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Association between a history of clinical depression and dementia, and the role of sociodemographic factors: population-based cohort study

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Background

Depression is associated with an increased dementia risk, but the nature of the association in the long-term remains unresolved, and the role of sociodemographic factors mainly unexplored.

Aims

To assess whether a history of clinical depression is associated with dementia in later life, controlling for observed sociodemographic factors and unobserved factors shared by siblings, and to test whether gender, educational level and marital status modify the association.

Method

We conducted a national cohort study of 1 616 321 individuals aged 65 years or older between 2001 and 2018 using administrative healthcare data. A history of depression was ascertained from the national hospital register in the period 15–30 years prior to dementia follow-up. We used conventional and sibling fixed-effects Cox regression models to analyse the association between a history of depression, sociodemographic factors and dementia.

Results

A history of depression was related to an adjusted hazard ratio of 1.27 (95% CI 1.23–1.31) for dementia in the conventional Cox model and of 1.55 (95% CI 1.09–2.20) in the sibling fixed-effects model. Depression was related to an elevated dementia risk similarly across all levels of education (test for interaction, $P = 0.84$), but the association was weaker for the widowed than for the married ($P = 0.003$), and stronger for men than women ($P = 0.006$). The excess risk among men attenuated following covariate adjustment ($P = 0.10$).

Discussion

This study shows that a history of depression is consistently associated with later-life dementia risk. The results support the hypothesis that depression is an aetiological risk factor for dementia.

Keywords

Dementia; depressive disorders; epidemiology; socioeconomic status; life course.

Background

Depression and dementia are highly disabling disorders contributing to the global disease burden and challenging the sustainability of healthcare systems.[1,2] Depressive symptoms commonly coexist with dementia,[3] and recently, late-life depression was estimated to contribute to 4% of all worldwide dementia cases.[4] Despite systematic review evidence on depression doubling the risk of dementia onset,[5] the question about whether depression is an aetiological risk factor for dementia remains unresolved. This is because late-life depression or depressive symptoms in close proximity to dementia onset may in fact be prodromal features of dementia itself.[6,7] An important limitation of previous studies is that they have not considered the temporal dimension in the association between depression and dementia onset. Only a few studies have analysed the association separately for earlier- and late-life depression.[8] Although some such studies reported a consistent association between depression and dementia as long as 20 years apart,[9–12] other studies only observed an association when depression occurred less than about 10 years before dementia diagnosis[6,7] or after the age of 45 or 50 years.[13,14] The inconsistency in findings may relate to differences in measurement of depression, follow-up times and characteristics of the study populations. Furthermore, only a few studies[9,14] have been able to control for childhood family background to account for the strong familial aggregation of both depression and dementia. For example, the low socioeconomic position of the childhood family may increase the risk of both depression and dementia.

Although many of the previous studies have controlled for sociodemographic factors, the modifying effects remain mainly unexplored. Prior studies have investigated gender and education modification in prodromal depression[8,15] but, to the best of our knowledge, no previous study has explicitly analysed the role of sociodemographic factors in the association between depression and dementia in the long term. Identifying susceptible population subgroups may elucidate potential mechanisms linking depression and dementia and help target dementia interventions effectively. In Finland, depression is among the leading causes of disability in the working-age population and about 10% of adults have experienced depression within the past 12 months.[16] At the same time, the number of people living with dementia is rapidly increasing, dementia already being the third leading cause of death in Finland. The high prevalence of depression and the growing elderly population suggest an urgent need to enhance understanding and awareness of the association between depression and dementia.

Aims of study

We conducted a register-based cohort study on Finnish older adults to estimate the association between a history of clinical depression and dementia, and to assess whether sociodemographic factors including gender, educational level and marital status modify the association. We also estimated sibling fixed-effects models controlling for unobserved early-life familial conditions and genetic factors shared by siblings that might confound the association between

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depression and dementia. As the preclinical and prodromal stages of dementia generally begin 10–15 years before the clinical stage,[17] we used information on depression diagnoses observed in hospital registers in the period from 15 to 30 years before the follow-up for dementia in order to reduce bias arising from depressive symptoms reflecting preclinical and prodromal stages of dementia.

Method

Data and variables

We used population register data on all Finns born between 1900 and 1950 obtained from Statistics Finland. The cohort was followed, through record linkage using personal identification codes assigned to all permanent residents, for incident dementia at the age of 65 years and above in administrative health registers from 2001 through 2018. The baseline for follow-up thus varied from year 2000 to 2015 according to the year of birth. Information on sociodemographic characteristics was obtained from population censuses conducted in 1970, 1975, 1980 and 1985 and from the population register from 1987 to 2018. The sibling analysis was based on a 10% household sample from the 1950 Finnish population census that has been linked to subsequent census records and the population register. Children living in the same family at the age of 0 to 15 years in 1950 were identified as siblings by means of unique family identifiers. The family is defined based on the youngest generation in the household dwelling-unit, and thus siblings could only be identified if they did not have children of their own. We therefore limited the age range to 15 years, when childbearing was still rare. The sibling subsample thus included cohorts born between 1935 and 1950.

We identified dementia using the medication reimbursement register of the Social Insurance Institution of Finland and the hospital care register of the Finnish Institute for Health and Welfare. Thus our definition of dementia only included people on dementia medication or receiving hospital care. We collected the beginning (month and year) of entitlement to special state reimbursement of antidementia medication, and the dates of state-reimbursed purchases of antidementia medication using the World Health Organization Anatomical Therapeutic Chemical (ATC) code N06D. Specialised out-patient care and in-patient hospital admissions with a dementia diagnosis were collected with World Health Organization ICD-10[18] codes F00–03, F05.1 and G30. The earliest entry in any of these registers was set as the date of dementia incidence. These data sources present good sensitivity and high precision for dementia diagnosis,[19] and the age-specific incidence rates observed in our data (Supplementary Table 1 available at https://doi.org/10.1192/bjp.2021.217) are consistent with reports for screened community samples.[20]

To restrict the study population to initially dementia-free individuals, we excluded those with pre-baseline reimbursements of antidementia medication (reimbursement became available in 1999) or hospital admissions with a dementia diagnosis indicated by ICD-10 codes in 1996–2000 and ICD-9[21] codes 290, 2912A, 2928C, 2941A, 3310, 3311 and 4378A in 1987–1995 ($n = 24\,543$). Because dementia is among the main indications of institutional residence, we further restricted the study population to those living in private households at baseline ($n = 49\,384$ excluded).

Data on clinical depression 15 to 30 years before baseline was collected from the hospital care register. In-patient care episodes with a depression diagnosis were identified using ICD-8[22] codes 2960, 2980, 3004 and 3011 in 1971–1986, ICD-9 codes 2961, 2968, 3004, 3009 and 3090 in 1987–1995, and ICD-10 codes F32, F33, F34.1 and F38.1 in 1996–2000. Individuals with at least one care episode with a depression diagnosis were classified as having a history of clinical depression.

Information on educational level and marital status was collected from the period 15 to 30 years before baseline. Education was indicated as the highest achieved qualification, categorised as tertiary (generally ≥13 years of education), secondary (10–12 years) and basic education or less (up to 9 years). Marital status was classified as married, divorced, widowed and never married. If education or marital status changed during the observation period, we considered the most recent status. We further included other medical conditions as covariates to indicate vascular risk factors (for example smoking, excessive alcohol use, diabetes) and cardiovascular diseases (CVDs) that are shown to be comorbid to depression[23] and to influence dementia risk.[24,25] These conditions were measured from 15 to 30 years before baseline from the hospital care register, and included alcohol-related diseases and accidental poisoning by alcohol, chronic obstructive pulmonary disease (COPD) or asthma, diabetes, coronary heart disease (CHD), and other non-stroke CVDs. Stroke was excluded because of the direct short-term effect on (post-stroke) dementia (for ICD-codes see Supplementary Table 2). Because depression history and the covariates could only be defined for Finnish residents, we excluded those living abroad over the period 15 to 30 years prior to baseline ($n = 14\,914$).

Statistical analyses

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% CI for the association between a history of clinical depression and dementia between 1 January 2001 and 31 December 2018. Cohorts turning 65 years in year 2001 or later entered the analysis on the 1 January following their 65th birthday. Attained age in years was used as the underlying timescale in the analyses. Individuals were censored on the date of death, at the end of the year preceding emigration or at the end of 2018, whichever came first.

We first used conventional Cox models to estimate the association between a history of clinical depression and dementia, controlling for observed characteristics. In addition to underlying attained age, model 1 adjusted for gender and calendar year. Model 2 accounted additionally for education and marital status, and model 3 further adjusted for comorbid medical conditions. Second, we used Cox regression with sibling fixed-effects by assuming a separate baseline hazard for each childhood family ($n = 23\,626$) to control for all time-invariant characteristics shared by siblings.[26] We further controlled for the same observed characteristics as in the conventional Cox models. Third, modification by gender, educational level and marital status was analysed in the full cohort, with basic (model 1) and full adjustments (model 3). The significance of interaction was analysed using the likelihood ratio test. All analyses were performed with Stata 16.0.

Sensitivity analyses

As selection for health and survival may bias the estimates in studies of older people,[24,27] we conducted age-stratified analyses to assess whether the associations changed with increasing age at study inclusion. We used three groups: cohorts born in 1935–1950 (aged 65 years at baseline), cohorts born in 1920–1934 (66–80 years) and cohorts born in 1900–1919 (81–100 years).

Ethics of research

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by Statistics Finland Board of Ethics (permit no. TK-53-1490-18). Participant consent

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was not required as administrative register data can be used for scientific purposes under the Personal Data Act and the Statistics Act. Statistics Finland pseudonymised the data prior to providing it to researchers.

Results

In the full cohort of 1 616 321 individuals (55.9% female), we identified 23 959 (1.5%) individuals with a history of clinical depression. In the subsample of 63 445 siblings (51.3% female), depression had been diagnosed for 948 (1.5%) individuals. Mean (s.d.) baseline age of the full cohort was 68.9 (6.2) years, and the sibling subsample was by definition 65 years at baseline. Table 1 shows the frequencies and descriptive values of sociodemographic and health variables.

During 14 725 473 person-years at risk (mean follow-up time 9.1 years), 274 817 individuals were identified with dementia in the full cohort.

Table 2 displays the results from the conventional Cox regression for the full cohort. In the minimally adjusted model 1, depression was associated with a significantly increased hazard of dementia (HR = 1.32, 95% CI 1.28–1.36). Also, secondary (HR = 1.11, 95% CI 1.10–1.13) and basic education (HR = 1.18, 95% CI 1.16–1.19), and all unmarried statuses (HR = 1.12; 95% CI 1.10–1.13 for divorced; HR = 1.04, 95% CI 1.03–1.06 for widowed; HR = 1.05, 95% CI 1.04–1.07 for never married) were associated with dementia at the 95% confidence level.

The hazard of dementia was also elevated for those with alcohol-related conditions (HR = 1.33, 95% CI 1.28–1.37), COPD/asthma (HR = 1.07, 95% CI 1.04–1.09), diabetes (HR = 1.52, 95% CI 1.45–1.60), CHD (HR = 1.10, 95% CI 1.08–1.12) and other CVDs (HR = 1.04, 95% CI 1.03–1.05). In model 2, adjusting for education and marital status, the associations of depression, education and marital status with dementia remained substantially unchanged. In the fully adjusted model further adjusting for medical conditions (model 3), depression was associated with a 27% (95% CI 1.23–1.31) excess hazard of dementia.

In the sibling subsample, 4508 individuals during 546 129 person-years at risk (mean follow-up time 8.6 years) were identified with dementia. Table 3 presents the results from the sibling fixed-effects models. Adjusting for the unobserved factors shared by siblings, the association between a history of clinical depression and dementia was stronger than in the conventional model but the confidence interval also became wider (HR = 1.65, 95% CI 1.17–2.33; model 1). In addition, having never married (HR = 1.21; 95% CI 1.03–1.42), alcohol-related conditions (HR = 1.82; 95% CI 1.27–2.61) and diabetes (HR = 3.40; 95% CI 1.97–5.88) were associated with dementia. In the model further adjusting for observed education and marital status (model 2), the excess hazard related to depression slightly attenuated (HR = 1.60; 95% CI 1.13–2.27). Adjusting additionally for observed medical conditions (model 3), depression was associated with a HR of 1.55 (95% CI 1.09–2.20) for dementia.

Compared with individuals without a history of clinical depression, the excess hazard of dementia related to depression was stronger among men (HR = 1.41, 95% CI 1.34–1.49) than women (HR = 1.29, 95% CI 1.24–1.34; test for interaction $x^2(1) = 7.72$, $P = 0.006$) (Fig. 1(a)). Adjustment for other sociodemographic and medical conditions, however, attenuated the association to the same level for both genders ($x^2(1) = 2.69$, $P = 0.10$). Further inspection revealed that alcohol-related conditions in particular explained the stronger association among men (results not shown). A history of clinical depression was associated with an elevated hazard of dementia similarly across all levels of education ($x^2(2) = 0.34$; $P = 0.84$) (Fig. 1(b)). By contrast, the association between depression and dementia differed by marital status ($x^2(3) = 13.97$; $P = 0.003$) (Fig. 1(c)). Specifically, the association was weaker among the widowed (HR = 1.16, 95% CI 1.07–1.26) than the married (HR = 1.36, 95% CI 1.31–1.41). The moderation was not explained by the covariates ($x^2(3) = 13.35$, $P = 0.004$).

Sensitivity analyses

Age-stratified analyses indicated that our main results primarily reflect associations observed in cohorts born in 1920–1934, who experienced most of the observed incident dementia cases (Supplementary Table 3). Among cohorts born in 1935–1950, the association between depression and dementia (HR = 1.53, 95% CI

Table 1 Descriptive characteristics of the full cohort and the sibling subsample

Variable	Study cohort			
	Full cohort		Sibling subsample	
	History of clinical depression		History of clinical depression	
	Yes (n = 23 959)	No (n = 1 592 362)	Yes (n = 948)	No (n = 62 497)
Age, years: mean (s.d.)	68.5 (5.6)	68.9 (6.2)	65.0 (–)	65.0 (–)
Gender, n (%)				
Men	8865 (37.0)	704 429 (44.2)	413 (43.6)	30 454 (48.7)
Women	15 094 (63.0)	887 933 (55.8)	535 (56.4)	32 043 (51.3)
Education, n (%)				
Tertiary	3415 (14.3)	302 677 (19.0)	175 (18.5)	14 872 (23.8)
Secondary	5855 (24.4)	374 279 (23.5)	302 (31.9)	19 107 (30.6)
Basic or less	14 689 (61.3)	915 406 (57.5)	471 (49.7)	28 518 (45.6)
Marital status, n (%)				
Married	13 128 (54.8)	1 134 560 (71.3)	528 (55.7)	45 513 (72.8)
Divorced	5579 (23.3)	174 547 (11.0)	234 (24.7)	8344 (13.4)
Widowed	2229 (9.3)	120 902 (7.6)	45 (4.7)	1759 (2.8)
Never married	3023 (12.6)	162 353 (10.2)	141 (14.9)	6881 (11.0)
Medical conditions, n (%)				
Alcohol related[a]	2994 (12.5)	20 785 (1.3)	135 (14.2)	916 (1.5)
COPD/asthma	1004 (4.2)	32 244 (2.0)	30 (3.2)	1133 (1.8)
Diabetes	361 (1.5)	10 972 (0.7)	14 (1.5)	462 (0.7)
CHD	1420 (5.9)	45 525 (2.9)	34 (3.6)	993 (1.6)
Other CVDs	4420 (18.5)	213 597 (13.4)	147 (15.5)	7586 (12.1)

COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cardiovascular disease.
a. Alcohol-related diseases and accidental poisoning by alcohol.

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Table 2 Hazard ratios for dementia by a history of clinical depression and covariates in the conventional Cox regression on the full cohort

Exposure variable	Hazard ratio (95% CI)		
	Model 1[a]	Model 2[b]	Model 3[b]
History of clinical depression			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.32 (1.28–1.36)	1.30 (1.27–1.34)	1.27 (1.23–1.31)
Education			
Tertiary	1 (Reference)	1 (Reference)	1 (Reference)
Secondary	1.11 (1.10–1.13)	1.11 (1.09–1.13)	1.11 (1.09–1.12)
Basic	1.18 (1.16–1.19)	1.17 (1.16–1.19)	1.17 (1.16–1.18)
Marital status			
Married	1 (Reference)	1 (Reference)	1 (Reference)
Divorced	1.12 (1.10–1.13)	1.11 (1.09–1.12)	1.10 (1.09–1.12)
Widowed	1.04 (1.03–1.06)	1.04 (1.02–1.05)	1.03 (1.02–1.05)
Never married	1.05 (1.04–1.07)	1.06 (1.04–1.07)	1.06 (1.04–1.07)
Medical conditions[c]			
Alcohol related[d]	1.33 (1.28–1.37)	–	1.25 (1.21–1.30)
COPD/asthma	1.07 (1.04–1.09)	–	1.05 (1.02–1.08)
Diabetes	1.52 (1.45–1.60)	–	1.50 (1.43–1.58)
CHD	1.10 (1.08–1.12)	–	1.08 (1.06–1.10)
Other CVDs	1.04 (1.03–1.05)	–	1.04 (1.02–1.05)

COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cardiovascular disease.
a. Each exposure variable modelled separately; adjusted for gender and calendar year.
b. Exposure variables mutually adjusted; adjusted for gender and calendar year.
c. Reference: not having this particular condition.
d. Alcohol-related diseases and accidental poisoning by alcohol.

1.44–1.61; Supplementary Table 4) reflected estimates obtained in the sibling analysis (Table 3). In these cohorts, depression was tentatively more strongly associated with dementia among women than men (Supplementary Figure 1). Furthermore, the association was stronger for those with a basic education compared with those who were more highly educated (Supplementary Figure 2) but no differences emerged by marital status (Supplementary Figure 3). Among the oldest cohorts born in 1900–1919, a history of clinical depression was not associated with dementia (Supplementary Table 5).

Discussion

In a large register-based cohort study of 1 616 321 individuals, we found an elevated risk of dementia related to having been diagnosed with depression 15 to 30 years before baseline. Cohort members with a history of clinical depression had around a 30% higher hazard of developing dementia compared with those with no history of depression, even after accounting for differences in educational level, marital status and several comorbid medical conditions. A similar association was found when we compared siblings to each other, adjusting for unobserved characteristics shared by siblings in addition to the observed characteristics. Our results thus align with the hypothesis that depression is an aetiological risk factor for dementia. Furthermore, our results show that depression is related to an elevated dementia risk similarly across all levels of education, but the association is generally stronger for men than women, and weaker for the widowed than for the married.

To our knowledge, this is the first study to explicitly assess whether sociodemographic factors modify the long-term association between depression and dementia. Our results show that the association was not specific to any of the assessed sociodemographic subpopulations, although the strength of association varied in terms of gender and marital status. The stronger association among men attenuated, however, to a statistically non-significant level following covariate adjustment. Our supplementary analyses indicated that the attenuation was mainly the result of adjustment for alcohol-related conditions. Alcohol use disorder is frequently comorbid with major depression, especially among men,[28] and heavy alcohol use is associated with an increased risk of dementia.[25] Nevertheless, our sensitivity analyses suggested that in younger cohorts born in 1935–1950, the association between a history of depression and dementia may in fact be stronger among women than men, despite the higher prevalence of alcohol-related conditions among men. Because the different cohorts were followed for incident dementia partly at different ages, these analyses do not disclose whether the stronger association among women in these cohorts reflects a cohort effect (the stronger association among women will persist with age) or an age effect (the stronger

Table 3 Hazard ratios for dementia by a history of clinical depression and covariates in the sibling fixed-effects Cox regression on the sibling subsample

Exposure variable	Hazard ratio (95% CI)		
	Model 1[a]	Model 2[b]	Model 3[b]
History of clinical depression			
No	1 (Reference)	1 (Reference)	1 (Reference)
Yes	1.65 (1.17–2.33)	1.60 (1.13–2.27)	1.55 (1.09–2.20)
Education			
Tertiary	1 (Reference)	1 (Reference)	1 (Reference)
Secondary	1.05 (0.89–1.24)	1.03 (0.87–1.22)	1.02 (0.86–1.20)
Basic	1.11 (0.94–1.31)	1.09 (0.92–1.29)	1.08 (0.92–1.28)
Marital status			
Married	1 (Reference)	1 (Reference)	1 (Reference)
Divorced	1.12 (0.97–1.31)	1.11 (0.96–1.29)	1.09 (0.94–1.27)
Widowed	1.17 (0.90–1.51)	1.16 (0.90–1.50)	1.14 (0.88–1.47)
Never married	1.21 (1.03–1.42)	1.20 (1.02–1.41)	1.19 (1.01–1.40)
Medical conditions[c]			
Alcohol-related[d]	1.82 (1.27–2.61)	-	1.63 (1.13–2.35)
COPD/asthma	0.92 (0.65–1.30)	-	0.88 (0.62–1.26)
Diabetes	3.40 (1.97–5.88)	-	3.28 (1.89–5.71)
CHD	1.31 (0.90–1.90)	-	1.23 (0.85–1.80)
Other CVDs	1.05 (0.91–1.21)	-	1.04 (0.90–1.20)

COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CVD, cardiovascular disease.
a. Each exposure variable modelled separately; adjusted for gender and calendar year.
b. Exposure variables mutually adjusted; adjusted for gender and calendar year.
c. Reference: not having this particular condition.
d. Alcohol-related diseases and accidental poisoning by alcohol.

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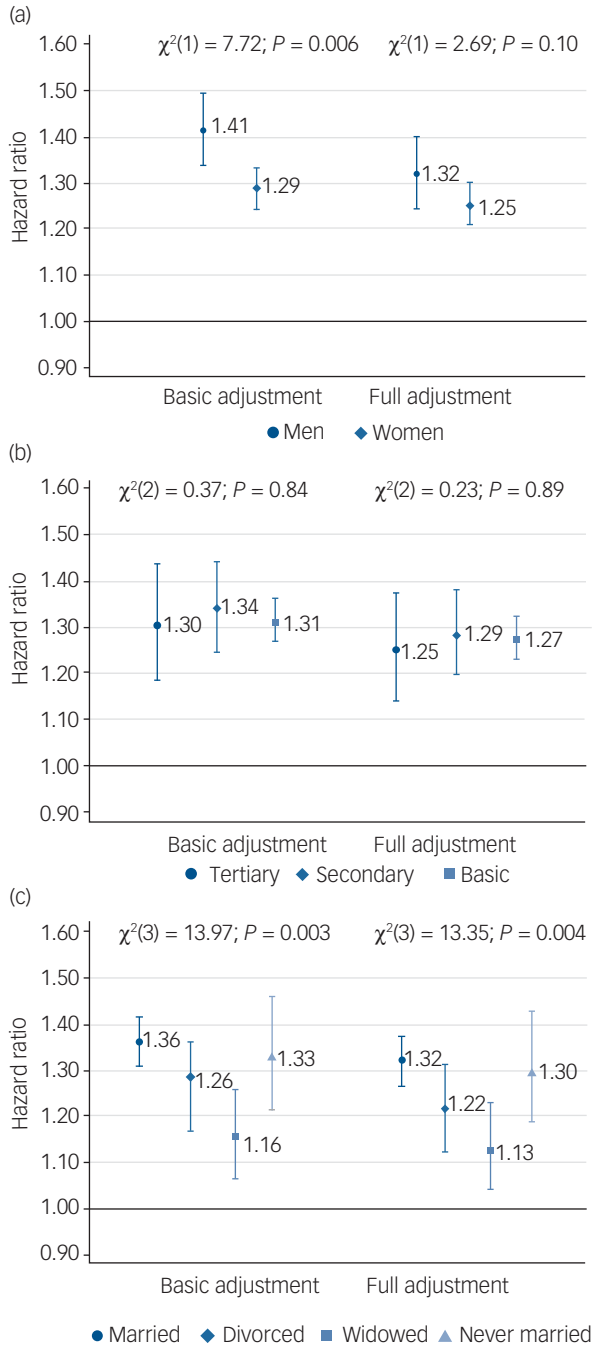

Fig. 1 Association between a history of clinical depression and dementia by (a) gender, (b) educational level, and (c) marital status.

Hazard ratio = 1.00 for no history of clinical depression. Error bars indicate 95% CIs.

association will attenuate with age). The nature of the gender difference will be an important point for future enquiry.

The association between a history of clinical depression and dementia was weaker among the widowed compared with the married. This finding may arise from selective survival: widowhood is related to higher mortality,[29] and thus the surviving widow(er)s may be more selected on health characteristics. Furthermore, our sensitivity analyses suggest that selective survival may also attenuate the overall association between depression and dementia. Similar attenuation and even reversal of association with increasing age has also been reported for other dementia risk factors including smoking,[24] suggesting that individuals with certain risk factors and susceptible to developing dementia do so before reaching the oldest old age.

These findings add to the existing evidence base showing a long-term association between depression and dementia.[9–12] Our analysis on siblings suggest that the association between depression and dementia is not likely to arise from early-life familial background such as childhood adversity or genetic factors shared by siblings. Similar findings have previously been reported by a Swedish register study[9] and a US twin study, although the latter did not observe statistically significant results for early-onset depression in either conventional (risk ratio 1.4, 95% CI 0.7–2.9) or sibling stratified (risk ratio 1.6, 95% CI 0.5–5.3) analysis.[14] In contrast to the previous studies,[9,14] we also adjusted for differences in educational level between those with and without a history of depression. Education is a strong determinant of both depression and dementia, and thus it was important to explicitly assess the extent to which education confounded the association between the two conditions. Our analysis shows that the association was not explained by shared family background or educational level, thus providing more evidence for a non-spurious relationship between depression and dementia.

In light of these and previous results, it seems likely that both explanations for an association between depression and dementia are valid: depressive symptoms reflect prodromal stages when they appear in close proximity to dementia onset, and depression earlier in life may increase the risk of neurodegeneration itself. This is also reflected in the study by Singh-Manoux et al,[6] which found that individuals with dementia had more depressive symptoms not only less than 10 years before dementia diagnosis but also more than 20 years before diagnosis compared with individuals without dementia. The results of their prospective analysis did not, however, reach statistical significance.[6] This highlights the considerable demands on data, especially in cohort studies of older people. In such studies, the most vulnerable and frail individuals tend to drop-out from follow-up; consequently, the numbers of cases of people with depression and dementia becomes small. We were in a fortunate position to overcome these potential problems as we used large register-based data without bias because of self-selection or non-random attrition.

The causal mechanisms through which depression may contribute to dementia risk are still not fully known. The suggested pathways relate to hippocampal atrophy because of the activation of the hypothalamic–pituitary–adrenal axis and increased glucocorticoid production, and raised levels of proinflammatory cytokines.[30] Furthermore, depression is associated with several vascular risk factors and CVD,[23] establishing a potential mediating pathway to increased dementia risk.[4,31] Our adjustments for comorbid medical conditions cover part of these mediating factors but accounting for these attenuated the association only modestly. Although we cannot exclude the possibility of residual confounding, our analysis provides strong evidence for a long-term association between the two conditions.

Impact and relevance

The consistent long-term association between a history of clinical depression and later-life dementia risk highlight that patients presenting with depression at working age, especially if severe, should be monitored for cognitive function in the long term. Furthermore, information about a patient's depression history should be utilised in the assessment of cognitive impairment and timely detection of dementia. The results also suggest that any success in fighting depression in those of working age will have an outsized societal impact throughout adult life in terms of, for

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example, improved workability and delayed or avoided early exit from the labour force and the need for long-term institutional care.

Strengths and limitations

The long follow-up in population and health registers provided an opportunity to study the long-term association between depression and dementia. All our measures came from administrative registers, and were thus collected prospectively and were not subject to self- or surrogate reporting biases. Both depression and dementia were diagnosed by a physician, entailing high specificity.

We also acknowledge the limitations of the study. First, the study is observational in design and thus cannot demonstrate a causal relationship between depression and dementia. The long gap between depression diagnosis and dementia follow-up, however, reduces the likelihood that our results are biased by preclinical symptoms of dementia. Second, the use of hospital diagnoses entails that less severe depressive episodes not requiring hospital care remained undetected, and thus the results reflect first and foremost an association for hospital-treated depression. Third, despite the reasonably good sensitivity of our register-based measure of dementia,[19] not all people with dementia could be identified. However, since the age-specific incidence rates were consistent with those obtained from screened community samples,[20] we believe that our results are not biased because of people with undiagnosed cases. Finally, although the sibling fixed-effects model controls for all unmeasured time-invariant characteristics shared by siblings, it is likely that many other characteristics are not shared by siblings. For example, only half of the genes are shared and thus the model does not fully exclude the possibility of common genetic antecedents. Also, other non-shared characteristics might confound the association, but we believe that these differences were at least partly captured by controlling for observed individual characteristics including educational level and health characteristics.

In conclusion, our results showed a consistent long-term association between a history of clinical depression and dementia, in line with the aetiological risk-factor hypothesis. Although the causal mechanisms are not yet clear, better management and treatment of mental health problems when people are working age should play a role in dementia prevention.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2021.217.

Data availability

The data that support the findings of this study are available from Statistics Finland, the Finnish Institute for Health and Welfare and the Social Insurance Institution of Finland. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors with the permission of Statistics Finland and the Social and Health Data Permit Authority Findata.

Author contributions

K.K. conceived the study. P.M. acquired the data. K.K. designed the analysis, with input from L.T., T.L., E.E. and P.M.. The analysis and interpretation of the data was carried out by K.K., with contributions from L.T., T.L., E.E. and P.M.. The initial version of the manuscript was written by K.K. All authors contributed to the final version, revising it critically for intellectual content and gave final approval of the version to be published.

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Declaration of interest

None.

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Psychiatry in History

Charles Arthur Mercier

C. V. Haldipur

Charles Mercier (1852–1919), a contemporary of Dr Henry Maudsley, lectured on insanity at Westminster Hospital and London School of Medicine for Women and later held a post at Charing Cross Hospital in London. He authored several books, whose titles (*Astrology in Medicine*, *Crime and Insanity*, *A New Logic*) attest to the breadth of his interests and knowledge. He wrote for the *Journal of Mental Science* and was President of the Medico-Psychological Association of Great Britain and Ireland in 1908–1909. Mercier addressed some thorny issues in psychiatry that continue to be controversial to this day: the nature of insanity and the definition of disease.

Insanity, he argued, is a disorder of conduct. The statement does not seem that outlandish when one considers that we base our diagnosis on the patient's behaviour and what he or she says.

His two-part essay 'What is a Disease?' was published on both sides of the Atlantic, in England as well as in the USA, in 1917. There is the commonly held notion that diseases exist in nature and that clinicians 'discover' them in much the same way as Columbus discovered America; indeed, we sometimes honour the discoverer by naming the disease after the clinician. Disease, Mercier averred, is a 'mental construct or concept, consisting of a symptom or a group of symptoms, correlated with or by a single intra-corporeal cause'.

As a forensic psychiatrist he was aware of the problem that our inability to define insanity presents in courts of law. With his characteristic sense of humour he suggested that, if counsel were to ask a psychiatrist to define mental disease in the courtroom, the psychiatrist should confound the lawyer by responding with a counterquestion to define law.

Mercier's views of insanity as a conduct disorder and of diseases as mental constructs were controversial then as they are likely to be today. Nevertheless, as the debate about how diseases are defined continues a century after these views were published, his proposed definition may be worth re-examining.

Sir William Osler, in his obituary of Mercier, described him as having a 'rich vocabulary and a keen wit, he had no equal among us as a controversialist'.

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