ronksley PE, Tonelli M, Quan H, et al.; Alberta Kidney Disease Network. Validating a case definition for chronic kidney disease using administrative data. Nephrol Dial Transplant 2012;27:1826–1831
25. Shah BR, Victor JC, Chiu M, et al. Cardiovascular complications and mortality after diabetes diagnosis for South Asian and Chinese patients: a population-based cohort study. Diabetes Care 2013;36:2670–2676
26. Okrainec K, Booth GL, Hollands S, Bell CM. Impact of language barriers on complications and mortality among immigrants with diabetes: a population-based cohort study. Diabetes Care 2015;38:189–196
27. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;170:244–256
28. Exalto LG, Biessels GJ, Karter AJ, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol 2013;1:183–190
29. Bruce DG, Davis WA, Starkstein SE, Davis TM. Mid-life predictors of cognitive impairment and dementia in type 2 diabetes mellitus: the Fremantle Diabetes Study. J Alzheimers Dis 2014;42(Suppl. 3):S63–S70
30. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: is Alzheimer's a vascular disorder? Am J Cardiovasc Dis 2013;3:197–226
31. Tzourio C, Anderson C, Chapman N, et al.; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069–1075
32. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–977
33. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
34. Yaffe K, Falvey CM, Hamilton N, et al.; Health ABC Study. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med 2013;173:1300–1306
35. Llibre Rodriguez JJ, Ferri CP, Acosta D, et al.; 10/66 Dementia Research Group. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. Lancet 2008;372:464–474
36. Booth GL, Bishara P, Lipscombe LL, et al. Universal drug coverage and socioeconomic disparities in major diabetes outcomes. Diabetes Care 2012;35:2257–2264
37. Booth GL, Creatore MI, Moineddin R, et al. Unwalkable neighborhoods, poverty, and the risk of diabetes among recent immigrants to Canada compared with long-term residents. Diabetes Care 2013;36:302–308
38. Rosella LC, Manuel DG, Burchill C, Stukel TA; PHIAT-DM team. A population-based risk algorithm for the development of diabetes: development and validation of the Diabetes Population Risk Tool (DPoRT). J Epidemiol Community Health 2011;65:613–620
39. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement 2015;11:718–726
40. Di Marco LY, Marzo A, Muñoz-Ruiz M, et al. Modifiable lifestyle factors in dementia: a systematic review of longitudinal observational cohort studies. J Alzheimers Dis 2014;42:119–135
41. Janz T. Statistics Canada. Health at a glance: current smoking trends. Available from http://www.statcan.gc.ca/pub/82-624-x/2012001/article/11676-eng.htm. Accessed 2 June 2015
42. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009;15:CD003160
43. Anderson C, Teo K, Gao P, et al.; ONTARGET and TRANSCEND Investigators. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol 2011;10:43–53
44. Williamson JD, Launer LJ, Bryan RN, et al.; Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Investigators. Cognitive

function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med 2014;174:324–333
45. Peters R, Beckett N, Forette F, et al.; HYVET investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008;7:683–689
46. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J Alzheimers Dis 2011;24:485–493
47. Peters R, Booth A, Peters J. A systematic review of calcium channel blocker use and cognitive decline/dementia in the elderly. J Hypertens 2014;32:1945–1957; discussion 1957–1958