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Hospital-treated mental and behavioral disorders and risk of Alzheimer's disease: A nationwide nested case-control study

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ABSTRACT

Background: Studies investigating psychiatric disorders as Alzheimer's disease (AD) risk factors have yielded heterogeneous findings. Differences in time windows between the exposure and outcome could be one explanation. We examined whether (1) mental and behavioral disorders in general or (2) specific mental and behavioral disorder categories increase the risk of AD and (3) how the width of the time window between the exposure and outcome affects the results.
Methods: A nationwide nested case-control study of all Finnish clinically verified AD cases, alive in 2005 and their age, sex and region of residence matched controls (*n* of case-control pairs 27,948). History of hospital-treated mental and behavioral disorders was available since 1972.
Results: Altogether 6.9% (*n* = 1932) of the AD cases and 6.4% (*n* = 1784) of controls had a history of any mental and behavioral disorder. Having any mental and behavioral disorder (adjusted OR = 1.07, 95% CI = 1.00–1.16) or depression/other mood disorder (adjusted OR = 1.17, 95% CI = 1.05–1.30) were associated with higher risk of AD with 5-year time window but not with 10-year time window (adjusted OR, 95% CI 0.99, 0.91–1.08 for any disorder and 1.08, 0.96–1.23 for depression).
Conclusions: The associations between mental and behavioral disorders and AD were modest and dependent on the time window. Therefore, some of the disorders may represent misdiagnosed prodromal symptoms of AD, which underlines the importance of proper differential diagnostics among older persons. These findings also highlight the importance of appropriate time window in psychiatric and neuroepidemiology research.

1. Introduction

It is estimated that 47 millions people suffered from dementia in 2015 and the amount is expected to nearly double every 20 years [1] The most common cause of dementia is Alzheimer's disease (AD), which is one of the costliest chronic diseases to society [2]. Identification of potential AD/dementia risk factors is important, because it may aid in targeting or developing potential strategies to prevent or delay the dementia onset.

Previous studies have mainly assessed specific mental and behavioral disorders, most commonly affective disorders [3], as AD risk factors. Two studies [4,5] reported a higher prevalence of psychiatric illness history among persons with AD, but we are not aware of other studies assessing whether mental and behavioral disorders in general are related to AD risk.

Most of the previous studies have assessed the association between depression and AD, with inconsistent findings [6]. A meta-analysis [7] concluded that depression is a risk factor rather than a prodromal symptom of AD as the width of time window between exposure and outcome was positively related to the risk of developing AD. Controversially, another study [8] concluded that 1-year increase in time window decreases the likelihood of dementia by 8%, suggesting that depression is a prodromal symptom of dementia rather than a risk factor. Similarly, the debate on whether early-life or late-life depression is more important risk factor is ongoing [3,6,8–13]. The results of studies

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investigating the association between bipolar disorder and dementia [14–17] and late-life schizophrenia and dementia [18–21] have been equally heterogeneous.

Many of these studies have been hampered by methodological issues such as narrow time windows between the exposure (mental and behavioral disorders) and outcome (AD/dementia) or cross-sectional study design [13,22,23]. Thus, in these studies the mental and behavioral disorders can actually have been prodromal symptoms or consequences of AD [6]. Due to the long latency period of AD/dementia, having an adequate time window between exposure and outcome (i.e., allowing a large enough time gap between them) is crucial. Otherwise the identified "risk factors", may actually be manifestations of the outcome.

Our nationwide nested case-control study was conducted to examine whether (1) mental and behavioral disorders in general or (2) specific mental and behavioral disorder categories increase the risk of AD and (3) how the width of the time window between the exposure and outcome affects the results.

2. Methods

2.1. Study population

The study was conducted in the MEDALZ-2005 (Medication use and Alzheimer's disease) study population [24]. This is a nested case-control study of the population of Finland, including all AD cases with clinically verified diagnosis (n = 28,093) and their age-, sex-, and region of residence matched controls (n of matched case-control pairs = 28,093). To be included in the study sample, the participants had to be alive on December 31, 2005, and community-dwelling. Data were available on all residents of Finland who had a unique personal identity code [25], i.e., all citizens and residents who lived in Finland for at least 2 years and had not resided abroad for more than 1 year on December 31, 2005. Controls were identified from a register of all residents with a personal identity code. Some of the controls had temporarily been entitled to reimbursed AD medication before January 1, 2006 (n = 145) and they, together with their matched AD cases (n = 145), were excluded from the analyses.

2.2. Data sources

The AD cases were identified from the Special Reimbursement Register maintained by Social Insurance Institution (SII). The Special Reimbursement Register contains information on reimbursement due to specific chronic diseases such as AD. To be included in this register, the diagnosis must be based on explicit predefined criteria and written documentary evidence, including results of a diagnostic test, such as computed tomography or magnetic resonance imaging scan, must be provided to the SII by a physician.

The Hospital Discharge Register contains data on inpatient hospital admissions. The register contains information of each admission, including date, reason for hospital stay (coded according to ICD-8, ICD-9 and ICD-10). The diagnoses for each hospital visit are made by attending physician. The detailed history of The Hospital Discharge register is described in Sund et al. [26].

The register maintainers retrieved the data from different registers using the personal identity codes and de-identified the data before submitting it to the research team. Because all data were de-identified and participants were not contacted, ethical approval was not required according to Finnish legislation.

2.3. Identification of cases with AD

The diagnostic criteria for probable AD were based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria [27,28]. AD cases were identified from the Special Reimbursement Register and had to fulfil the requirements of the reimbursement which were:

- symptoms consistent with AD;
- experienced a decrease in social capacity over a period of at least 3 months;
- a computed tomography or magnetic resonance imaging scan;
- exclusion of alternative diagnoses;
- confirmation of the diagnosis by a registered neurologist or geriatrician [29].

The requirements for reimbursement were consistent during 1999–2005. Summary of anamnestic information from the patients and family, as well findings from clinical examination and all diagnostic and laboratory findings, were submitted to the SII, where a geriatrician/neurologist systematically evaluated the diagnostic evidence for each AD case and confirmed whether the pre-specified criteria are met. The physician also needs to confirm whether the patient has other dementing diseases, such as mixed dementia, multi-infarct dementia or Lewy body dementia. However, patients with these diseases are also entitled to reimbursed medicines if the symptoms are considered to be mainly caused by AD.

2.4. Extraction of mental and behavioral disorders

Diagnoses of mental and behavioral disorders (Chapter V of the ICD-10 classification, code F*) during 1972–2005 were extracted from the Hospital Discharge Register. ICD-8 and ICD-9 codes were converted to ICD-10 codes (Supplementary table). The conversion was made by using classification of National Centre for Health Statistics and the code lists of the Finnish National Institute for Health and Welfare. The mental and behavioral disorder diagnoses were categorized according to previously applied classification [30]: 'Mental and behavioral disorders due to psychoactive substance use' (F10–F19); 'schizophrenia, schizotypal and delusional disorders' (F20–F29); 'manic episode and bipolar affective disorder' (F30–F31); 'depression and other mood disorders' (F32–F39); 'neurotic, stress-related and somatoform disorders' (F40–F48); 'disorders of adult personality and behavior' (F60–F69) and 'other disorders' (F00–F09, F50–F59, F60–F69, F70–F79, F80–F89, F90–F98, F99–F99).

Due to small number of persons with 'manic episode and bipolar affective disorder' and 'disorders of adult personality and behavior' these categories were combined with 'other disorders' category, which thereafter contained 'organic, including symptomatic, mental disorders' (F00–F09); 'manic episode or bipolar affective disorder' (F30–F31); 'behavioral syndromes associated with physiological disturbances and physical factors' (F50–F59); 'disorders of adult personality and behavior' (F60–F69); 'mental retardation' (F70–F79); 'disorders of psychological development' (F80–F89); 'behavioral and emotional disorders with onset usually occurring in childhood and adolescence' (F90–F98) and 'unspecified mental disorder' (F99–F99).

2.5. Confounders

Data on chronic diseases were identified from the Special Reimbursement Register. A modified Charlson Comorbidity Index [31] was calculated using the following diseases with corresponding scores: heart failure, coronary artery disease, type 1 or 2 diabetes, chronic asthma or chronic obstructive pulmonary