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RESEARCH ARTICLE

Risk of depression in persons with Alzheimer's disease: A national cohort study

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Abstract

INTRODUCTION: Depression is a risk factor and possible prodromal symptom of Alzheimer's disease (AD), but little is known about subsequent risk of developing depression in persons with AD.

METHODS: National matched cohort study was conducted of all 129,410 persons diagnosed with AD and 390,088 with all-cause dementia during 1998–2017 in Sweden, and 3,900,880 age- and sex-matched controls without dementia, who had no prior depression. Cox regression was used to compute hazard ratios (HRs) for major depression through 2018.

RESULTS: Cumulative incidence of major depression was 13% in persons with AD and 3% in controls. Adjusting for sociodemographic factors and comorbidities, risk of major depression was greater than two-fold higher in women with AD (HR, 2.21; 95% confidence interval [CI], 2.11–2.32) or men with AD (2.68; 2.52–2.85), compared with controls. Similar results were found for all-cause dementia.

DISCUSSION: Persons diagnosed with AD or related dementias need close follow-up for timely detection and treatment of depression.

KEYWORDS
Alzheimer disease, cohort studies, dementia, depression, mental health

Highlights

- In a large cohort, women and men with AD had >2-fold subsequent risk of depression.
- Risks were highest in the first year (>3-fold) but remained elevated ≥3 years later.
- Risk of depression was highest in persons aged ≥85 years at AD diagnosis.
- Persons with AD need close follow-up for detection and treatment of depression.

1 | BACKGROUND

Alzheimer's disease (AD) has a global prevalence of 5%–8% in adults aged ≥60 years and is a leading cause of morbidity and mortality.[1] AD and related dementias currently affect > 50 million people worldwide, and this number is expected to triple by 2050.[2,3] The cognitive decline that occurs in AD may be accompanied by psychological symptoms such as depression, which may further compromise overall functioning, quality of life, and health outcomes.[4–6] Depression is a reported risk factor and possible prodromal symptom of AD,[7–9] but less is

known about the subsequent risk of developing depression in persons diagnosed with AD. A better understanding of the long-term risks of depression and high-risk subgroups is needed to guide interventions that may improve function, quality of life, and health outcomes in persons with AD.

Persons with dementia have been reported to have a higher prevalence of clinically significant depression (20%) than other adults without dementia (11%), based on family-reported symptoms.[10] Other studies have found that 30% to 50% of persons diagnosed with AD experience various symptoms consistent with depression, including mood changes, social withdrawal, apathy, or suicidal ideation.[11,12] A meta-analysis reported that the prevalence of major depression based on diagnostic criteria is 15% in persons with AD and 16% in those with all-cause dementia.[13] However, most studies have been based on selected clinical samples of < 1000 patients and have lacked sufficient sample sizes or follow-up time to estimate long-term risks or delineate the highest-risk subgroups. To our knowledge, no studies have examined the risk of major depression following AD diagnosis in a large population-based cohort.

We sought to address these knowledge gaps using nationwide data in Sweden. Our goals were to: (1) determine risks of major depression following diagnosis with AD or all-cause dementia (for comparison with AD) in a large population-based cohort, adjusting for sociodemographic factors and comorbidities; (2) identify periods of heightened risk; and (3) assess for potential age- or sex-specific differences. We hypothesized that women and men of any age who are diagnosed with AD have increased subsequent risk of major depression.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using Pubmed. Prior studies have reported high prevalence of depression in persons with Alzheimer's disease (AD). However, most studies have been based on selected clinical samples of < 1000 patients and lacked sufficient sample sizes or follow-up to identify long-term risks or highest-risk subgroups.
2. **Interpretation**: In a national cohort of > 4 million people, after adjusting for sociodemographic factors and comorbidities, women and men diagnosed with AD had greater than two-fold higher subsequent risk of major depression compared with population-based controls. Risks were highest in the first year (greater than three-fold), then declined but remained significantly elevated (1.1- to 1.3-fold) ≥3 years after AD diagnosis. Persons with AD need close clinical follow-up for timely detection and treatment of depression.
3. **Future directions**: Interventional studies are needed to assess long-term function, quality of life, and health outcomes associated with screening and treatment for depression in persons with AD.

2 | METHODS

2.1 | Study population and dementia ascertainment

Using the Swedish Hospital and Outpatient Registers, we identified 134,347 persons diagnosed with AD and 407,663 persons diagnosed with all-cause dementia during 1998–2017. AD and all-cause dementia were identified using *International Classification of Diseases, Tenth Revision* (ICD-10) codes (AD: F00, G30; all-cause dementia: F00-F03, G30). The Hospital Register started in 1964 and contains all primary and secondary hospital discharge diagnoses with 100% coverage of the Swedish population since 1987.[14] The Outpatient Register started in 2001 and contains all diagnoses from specialty clinics with approximately 87% nationwide coverage.[15] Dementia diagnoses in these registers have been found to be highly reliable, with positive predictive values near 90%.[16]

We excluded 4937 persons diagnosed with AD and 17,575 with all-cause dementia who had a preceding diagnosis of major depression (ICD-10 codes F32-F33) in the Hospital or Outpatient Registers or primary care records, leaving 129,410 persons with AD and 390,088 persons with all-cause dementia available for analysis. Primary care diagnoses previously collected by our group[17] were available for 20% of the Swedish population starting in 1998, 45% starting in 2001, and 90% starting in 2008 and onward.

Each person with AD or all-cause dementia was matched to 10 persons randomly sampled from the general population who had the same sex, birth year and month; were living in Sweden on the date of dementia diagnosis for the respective case (i.e., index date); and had no prior diagnosis of major depression. This study was approved by the Regional Ethical Review Board in Lund, Sweden. Participant consent was not required because this study used only pseudonymized registry-based secondary data.

2.2 | Outcome ascertainment

The study outcome was the earliest diagnosis of major depression ascertained from the index date (respective case's dementia diagnosis date) through December 31, 2018. Major depression was identified using ICD-10 codes F32-F33 in the Swedish Hospital and Outpatient Registers and primary care records (as described above). Prior studies have suggested that major depression diagnoses in these data sources have high validity based on their prevalence, sex ratio, and sibling and twin correlations.[17,18]

2.3 | Covariates

Other characteristics that may be associated with AD and depression were identified using Swedish national census and health registry data,

which were linked using a pseudonymous serial number. Sex and birth date were adjusted for as matching variables. Covariates included birth country (Sweden/other), marital status (married/not married), education level (≤9, 10–12, > 12 years), region (large cities, other/Southern, other/Northern, unknown), and prior history of other mental disorders (anxiety disorder, bipolar disorder, schizophrenia) or medical comorbidities (hypertension, diabetes, lipid disorders, ischemic heart disease) at the index date, each modeled as a separate covariate. Cardiometabolic comorbidities were included because they have previously been associated with depression in persons with AD.[19] All comorbidities were ascertained from the Swedish Hospital and Outpatient Registers and primary care records using ICD-10 codes (Table S1 in the Supplement). All covariates were > 93% complete. Missing data were modeled as a separate category and had little effect on risk estimates because of their rarity.

2.4 | Statistical analysis

Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for major depression associated with AD or all-cause dementia while stratifying on matched sets. The observation period for each study participant (dementia cases and their matched controls) began at the index date (date of AD or all-cause dementia diagnosis for the respective case) and ended at the date of earliest diagnosis of major depression or December 31, 2018, whichever came first. Persons were censored at the date of death as identified in the Swedish Death Register (n = 255,675) or the date of emigration as determined by absence of a Swedish residential address in census data (n = 106,623). Analyses were adjusted first only for age and sex (via matching variables) and then further for all covariates (as defined above). The proportional hazards assumption was evaluated by examining log-log survival plots, which showed no substantial departures.

Sex-specific differences were assessed by stratifying on sex and formally testing for additive or multiplicative interaction between AD or all-cause dementia and sex in relation to major depression risk. To assess periods of heightened susceptibility during the follow-up period, HRs were estimated within narrower time intervals after dementia diagnosis (< 1, 1 to < 2, 2 to < 3, ≥3 years) in separate analyses among persons still living in Sweden without a prior diagnosis of major depression at the beginning of the respective interval. Age-specific differences were assessed by stratifying on age at the index date (< 65, 65–74, 75–84, ≥85 years), while adjusting for age within each stratum.

In secondary analyses, the study outcome was expanded to include (1) dysthymia and "other persistent mood disorders" (ICD-10 code F34) in the Swedish Hospital and Outpatient Registers and primary care records (as described above); or (2) prescription of any antidepressant medication (code N06A) in the Swedish Pharmacy Register, which includes all prescriptions dispensed nationwide starting on July 1, 2005.

Two sensitivity analyses were also performed. Because the primary aim of this study was to assess new-onset major depression after dementia diagnosis, a sensitivity analysis was performed that started follow-up for major depression 1 year after the index date to help exclude latent cases of depression (i.e., preceding the index date but still undiagnosed at the time of dementia diagnosis) and the possibility of detection bias due to increased screening in persons newly diagnosed with dementia. In addition, a sensitivity analysis was performed that accounted for death as a competing event using Fine-Gray competing risks models, to assess for potential bias that may result from earlier mortality in persons with versus without dementia.[20] All statistical tests were two-sided and used a significance level of 0.05. All analyses were conducted using Stata version 16.1.

3 | RESULTS

The median age at diagnosis with AD was 80 years (interquartile range [IQR], 75 to 85) and with all-cause dementia was 83 years (IQR, 77 to 88). The median follow-up time was 8 years (IQR, 4 to 13) for persons with either AD or all-cause dementia. In 10 million person-years of follow-up, 164,608 persons (with or without dementia) were diagnosed with major depression. The median ages at diagnosis of major depression were 81 years in persons with AD, 83 years in those with all-cause dementia, and 84 years in controls. At 10 years of follow-up, the cumulative incidence of major depression was 13% in persons with AD, 11% in those with all-cause dementia, and 3% in control persons without dementia.

Table 1 shows characteristics of persons with AD or all-cause dementia, control persons without dementia, and all persons diagnosed with major depression. Over 60% of all persons diagnosed with AD or all-cause dementia and 78% of those with major depression were women. Persons diagnosed with AD, all-cause dementia, or major depression were more likely to have high education level, live in large cities, or have comorbidities than all control persons without dementia.

3.1 | AD or all-cause dementia and risk of major depression

Persons diagnosed with AD or all-cause dementia had a greater than two-fold higher subsequent risk of major depression compared with controls, after adjusting for sociodemographic factors and comorbidities (AD: adjusted HR, 2.38; 95% CI, 2.29–2.47; all-cause dementia: HR, 2.30; 95% CI, 2.25–2.35) (Table 2). These risks were elevated among both women (HRs, 2.21 and 2.15, respectively) and men (2.68 and 2.52, respectively).

In persons either with or without AD or all-cause dementia, the incidence of major depression was higher among women than men (Tables S2 and S3 in the Supplement). Interaction tests showed a positive additive but negative multiplicative interaction between AD or all-cause dementia and female sex (i.e., the combined effect of AD or all-cause dementia and female sex on risk of major depression exceeded the sum but was less than the product of their separate effects) (Tables S2 and S3 in the Supplement). The positive additive interaction indicates

TABLE 1 Characteristics of study participants, 1998–2018, Sweden

Parameter	AD *N* = 129,410 *n* (%)	All-cause dementia *N* = 390,088 *n* (%)	Controls *N* = 3,900,880 *n* (%)	Major depression *N* = 186,117 *n* (%)
Age at index date (years)				
< 65	7234 (5.6)	19,342 (4.9)	193,420 (5.0)	19,685 (10.6)
65–74	24,671 (19.1)	52,985 (13.6)	529,850 (13.6)	34,927 (18.8)
75–84	63,971 (49.4)	167,354 (42.9)	1,673,540 (42.9)	85,488 (45.9)
≥85	33,534 (25.9)	150,407 (38.6)	1,504,070 (38.5)	46,017 (24.7)
Sex (female)	83,310 (64.4)	245,238 (62.9)	2,452,380 (62.9)	145,193 (78.0)
Sweden-born	115,372 (89.2)	350,404 (89.8)	3,504,040 (89.8)	164,272 (88.3)
Marital status				
Married	78,699 (60.8)	212,043 (54.4)	1,460,594 (37.4)	107,053 (57.5)
Not married	50,702 (39.2)	178,018 (45.6)	2,172,528 (55.7)	79,062 (42.5)
Unknown	9 (< 0.1)	27 (< 0.1)	267,758 (6.9)	2 (< 0.1)
Education (years)				
≤9	66,768 (51.6)	228,449 (58.6)	2,425,382 (62.2)	95,884 (51.5)
10–12	42,763 (33.0)	115,198 (29.5)	878,355 (22.5)	61,429 (33.0)
> 12	19,669 (15.2)	45,679 (11.7)	379,385 (9.7)	28,607 (15.4)
Unknown	210 (0.2)	762 (0.2)	217,758 (5.6)	197 (0.1)
Region				
Large cities	65,503 (50.6)	188,281 (48.3)	1,646,766 (42.2)	106,642 (57.3)
Other/Southern	35,706 (27.6)	122,740 (31.5)	1,400,511 (35.9)	54,456 (29.3)
Other/Northern	28,163 (21.8)	78,929 (20.2)	661,363 (17.0)	24,973 (13.4)
Unknown	38 (< 0.1)	138 (< 0.1)	192,240 (4.9)	46 (< 0.1)
Prior diagnoses				
Anxiety disorder	12,103 (9.4)	40,672 (10.4)	229,803 (5.9)	36,267 (19.5)
Bipolar disorder	719 (0.6)	3,148 (0.8)	18,341 (0.5)	2414 (1.3)
Schizophrenia	427 (0.3)	2737 (0.7)	27,691 (0.7)	749 (0.4)
Hypertension	50,750 (39.2)	169,253 (43.4)	1,176,997 (30.2)	94,965 (51.0)
Diabetes	17,631 (13.6)	65,976 (16.9)	536,283 (13.8)	26,392 (14.2)
Lipid disorders	11,905 (9.2)	34,534 (8.9)	233,904 (6.0)	21,561 (11.6)
Myocardial infarction	17,509 (13.5)	67,102 (17.2)	628,379 (16.1)	25,772 (13.9)

that AD and all-cause dementia accounted for more diagnoses of major depression among women than men.

Relative rates of major depression were highest (greater than three-fold) within the first year after diagnosis with either AD or all-cause dementia, then declined but remained significantly elevated (1.1- to 1.3-fold) even ≥ 3 years after diagnosis (Figure 1 and Table S4 in the Supplement). Risk of major depression was elevated regardless of age at diagnosis with either AD or all-cause dementia but was highest among those aged ≥ 85 years (Figure 2 and Table S5 in the Supplement).

3.2 | Secondary analyses

Expansion of the outcome to include dysthymia and other persistent mood disorders (ICD-10 code F34) yielded virtually identical risk estimates as the main analyses (e.g., AD: adjusted HR, 2.37; 95% CI, 2.29–2.46; all-cause dementia: HR, 2.30; 95% CI, 2.24–2.35). Inclusion of antidepressant prescriptions yielded somewhat higher risk estimates (AD: adjusted HR, 3.00; 95% CI, 2.94–3.07; all-cause dementia: HR, 2.87; 95% CI, 2.83–2.91).

In sensitivity analyses that started follow-up for major depression 1 year after the index date, all HRs were moderately reduced but remained significantly elevated ($P < 0.001$ for each). For example, adjusted HRs for major depression among women or men with AD were 1.79 (95% CI, 1.69–1.90) and 1.99 (1.85–2.14), respectively, and the corresponding HRs associated with all-cause dementia were 1.59 (1.53–1.66) and 1.72 (1.64–1.80), respectively.

In sensitivity analyses that accounted for death as a competing event, all results were similar to those from the main analyses. For example, adjusted subdistribution HRs[20] for major depression among

TABLE 2 Relative rates of major depression through 2018 in persons diagnosed with AD or all-cause dementia (1998–2017), compared with population-based controls

Parameter	Dementia cases		Controls		Age- and sex-adjusted model HR (95% CI)	Fully adjusted model[a] HR (95% CI)
	No. with depression	Rate[b]	No. with depression	Rate[b]		
AD						
All	9467	1573.9	15,391	650.0	2.82 (2.73, 2.92)	2.38 (2.29, 2.47)
Women	6693	1890.2	10,625	981.1	2.57 (2.47, 2.68)	2.21 (2.11, 2.32)
Men	2774	1121.2	4766	370.9	3.35 (3.16, 3.54)	2.68 (2.52, 2.85)
All-cause dementia						
All	23,379	1209.2	38,694	478.0	2.88 (2.82, 2.95)	2.30 (2.25, 2.35)
Women	15,987	1432.8	24,997	683.5	2.64 (2.57, 2.72)	2.15 (2.08, 2.21)
Men	7392	904.0	13,697	308.6	3.30 (3.19, 3.41)	2.52 (2.43, 2.62)

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, birth country, marital status, education, region, and prior history of psychiatric disorders (bipolar disorder, schizophrenia, anxiety disorder, major depression) or cardiometabolic disorders (hypertension, diabetes, lipid disorders, myocardial infarction) at index date.
[b]Incidence rate for major depression per 100,000 person-years.

women or men with AD were 2.35 (95% CI, 2.24–2.47) and 2.87 (95% CI, 2.69–3.06), respectively, and the corresponding results for all-cause dementia were 2.26 (95% CI, 2.18–2.33) and 2.67 (95% CI, 2.57–2.78), respectively.

4 | DISCUSSION

In this large national cohort, women and men diagnosed with AD or all-cause dementia had more than double the risk of major depression compared to population-based controls without dementia, after adjusting for sociodemographic factors and comorbidities. These risks were highest within the first year (greater than three-fold), then subsequently declined but remained significantly elevated (1.1- to 1.3-fold) even ≥ 3 years after diagnosis with dementia. Relative risks were elevated regardless of age but were highest among persons aged ≥85 years at the time of diagnosis with dementia.

To our knowledge, this is the first study to examine risks of major depression following AD or all-cause dementia diagnosis in a large population-based cohort. Most prior studies of depression in AD patients have had selected samples with < 1000 people. In a US study of 851 adults aged ≥ 70 years, dementia patients had a higher prevalence of clinically significant depression (20%) than other older adults (11%) based on family-reported symptoms, and a three-fold odds of depression after adjusting for sociodemographic factors and comorbidities (odds ratio, 3.00; 95% CI, 1.36–6.60).[10] A meta-analysis of 63 studies (mean sample size < 400 participants) found that the prevalence of depression was 13% using diagnostic codes (based on 25 studies with 7549 dementia patients) and 42% using more specific criteria for depression in persons with AD (32 studies with 11,842 dementia patients).[21] Another meta-analysis of 20 studies with 5897 dementia patients (mean sample size < 300) reported that the overall pooled prevalence of depression was 39%, with a range of 10% to 78% and no difference by dementia stage or type.[22] These meta-analyses found high heterogeneity among studies and lacked a comparison group of persons without dementia.

The present study extends prior evidence by examining long-term risks of major depression in a national cohort of persons with AD or all-cause dementia compared with population-based controls, and potential age- or sex-specific differences. We found that persons newly diagnosed with AD or all-cause dementia had markedly higher subsequent risks of major depression, especially within the first year, which remained elevated even ≥ 3 years later. This pattern is broadly consistent with previous smaller studies that reported highest prevalence of depression within the first year after AD diagnosis, then subsequently declining.[23,24] In a secondary analysis, we found that inclusion of antidepressant prescriptions resulted in even higher risk estimates than those based on clinical diagnoses of major depression. However, those findings should be interpreted with caution because antidepressants are commonly prescribed for other conditions, including insomnia and anxiety,[25,26] and thus do not necessarily represent depressive symptoms or clinical depression.

Some[27] but not all[19,24] prior studies have reported that the prevalence and severity of depression are higher in women versus men with AD, as in the general population.[28] We found that both women and men had greater than two-fold increased risks, but AD accounted for significantly more cases of major depression among women. In addition, we found that relative risks were highest among persons aged ≥85 years at diagnosis with AD or all-cause dementia. This finding warrants further confirmation and differs from smaller studies suggesting highest risk among younger adults[19,29] or no age differences.[23,24] In contrast with prior studies,[30–32] persons diagnosed with dementia in the present cohort were also more likely to have a high education level, possibly related to greater health care utilization among more highly educated older adults in this population. In addition, urban residence was more common in persons with either major depression

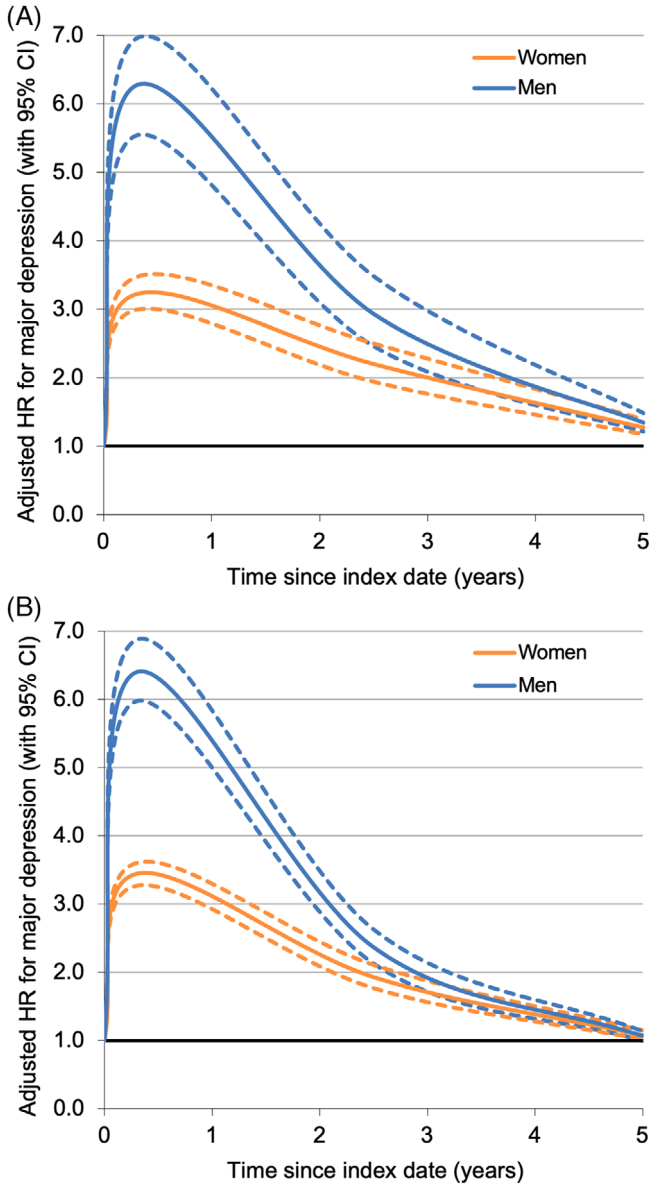

FIGURE 1 Adjusted HRs for major depression through 2018 associated with AD (A) or all-cause dementia (B) in women or men (1998–2017) by time since index date (dotted lines represent 95% CI). AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio

or dementia than in controls. Urbanicity is a reported risk factor for depression in older adults[33,34] and in the general population,[35] whereas higher dementia risks have been reported in rural than in urban areas, possibly explained by differences in education levels.[36,37]

These findings add to prior evidence that AD patients may experience psychological sequelae that could potentially worsen quality of life and long-term outcomes. Depression is not only a psychological burden but may have other important life consequences such as reduced functioning and self-care ability, earlier institutionalization, and worse quality of life for both patients and their caregivers.[4–6,38,39] The US Preventive Services Task Force has recommended routine screening for depression in the general adult population, including older adults (ages ≥70 years),[40] for whom depression screening and treatment have been shown to be effective.[41] More specific criteria have been proposed for diagnosis of depression in persons with AD.[42,43] Our findings underscore the importance of long-term monitoring for psychosocial distress and depression in persons with AD or related dementias. Patients with positive depression screens need further evaluation for appropriate treatment and psychosocial support. Psychosocial interventions including cognitive-behavioral therapy and behavioral activation have been found to be effective in reducing depression symptoms and improving quality of life and overall function in AD patients.[44–46]

Priorities for future research include elucidation of underlying mechanisms for the development of depression in persons with AD, and improvement of detection, treatment, and outcomes of depression in this population. Blood biomarker profiles have recently been identified that may reveal heterogeneity of brain phenotypes in AD.[47] Further extension of this work could potentially help identify underlying biologic pathways for depressive states in persons with AD and novel therapeutic targets.

4.1 | Strengths and limitations

A key strength of the present study was its large national cohort design, which provided high statistical power needed to examine major depression associated with AD and all-cause dementia, periods of susceptibility, and age- and sex-specific differences, while controlling for multiple potential confounders. Clinical diagnoses from all health care settings, including primary care, allowed more complete ascertainment of major depression than in most prior studies, thus enabling more valid risk estimates based on a national cohort. Previously reported incidence rates for depression are comparable between Sweden and the United States.[17,48]

This study also had certain limitations. Major depression diagnoses were identified using nationwide ICD codes, whereas more detailed clinical data needed for validation were unavailable. However, high validity of these diagnoses is previously supported by their prevalence, sex ratio, sibling and twin correlations, and associations with well-documented psychosocial risk factors.[17,18] Depression is commonly underdiagnosed; thus, the prevalences that we observed are likely underestimates that may reflect the most severe cases. However, the inclusion of diagnoses from primary care settings enabled more complete capture in a large cohort than has been possible in prior studies. Depression that preceded dementia diagnosis was also likely underdetected; however, a sensitivity analysis that excluded diagnoses within 1 year after the index date still showed substantially elevated depression risks in persons with AD or all-cause dementia compared with controls.

Dementia diagnoses in the Swedish registers have been reported to have high positive predictive values but low sensitivity,[16] which may result in substantial numbers of people with dementia being misclassified as controls, thus influencing results toward the null hypothesis. Information on dementia severity was also unavailable, although prior studies have suggested that depression has a similar prevalence across different levels of dementia severity.[22,49] Last, this study was limited to

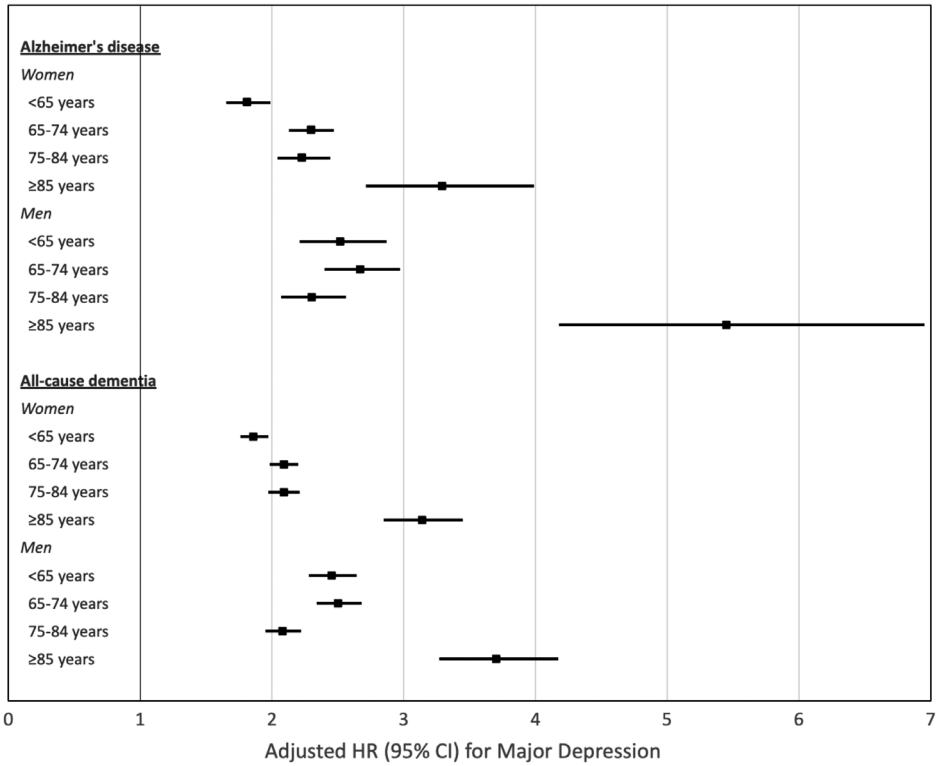

FIGURE 2 Adjusted HRs for major depression through 2018 associated with AD or all-cause dementia (1998–2017), stratified by sex and age at index date. AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratios

Sweden and will need replication in other populations when feasible, including assessment of potential racial/ethnic differences.

5 | CONCLUSIONS

In this large national cohort, women and men diagnosed with AD or all-cause dementia had more than two-fold higher subsequent risks of major depression compared to population-based control persons without dementia. These risks remained elevated more than 3 years later and were highest among persons aged ≥ 85 years at dementia diagnosis. Persons diagnosed with AD or related dementias need close clinical follow-up, particularly in the first year, for timely detection and treatment of depression.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information

CONSENT STATEMENT

Participant consent was not required because this study used only pseudonymized registry-based secondary data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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