Effect of Depression and Diabetes Mellitus on the Risk for Dementia
A National Population-Based Cohort Study

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IMPORTANCE Although depression and type 2 diabetes mellitus (DM) may independently increase the risk for dementia, no studies have examined whether the risk for dementia among people with comorbid depression and DM is higher than the sum of each exposure individually.

OBJECTIVE To examine the risk for all-cause dementia among persons with depression, DM, or both compared with persons with neither exposure.

DESIGN, SETTING, AND PARTICIPANTS We performed a national population-based cohort study of 2,454,532 adults, including 477,133 (19.4%) with depression, 223,174 (9.1%) with DM, and 95,691 (3.9%) with both. We included all living Danish citizens 50 years or older who were free of dementia from January 1, 2007, through December 31, 2013 (followed up through December 31, 2013). Dementia was ascertained by physician diagnosis from the Danish National Patient Register or the Danish Psychiatric Central Register and/or by prescription of a cholinesterase inhibitor or memantine hydrochloride from the Danish National Prescription Registry. Depression was ascertained by psychiatrist diagnosis from the Danish Psychiatric Central Research Register or by prescription of an antidepressant from the Danish National Prescription Registry. Diabetes mellitus was identified using the National Diabetes Register.

MAIN OUTCOMES AND MEASURES We estimated the risk for all-cause dementia associated with DM, depression, or both using Cox proportional hazards regression models that adjusted for potential confounding factors (eg, demographics) and potential intermediates (eg, medical comorbidities).

RESULTS During 13,834,645 person-years of follow-up, 59,663 participants (2.4%) developed dementia; of these, 6466 (10.8%) had DM, 15,729 (26.4%) had depression, and 4022 (6.7%) had both. The adjusted hazard ratio for developing all-cause dementia was 1.83 (95% CI, 1.80-1.87) for persons with depression, 1.20 (95% CI, 1.17-1.23) for persons with DM, and 2.17 (95% CI, 2.10-2.24) for those with both compared with persons who had neither exposure. The excess risk for all-cause dementia observed for individuals with comorbid depression and DM surpassed the summed risk associated with each exposure individually, especially for persons younger than 65 years (hazard ratio, 4.84 [95% CI, 4.21-5.55]). The corresponding attributable proportion due to the interaction of comorbid depression and DM was 0.25 (95% CI, 0.13-0.36; P < .001) for those younger than 65 years and 0.06 (95% CI, 0.02-0.10; P = .001) for those 65 years or older.

CONCLUSIONS AND RELEVANCE Depression and DM were independently associated with a greater risk for dementia, and the combined association of both exposures with the risk for all-cause dementia was stronger than the additive association.

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Diabetes mellitus (DM) and major depression are very common in Western populations. Type 2 DM occurs in approximately 8% to 14% of most Western populations, whereas approximately 25% of women and 16% of men will have a major depressive episode during their lifetime. As many as 20% of persons with type 2 DM have comorbid depression. Furthermore, a recent meta-analysis has established a bidirectional link between depression and DM. Patients with comorbid depression and DM have poorer adherence to diet, smoking cessation, exercise, and medication regimens to control DM. Depression is also associated with increased cortisol levels, autonomic nervous system dysregulation, and increased inflammation, all of which worsen glycemic control. Therefore, patients with comorbid depression and DM have an increased risk for microvascular and macrovascular complications and mortality.

An extensive literature has also identified DM and depression as independent risk factors for dementia. A meta-analysis found that persons with DM have a 47% increased risk for all-cause dementia. Two recent meta-analyses found that depression doubled the subsequent risk for all-cause dementia. Two additional studies have shown that comorbid depression and type 2 DM were associated with a 2-fold greater risk for developing all-cause dementia compared with DM alone. A study of more than 29,000 patients with type 2 DM developed a 10-year risk prediction model for dementia that identified depression as an important risk factor. Another recent study using data from a large randomized clinical trial aimed at optimum control of glycemic and cardiovascular risk factors in patients with DM found that those with comorbid depression and type 2 DM compared with DM alone had a greater risk for cognitive decline during a 40-month period.

However, these prior studies have all been limited to cohorts of patients with DM and so could not ascertain whether people with depression and DM have an elevated risk for dementia owing to an additive (or more than additive) interaction between the two. Given the increasing incidence of dementia in aging modern societies, understanding the risk associated with potentially modifiable depression and DM disease trajectories is essential.

In a population-based cohort of 2.4 million adults, we aimed to study the risk for all-cause dementia among persons with DM, depression, or both compared with persons who had neither illness. Given the rapidly increasing incidence of DM in younger groups and the demographic, clinical, and prognostic differences in patients who develop DM in middle vs older age, we also examined whether age (<65 vs ≥65 years) modified the risk for all-cause dementia in this population.

Methods

Population
We conducted a population-based cohort study using data from the Danish Civil Registration System. This register includes information on sex and month of birth and continuously updated information on vital status and migration since 1968.
Registry (eAppendix 4 in the Supplement). The Danish National Patient Register contains information on all Danish medical hospitalizations since January 1, 1977, and all outpatient contacts since January 1, 1995. Approximately two-thirds of all dementia cases in Denmark are diagnosed within the secondary health care system. Although the diagnosis of all-cause dementia in the Danish National Patient Register or the Danish Psychiatric Central Research Register has a positive predictive value of 86%, the validity is lower among individuals younger than 65 years for dementia subtypes. We identified all inpatient or outpatient contacts with a diagnosis of dementia made from January 1, 1969, through December 31, 2013, based on a validated algorithm. In addition, we supplemented our definition of all-cause dementia with re-demption of at least 1 prescription for a cholinesterase inhibitor or memantine hydrochloride from January 31, 1995, through December 31, 2013. 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, DM, and the risk for dementia. We obtained marital status information (defined as married or living in a registered partnership or single) from the Danish Civil Registration System (eAppendix 5 in the Supplement). We used the Danish National Patient Register to obtain data on all hospital contacts from January 1, 1977, through December 31, 2013, for 1 or more of the following chronic diseases: ischemic heart disease, congestive heart failure, peripheral vascular disease, atrial fibrillation/flutter, cerebrovascular disease, traumatic brain injury, chronic pulmonary disease, renal disease, retinopathy, and neuropathy (eAppendix 6 in the Supplement).

Statistical Analysis
We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for the associations between depression and DM and the risk for all-cause dementia. Age was chosen as the underlying time scale, for which we corrected intrinsically. Individuals contributed at-risk time from January 1, 2007, or from their 50th birthday, whichever came last (delayed entry). Censoring occurred at the day of the dementia diagnosis, diagnosis of schizophrenia or bipolar disorder, death, immigration from Denmark, 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 sex, marital status, and calendar period. Next, we adjusted for potential intermediates on the pathway from depression and DM to dementia, including medical comorbidities (ie, ischemic heart disease, congestive heart failure, peripheral vascular disease, atrial fibrillation/flutter, cerebrovascular disease, traumatic brain injury, and chronic pulmonary disease) and complications of DM (ie, renal disease, retinopathy, and neuropathy). 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, we added 2 years to the date of the initial diagnosis of depression or the initial prescription of an antidepressant. Furthermore, because guidelines recommend that individuals with suspected dementia have fasting blood glucose or hemoglobin A1c levels measured as part of the medical workup and are therefore likely to be diagnosed with DM soon after the dementia diagnosis, 1 year was added to the date of the initial diagnosis of DM. To validate this approach, we performed a sensitivity analysis in which we repeated our regression models stratified by time since the depression diagnosis and time since the DM diagnosis without postponement of these exposures; these models were adjusted for age, sex, and marital status.

We examined whether an additive interaction existed by testing the hypothesis of no excess hazard due to the interaction. We performed interaction analyses between DM and depression using the entire sample and stratifying by age (ie, ≥65 and <65 years) and calculated the attributable proportion 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 (represented by AP) is given by the following formula:

\[
AP = \frac{HR_{Depression + DM} - HR_{Depression} - HR_{DM} + 1}{HR_{Depression + DM}}
\]

All interaction analyses were adjusted for age, sex, marital status, and calendar period.

We conducted 2 secondary analyses. First, we created a categorical variable denoting early- vs late-onset DM using the median age of onset, 63 years, 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 the risk for diagnosis of Alzheimer disease or diagnosis of vascular dementia individually in regression models adjusted for age, sex, calendar period, and marital status. In a sensitivity analysis, we examined whether our findings were affected by expanding our definition of depression to include prescription of tricyclic antidepressants.

We used 2-sided significance tests for all analyses, with statistical significance set at P < .05. The proportional hazards assumption was assessed graphically for all variables using the log-minus-log plots, and we found no violations. All statistical analyses were performed using commercially available software (Stata, version 13; StataCorp).

Results
We followed up a cohort of 2,454,532 individuals for a total of 13,844,645 person-years, including 477,133 (19.4%) with a diagnosis of depression, 223,174 (9.1%) with a diagnosis of DM, and 95,691 (3.9%) with comorbid depression and DM. The mean age at the initial diagnosis of DM was 63.1 (SD, 12.0) years; at the initial diagnosis of depression, the mean age was 58.5 (SD, 13.5) years.

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

Compared with persons without depression or DM, DM alone was associated with a 20% greater risk for all-cause dementia (HR, 1.20 [95% CI, 1.17–1.23]); depression alone, with an 83% greater risk (HR, 1.83 [95% CI, 1.80–1.87]); and comorbid depression and DM, with a 117% greater risk (HR, 2.17 [95% CI, 2.10–2.24]) after adjustment for age, sex, 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 the diagnosis of depression, the associated hazard for all-cause dementia was elevated nearly 7-fold (HR, 6.75 [95% CI, 6.55–6.97]).
but thereafter it decreased consistently to approximately 2.00 (compared with individuals without depression). As shown in Figure 2, during the first year after the diagnosis of DM, the associated hazard for all-cause dementia was elevated 31% (HR, 1.31 [95% CI, 1.22-1.40]), with a decrease in subsequent years. The long-term HR rose 42% at 10 years after the diagnosis of DM (HR, 1.42 [95% CI, 1.38-1.47]).

Among participants younger than 65 years, the HRs for all-cause dementia were 2.93 (95% CI, 2.71-3.16) with depression alone, 1.71 (95% CI, 1.49-1.97) with DM alone, and 4.84 (95% CI, 4.21-5.55) with comorbid depression and DM (Table 3). The combined effect of the 2 illness exposures on all-cause dementia risk was larger than the sum of the 2 individual diseases; that is, the attributable proportion owing to the interaction was 0.25 (95% CI, 0.13-0.36; $P < .001$) for persons younger than 65 years and 0.06 (95% CI, 0.02-0.10; $P = .001$) for those 65 years or older. When we examined the impact of age at onset of DM, the HR for the association between early-onset DM and the risk for all-cause dementia was significantly higher (HR, 1.82 [95% CI, 1.73-1.91]) than that for late-onset DM (HR, 1.30 [95% CI, 1.24-1.36] ($P < .001$).

**Table 2. Adjusted HRs for the Risk of All-Cause Dementia by Exposure Disease**

<table>
<thead>
<tr>
<th>Adjustment Model</th>
<th>Exposure, HR (95% CI)</th>
<th>No Depression or DM</th>
<th>DM</th>
<th>Depression</th>
<th>Depression and DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary$^a$</td>
<td>1 [Reference]</td>
<td>1.20 (1.17-1.23)</td>
<td>1.83 (1.80-1.87)</td>
<td>2.17 (2.10-2.24)</td>
<td></td>
</tr>
<tr>
<td>Second$^b$</td>
<td>1 [Reference]</td>
<td>1.14 (1.11-1.17)</td>
<td>1.68 (1.65-1.71)</td>
<td>1.88 (1.82-1.94)</td>
<td></td>
</tr>
<tr>
<td>Third$^c$</td>
<td>1 [Reference]</td>
<td>1.15 (1.12-1.18)</td>
<td>1.83 (1.79-1.86)</td>
<td>2.07 (2.00-2.14)</td>
<td></td>
</tr>
<tr>
<td>Final$^d$</td>
<td>1 [Reference]</td>
<td>1.11 (1.08-1.14)</td>
<td>1.68 (1.64-1.71)</td>
<td>1.82 (1.76-1.89)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; HR, hazard ratio.

$^a$ Adjusted for age, sex, calendar period, and marital status.

$^b$ Adjusted as in the primary model and for complications of DM (ie, retinopathy, renal disease, and neuropathy).

$^c$ Adjusted as in the primary model and for the diseases in the second and third models.

**Table 3. Interaction Analyses of Exposure Diseases**

<table>
<thead>
<tr>
<th>Risk for Dementia by Exposure, HR (95% CI)</th>
<th>No Depression or DM</th>
<th>Depression</th>
<th>DM</th>
<th>Depression and DM</th>
<th>AP Due to Interaction (95% CI)</th>
<th>$P$ Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1 [Reference]</td>
<td>1.83 (1.80-1.87)</td>
<td>1.20 (1.17-1.23)</td>
<td>2.17 (2.10-2.24)</td>
<td>0.06 (0.03-0.10)</td>
<td>.001</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>1 [Reference]</td>
<td>2.93 (2.71-3.16)</td>
<td>1.71 (1.49-1.97)</td>
<td>4.84 (4.21-5.55)</td>
<td>0.25 (0.13-0.36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥65</td>
<td>1 [Reference]</td>
<td>1.78 (1.75-1.82)</td>
<td>1.18 (1.15-1.21)</td>
<td>2.08 (2.01-2.16)</td>
<td>0.06 (0.02-0.10)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: AP, attributable proportion; DM, diabetes mellitus; HR, hazard ratio.

$^a$ Indicates $P$ value for the test of the null hypothesis that the AP = 0.
Depression, DM, and their comorbid combination were all associated with an increased risk for Alzheimer disease (HR for DM alone, 1.06 [95% CI, 1.01-1.11]; HR for depression alone, 1.39 [95% CI, 1.35-1.44]; HR for comorbid depression and DM, 1.46 [95% CI, 1.37-1.55]). However, the magnitude of the associations of DM, depression, and their comorbid combination with the risk for vascular dementia was more pronounced (HR for DM alone, 1.55 [95% CI, 1.44-1.66]; HR for depression alone, 2.42 [95% CI, 2.29-2.55]; HR for comorbid depression and DM, 3.56 [95% CI, 3.28-3.86]). Finally, our results were unaffected by expanding our definition of depression to include redemp-tion of a tricyclic antidepressant prescription (HR for DM alone, 1.20 [95% CI, 1.17-1.24]; HR for depression alone, 1.79 [95% CI, 1.75-1.82]; HR for comorbid depression and DM, 2.07 [95% CI, 2.01-2.14]).

Discussion

In a nationwide, population-based cohort study of more than 2.4 million persons 50 years or older, DM and depression were associated with an increased risk for all-cause dementia, and the combined effect of both disorders appeared more than additive, especially among younger persons. Among those with comorbid depression and DM in our cohort, 6% of incident dementia may be accounted for by the interaction between depression and DM overall, and 25% may be accounted for among those younger than 65 years. Although the underlying risk for dementia is low in this younger group, the marked increase in the incidence of DM in younger groups makes this finding quite worrisome.

Our study extends beyond prior studies by identifying that, compared with a population without depression or DM, depression alone is associated with the highest relative risk for all-cause dementia. Further, we found similar results when examining associations with the risk for Alzheimer disease or vascular dementia, although the magnitude of the associations of depression and of comorbid depression and DM with the risk for vascular dementia was more pronounced, in line with the results of a recent meta-analysis. In addition, we found that having comorbid depression and DM is associated with a level of risk greater than that of the sum of the 2 illnesses. Although underlying causal mechanisms are unclear, one explanation could be that depression and DM have many shared risk factors for dementia, including increased inflammation, decreased insulin sensitivity, autonomic nervous system dysregulation, obesity, and vascular disease.

Prior studies have found that patients with comorbid depression and DM are younger than those with DM alone and were diagnosed as having DM approximately 5 years earlier. Also, depression earlier in life may be a risk factor for developing type 2 DM. Given that depression in patients with DM is associated with poor self-care, nonadherence to treatment regimens, and adverse psychobiological changes, this younger group with comorbid depression and DM may be vulnerable to developing dementia later in life.

From a public health perspective, developing screening and interventions to improve the quality of treatment of depression and DM in this subgroup of patients could be important in reducing the risk for dementia. A recent prospective cohort study of 1433 older adults with DM found that effective treatment of DM and depression and an improved diet could lead to as much as a 20% decrease in incident dementia. 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 DM and heart disease. Although adequately powered trials of these interventions to test their effects on preventing dementia may require very large sample sizes (eg, >50 000 participants) and long durations (eg, 15-20 years), they are warranted given the societal costs of dementia.

Our study has several strengths and limitations. We followed up a nationwide cohort virtually without any losses, making nonresponse bias an unlikely explanation for our findings. Also, information on DM, 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 a relatively homogenous population, therefore limiting generalizability. However, this factor should improve internal validity, because 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, because patients with more severe depression are more likely to be prescribed antidepressants and/or referred to psychiatrists. This issue is further complicated by our inability to capture individuals with depression who have not sought treatment. Similarly, the use of codes from the 8th and 10th revisions of the International Classification of Diseases to identify dementia and DM cases could miss patients with initial symptoms of these illnesses until symptoms or functional impairments become more prominent and limit our ability to differentiate dementia subtypes accurately. A further limitation was the 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 herein, and previous studies did not find attenuation of the association of comorbid depression and DM with the risk for dementia after adjusting for health-risk behaviors. Finally, residual confounding remains a possibility, as in any observational study.

Conclusions

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

**REFERENCES**


Promoting Healthy Brain Aging

Charles F. Reynolds III, MD

The co-occurrence of diabetes mellitus and depression, especially in persons younger than 65 years, poses an important hazard to healthy brain aging and cognitive fitness in the later years of life. Katon and colleagues1 from Denmark contribute this key observation in this issue of JAMA Psychiatry. This observation raises questions about the biology of aging and about promotion of ways of aging well, not just living a long life. First, with respect to the basic biology of aging, how does aging enable disease? Second, from the perspective of population health, how can we narrow the gap between life span and health span, compressing the period of functional morbidity (especially related to dementia) in the later years of life? The answers to the first question will likely provide important clues for answering the second.2

Geroscience: Linking Aging to Chronic Disease

The trans–National Institutes of Health Geroscience Interest Group (GSIG) has advanced the thesis that mammalian aging can be delayed through a variety of approaches, including genetic, dietary, and pharmacologic.2 To this list should be added modifications of lifestyle, especially physical activity, which is neuroprotective and which may diminish the toxic effects of diabetes mellitus and depression on the brain. The GSIG has posited the following “7 pillars of aging,” underscoring the multifactorial nature of the biology of aging and the interconnectiveness of the biological processes that underlie aging: macromolecular damage, epigenetics, inflammation, adaptation to stress, proteostasis (ie, the concept of integrated and competing pathways within cells that control the biogenesis, folding, trafficking, and degradation of proteins present within and outside the cell), stem cells and regeneration, and metabolism. Important research goals flow from each pillar. Of particular relevance to the observations contributed by Katon et al1 are the need to bridge the continuum from psychological to molecular stresses, to develop biomarkers that disambiguate chronicologic and biological aging, to differentiate adaptive and maladaptive inflammatory processes, to generate system-level understanding of types of macromolecular damage, and to identify proteostatic pathways that are overwhelmed in specific chronic disease states.

Other hallmarks of the biology of aging may have further relevance to depression, including genomic instability, telomere attrition, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, and altered intercellular communication.3 For example, depression is now known to be associated with acceleration of telomere attrition, although whether antidepressant treatment reactivates telomerase is unknown.4 Candidate biomarkers of aging in epidemiologic studies such as those of Katon and colleagues include interleukin 6 as a marker of inflammation, telomere length as a marker of cellular senescence and oxidation, end products of advanced glycation as types of macromolecular damage, insulinlike growth factor as a marker of energy homeostasis, and klotho (termed the longevity protein) as a marker of oxidative stress and metabolism. All meet the following required criteria for understanding aging processes in epidemiologic studies: biological plausibility; measurability in high-throughput, precise accurate assays; association with aging outcomes; and attenuation of the effect of chronicologic age on outcomes.5 An example of a particularly interesting hypothesis is that reduced signaling of insulinlike growth factor 1 may be a marker for longevity in humans. Caloric restriction, which is accompanied by a decrease in insulinlike growth factor 1 levels, leads to greater life span in rodent models, perhaps through improved glycemic control.

Translational and Clinical Science of Aging and Depression

We do not yet know whether the treatment of prevalent cases of depression protects brain health and delays the onset of dementia, although this hypothesis is plausible for several reasons. First, we know that evidence-based treatment of depression in older adults improves but does not...