*Extended Abstract*

*Call for Papers for the Population Association of America Annual Meeting 2019*

# Earlier-Life Depression and Dementia Risk Twenty Years Later: A Population-Based Register Study in Finland

Kaarina Korhonen[1], Elina Einiö[1,2,3], Taina Leinonen[4], Lasse Tarkiainen[1], Pekka Martikainen[1, 3, 5]

[1] Population Research Unit, Faculty of Social Sciences, University of Helsinki, Helsinki, Finland
[2] London School of Economics and Political Science, Department of Social Policy, London, United Kingdom
[3] Max Planck Institute for Demographic Research, Rostock, Germany
[4] Finnish Institute of Occupational Health, Helsinki, Finland
[5] Department of Public Health Sciences, Stockholm University, Stockholm, Sweden

## Introduction

Depression is a common comorbid disorder among dementia patients and depressive symptoms may be early markers of dementia.[1] Depression may also cause pathological changes in the brain and thus increase the risk of developing dementia.[2] However, the causal relationship between depression and dementia has proven difficult to establish; depression may also develop in reaction to the decline in cognitive and functional abilities (reverse causation), or it may be a prodromal symptom of dementia whereby the underlying neurodegenerative condition causes both depressive symptoms and dementia (confounding).

Much attention has been directed to the association between old-age depression and dementia, a recent meta-analysis reporting that 4% of all dementia cases are attributable to old-age depression.[3] However, the closer the measurement of depression is to the onset of dementia the more likely the association is to reflect reverse causation or confounding by a shared neuropathological cause. Furthermore, recent studies indicate that the neurodegenerative disorder that causes dementia may start to develop already in midlife[4] and, thus, depression experienced earlier in life may be most relevant to later dementia risk. Earlier-life depression defined as self-reported depression before the age of 60 was related to a 3.8-fold hazard of Alzheimer's disease in a prospective cohort study in the Netherlands.[5] However, because the follow-up for Alzheimer's disease began at the age of 60, the results are still subject to reverse causation and confounding. Another US study only considered depression four or more years before dementia onset, finding a hazard ratio of 2.0 among men and no association among women.[6] A case-control study extended the time lag to 25 years finding that earlier-life depression increased the odds of dementia 1.7-fold.[7] The timing of depression was, however, reported by the spouse or adult offspring, which may induce considerable reporting bias. A recent prospective study on the Whitehall II cohort found no long-term effects of depressive symptoms on dementia risk.[8] Instead, depressive symptoms were elevated only up to 11 years before dementia onset compared to individuals who did not develop dementia suggesting that depression is more likely a prodromal symptom rather than risk factor for dementia.

In the current study, we aim to provide stronger evidence on the role of depression in dementia. More specifically, we investigate whether a history of hospital-treated depression increases the risk of incident dementia. This study adds to the literature in three important ways. First, we avoid the possibility of reverse causation and confounding by shared neuropathological causes by measuring depression already 20–29 years before the dementia follow-up. This time frame is more likely to capture depression that precedes the development of the neurodegenerative disorder. We further focus on earlier-life depression defined as depression before the age of 50 to minimize the possibility of confounding. Second, we assess whether the effect of depression on dementia risk is modified by education, a commonly used proxy for cognitive reserve. Finally, our measure of depression comes from administrative health care registers and thus is not subject to

recall or surrogate-reporting bias. The analyses are based on a population-representative cohort in Finland with 146,709 older adults being followed up for incident dementia over the years 2000–2012.

## Methods

### Data and variables

The present study used an 11% random sample of the Finnish population in 1987–2007 drawn from the Statistics Finland population register, which covers all permanent residents. Statistics Finland linked the sample with longitudinal information from various administrative registers including the Death Register and healthcare registers using unique personal identification numbers assigned to all permanent residents.

We followed up individuals for incident dementia at the age of 65 and over in 2000–2012. The included cohorts were born in 1896–1946. 31 December 1999 was set as the baseline for cohorts born before 1935, and 31 December of the year of the 65$^{th}$ birthday for the younger cohorts. We excluded individuals who were not registered as Finnish residents in the quinquennial population censuses 20–29 years before the baseline (n=4,203) because history of depression of these individuals could not be measured. We further excluded individuals with pre-baseline dementia (n=1,559) and those living in institution at baseline (n=4,781). The analytic sample consisted of 146,709 individuals.

We identified dementia using the diagnostic records of the Hospital Discharge Register collected by the National Institute for Health and Welfare. The International Classification of Diseases 10$^{th}$ revision (ICD-10) codes for dementia included F00–03, F05.1 and G30. For pre-baseline dementia, ICD-10 (1996–2011) and ICD-9 (1987–1995) codes (290, 2912A, 2928C, 2941A, 4378A and 3310) were used. Both primary and secondary diagnoses were considered. The date of incident dementia was defined as the date of hospital admission. We identified 15,074 individuals with incident dementia during the follow-up.

A history of depression was defined as having received hospital care for depression in the 10-year period 20 to 29 years before the baseline. Depression was identified from the Hospital Discharge Register of 1970–1991 with ICD-8 codes 2960, 2980, 3004 and 3011 (1970–1986) and ICD-9 codes 2961, 2968, 3004, 3009 and 3090 (1987–1991).

We included socio-demographic characteristics of individuals as covariates in the analyses. To account for confounding, they were measured from the same period as depression (20–29 years before baseline). Education indicated the highest attained educational qualification categorized as 1) tertiary, 2) secondary and 3) basic education. Occupational social class was classified as 1) white-collar employee, 2) manual worker, 3) farmer, 4) other self-employed and 5) other or unknown. Marital status was coded as 1) married, 2) divorced, 3) widowed and 4) never-married.

We included a set of dummy indicators for earlier-life health conditions that may confound the association between depression and dementia. Stroke, coronary heart disease, heart failure, diabetes, asthma and other chronic obstructive pulmonary diseases, head injuries and alcohol-related diseases and accidental poisoning by alcohol were identified from the Hospital Discharge Register in the same time period as depression (20–29 years before baseline). Because the same health conditions may also operate as mechanisms that link depression to dementia, we included another set of indicators for later-life health conditions, measured from the time after depression measurement (up to 19 years before baseline) and updated at incidence if occurred during the follow-up.

### Statistical analyses

We used Cox proportional hazards regression to estimate the effect of a history of depression on incident dementia at the age of 65+. Age in years was used as the time scale. Individuals were censored at death, at the end of the year preceding emigration or at the end of 2012, whichever came first. Model 1 was adjusted for

gender, region of residence and calendar year. We further adjusted for socio-demographic characteristics in model 2 and earlier-life health conditions in model 3. Finally in model 4, we included later-life health conditions to assess to what extent depression affects dementia risk through these factors. We next restricted the analytic sample to cohorts aged below 50 at the time of depression measurement (cohorts born in 1930–1946) and estimated the same models as for the total sample. Interaction with education was tested using likelihood ratio test. We also tested for gender interactions in model 1 and found them statistically nonsignificant (p=0.618 in the total sample and p=0.892 in the restricted sample). All analyses were performed with Stata 14.2.

**Results**

The characteristics of the total and restricted samples and proportions with history of depression are shown in Table 1. The restricted sample was (by definition) younger and also more highly educated. A history of hospital-treated depression was very rare; the 10-year prevalence was 0.7% in both samples. Individuals with earlier-life health conditions were also more likely to have depression. Table 2 displays the Cox regression models for incident dementia by history of depression. In the total population, depression was related to a 1.43-fold hazard (95% CI 1.21–1.68) of dementia (model 1). This excess hazard was not related to earlier-life socio-demographic factors (model 2) and only modestly to earlier-life health conditions (model 3). Adjustment for later-life health conditions in model 4 attenuated the effects by about 20%. When further restricted to depression before the age of 50, the effect of depression was somewhat stronger (HR=1.94, 95% CI 1.46–2.58), and greater attenuation was observed with each set of adjustments. Interaction between depression and education was statistically non-significant in both the total sample (p=0.713) and the restricted sample (p=0.353).

**Conclusions**

We found that individuals with a history of hospital-treated depression had a 40–90% excess risk of dementia. Because depression was measured more than two decades before the dementia follow-up, and before the age of 50 in the analysis on the restricted sample, our measure is unlikely to reflect any prodromal symptoms of dementia. Instead, the results provide evidence for a causal relationship between depression and dementia. Later-life health conditions such as stroke and diabetes accounted for about 20–35% of the excess risk related to depression, and thus make important targets for intervention. In contrast to our hypothesis, education did not moderate the association, indicating that higher levels of cognitive reserve cannot offset the adverse consequences of depression for dementia risk.

**References**

1. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The Temporal Relationship Between Depressive Symptoms and Dementia: A Community-Based Prospective Study. *Arch Gen Psychiat* 1999;**56**:261–66.
2. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol* 2011;**7**:323–31.
3. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017;**390**:2673–734.
4. Ritchie K, Ritchie CW, Yaffe K, Skoog I, Scarmeas N. Is late-onset Alzheimer's disease really a disease of midlife? *Alzheimers Dement* 2015;**1**:122–30.
5. Geerlings MI, Heijer T den, Koudstaal PJ, Hofman A, Breteler MMB. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology* 2008;**70**:1258–64.
6. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann Neurol* 2005;**57**:381–87.
7. Green RC, Cupples LA, Kurz A, et al. Depression as a Risk Factor for Alzheimer Disease: The MIRAGE Study. *Arch Neurol* 2003;**60**:753–59.
8. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA Psychiat* 2017;**74**:712–18.

Table 1. Characteristics of the total sample and the restricted sample (cohorts born in 1930–1946)

| | Total sample | | Restricted sample | |
|---|---|---|---|---|
| | % | % with a history of depression | % | % with a history of depression |
| Mean age at baseline (SD) | 69.6 (6.5) | | 65.5 (1.1) | |
| Gender | | | | |
| Male | 43.0 | 0.6 | 46.9 | 0.6 |
| Female | 57.0 | 0.9 | 53.1 | 0.9 |
| Education | | | | |
| Tertiary | 16.1 | 0.5 | 19.8 | 0.5 |
| Secondary | 19.1 | 0.7 | 23.2 | 0.7 |
| Basic | 64.8 | 0.8 | 57.1 | 0.8 |
| Occupational social class | | | | |
| White-collar | 38.3 | 0.6 | 43.5 | 0.6 |
| Manual | 40.1 | 0.9 | 39.8 | 0.9 |
| Farmer | 14.6 | 0.7 | 10.1 | 0.6 |
| Other self-employed | 6.0 | 0.7 | 5.8 | 0.7 |
| Other or unknown | 1.0 | 0.9 | 0.9 | 1.2 |
| Marital status | | | | |
| Married | 81.0 | 0.7 | 81.4 | 0.6 |
| Divorced | 5.0 | 1.6 | 6.0 | 1.6 |
| Widowed | 3.0 | 0.7 | 1.1 | 1.1 |
| Never married | 11.0 | 0.9 | 11.5 | 1 |
| Earlier-life health conditions | | | | |
| Stroke | 0.7 | 2.2 | 0.5 | 2.6 |
| Coronary heart disease | 1.9 | 2.0 | 1.0 | 2.7 |
| Heart failure | 0.4 | 1.6 | 0.1 | 1.7 |
| Diabetes | 0.7 | 1.9 | 0.6 | 1.7 |
| Asthma or COPD[a] | 1.4 | 1.3 | 1.3 | 1.4 |
| Head injury | 1.3 | 2.5 | 1.3 | 2.8 |
| Alcohol-related diseases | 1.0 | 10.3 | 1.2 | 10.7 |
| Total | 146709 (100.0) | 1090 (0.7) | 93909 (100.0) | 683 (0.7) |

[a] other chronic obstructive pulmonary diseases

Table 2. Hazard ratios and 95% confidence intervals for incident dementia by history of depression in total and restricted (cohorts born in 1930–1946) samples, 2000–2012

| | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** | **HR** | **95% CI** |
| Total sample | | | | | | | | |
| Depression | | | | | | | | |
| No | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Yes | 1.43 | (1.21-1.68) | 1.42 | (1.20-1.67) | 1.38 | (1.17-1.62) | 1.30 | (1.10-1.53) |
| n | 146709 | | | | | | | |
| events | 15074 | | | | | | | |
| | | | | | | | | |
| Restricted sample | | | | | | | | |
| Depression | | | | | | | | |
| No | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Yes | 1.94 | (1.46-2.58) | 1.86 | (1.40-2.47) | 1.71 | (1.28-2.29) | 1.46 | (1.09-1.95) |
| n | 93909 | | | | | | | |
| events | 3870 | | | | | | | |

Model 1 adjusted for gender, region of residence and calendar year
Model 2: model 1 + earlier-life education, occupational social class and marital status
Model 3: model 2 + earlier-life health conditions
Model 4: model 3 + later-life health conditions