Published in final edited form as:

Aging Ment Health. 2019 July ; 23(7): 880–886. doi:10.1080/13607863.2018.1455167.

Depression in Type 1 Diabetes and Risk of Dementia

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Abstract

Objective: Depression afflicts 14% of individuals with type 1 diabetes (T1D). Depression is a robust risk factor for dementia but it is unknown if this holds true for individuals with type 1 diabetes, who recently started living to an age conferring dementia risk. We examined if depression is a risk factor for dementia among elderly individuals with type 1 diabetes.

Methods: 3,742 individuals with T1D age ≥ 50 were followed for dementia from 1/1/96–9/30/2015. Depression, dementia, and comorbidities were abstracted from electronic medical records. Cox proportional hazard models estimated the association between depression and dementia adjusting for demographics, glycosylated hemoglobin, severe dysglycemic episodes, stroke, heart disease, nephropathy, and end stage renal disease. The cumulative incidence of dementia by depression was estimated conditional on survival dementia-free to age 55.

Results: Five percent (N=182) were diagnosed with dementia and 20% had baseline depression. Depression was associated with a 72% increase in dementia (fully adjusted HR=1.72; 95% CI: 1.12–2.65). The 25-year cumulative incidence of dementia was more than double for those with versus without depression (27% vs. 12%).

Conclusions: For people with type 1 diabetes, depression significantly increases dementia risk. Given the pervasiveness of depression in type 1 diabetes, this has major implications for successful aging in this population recently living to old age.

Keywords

type 1 diabetes; dementia; cohort; depression

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The authors report no conflicts of interest.

1. INTRODUCTION

Depression is three times as common among people with type 1 diabetes compared to the general population and tends to occur in early adulthood or adolescence (Korczak, Pereira, Koulajian, Matejcek, & Giacca, 2011; Kovacs, Goldston, Obrosky, & Bonar, 1997; Roy & Lloyd, 2012). This is especially concerning as depression is associated with worse self-care, poorer adherence and increased risk of complications (Bauer et al., 2017; Grey, Whittemore, & Tamborlane, 2002; Johnson, Eiser, Young, Brierley, & Heller, 2013; Korczak et al., 2011). Furthermore, a bidirectional relationship between depression and glycemic control may lead to a harmful cycle in which poor glycemic controls leads to depressed mood further exacerbating poor self-care (Holt, de Groot, & Golden, 2014; Johnson et al., 2013). Adolescent-onset depression tends to be chronic and recurrent (Johnson et al., 2013; Wilson, Hicks, Foster, McGue, & Iacono, 2014) thus depression remains a concern into adulthood.

Recent advancements in medical care have led to large increases in the life expectancy of people with type 1 diabetes (Miller, Secrest, Sharma, Songer, & Orchard, 2012; Secrest, Becker, Kelsey, LaPorte, & Orchard, 2010). The life expectancy at birth for individuals with type 1 diabetes for individuals diagnosed between 1965 and 1980 was estimated to be 68.8 years, 15 years greater than for individuals diagnosed between 1950 and 1964 (Miller et al., 2012). For the first time individuals with type 1 diabetes are entering an age group at risk for dementia. Starting at age 65, the incidence of dementia in the general population approximately doubles every five years (Jorm & Jolley, 1998). Emerging evidence suggests people with type 1 diabetes are at higher risk of dementia compared to individuals without type 1 or type 2 diabetes (Smolina, Wotton, & Goldacre, 2015). Depression is a known risk of dementia in the general population (Barnes et al., 2012; Chen et al., 2008; da Silva, Gonçalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013; Dotson, Beydoun, & Zonderman, 2010; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006) and among people with type 2 diabetes (L. G. Exalto et al., 2013; W. Katon et al., 2012). However, there is uncertainty whether depression is an early symptom of dementia (Richard, Reitz, Honig, & et al., 2013) or is indeed a true causal risk factor (O'Brien et al., 2003; Richard et al., 2013; Taylor, Aizenstein, & Alexopoulos, 2013). Lifecourse epidemiology has provided additional, suggestive evidence showing an association between midlife depression and late-life dementia (Barnes et al., 2012).

If depression earlier in the lifecourse is truly a risk factor for dementia this is particularly concerning for people with type 1 diabetes who tend to be diagnosed with depression in mid-adulthood or earlier. Increases in prevalence of type 1 diabetes among children and adults (DIAMOND Group, 2006) coupled with increases in an aging population heightens the public health importance of understanding possible negative brain health sequela of type 1 diabetes among an aging population. The objectives of this study are to assess if depression is associated with greater risk of dementia among a cohort of individuals with type 1 diabetes and if the magnitude of risk varies when examining risk of dementia over different follow-up time periods.

2. METHODS

2.1 Study population.

We identified individuals with type 1 diabetes by screening the electronic health records of members of the Kaiser Permanente Northern California (KPNC) Diabetes Registry, which is an amalgamation of all KPNC members with diabetes mellitus. Since 1993 the Diabetes Registry has incorporated various sources of data to identify individuals with diabetes, including laboratory data, pharmacy records, and inpatient and outpatient diagnoses of diabetes (Karter et al., 2002; Karter et al., 2013). Overall, KPNC provides comprehensive medical services to over 3 million members. Members are generally representative of the overall population of the region, except for underrepresentation of the extreme tails of the income distribution (Gordon & Kaplan, 1991; Krieger, 1992; NP, 2012). Individuals were considered to have a type 1 diabetes diagnosis if they met the following three criteria during a review of electronic health records for all Diabetes Registry members: 1) at least 75% of their diabetes diagnostic codes indicate type 1 diabetes versus type 2 diabetes; 2) filled an insulin prescription at any time during the study period; and c) did not fill prescriptions of any hypoglycemic agents other than insulin (Klompas et al., 2013). Members with type 1 diabetes were eligible if they were 50 years old during the study period (01/01/1996 to 9/30/2015) and had no previous diagnosis for dementia at baseline. Baseline date was defined as the first date between 01/01/1996 and 9/30/2015 that an individual with type 1 diabetes turned 50. The final analytic sample included 3,742 individuals with type 1 diabetes. This study was approved by the Kaiser Permanente Internal Review Board.

2.2 Depression diagnosis.

Depression diagnoses were identified from electronic health records using the following ICD-9 codes: major depressive disorder (296.2x and 296.3x), depressive type psychosis (298.0x), dysthymic disorder (300.4x), adjustment disorder with depressed mood (309.0x) or with mixed anxiety and depressed mood (309.28), and depressive disorder not otherwise classified (311).

2.3 Dementia diagnosis.

Dementia diagnoses were identified from inpatient and outpatient visits extracted from electronic medical records using the following International Statistical Classification of Diseases, ninth edition (ICD-9) codes: Alzheimer's disease (331.0), vascular dementia (290.4x), and other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.1, 294.2x, and 294.8). Dementia has been successfully identified using ICD-9 codes in previous studies in this population (L. G. Exalto et al., 2013; Lieza G. Exalto et al., 2014; Mayeda, Glymour, Quesenberry, & Whitmer, 2016; Mayeda et al., 2014; Whitmer et al., 2008; Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005) and a similar set of ICD-9 codes had a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia utilizing medical records review, physical examination, structured interview, and a neuropsychiatric battery (W. J. Katon et al., 2010).

2.4 Death.

Dates of death were extracted from hospital records, California death certificates, and Social Security Administration datasets.

2.5 Covariates.

Age, sex, and race/ethnicity were retrieved from KPNC health plan membership databases. Race/ethnicity was collapsed and reclassified as White, Asian, or “Other racial/ethnic group”. Baseline glycosylated hemoglobin (HbA1c) was obtained from the most recent prior KP laboratory measurement to baseline. The following baseline diabetes characteristics previously associated with dementia risk (G. J. Biessels, M. W. Strachan, F. L. Visseren, L. J. Kappelle, & R. A. Whitmer, 2014; Ramirez et al., 2015) were ascertained from the KPNC electronic health record between 01/01/1996 and 9/30/2015 (ICD-9 and Current Procedural Terminology, 4th edition (CPT-4) procedural code definition in Supplemental Table 1): severe hypoglycemic and hyperglycemic episodes, stroke, ischemic heart disease, nephropathy, and end stage renal disease (ESRD). Studies among individuals with type 2 diabetes have shown an increased risk of dementia associated with HbA1c (Ramirez et al., 2015), acute dysglycemic events (G. J. Biessels, M. W. J. Strachan, F. L. J. Visseren, L. J. Kappelle, & R. A. Whitmer, 2014; L. G. Exalto et al., 2013; Whitmer et al., 2009), and microvascular (G. J. Biessels et al., 2014; L. G. Exalto et al., 2013; Tamura & Yaffe, 2011) and macrovascular (G. J. Biessels et al., 2014; L. G. Exalto et al., 2013) complications. A missing indicator was used for individuals missing data on race/ethnicity; there were no other missing data.

2.6 Statistical analysis.

We examined the distribution of characteristics of members with and without depression using chi-squares and t-tests. There was no missing data on depression, dementia, or any of the covariates. Cox proportional hazards models with age as a time scale were implemented to estimate the effect of depression on dementia risk. Covariates were added to the model in four groups: demographics (age, race (Whites as reference group), sex (females as reference group)), glycemic control indicators (HbA1c, severe hypoglycemic or hyperglycemic episodes), macrovascular risk indicators (stroke, ischemic heart disease), and microvascular indicators (nephropathy, ESRD). To examine if the association between depression and dementia may vary by time due to depression being a prodrome of dementia, we conducted a series of Cox proportional hazards models including dementia cases occurring: any time after baseline, or three, five, and 10 years after baseline. We implemented Fine and Gray models to examine the association between baseline depression and dementia anytime during follow-up accounting for the competing risk of death (Fine & Gray, 1999). Possible effect modification of the associations between baseline depression and dementia three years after baseline by race and sex was tested using interaction terms. We choose this outcome in order to reducing the likelihood of capturing depression as part of the prodromal period of dementia while including as many dementia cases as possible. Individuals were censored at first diagnosis of dementia, death, lapse in membership greater than 90 days, or end of study period on September 30, 2015.

We also estimated the cumulative incidence of dementia (in 5-year increments from 5 to 35 years) conditional on survival free of dementia until age 55 by using the Practical Incidence Estimator macro, which incorporates information on the competing risk of death (Beiser, D'Agostino, Seshadri, Sullivan, & Wolf, 2000). All analyses were conducted on SAS statistical software version 9.3 (SAS Institute Inc, Cary North Carolina).

3. RESULTS

The sample's mean age at entry was 56.1 years (standard deviation=8.5) and 20% of the sample had prevalent depression at baseline (Table 1). Individuals with depression were more likely to have hypoglycemic and hyperglycemic events as well as macrovascular and microvascular complications than their non-depressed counterparts. During follow-up (mean=6.3 years; range: 0.003–19.7 years), 5% of members received a dementia diagnosis, 17% died, and 26% were censored due to a lapse in membership. At the end of follow-up, 52% of the sample survived and were dementia free members of KPNC. The time to dementia diagnosis ranged from 0.05 years to 19.63 years with a mean of 8.57 years (standard deviation=5.72). The mean time to dementia diagnosis was shorter among individuals with baseline depression than individuals without depression (7.58 vs. 8.76 years).

Depression was associated with almost double the risk of dementia anytime after baseline adjusting for demographics (HR=1.98; 95% CI: 1.30, 3.01). This risk persisted even after adjusting for HbA1c, acute dysglycemic events, and macrovascular and microvascular risk indicators (fully adjusted model: HR=1.72; 95% CI: 1.12, 2.65) (Table 2). Analyses restricted to dementia diagnosis occurring at least 3, 5, 7, or 10 years after baseline each showed an association between depression and dementia (Table 2). (See Supplemental Table 3 for results including effect estimates of covariates for the relationship between depression and dementia at least 3 years after baseline.) For example, baseline depression was associated with 126% greater risk of dementia occurring at least 5 years after baseline (HR=2.26; 95% CI: 1.24, 4.11). The effect persists in fully adjusted models looking at dementia risk 3+ or 5+ years after baseline; the effect estimates of depression on dementia 7+ and 10+ years after baseline are elevated but non-significant likely due to decreasing dementia cases. Depression was not associated with dementia in models accounting for the competing risk of death and adjusting for demographics (HR=1.18; 95% CI: 0.77, 1.76; Supplemental Table 2). There continue to be no evidence of an association between depression and dementia in competing risk models further adjusting for HbA1c, acute dysglycemic events, and macro-and microvascular indicators (HR=1.18, 95% CI: 0.76, 1.77). There was no evidence of effect modification by race or sex on the relationship between baseline depression and dementia at least three years later (sex*depression interaction term p-value= 0.13; race/ethnicity*depression interaction term p-value=0.70).

The cumulative incidence of dementia any time after baseline conditional on survival to age 55 without dementia (Table 3 and Figure 1) were consistently higher among members with depression compared those without depression. 25-year cumulative dementia risk at age 55 was 27% (95% CI: 19%, 32%) for members with depression versus 12% (95% CI: 7%, 15%) for members without depression.

4. DISCUSSION

In the first study of dementia and depression among older adults with type 1 diabetes, depression is a strongly associated with dementia. Those with depression had between 98% to 132% increase in risk of dementia adjusting for demographics. The risk for dementia anytime after baseline, at least 3 years after baseline, and at least 5 years after baseline persisted even after adjusting for HbA1c, acute dysglycemic events, and macrovascular and microvascular risk indicators. The association between baseline depression and dementia persisted 3-, 5-, 7-, and 10-years after baseline suggesting that this association is not due to depression in the prodromal period of dementia. The risk of dementia was approximately twice as large among type 1 diabetes with comorbid depression when only including dementia cases occurring at least three years after baseline and adjusting for demographics and glycemic control indicators. The effect was only slightly attenuated when further adjusting for macrovascular and microvascular risk indicators. 25-year cumulative incidence of dementia at age 55 was 27% (95% CI: 19%, 32%) for members with diabetes and depression versus 12% (95% CI: 7%, 15%) for members without comorbid depression. Depression was not associated with dementia in models accounting for the competing risk of death. There was no evidence that the association between depression and dementia differed by sex or race.

Though the increased prevalence of depression among children and adolescents with type 1 diabetes is well described, less is known about the prevalence and effect of depression among older populations of individuals with type 1 diabetes. In systematic reviews, the prevalence of clinical depression among adults with type 1 diabetes has been estimated to be 12% compared to 3% among the control groups without type 1 diabetes (Barnard, Skinner, & Peveler, 2006; Roy & Lloyd, 2012). This prevalence is lower than the 20% of our cohort who had a depression diagnosis at baseline.

Our study estimates depression is associated with almost double the risk of dementia among individuals with type 1 diabetes. This is consistent with prior estimates that depression elevates dementia risk by 87–162 % in the general population (Chen et al., 2008; Dotson et al., 2010) and by 100–169% among individuals with type 2 diabetes (W. Katon et al., 2012; W. J. Katon et al., 2010). A study also conducted among KPNC members found that depressive symptoms in midlife and late life each increased the risk of dementia and that the risk was greatest among people with depression at both life stages (Barnes et al., 2012). The possibility that dementia risk may increase with longer duration of depression is particularly concerning for people with type 1 diabetes who have an earlier age of depression onset compared to people with type 2 diabetes or the general population increasing the length of depression exposure (Zhao, Chen, Lin, & Sigal, 2006).

The specific mechanisms linking type 1 diabetes and depression remain unknown. The psychological burden of the complex self-care required is a commonly cited link between depression and type 1 diabetes (Holt et al., 2014; Moulton, Pickup, & Ismail, 2015; Roy & Lloyd, 2012). Physiological pathways have also been proposed. Increases in cytokines production due to hyperglycemia may increase the risk of depression by activating the hypothalamic-pituitary-adrenal (HPA) axis (Korczak et al., 2011). Alternatively, low levels

of insulin may hinder the ability of the brain to make serotonin, a neurotransmitter associated with depression, by altering the ratio of amino acids that cross the blood-brain barrier (Korczak et al., 2011).

Depression, in turn, may lead to dementia in people with type 1 diabetes through pathways present in the general population or through mechanisms specific to type 1 diabetes or both. Depression is known to increase the risk of vascular risk factors of dementia such as hypertension and stroke (Gilsanz et al., 2017; Pan, Sun, Okereke, Rexrode, & Hu, 2011; Trudel-Fitzgerald, Gilsanz, Mittleman, & Kubzansky, 2015). Magnetic resonance imaging studies show deterioration of the hippocampus in both people with depression as well as people with diabetes (Ho, Sommers, & Lucki, 2013). Depression may also directly affect brain health by causing hippocampal damage due to elevated levels of glucocorticoids (Korczak et al., 2011). This atrophy is associated with duration of depression across the lifecourse (Butters et al., 2008) possibly resulting in greater atrophy among people with type 1 diabetes than the general population. Hypoglycemic events are associated with reduced cognitive function among people with type 1 diabetes (Korczak et al., 2011) and may be triggered by depression related to poor glycemic control.

Strengths of this study including a large well characterized sample of individuals with type 1 diabetes age 50+ with access to a wide range of possible confounders including HbA1c levels and micro-and macrovascular complications; putting us in a unique position to take into account comorbid conditions specific to type 1 diabetes. We defined depression, dementia, and comorbidities using ICD codes; as KPNC patients receive virtually every aspect of care at KPNC facilities and every clinical interaction and diagnosis is captured in the comprehensive electronic medical record we have no missing data regarding comorbidities. Nevertheless, the possibility of misclassification (e.g., undiagnosed depression or dementia) remains. Assuming depression is associated with dementia, the underdiagnoses of depression would lead to an underestimate of the depression-dementia association. The identification of depression through clinical diagnosis instead of symptom scales decreases the likelihood of misclassifying people with diabetes distress as having depression (Fisher et al., 2016). However, we were unable to examine the association between depression symptom severity and dementia risk. We were also able to follow individuals longitudinally and determine if depression is associated with dementia 7–10 years after baseline. Limitations of this study include our inability to examine the direct effect of depression on brain health due to a lack of brain imaging. Nor does this study include measures of cognitive function so we are unable to determine if depression impacts certain domains of cognition in this population. Unfortunately, age of diabetes onset was unknown, thus we don't know if those with younger age of type 1 diabetes onset are more or less likely to have depression. We are not able to account for confounding by socioeconomic status, education, health risk behaviors, or subclinical cerebrovascular disease, such as white matter hyper-intensities, microinfarcts, or other markers of brain vascular injury. We do not know if individuals who were censored due to a membership gap greater than 90 days went on to develop dementia and it is unclear how this affects our results. However, individuals censored due to a lapse in membership were overall healthier and less likely to have depression. Although we did not see evidence of effect modification using interaction terms

between depression and sex and race, we were likely underpowered and future research should examine these associations in larger diverse samples.

Depression is a significant public health issue for those with type 1 diabetes over the life span. Depression warrants intervention not only due to its own burden but also because it is linked with increased risk of cardiovascular disease, stroke, and over the long-term may have consequences for brain health. Due to the enormous impact depression has on glycemic control and self-care in the context of type 1 diabetes it is alarming that it is linked with increased risk of dementia in this population. Our study found that depression is robustly associated with dementia risk in this large sample of individuals with type 1 diabetes independent of vascular comorbidities and proximal glycemic control. Research needs to continue to identify intervening pathways from type 1 diabetes to depression and depression to dementia. Delineation of mechanisms could reduce the burden of dementia in an aging cohort of people with type 1 diabetes and improve diabetes care. Fortunately, depression may be treated and future research should examine if effective treatment mitigates dementia risk in this unique and vulnerable population with a chronic disease requiring constant vigilance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by grant number R01 AG047500 (PI: Dr. Whitmer). Dr. Gilsanz is supported by the UCSF Training for Research on Aging and Chronic Disease (T32 AG049663).

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Figure 1.
Cumulative incidence of dementia by baseline depression status conditional on survival without dementia until age 55

Table 1.

Baseline characteristics by baseline depression status

	No depression (N=2,990)	Depression (N=752)	Total (N=3,742)	P-values
Dementia				
Any time after baseline, n(%)	153 (5.1)	29 (3.9)	182 (4.9)	0.15
At least 3 yrs. after baseline, n(%)	100 (3.3)	17 (2.3)	117 (3.1)	0.13
At least 5 yrs. after baseline, n(%)	72 (2.4)	14 (1.9)	86 (2.3)	0.37
At least 7 yrs. after baseline, n(%)	61 (2.0)	10 (1.3)	71 (1.9)	0.20
At least 10 yrs. after baseline, n(%)	43 (1.4)	<10	<53	0.28
Sociodemographic				
Birth year, mean (SD)	1947.3 (12.0)	1954.7 (8.8)	1948.8 (11.8)	<.0001
median (range)	1950 (1906, 1965)	1957 (1900, 1965)	1951 (1900, 1965)	
Age at baseline, mean (SD)	57.0 (8.7)	52.3 (6.0)	56.1 (8.5)	<.0001
Male, n(%)	1,660 (55.5)	310 (41.2)	1,970 (52.6)	<.0001
Race				<.0001
White, n(%)	2,350 (78.6)	606 (80.6)	2,956 (79.0)	
Black, n(%)	150 (5.0)	37 (4.9)	187 (5.0)	
Hispanic, n(%)	156 (5.2)	52 (6.9)	208 (5.6)	
Asian, n(%)	126 (4.2)	20 (2.7)	146 (3.9)	
Other/mixed, n(%)	90 (3.0)	29 (3.9)	119 (3.2)	
Missing, n(%)	96 (3.2)	3 (0.4)	99 (2.6)	
Glycemic risk indicators				
HbA1c% mean (SD)	8.2 (1.9)	8.4 (1.9)	8.3 (1.9)	0.10
median (range)	7.8 (4.7, 20.7)	8.0 (4.2, 16.2)	7.9 (4.2, 20.7)	
Severe hypoglycemic episode, n(%)	342 (11.4)	200 (26.6)	542 (14.5)	<.0001
Severe hyperglycemic episode, n(%)	158 (5.3)	158 (21.0)	316 (8.4)	<.0001
Macrovascular complications				
Stroke, n(%)	91 (3.0)	59 (7.8)	150 (4.0)	<.0001
Ischemic heart disease, n(%)	258 (8.6)	124 (16.5)	382 (10.2)	<.0001
Microvascular complications				
Nephropathy, n(%)	401 (13.4)	256 (34.0)	657 (17.6)	<.0001

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	No depression (N=2,990)	Depression (N=752)	Total (N=3,742)	P-values
End stage renal disease, n(%)	120 (4.0)	71 (9.4)	191 (5.1)	<.0001

Note: Column percent presented.

Table 2:
Depression and Risk of Dementia from Cox Proportional Hazard Models Using Age as the Time scale

Adjusted for:	Dementia any time after baseline (182 cases)	Dementia 3+ years after baseline (117 cases)	Dementia 5+ years after baseline (86 cases)	Dementia 7+ years after baseline (71 cases)	Dementia 10+ years after baseline (50 cases)
Model 1: Demographics	1.98 (1.30, 3.01) *	2.02 (1.18, 3.45) *	2.26 (1.24, 4.11) *	2.21 (1.11, 4.40) *	2.32 (1.01, 5.28) *
Model 2: Model 1+HbA1c	2.02 (1.33, 3.07) *	2.06 (1.21, 3.52) *	2.33 (1.28, 4.25) *	2.30 (1.16, 4.59) *	2.44 (1.07, 5.59) *
Model 3: Model 2+Acute dysglycemic event	1.91 (1.25, 2.94) *	1.99 (1.16, 3.42) *	2.18 (1.18, 4.01) *	2.21 (1.11, 4.44) *	2.28 (0.99, 5.25)
Model 4: Model 3+ macrovascular indicators	1.70 (1.11, 2.62) *	1.80 (1.05, 3.11) *	1.98 (1.08, 3.64) *	1.98 (0.99, 3.98)	2.01 (0.91, 4.84)
Model 5: Model 4+microvascular indicator	1.72 (1.12, 2.65) *	1.84 (1.07, 3.18) *	1.97 (1.07, 3.62) *	1.91 (0.95, 3.85)	2.02 (0.87, 4.66)

Notes: Demographics: age, sex, race/ethnicity; Acute dysglycemic events: severe hypoglycemic episode, severe hyperglycemia episode; Macrovascular risk indicators: stroke, ischemic heart disease;
Microvascular risk indicators: nephropathy, end stage renal disease

*
p-values <0.05

Table 3:

Estimates of cumulative incidence of dementia adjusted for death rates and conditional on survival free of dementia up to age 55

	Not depressed Cumulative Incidence (95% CI)	Depressed Cumulative Incidence (95% CI)
5 year risk	0.6 (0.0, 1.2)	1.9 (0.8, 3.0)
10 year risk	1.3 (0.3, 2.2)	4.3 (2.5, 6.0)
15 year risk	3.7 (1.6, 5.3)	12.4 (8.4, 15.6)
20 year risk	7.9 (4.4, 10.5)	20.7 (14.5, 25.2)
25 year risk	12.1 (6.8, 15.4)	27.0 (18.8, 32.1)
30 year risk	16.9 (8.7, 20.7)	30.4 (20.7, 35.8)
35 year risk	18.9 (7.3, 23.0)	33.6 (19.3, 39.5)