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

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Original article

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

Vesa Tapiainen\textsuperscript{a,b}, Sirpa Hartikainen\textsuperscript{a,c,d}, Heidi Taipale\textsuperscript{a,d}, Jari Tiihonen\textsuperscript{e,f,g}, Anna-Maija Tolppanen\textsuperscript{a,b}

\textsuperscript{a}School of Pharmacy, University of Eastern Finland, Kuopio, Finland
\textsuperscript{b}Research Centre for Comparative Effectiveness and Patient Safety (RECEPS), University of Eastern Finland, Kuopio, Finland
\textsuperscript{c}Department of Psychiatry, Kuopio University Hospital, Kuopio, Finland
\textsuperscript{d}Kuopio Research Centre of Geriatric Care, University of Eastern Finland, Kuopio, Finland
\textsuperscript{e}Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
\textsuperscript{f}National Institute for Health and Welfare, Helsinki, Finland
\textsuperscript{g}Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland

Corresponding author: Vesa Tapiainen, School of Pharmacy, University of Eastern Finland, PO Box 1627, 70211 Kuopio, Finland. E-mail: vesa.tapiainen@gmail.com. Phone number: +358509121140.

Conflicts of Interest and Source of Funding

Vesa Tapiainen, Sirpa Hartikainen, Heidi Taipale and Anna-Maija Tolppanen report no competing interests. Jari Tiihonen reports serving as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon. He has received fees for giving expert opinions to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka and Pfizer, and lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer; and grant from Stanley Foundation and Sigrid Jusélius Foundation. He is a member of advisory board in AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka.

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Key words: Addiction (consumption/abuse/dependence); Affective disorders; Anxiety disorders; Schizophrenia and psychosis; Alzheimer disease; Epidemiology
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=1,932) of the AD cases and 6.4% (n=1,784) 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 million people suffered from dementia in 2015 and the amount is expected to nearly double every 20 years. The most common cause of dementia is Alzheimer’s disease (AD), which is one of the costliest chronic diseases to society. 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, as AD risk factors. Two studies 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. A meta-analysis 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 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. The results of studies investigating the association between bipolar disorder and dementia and late-life schizophrenia and dementia 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. Thus, in these studies the mental and behavioral disorders can actually have been prodromal symptoms or consequences of AD. 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. This is a nested case-control study of the population of Finland, including all AD cases with clinically verified diagnosis and their age-, sex-, and region of residence matched controls. To be included in the study, 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, 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, and they, together with their matched AD cases, 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: 1) symptoms consistent with AD; 2) experienced a decrease in social capacity over a period of at least 3 months; 3) a computed tomography or magnetic resonance imaging scan; 4) exclusion of alternative diagnoses ; and 5) 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 disease, disseminated connective tissue diseases, rheumatoid arthritis and other comparable conditions (score of 1); uremia requiring dialysis, severe anemia in connection with chronic renal failure, leukemia, other malignant diseases of blood and bone marrow including malignant diseases of the lymphatic system and all cancers (score of 2). The comorbidity score was summed to each person at the index date (December 31, 2005). Due to skewed distribution the score was categorized to “0”, “1”, “2,” and “≥3”.

A composition variable indicating substance abuse was created on the basis of the following data from the Hospital Discharge Register: mental and behavioral disorders due to psychoactive substance use (ICD-10 codes F10–F19), alcohol-induced chronic pancreatitis (ICD-10 codes K86.00, K86.01 and K86.08) and hospitalizations due to substance abuse.

2.6 Statistical analysis
All analyses were performed using Stata, version 12.1 (StataCorp, College Station, Tex.). Student’s t test was used for comparing the age differences between groups. Other continuous variables were compared with Wilcoxon rank-sum test due to skewed distribution. Differences in categorical variables were investigated with Pearson’s chi-square test. Associations between mental and behavioral disorders and AD were assessed with conditional logistic regression. Odds ratios (ORs) are represented with 95% confidence intervals (CIs). To account for reverse causality, only those mental and behavioral disorders and confounders that occurred at least 5 or 10 years before AD diagnosis date of the case were taken into account. Both 5- and 10-year time windows were used when assessing associations between mental and behavioral disorders and AD. In addition to unadjusted analyses, the analyses were adjusted for 1) modified Charlson Comorbidity Index and 2) modified Charlson Comorbidity Index and substance abuse. In order to further illustrate the impact of time window, we calculated odds ratios for the associations between exposures and AD for 0–33-year time window between exposure and outcome. All statistical tests were two-sided.

3 RESULTS

3.1 Characteristics of study population
Characteristics of study population are shown in Table 1. The mean age of the study population was 79.7 (SD 6.8) and majority of the population were ≥75 years old (80.5%). Proportion of women was 67.7%. AD cases had slightly more chronic diseases compared to controls. Altogether 6.5% (n=3,649) of the whole study population had a history of any mental and behavioral disorder requiring hospital treatment and of them, ‘depression and other mood disorders’ were the most frequent (37.5% of persons with mental and behavioral disorders). With the 5-year time window between exposure and outcome, history of mental and behavioral disorders, was more frequent in AD cases than in controls. Findings were similar for individual
categories, except for ‘schizophrenia, schizotypal and delusional disorders’. The persons with mental and behavioral disorders were younger with mean age of 78.7 (SD 7.3) vs 79.7 (SD 6.8) and had more chronic diseases than people without mental and behavioral disorders. There were no sex differences between these groups. When 5-year time window was used, the mean difference between the first hospital admission due to any mental and behavioral disorder and date of AD diagnosis was 18.1 years (SD 8.9) for AD cases, 19.4 years for controls (SD 9.0; calculated from the AD diagnosis date of the matched case).

3.2 Associations of mental and behavioral disorders with Alzheimer’s disease

The associations of mental and behavioral disorders with AD are shown in Table 2. In the crude analyses with 5-year time window, any mental and behavioral disorder (OR=1.09, 95% CI=1.02–1.17) and ‘depression and other mood disorders’ (OR=1.18, 95% CI=1.06–1.32) were associated with higher risk of AD. Adjustments slightly weakened both associations. These associations disappeared when the 10-year time window was applied. The negative association between ‘schizophrenia, schizotypal and delusional disorders’ and risk of AD strengthened after the time window was widened, but the confidence interval was wide and included also 1 (adjusted OR=0.87, 95% CI=0.73–1.02).

More detailed investigation of the changes in OR depending on the time of exposure is illustrated in Figures 1 and 2. The association between any mental and behavioral disorder (the entire chapter V of the ICD-10 classification) was highly dependent on the time window. Those with the longest time window (>20 years) had lower odds of AD in comparison to persons without a history of any mental and behavioral disorder, and the OR was not different from 1 when those with a mental disorder diagnosed 5-20 years before AD were included (Figure 1). The association became evident only with those with <5 years time window, as illustrated from the exponential increase in these diagnoses among AD cases around the same timepoint (Supplementary figure 1). The association of ‘schizophrenia, schizotypal and delusional disorders’ and ‘neurotic, stress-related and somatoform disorders’ followed a similar pattern (Figure 2). For ‘depression and other mood disorders’ and ‘mental and behavioral disorders due to psychoactive substance use’ an inverse association with longer time windows was not observed, but also with these categories, the association became evident with shorter time windows. Similar exponential increase of diagnoses among AD cases was seen in specific mental and behavioral disorder categories as in any mental and behavioral disease. (Supplementary figure 2). The differences were higher for ‘schizophrenia, schizotypal and delusional disorders’ and ‘depression and other mood disorders’ and relatively small for ‘mental and behavioral disorders due to psychoactive substance use’ and ‘neurotic, stress-related and somatoform disorders’.

4 DISCUSSION

Our study showed that the width of time window affects the association between mental and behavioral disorders and AD. Having any mental and behavioral disorder or ‘depression and other mood disorders’ were associated with an increased risk of AD when a 5-year time window was applied but the associations disappeared when the time window was extended to 10 years. More detailed investigations revealed that the narrower time window between exposure and AD, especially <5-year time window, the higher the odds of AD and larger the difference in the cumulative annual prevalence. Similar tendency was also observed for other mental and behavioral disease categories (‘mental and behavioral disorders due to psychoactive substance use’, ‘schizophrenia, schizotypal and delusional disorders’, ‘depression and other mood disorders’ and ‘neurotic, stress-related and somatoform disorders’). These results may be due to misdiagnosis of prodromal symptoms of AD as mental and behavioral disorders. It might be that some AD cases, possibly with mixed forms of dementia (Lewy body disease in addition
to AD), had symptoms like delusions and hallucinations which could have been misdiagnosed as very late-onset schizophrenia-like psychosis, that starts after age of 60 years (32). However, that is a rare disease and the entity is still under discussion.

Interestingly, the exponential increase of ‘depression and other mood disorders’ from 7 years before AD diagnosis was similar to a previous study (33) in which the change in the Center for Epidemiologic Studies-Depression (CES-D) scale in relation to AD diagnosis was investigated. In that study, the CES-D score of AD cases separated from that of the controls 7 years before AD diagnosis. The cumulative prevalence of any mental and behavioral disorder increases exponentially among AD cases as the time window got closer to AD diagnosis. Note that Tables 1 and 2 were made with 5-year time window so that they were dated right at the beginning of the exponential growth (Supplementary figure 1).

The inverse association between any mental and behavioral disorder and AD was observed with time windows of >20 years. One possible explanation could be use of lithium as treatment. Lithium was mainly used as a mood stabilizer to treat bipolar disorders and it was also used to treat depression, schizoaffective and schizophrenic disorders if there is no response to conventional medicines (i.e. antidepressants and antipsychotics) (34). Several studies have shown that lithium use could have preventive effect to AD/dementia (35-37) and that it could decrease P-tau concentration in cerebrospinal fluid and improve cognitive skills among mild cognitive impairment patients (38). Lithium used for treatment of mental and behavioral disorders could therefore protect these patients from AD. Similar inverse association was seen with ‘schizophrenia, schizotypal and delusional disorders’ and ‘neurotic, stress-related and somatoform disorders’. However, the number of persons with long-term psychiatric history is relatively small and also some selection via mortality has very likely occurred, for example, among those with the longest history of neurotic and stress-related disorders and schizophrenia.

To our knowledge, ours was the first large scale study to assess the association of any mental and behavioral disorder and AD. Our findings are in line with previous studies on the higher prevalence of psychiatric morbidity in AD patients (4, 5) and studies that investigated depression (7, 8, 39) as a risk factor for AD. Previous studies with narrow or non-existent time window between depression and AD/dementia reported an association between depression and AD/dementia (5,22,23) while studies with wider time window yielded inconsistent results (5,8,10,40). Taken together, our findings and the previous research highlight the importance of choosing an appropriate time window for analyses.

4.1 Strengths
The strengths of our study were clinically verified diagnosis of AD, representativeness and the length of the follow-up time. All AD diagnoses were clinically verified and the positive predictive value of diagnoses is good (PPV 97.1%(41)). The Finnish health care system (and thus the registers applied in this study) includes all citizens despite their age and income. Therefore, these data represent all socioeconomic classes instead of members of a certain private health care insurance scheme. The long-term follow-up of over 30 years enabled us to investigate the effect of time window selection and thus, we were also able to account for reverse causality (i.e. mental and behavioral disorders would be caused by AD). Too narrow time window could cause bias as mental and behavioral disorders could be a reaction to early cognitive deficits or the symptoms of pre-dementia stage of AD could be misdiagnosed as mental and behavioral disorders. As a register based study, this study does not rely on self-report and therefore, it is not subject to recall bias.
4.2 Limitations

The mortality of persons with mental and behavioral disorders, especially with ‘mental and behavioral disorders due to psychoactive substance use’, is significantly higher compared to general population (42, 43). Due to the higher mortality, our prevalence figures represent only those persons who survived to be old enough to develop AD, not the entire population. We accounted for the decreased life expectancy by matching the AD cases and controls by age and sex. In this way, the decreased life expectancy should affect similarly both cases and controls. In addition, we adjusted the analyses for substance abuse. Although the register data on substance abuse captures only the most serious cases and thus, is an underestimation, the degree of underestimation is likely to be independent of exposure and outcome and it should not bias the results.

The Hospital Discharge Register includes stays in hospitals but does not include information from outpatient clinics and thus, mental and behavioral disorders were restricted to more serious cases and do not represent the entire spectrum of these diseases. Especially, the findings with ‘depression and other mood disorders’ and ‘neurotic, stress-related and somatoform disorders’ represent the association with most severe forms of these disorders as they are mainly treated in outpatient clinics. On the other hand, previous validation studies have shown that the Hospital Discharge Register is able to capture nearly all persons with schizophrenia, schizotypal and delusional disorders (44, 45).

Although all AD diagnoses were clinically verified according to a standard protocol, one limitation is that the diagnoses were probable AD rather than definite AD. However, the validity was improved by the practice that diagnoses were assessed by two independent specialists in clinical practice, and further evaluation was done in the SII according to the predefined criteria. In addition, national studies with definite AD diagnosis were not possible in the study period, as definite AD diagnoses could only be made post mortem. To our knowledge, the same limitation is present in all other studies of this topic.

Because our data were representative only of the most severe forms of mental and behavioral disorders e.g., depression, it would be important to examine the association between mental and behavioral disorders and AD with data that includes also those mental and behavioral disorders diagnosed in outpatient clinics. Further, the association between depression and AD/dementia may be dependent on the age when depression was diagnosed, or severity or episodic nature of the disease (3, 6), but this was beyond the scope of our study.

4.3 Conclusion

Our nationwide nested case-control study did not detect a strong association between mental and behavioral disorders and AD. Although some associations were detected with narrow time windows, they disappeared when a wider time window was applied. This suggests that some of these mental and behavioral disorders might actually have been prodromal symptoms of AD and thus, underlines the importance of proper differential diagnostics of AD and mental and behavioral disorders. In addition, these findings highlight the importance of appropriate time window in psychiatric and neuroepidemiology research.

5 ACKNOWLEDGEMENTS

This work was supported by European Regional Development Fund (Regional Council of Pohjois-Savo) [32198 to VT, HT and AMT]. The funder had no role in study design; in the collection, analysis, and interpretation of data, in the writing of the report; and in the decision to submit the paper for publication.
6 AUTHOR CONTRIBUTIONS
SH and AMT planned the research project, VT drafted the first version on the manuscript, performed statistical analyses and acts as guarantor. VT, SH, HT, JT and AMT interpreted the data, revised the draft version and accepted the final manuscript.

7 CONFLICTS OF INTEREST
VT, SH, HT and AMT report no competing interests. JT reports serving as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon. He has received fees for giving expert opinions to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka and Pfizer, and lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer; and grant from Stanley Foundation and Sigrid Jusélius Foundation. He is a member of advisory board in AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka.
8 REFERENCES


## TABLES

**Table 1.** Characteristics of the study population at the index date (December 31, 2005) with 5-year time window between exposure and outcome.

<table>
<thead>
<tr>
<th></th>
<th>AD(^a) case (n=27948)</th>
<th>Control (n=27948)</th>
<th>Mental and behavioral disorder (n=3716)</th>
<th>No mental and behavioral disorder (n=52180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Age in 2005</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>764   2.7</td>
<td>764   2.7</td>
<td>158   4.3</td>
<td>1,370   2.6</td>
</tr>
<tr>
<td>65–74</td>
<td>4,693 16.8</td>
<td>4,693 16.8</td>
<td>730   19.6</td>
<td>8,656  16.6</td>
</tr>
<tr>
<td>75–84</td>
<td>15,982 57.2</td>
<td>15,982 57.2</td>
<td>2,056  55.3</td>
<td>29,908 57.3</td>
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<tr>
<td>≥85</td>
<td>6,509 23.3</td>
<td>6,509 23.3</td>
<td>772   20.8</td>
<td>12,246 23.5</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18,934 67.7</td>
<td>18,934 67.7</td>
<td>2,545  68.5</td>
<td>35,323 67.7</td>
</tr>
<tr>
<td>Male</td>
<td>9,014 32.3</td>
<td>9,014 32.3</td>
<td>1,171  31.5</td>
<td>16,857 32.3</td>
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<tr>
<td><strong>Mental and behavioral disorders(^b)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mental and behavioral disorder (F00–F99)</td>
<td>1,932 6.9</td>
<td>1,784 6.4</td>
<td></td>
<td></td>
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<tr>
<td>Mental and behavioral disorders due to psychoactive substance use (F10–F19)</td>
<td>347 1.2</td>
<td>309 1.1</td>
<td>656 17.7</td>
<td></td>
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<tr>
<td>Schizophrenia, schizotypal and delusional disorders (F20–F29)</td>
<td>336 1.2</td>
<td>354 1.3</td>
<td>690 18.9</td>
<td></td>
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<tr>
<td>Depression and other mood disorders (F32–F39)</td>
<td>754 2.7</td>
<td>641 2.3</td>
<td>1,395 37.5</td>
<td></td>
</tr>
<tr>
<td>Neurotic, stress-related and somatoform disorders (F40–F48)</td>
<td>468 1.7</td>
<td>417 1.5</td>
<td>885 23.8</td>
<td></td>
</tr>
<tr>
<td>Other disorders (F00-F09, F30-F31, F50-F59, F60-F69 F70-F79, F80-F89, F90-F98, F99-F99)</td>
<td>569 2.0</td>
<td>524 1.9</td>
<td>1,093 29.4</td>
<td></td>
</tr>
<tr>
<td><strong>Modified Charlson Comorbidity Index</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0</td>
<td>19,028 68.1</td>
<td>19,627 70.2</td>
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<td>36,282 69.5</td>
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<td>1</td>
<td>6,467 23.1</td>
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<td>941   25.3</td>
<td>11,668 22.4</td>
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<td>2</td>
<td>2,013  7.2</td>
<td>1,766  6.3</td>
<td>315   8.5</td>
<td>3,464  6.6</td>
</tr>
<tr>
<td>≥3</td>
<td>440   1.6</td>
<td>413   1.5</td>
<td>87    2.3</td>
<td>766   1.5</td>
</tr>
</tbody>
</table>

\(^a\)Alzheimer’s disease

\(^b\)ICD-10 codes between parentheses
Table 2. Associations between mental and behavioral disorders and Alzheimer’s disease.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>n</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted for modified Charlson Comorbidity Index OR (95% CI)</th>
<th>Adjusted for modified Charlson Comorbidity Index and drug abuse OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mental and behavioral disorder (F00–F99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year time window</td>
<td>3,716</td>
<td>1.09 (1.02–1.17)</td>
<td>1.08 (1.01–1.16)</td>
<td>1.07 (1.00–1.16)</td>
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<tr>
<td>10-year time window</td>
<td>2,812</td>
<td>1.02 (0.94–1.10)</td>
<td>1.01 (0.93–1.09)</td>
<td>0.99 (0.91–1.08)</td>
</tr>
<tr>
<td>Mental and behavioral disorders due to psychoactive substance use (F10–F19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year time window</td>
<td>656</td>
<td>1.13 (0.96–1.32)</td>
<td>1.12 (0.96–1.31)</td>
<td></td>
</tr>
<tr>
<td>10-year time window</td>
<td>504</td>
<td>1.09 (0.92–1.31)</td>
<td>1.08 (0.91–1.29)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia, schizotypal and delusional disorders (F20–F29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year time window</td>
<td>690</td>
<td>0.95 (0.82–1.10)</td>
<td>0.95 (0.82–1.11)</td>
<td>0.94 (0.81–1.10)</td>
</tr>
<tr>
<td>10-year time window</td>
<td>567</td>
<td>0.87 (0.74–1.03)</td>
<td>0.87 (0.74–1.03)</td>
<td>0.87 (0.73–1.02)</td>
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<tr>
<td>Depression and other mood disorders (F32–F39)</td>
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<tr>
<td>5-year time window</td>
<td>1,395</td>
<td>1.18 (1.06–1.32)</td>
<td>1.18 (1.06–1.31)</td>
<td>1.17 (1.05–1.30)</td>
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<tr>
<td>10-year time window</td>
<td>988</td>
<td>1.10 (0.97–1.25)</td>
<td>1.09 (0.96–1.24)</td>
<td>1.08 (0.96–1.23)</td>
</tr>
<tr>
<td>Neurotic, stress-related and somatoform disorders (F40–F48)</td>
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<td></td>
<td></td>
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<tr>
<td>5-year time window</td>
<td>885</td>
<td>1.12 (0.98–1.28)</td>
<td>1.12 (0.98–1.28)</td>
<td>1.11 (0.97–1.27)</td>
</tr>
<tr>
<td>10-year time window</td>
<td>735</td>
<td>1.07 (0.93–1.24)</td>
<td>1.06 (0.91–1.22)</td>
<td>1.05 (0.91–1.22)</td>
</tr>
<tr>
<td>Other disorders (F00–F09, F30–F31, F50–F59, F60–F69 F70–F79, F80–F89, F90–F98, F99–F99)</td>
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<td></td>
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<tr>
<td>5-year time window</td>
<td>1,093</td>
<td>1.09 (0.96–1.23)</td>
<td>1.08 (0.96–1.22)</td>
<td>1.07 (0.95–1.21)</td>
</tr>
<tr>
<td>10-year time window</td>
<td>690</td>
<td>0.98 (0.84–1.13)</td>
<td>0.97 (0.84–1.13)</td>
<td>0.97 (0.83–1.12)</td>
</tr>
</tbody>
</table>

aICD-10 codes between parentheses
## Supplementary table. Conversion of ICD codes.

<table>
<thead>
<tr>
<th>Category</th>
<th>ICD-10 codes</th>
<th>ICD-9 codes</th>
<th>ICD-8 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental and behavioral disorders due to psychoactive substance use</td>
<td>F10-F19</td>
<td>291, 292, 303, 304, 305</td>
<td>291, 303, 304</td>
</tr>
<tr>
<td>Schizophrenia, schizotypal and delusional disorders</td>
<td>F20-F29</td>
<td>295, 297, 298, 298, 301.2</td>
<td>295, 297, 298, 299.99, 301.20</td>
</tr>
<tr>
<td>Manic episode and bipolar affective disorders</td>
<td>F30-F31</td>
<td>296.2, 296.3*, 296.4, 296.7</td>
<td>296.10, 296.20*, 296.30, 296.99, 296.88</td>
</tr>
<tr>
<td>Depression and other mood disorders</td>
<td>F32-F39</td>
<td>296.1, 296.3*, 296.8, 300.4, 301.1</td>
<td>296.00, 296.20*, 300.40</td>
</tr>
<tr>
<td>Neurotic, stress-related and somatoform disorders</td>
<td>F40-F48</td>
<td>300</td>
<td>300, 305</td>
</tr>
<tr>
<td>Disorders of adult personality and behavior</td>
<td>F60–F69</td>
<td>301, 302, 312</td>
<td>301 excluding 301.20, 302</td>
</tr>
</tbody>
</table>

*Manic depressive psychosis, depressed type; not possible to differentiate whether these cases have depression or mania.*
Figure 1. The association between any mental and behavioral disorder (ICD-10 codes F00-F99) and Alzheimer’s disease (AD) with different time windows between exposure and outcome. Number of exposed persons is calculated cumulatively at each time point.
Figure 2. The association between a) mental and behavioral disorders due to psychoactive substance use (ICD-10 codes F10–F19), b) schizophrenia, schizotypal and delusional disorders (F20–F29), c) depression and other mood disorders (F32–F39) and d) neurotic, stress-related and somatoform disorders (F40–F48) and Alzheimer’s disease (AD) with different time windows between exposure and outcome. Number of exposed persons is calculated cumulatively at each time point.
Supplementary figure 1. The cumulative prevalence of any mental and behavioral disorder (ICD-10 codes F00-F99) in relation to Alzheimer’s disease (AD) diagnosis.
Supplementary figure 2. The cumulative prevalence of mental and behavioral disorder categories in relation to Alzheimer’s disease (AD) diagnosis: a) mental and behavioral disorders due to psychoactive substance use (ICD-10 codes F10–F19), b) schizophrenia, schizotypal and delusional disorders (F20–F29), c) depression and other mood disorders (F32–F39) and d) neurotic, stress-related and somatoform disorders (F40–F48).