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Impact of Depression and Diabetes on Risk of Dementia In a National Population-Based Cohort

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Abstract

Importance—Although depression and type 2 diabetes may independently increase dementia risk, no studies have examined whether the risk of dementia among people with both is higher than the sum of each individually.

Objective—To examine risk of all-cause dementia among persons with depression, diabetes or both compared to those with neither.

Design—A population-based cohort study of 2,454,532 adults, including 477,133 (19.4%) with depression, 223,174 (9.1%) with diabetes and 95,691 (3.9%) with both.

Setting—Denmark

Participants—All dementia-free Danish citizens ≥50 years old between January 1, 2007 through 2013.

Main outcome measure—Dementia was ascertained by physician diagnosis from the Danish National Patient Register, the Danish Psychiatric Central Register (DPCR), and/or prescription of a cholinesterase inhibitor or memantine from the Danish National Prescription Registry (DNPR). Depression was ascertained by psychiatrist diagnosis from the DPCR or antidepressant prescription from the DNPR. Diabetes was identified using the Danish National Diabetes Register. The risk of all-cause dementia associated with diabetes, depression or both was estimated using

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Access to Data and Data Analysis: Dr. Vestergaard 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.

Cox proportional hazards regression models that adjusted for potential confounding factors such as demographics and potential intermediates such as medical comorbidity.

Results—During 13,834,645 million person-years of follow-up, 59,663 (2.4%) developed dementia of whom 6,466 (10.8%) had diabetes, 15,729 (26.4%) had depression and 4,022 (6.7%) had both. The adjusted hazard ratio of developing all-cause dementia was 1.83 (95% confidence interval: 1.80, 1.87) for persons with depression, 1.20 (95% CI: 1.17, 1.23) for persons with diabetes, and 2.17 (95% CI: 2.10, 2.24) for those with both as compared to those with neither. The excess risk of all-cause dementia observed for individuals with comorbid depression and diabetes surpassed the summed risk associated with the two individually, especially for younger persons. The corresponding Attributable Proportion due to the interaction of comorbid depression and diabetes was 0.25 (95% CI = 0.13, 0.36; $P<0.001$) for those under 65 years old and 0.06 (95% CI = 0.02, 0.10; $P=0.001$) for those over 65.

Conclusions—Depression and diabetes were independently associated with greater dementia risk and the combined association of the two disorders with risk of all-cause dementia was stronger than additive.

INTRODUCTION

Diabetes and major depression are very common in western populations. Type 2 diabetes occurs in approximately 8–14% of most western populations,[1] while approximately 25% of women and 16% of men will have a major depressive episode over their lifetime.[2] Up to 20% of persons with type 2 diabetes have comorbid depression.[3] Furthermore, a recent meta-analysis has established a bidirectional link between depression and diabetes.[4] Patients with comorbid depression and diabetes have poorer adherence to diet, smoking cessation, exercise, and diabetes-controlling medications.[5] Depression is also associated with increased cortisol levels,[6] autonomic nervous system dysregulation[7] and increased inflammation,[8] all of which worsen glycemic control. Therefore, it is not surprising that patients with comorbid depression and diabetes have increased risk of microvascular and macrovascular complications as well as mortality.[9]

An extensive literature has also identified that diabetes and depression are independent risk factors for dementia. A meta-analysis found that persons with diabetes have a 47% increased risk of all-cause dementia.[10] Two recent meta-analyses found that depression doubled subsequent all-cause dementia risk.[11,12] Two additional studies have shown that comorbid depression and type 2 diabetes was associated with a two-fold greater risk of developing all-cause dementia versus diabetes alone.[13,14] A study of over 29,000 patients with type 2 diabetes developed a 10-year risk prediction model for dementia, identifying depression as an important risk factor.[15] Another recent study using data from a large randomized trial aimed at optimally controlling glycemic and cardiovascular risk factors in patients with diabetes found that those with comorbid depression and type 2 diabetes versus those with diabetes alone had greater risk of cognitive decline over a 40-month period.[16]

However, these prior studies have all been limited to diabetes cohorts[13–16] and so could not ascertain whether people with both depression and diabetes have an elevated dementia risk due to an additive (or more than additive) interaction between the two. Given the increasing

incidence of dementia in aging modern societies,[17] understanding the risk associated with potentially modifiable depression and diabetic disease trajectories is essential.

In a population-based cohort of 2.4 million adults, we aimed to study the risk of all-cause dementia among persons with diabetes, depression, and comorbid diabetes and depression versus those with neither illness. Given rapidly increasing diabetes incidence in younger age groups[18] and the demographic, clinical, and prognostic differences in patients who develop diabetes in middle versus older age,[19,20] we also examined whether age (comparing those younger than 65 versus those older than 65) modified the risk of all-cause dementia in this population.

METHODS

Population

We conducted a population-based cohort study using data from the Danish Civil Registration System.[21] This register includes information on gender, month of birth, and continuously updated information on vital status and migration since 1968. In this register, Danish citizens are each assigned a unique personal identification number, providing accurate linkage to person-level data.[21] Diagnoses in the registers are classified according to the Danish version of the International Classification of Diseases, 8th Revision [ICD-8][22] before January 1, 1994. Hereafter, diagnoses were classified according to the ICD-10.[23] Our cohort included all individuals who were ≥50 years of age between January 1, 2007 through 2013, born in Denmark, free of dementia, and alive as of January 1, 2007. We followed our sample from 2007 through 2013 in order to ensure maximum validity of dementia diagnoses[24] and homogenous calendar period.

The study protocol was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authority.

Primary Independent Variables

Our primary independent variables of interest were the presence of either depression, diabetes, or comorbid depression and diabetes. We identified individuals with depression by either a depression diagnosis made by a psychiatrist or redemption of at least one antidepressant prescription using data from the Danish Psychiatric Central Register (DPCR) [25] and the Danish National Prescription Registry (DNPR) (see Appendix 1).[26] The DPCR contains diagnostic information on all psychiatric admissions since 1969 and outpatient specialty mental health visits since 1995.[25] The DNPR contains information on all prescriptions dispensed at Danish pharmacies since 1995, including day of purchase and classification of drugs according to the Anatomical Therapeutic Chemical (ATC) Classification.[27] Individuals with schizophrenia, schizoaffective disorders or bipolar disorder were censored at the date of diagnosis (see Appendix 2). We supplemented our depression definition by identifying all antidepressant prescriptions (i.e. selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors, and other non-tricyclic (TCA) antidepressants) redeemed between 1995 and 2014 (see Appendix 1). Our primary depression definition did not include redemption of TCA prescriptions because of their

frequent use for insomnia and/or pain, nor bupropion or trazodone since neither was approved for the treatment of depression in Denmark during the study period.

Individuals diagnosed with diabetes between 1990 and 2014 were identified in the Danish National Diabetes Register using a validated algorithm[28] (see Appendix 3). The Register's registration of diabetes is considered complete from 1995 onwards with a sensitivity of 86% and a positive predictive value of 89%.[28]

Outcome of Interest

We identified incident all-cause dementia using data from the Danish National Patient Register,[29] the DPCR, and the DNPR (see Appendix 4). The Danish National Patient Register contains information on all Danish medical hospitalizations since 1977 as well as all outpatient contacts since 1995.[29] Approximately two-thirds of all dementia cases in Denmark are diagnosed within the secondary health care system.[24] While the diagnosis of all-cause dementia in either the Danish National Patient Register or the DPCR has a positive predictive value of 86%,[30] the validity is lower among individuals under age 65 for dementia sub-types.[31] We identified all inpatient or outpatient contacts with a diagnosis of dementia made between 1969 and 2014 based on a validated algorithm.[24] In addition, we supplemented our all-cause dementia definition with redemption of at least one prescription for a cholinesterase inhibitor or memantine between 1995 and 2014. We excluded all cases of dementia prevalent before January 1, 2007 to identify all incident cases of dementia.

Covariates of Interest

Covariates were chosen *a priori* based on their availability and prior research identifying their potential associations with depression, diabetes and dementia risk.[32]

We obtained marital status information (defined as married/living in a registered partnership or single) from the Danish Civil Registration System.

We used the Danish National Patient Register to obtain data on all hospital contacts between 1977 and 2014 for one or more of the following chronic diseases: ischemic heart disease, congestive heart failure (CHF), peripheral vascular disease, atrial fibrillation/flutter, cerebrovascular disease, traumatic brain injury (TBI), chronic pulmonary disease, renal disease, retinopathy and neuropathy (see Appendix 6).

Statistical Analysis

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% Confidence Intervals (95%CIs) for the associations between depression, diabetes and risk of all-cause dementia. Age was chosen as the underlying time scale and was thus intrinsically corrected for. Individuals contributed at-risk time from January 1, 2007 or from their 50th birthday, whichever came last (delayed entry). Censoring occurred at day of dementia, day of schizophrenia or bipolar disorder diagnosis, death, immigration from Denmark, at their 100th birthday or January 1, 2014, whichever came first.

Apart from using age as the time scale, our primary regression model was adjusted for gender, marital status and calendar period. Next, we adjusted for potential intermediates on

the pathway from depression and diabetes to dementia, including medical comorbidities (i.e. ischemic heart disease, CHF, peripheral vascular disease, atrial fibrillation/flutter, cerebrovascular disease, TBI, and chronic pulmonary disease) and diabetes complications (i.e. renal disease, retinopathy and neuropathy). [10–12] In order to minimize the possibility that any associations between depression and all-cause dementia risk could be confounded by similarities between late-life depressive symptoms and prodromal dementia,[33] we added two years to the date of initial depression diagnosis or initial antidepressant prescription.

Furthermore, because guidelines recommend that individuals with suspected dementia have fasting blood glucose or HbA1c levels drawn as part of the medical work-up[34] and are therefore likely to be diagnosed with diabetes soon after dementia diagnosis, one year was added to the date of initial diabetes diagnosis. To validate this approach, we performed a sensitivity analysis where we repeated our regression models stratified by time since depression and time since diabetes without postponement of these exposures; these models were adjusted for age, gender and marital status.

We examined whether there was an additive interaction by testing the hypothesis of no excess hazard due to the interaction.[35] We performed interaction analyses between diabetes and depression using the entire sample as well as stratifying by age (i.e. over/under 65 years) and calculated the attributable proportion (AP) due to interaction as a measure of the excess HR for individuals with both conditions not explained by the independent effects of either. In this setting, the attributable proportion is given by the following formula: $AP_{interaction} = (HR_{dep+dm}\text{-}HR_{dep}\text{-}HR_{dm}+1)/HR_{dep+dm}$.[35] All interaction analyses were adjusted for age, gender, marital status and calendar period.

We conducted two secondary analyses. First, we created a categorical variable denoting early-versus late-onset diabetes using the median age of onset, 63, as the cut-point. To facilitate this categorization based on the National Diabetes Register, this analysis was restricted to individuals born after 1932. Next, we ascertained the associations of our independent variables of interest with risk of Alzheimer's disease or vascular dementia diagnoses individually in regression models adjusted for age, gender, calendar period and marital status.

In a sensitivity analysis, we examined whether our findings were impacted by expanding our definition of depression to include TCA prescription(s).

We used two-sided significance tests for all analyses with statistical significance set at $P < 0.05$. The proportional hazards assumption was assessed graphically for all variables using the log-minus-log plots, finding no violations. All statistical analyses were performed using Stata 13 (StataCorp, College Station, Texas, USA).

RESULTS

We followed a cohort of 2,454,532 individuals for a total of 13,834,645 million person-years including 477,133 (19.4%) with a diagnosis of depression, 223,174 (9.1%) with diabetes and 95,691 (3.9%) with comorbid depression and diabetes. The mean age of initial diabetes diagnosis was 63.1 (Standard Deviation [SD]: 12.0) and 58.5 (SD: 13.5) for depression.

During the study period, 59,663 (2.4%) persons developed dementia. The mean age at first dementia diagnosis was 80.9 (SD: 8.7). Of those who developed dementia, 15,729 (26.4%) had depression alone, 6,466 (10.8%) had diabetes alone, and 4,022 (6.7%) had comorbid depression and diabetes (See Table 1).

Compared with persons without depression or diabetes, diabetes alone was associated with 20% greater risk of all-cause dementia (HR = 1.20, 95% CI = 1.17, 1.23), depression alone with 83% greater risk, (HR = 1.83, 95% CI = 1.80, 1.87) and comorbid depression and diabetes with 117% higher risk (HR = 2.17, 95% CI = 2.10, 2.24) after adjustment for age, gender, calendar period and marital status. The estimates decreased slightly after adjustment for chronic diseases (Table 2).

As shown in Figure 1, during the first year after depression, the associated hazard of all-cause dementia was elevated by nearly seven-fold (HR=6.75, 95% CI = 6.55, 6.95), but thereafter it decreased consistently to a constant hazard of approximately two (as compared to those without depression). As shown in Figure 2, during the first year after diabetes diagnosis, the associated hazard of all-cause dementia was 31% higher (HR=1.31, 95% CI = 1.22, 1.40), with a decrease in subsequent years. The long-term HR rose to 42% higher at 10 years post-diabetes diagnosis (HR=1.42, 95% CI = 1.38, 1.47).

Among participants under age 65, the HRs for all-cause dementia were 2.93 (95% CI = 2.71, 3.16) for depression alone, 1.71 (95% CI = 1.49, 1.97) for diabetes alone and 4.84 (95% CI = 4.21, 5.55) for those with both (See Table 3). The combined effect of the two illnesses on all-cause dementia risk was larger than the sum of the two individual diseases; i.e., the AP due to the interaction was 0.25 (95% CI = 0.13, 0.36; $P < 0.001$) for persons younger than 65 and 0.06, 95% CI = 0.02, 0.100; $P = 0.001$) for those older than 65.

When we examined the impact of age at diabetes-onset, the HR for the association between early onset-diabetes and all-cause dementia risk was significantly higher than that for late-onset diabetes (early-onset: HR = 1.82; 95% CI = 1.73, 1.91; late-onset: HR = 1.30, 95%CI = 1.24, 1.36; $P < 0.001$).

Diabetes, depression and their comorbid combination were all associated with increased Alzheimer's disease risk (diabetes alone: HR = 1.06, 95%CI = 1.01, 1.11; depression alone: HR = 1.39, 95%CI = 1.35, 1.44; comorbid depression and diabetes: HR = 1.46, 95%CI = 1.37, 1.55). However, the magnitude of the associations of diabetes, depression and their comorbid combination with vascular dementia risk were more pronounced (diabetes alone: HR = 1.55, 95%CI = 1.44, 1.66; depression alone: HR = 2.42, 95%CI = 2.29, 2.55; comorbid depression and diabetes: HR = 3.56, 95%CI = 3.28, 3.86).

Finally, our results were unaffected by expanding our depression definition to include TCA prescription(s) redemption (diabetes alone: HR = 1.20, 95%CI = 1.17, 1.24; depression alone: HR = 1.79, 95%CI = 1.75, 1.82; comorbid depression and diabetes: HR = 2.07, 95%CI = 2.01, 2.14).

DISCUSSION

In a nationwide, population-based cohort study of over 2.4 million persons ≥50 years old, diabetes and depression were associated with increased risk of all-cause dementia, and the combined effect of both disorders appeared more than additive, especially among younger persons. Among those with depression and diabetes in our cohort, six percent of incident dementia may be accounted for by the interaction between depression and diabetes overall, and 25% among those under age 65. Although the underlying risk of dementia is low in this younger age group, the marked increase in incidence of diabetes in younger age groups[18] makes this finding quite worrisome.

Our study extends beyond prior studies by identifying that compared to a population with neither depression nor diabetes, depression alone is associated with the highest relative risk of all-cause dementia. Further, we found similar results when examining associations with risk of Alzheimer's disease or vascular dementia, though the magnitude of the associations of depression as well as comorbid depression and diabetes with vascular dementia risk was more pronounced, in line with the results of a recent meta-analysis.[36] Additionally, we found that having both depression and diabetes is associated with a level of risk greater than the sum of the two illnesses. Although underlying causal mechanisms are unclear, one explanation could be depression and diabetes having many shared risk factors for dementia including increased inflammation, decreased insulin sensitivity, autonomic nervous system dysregulation, obesity and vascular disease.[37]

Prior studies have found that patients with depression and diabetes are younger than those with diabetes alone and were diagnosed with diabetes approximately five years earlier.[38] Also, depression earlier in life may be a risk factor for developing type 2 diabetes.[4] Given that depression in patients with diabetes is associated with poor self-care, treatment non-adherence and adverse psychobiologic changes,[5–8] this younger age group with comorbid depression and diabetes may be vulnerable to developing dementia later in life.

From a public health perspective, developing screening and interventions improving both quality of depression and diabetes treatment in this subgroup of patients could be important in reducing dementia risk. A recent prospective cohort study of 1,433 older adults with diabetes found that both effective treatment of diabetes and depression and improving diet could lead to as much as a 20% decrease in incident dementia.[39] Primary care-based collaborative care models have been developed and shown to reduce depressive symptoms in patients with comorbid depression and chronic medical illnesses such as diabetes and heart disease.[40–42] Although adequately powered trials of these interventions to test their effects on preventing dementia may require very large sample sizes (e.g., > 50,000 subjects) and long durations (e.g., 15–20 years), they are warranted given dementia's societal costs.

Our study has several strengths and limitations. We followed a nationwide cohort virtually without loss to follow-up making non-response bias an unlikely explanation for our findings. Also, information on diabetes, depression and dementia was collected prospectively and did not rely on patient or proxy recall. An important limitation of our study was that the population was from a single country with a well-developed national health care system and

relatively homogenous population, therefore limiting generalizability. However, this factor should improve internal validity since the role of socioeconomic factors in health care-seeking behavior is expected to be minimal. Further, our definition of depression was based on a combination of psychiatric diagnoses and antidepressant prescription records, thereby introducing selection bias since patients with more severe depression are more likely to be prescribed antidepressants and/or referred to psychiatrists.[43,44] This issue is further complicated by inability to capture depressed individuals who have not sought treatment.[45] Similarly, the use of ICD-8 and ICD-10 codes to identify dementia and diabetes cases could miss patients with initial symptoms of these illnesses until symptoms or functional impairments become more prominent, as well as limit ability to accurately differentiate dementia subtypes.[46,47] A further limitation was lack of data on possible confounders such as health-risk behaviors including smoking, obesity and sedentary lifestyle. However, these lifestyle factors may be mediators of the associations presented here, and previous studies did not find attenuation of the association of comorbid depression and diabetes with dementia risk after adjusting for health-risk behaviors.[13,14] Finally, residual confounding remains a possibility, as in any observational study.

In conclusion, we found that depression and diabetes were both associated with greater risk of all-cause dementia, as well as both Alzheimer's disease and vascular dementia. These associations appeared to be stronger among those with depression alone compared to those with diabetes alone. Persons with co-existing diabetes and depression appeared to have the highest relative risk of dementia, and this association tended to be stronger than additive. The interaction between diabetes and depression tended to be particularly strong for individuals under 65. In light of the increasing societal burden of chronic diseases, further research is needed to elucidate the pathophysiologic mechanisms linking depression, diabetes, and adverse outcomes such as dementia, as well as to develop interventions aimed at preventing these dreaded complications.

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APPENDICES

APPENDIX 1: Information on depression obtained from the Danish Psychiatric Central Register and the Danish National Prescription Registry

EXPOSURES (Appendices 1-3)

A diagnosis of depression was identified if at least one of the following criteria applied

1. Registration of a diagnosis of depression in the Danish Psychiatric Central Register.

   And/or

2. Registration of at least one prescription of antidepressants redeemed in the Danish National Prescription Registry

Diagnosis according to a record of depression in the Danish Psychiatric Central Register

ICD-8	ICD-10
296.09, 296.29, 296.99, 298.09, 300.49, and 300.19	F32, F33

Diagnosis according to a record of prescriptions for antidepressants in the Danish National Prescription Registry

Name	Drug	ATC-codes
SSRI (Selective serotonin re-uptake inhibitors)	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram	N06AB
MAOIs (Monoamine oxidase inhibitors)	Isocarboxazid and moclobemide	N06AF, N06AG
Other antidepressants	Mianserin, nefazodone, mirtazapine, venlafaxine, reboxetine, duloxetine, and agomelatine	N06AX
Tricyclic antidepressants (TCAs)	Desipramine, imipramine, imipramine oxide, clomipramine, opipramol, trimipramine, Iofepramine, dibenzepin, amitriptyline, nortriptyline, protriptyline, doxepin, iprindole, melitracen, butriptyline, dosulepin, amoxapine, dimetacrine, amineptine, maprotiline, quinupramine	N06AA

APPENDIX 2: Information on severe mental illness obtained from the Danish Psychiatric Central Register

	ICD-8	ICD-10
Schizophrenia	295 (excluding 295.79)	F20
Schizoaffective disorders	295.79, 296.8	F25
Bipolar affective disorders	296.19, 296.39	F30, F31

APPENDIX 3: Information on diabetes obtained from the Danish National Diabetes Register

Algorithm: Individuals were classified as having diabetes on the day where at least one of the following six criteria was met

1. A diagnosis of diabetes made at any Danish hospital as registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).
2. A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.
3. Five blood glucose measurements within one year as registered in the Danish National Health Service Register.
4. Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Service Register.
5. Two redemptions of oral anti-diabetic drugs within six months as registered in the Danish National Prescription Registry.
6. Two redemptions of prescribed insulin as registered in the Danish National Prescription Registry.

APPENDIX 4: Information on dementia obtained from the Danish Psychiatric Central Register, the Danish National Patient Register, and the Danish National Prescription Registry

OUTCOME

A diagnosis of dementia was identified if at least one of the following criteria applied

1. Registration of a diagnosis of dementia in the Danish Psychiatric Central Register or the Danish National Patient Register

   And/or

2. Registration of at least one prescription of anti-dementia drug redeemed in the Danish National Prescription Registry

Diagnosis according to a record of dementia in the Danish Psychiatric Central Register or the Danish National Patient Register

	ICD-8	ICD-10
AD (Alzheimer's disease)	290.10	F00.0, F00.1, F00.2,

	ICD-8	ICD-10
		F00.9, G30.0, G30.1, G30.8, G30.9
VaD (Vascular dementia)	293.09–19	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
FTD (Frontotemporal dementia)	290.11	F02.0
Dementia without specification	290.09–19	F03.9

Diagnosis according to a record of prescriptions for anti-dementia drugs in the Danish National Prescription Registry

Name	Drug	ATC-codes
Anticholinesterases		
	Tacrine	N06DA01
	Donepezil	N06DA02
	Rivastigmine	N06DA03
	Galantamine	N06DA04
	Donepezil and Memantine	N06DA52
Other anti-dementia drugs		
	Memantine	N06DX1

APPENDIX 5: Information on marital status obtained from the Danish Civil Registration System

COVARIATES

Family type/marital status
Single
Partners/married

APPENDIX 6: Information on chronic diseases and diabetic complications obtained from the Danish National Patient Register

	ICD-8	ICD-10
Ischemic heart disease	410–414	I20–I25
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445,	I70; I71; I72; I73; I74; I77
Atrial fibrillation or flutter	427.93, 427.94	I48

	ICD-8	ICD-10
Cerebrovascular disease	430–438	I60–I69; G45; G46
Traumatic Brain Injury	850.99, 851.29–854.99, 800.99–801.09, 803.99	S06.0, S06.1-S06.9, S02–S02.1, S02.7, S02.9
Chronic pulmonary disease	490–493, 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Renal Disease	249.02, 250.02, 403,404,580-583, 584, 590.09, 593.19, 753.10–753.19, 792	I12; I13; N00-N05; N07; N08.3, N11; N14; N17-N19; Q61 E10.2, E11.2, E14.2
Retinopathy	249.01, 250.01, 377.00	H33.4, H36.0, H43.1, H45.0, E10.3, E11.3, E14.3
Neuropathy	249.03, 250.03	G62.9, G63.2, E10.4, E11.4

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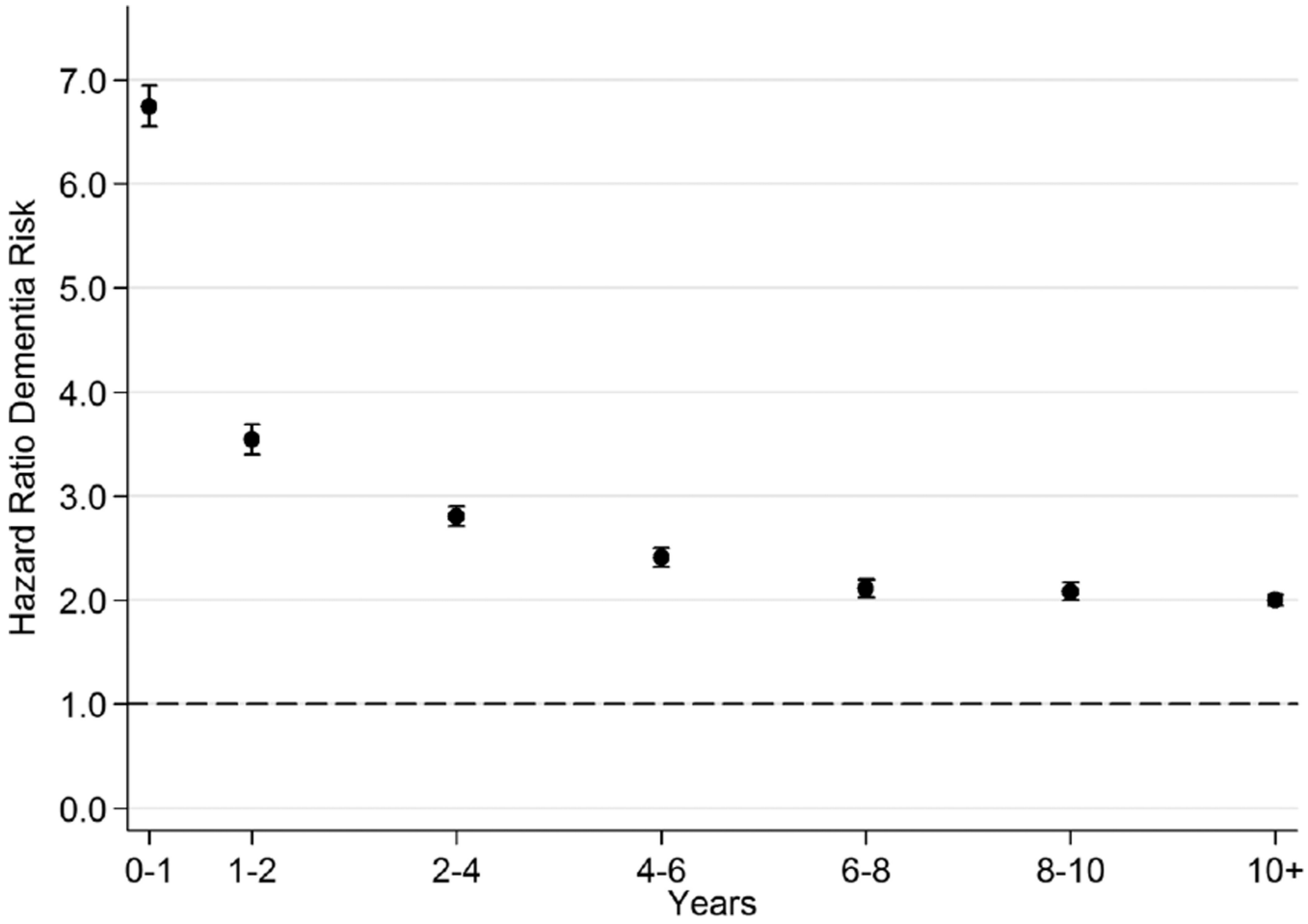

Figure 1.

Time Since Depression Diagnosis and All-Cause Dementia Risk*

* Adjusted for age, gender, calendar year, and marital status.

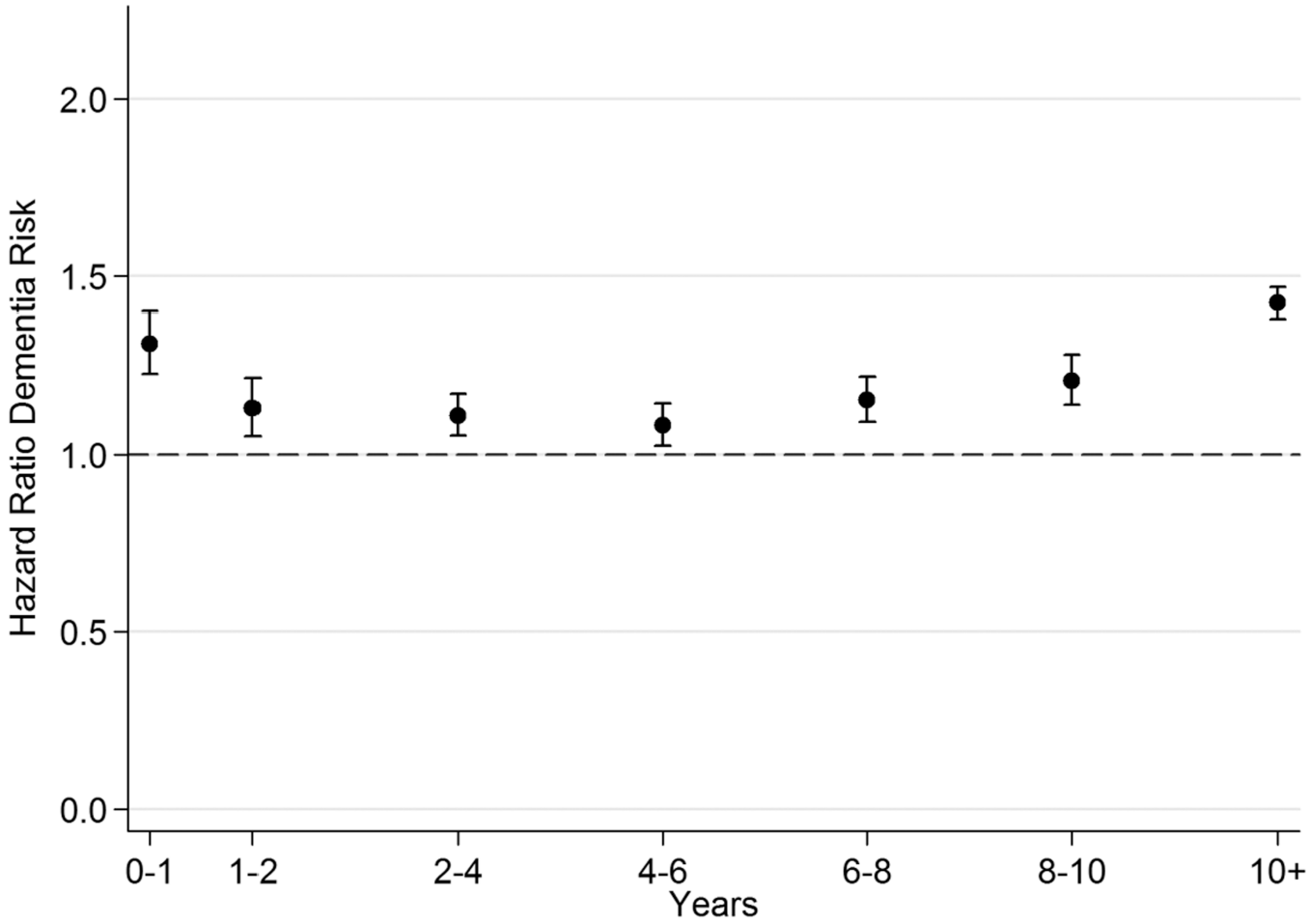

Figure 2.
Time Since Diabetes Diagnosis and All-Cause Dementia Risk*
* Adjusted for age, gender, calendar year, and marital status.

Table 1

Patient Characteristics from a Population-Based Danish Cohort (All Years)

	NO. WITH DEMENTIA	NO. WITHOUT DEMENTIA*	PERSON YEARS AT RISK
Total	59,663	2,394,869	13,834,645
Age			
<65 years	3,269	1,147,053	7,604,829
≥65 years	56,394	1,247,816	6,229,815
Gender			
Women	35,843	1,232,159	7,214,160
Men	23,820	1,162,710	6,620,485
Calendar period			
2007	8,545	50,572	1,920,880
2008	8,669	48,940	1,938,299
2009	9,109	49,185	1,954,875
2010	8,924	49,152	1,973,373
2011	8,296	47,250	1,994,020
2012	8,089	47,271	2,016,872
2013	8,031	2,102,499	2,036,325
Exposure diseases			
None	33,446	1,625,088	10,116,443
Diabetes	6,466	216,708	1,048,696
Depression	15,729	461,404	2,310,165
Depression and diabetes	4,022	91,669	359,341
Marital status			
Married	22,360	1,393,722	8,589,713
Single	35,329	968,408	5,084,545
Missing	1,974	32,739	160,386
Chronic diseases			
Ischemic heart disease	12,622	308,389	1,444,251
Congestive heart failure	5,909	120,500	410,542
Peripheral vascular disease	5,097	125,448	508,264
Atrial fibrillation or flutter	9,725	185,422	698,446
Cerebrovascular disease	14,713	231,213	971,917
Traumatic brain injury	5,601	155,803	744,497
Chronic pulmonary disease	7,024	221,382	927,227
Renal disease/Nephropathy	2,603	80,353	254,381
Retinopathy	1,526	42,222	208,846
Neuropathy	1,592	37,854	161,895
Duration of diabetes			

	NO. WITH DEMENTIA	NO. WITHOUT DEMENTIA*	PERSON YEARS AT RISK
No diabetes	49,175	2,086,492	12,426,608
0–2 years	9,322	223,292	1,213,969
2–4 years	763	39,848	130,709
4–6 years	372	32,469	56,967
> 6 years	31	12,768	6,392
Anti-diabetic treatment			
No insulin	57,386	2,327,123	13,526,400
Insulin	2,277	67,746	308,245

* Persons are assigned the category in which they are last observed in the study.

Table 2

Adjusted hazard ratios (HRs) for the risk of All-Cause of dementia among persons with depression alone, diabetes alone, and both diseases, compared to persons with neither disease

	Neither Depression Nor Diabetes	Diabetes	Depression	Depression and diabetes
HR(95%CI)[a]	1(ref)	1.20 (1.17;1.23)	1.83 (1.80;1.87)	2.17 (2.10;2.24)
HR(95%CI) [b]	1(ref)	1.14 (1.11;1.17)	1.68 (1.65;1.71)	1.88 (1.82;1.94)
HR(95%CI) [c]	1(ref)	1.15 (1.12;1.18)	1.83 (1.79;1.86)	2.07 (2.00;2.14)
HR(95%CI) [d]	1(ref)	1.11 (1.08;1.14)	1.68 (1.64;1.71)	1.82 (1.76;1.89)

[a] Adjusted for age, gender, calendar period and marital status

[b] As [a] but also adjusted for ischemic heart disease, congestive heart failure, peripheral vascular disease, atrial fibrillation or flutter, cerebrovascular disease, traumatic brain injury and chronic pulmonary disease

[c] As [a] but also adjusted for retinopathy, renal disease and neuropathy

[d] As [a] but also adjusted for the diseases in both [b] and [c]

Table 3

Interaction analyses: Hazard ratios (HRs) for the risk of All-Cause dementia among persons with depression alone, diabetes alone, and depression and diabetes, compared to persons with neither disease

	Neither Depression Nor Diabetes	Depression HR(95% CI)	Diabetes HR(95% CI)	Depression and diabetes HR(95% CI)	Attributable proportion due to interaction (95% CI)	P-value for H:AP=0
Total	1 (ref)	1.83 (1.80;1.87)	1.20 (1.17;1.23)	2.17 (2.10;2.24)	0.06 (0.03;0.10)	0.001
Age-stratified:						
<65 years	1 (ref)	2.93 (2.71;3.16)	1.71 (1.49;1.97)	4.84 (4.21;5.55)	0.25 (0.13;0.36)	<0.001
>65 years	1 (ref)	1.78 (1.75;1.82)	1.18 (1.15;1.21)	2.08 (2.01;2.16)	0.06 (0.02;0.10)	0.001