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Depressive symptoms predict incident dementia during short- but not long-term follow-up period

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Abstract

Background: Whether depression is a long-term risk factor for dementia or represents a dementia prodrome is unclear. Therefore, we examined the relationship between depressive symptoms and dementia during short and long follow-up in a population-based cohort.
Methods: In the Rotterdam Study, 4393 nondemented individuals were followed for incident dementia for 13.7 years by continuous monitoring. Cox proportional hazards models for different time intervals were used to estimate the risk of incident dementia.
Results: Five-hundred eighty-two participants developed dementia during 13.7 years. Persons with depressive symptoms had an 8% increased risk of dementia compared with those without depressive symptoms during the overall follow-up. The risk was highest in the short and intermediate follow-up, particularly in men. We did not find an association in the follow-up period beyond 10 years.
Conclusion: Our results suggest that late-life depressive symptoms are part of a dementia prodrome rather than an independent risk factor of dementia.

Keywords: Depression; Dementia; Population-based; Epidemiology

1. Introduction

Dementia poses a high burden on society and health care in terms of financial costs and suffering for patients and caregivers. Current estimates indicate a prevalence of 35.6 million patients worldwide with another 7.7 million incident cases occurring annually [1]. To develop effective preventive and therapeutic strategies, it is crucial to unravel the multifactorial etiology of dementia.

Depression and depressive symptoms are very common in the elderly and often co-occur with dementia [2]. Depression and dementia share many vascular risk factors [3], and various studies have shown that depression in late life is associated with a 2- to 5-fold increased risk of dementia [4–8]. Most studies investigated this association over a follow-up period of at most 7 years. In contrast, the Framingham study analyzed a follow-up period of 17 years and reported a 70% greater risk of incident dementia in depressed individuals; however, the investigators did not distinguish the risk between short- and long-term follow-up. Taken together, current data suggest a strong association between depression and incident dementia, but the question remains whether depression is a risk factor for dementia or merely a prodromal symptom of underlying dementia [9]. Given the long preclinical phase of dementia, it is conceivable that subclinical dementia causes depressive symptoms rather than depression being a true risk factor for dementia. One way to address this issue is to study the association of depression and dementia during a long follow-up and then explore the association over separate incremental periods of follow-up. The hypothesis to be tested is that there is a

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strong association between depression and dementia over a short follow-up period that attenuates with longer follow-up.

In addition, some studies have suggested a difference between men and women in the association of depression with dementia, but data are still scarce. Therefore, we studied the relationship of depressive symptoms and dementia over long and short follow-up periods in a population-based cohort. We further examined if the relationship between depression and dementia differs between men and women.

2. Methods

2.1. Setting

This study was embedded in the Rotterdam Study, which is an ongoing population-based prospective study of the elderly that started in 1990 and studies the incidence and determinants of chronic diseases in late life [10]. The Medical Ethics Committee of Erasmus Medical Center Rotterdam approved the study, and a written informed consent was obtained from all participants.

Every 3 to 4 years, all participants undergo an extensive home interview and a physical examination at the research center. In addition, all participants are continuously monitored for the occurrence of all major events during follow-up by linkage of the study database with medical files from general practitioners. The third examination round of the Rotterdam study constituted the baseline of this study because the data on depressive symptoms were complete and uniformly collected (using the Center for Epidemiology Depression Scale [CES-D] for the whole cohort).

2.2. Study population

Of the original cohort of 7983 persons in 1990, 4797 surviving persons participated at the third examination that took place from 1997 to 1999. From these 4797 individuals, 4602 (96%) completed the depression assessment questionnaire. Of these 4602, 110 participants did not consent to undergo dementia screening and were excluded. We also excluded 92 participants who were demented at baseline and 7 who were lost to follow-up. This yielded a total of 4393 individuals (92% of total survivors) available for final analysis who were followed for a maximum of 13.7 years (mean 8.7, standard deviation [SD] 3.5 years) for incident dementia. Follow-up started from the day of depressive symptom screening to the date of incident dementia, date of death, or the censor date January 1, 2011, whichever occurred first.

2.3. Assessment of depression

We used the validated Dutch version of the CES-D for assessment of depressive symptoms at baseline. The CES-D comprises 20 questions, each with a possible score of 0 to 3, and the score indicates clinically relevant depressive symptoms. Depressive symptom scores were used as a standardized continuous variable. z scores were calculated as weighted individual score minus mean score divided by the standard deviation. CES-D scores were weighted by missing values only if missing values did not exceed 25%. However, for descriptive purposes, a score of 16 or higher is considered suggestive of depressive symptoms [11].

2.4. Assessment of incident dementia

Participants were screened for dementia at baseline and follow-up examinations using a three-step protocol [12]. Screening was done using the Mini-Mental State Examination (MMSE) [13] and the Geriatric Mental Schedule (GMS) organic level [14]. Screen-positives (MMSE $<$ 26 or GMS organic level $>$ 0) subsequently underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) [15]. Participants who were suspected of having dementia underwent, if necessary, further neuropsychological testing. In addition, the total cohort was continuously monitored for dementia through computerized linkage between the study database and digitized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. In the end, a consensus panel, led by a neurologist, decided on the final diagnosis in accordance with standard criteria using the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R) criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA) for Alzheimer's disease [16]. If required for differential diagnosis, neuroimaging was used. Follow-up for incident dementia was virtually complete (98.63%) until January 1, 2011.

2.5. Covariates

In addition to age and gender, education level, smoking, cognition level at baseline, hypertension, diabetes mellitus, prevalent stroke, and use of antidepressant medication were considered possible confounders. Smoking, hypertension, diabetes, and stroke are well-documented risk factors for all types of dementia. A low education level has been found to be associated with increased risk of dementia, especially in females [17]. In subsequent models, we also adjusted for marital status, *APOE*-ε4 (*APOE* ε2/ε4, *APOE* ε3/ε4 or *APOE* ε4/ε4) carrier status, cognitive complains at baseline, and psychotropic medication use.

Education level was assessed during the interview, and people were classified into two categories: low level of education (primary only or primary and unfinished secondary) and intermediate to high (primary and secondary, vocational, or university) level of education. Cognition was assessed by the MMSE at baseline [13]. Inquiring about smoking habits, participants were categorized into current, former, and never smokers. Blood pressure was measured twice at the right arm in sitting position at the research center; the average of two

blood pressure readings was used. Hypertension was defined as systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater, or use of antihypertensive medication assessed by interview and pharmacy records [18]. Diabetes mellitus type II was diagnosed as fasting blood glucose of 126.13 mg/dL (multiply by factor 0.0555 to covert to mmol/L) or greater or use of antidiabetic medication evaluated by interview and pharmacy records [19]. Previous stroke was determined by reported events on interview and confirmed by medical records. In addition, participants are continuously monitored for all major events through automated linkage of the study database with general practitioner (GP) files [20]. Information on use of antidepressants (ATC code n06) was obtained by interview and medical and pharmacy records.

2.6. Statistical analysis

We used the Cox proportional hazards model to assess the relationship between clinically relevant depressive symptoms and incident dementia (all cause). We investigated not only the total follow-up period as a whole, but also separate 5-year time periods (0–5 years, 5–10 years, and >10 years of follow-up). This analysis was performed to study the timing of incident dementia in relation to the appearance of depressive symptoms. However, several studies have used a follow-up time range of 1 to 5 years to study the short-term effect of depression on dementia incidence [5,6,21–24]; there is no recommended cutoff of follow-up time to study depression as a dementia prodrome. In an alternative analysis, time periods were defined by ensuring an equal number of 100 cases in each period (five periods of 100 incident cases, the last period only counted 82 cases). This approach allows a more detailed assessment of risk ratio change over time and increases the power to detect changes. Hazard ratios (HRs) of dementia for each time period of 100 cases were calculated separately and cumulatively. The cumulative time approach in the main analysis and in the 100-case analysis was a method performed to ensure comparability with other studies because most studies have examined the association of depressive symptoms and dementia using a Cox model and using variable follow-up periods. Therefore, we first used a cumulative follow-up approach in which we examined the association between depression and dementia by increasing the years of follow-up by not changing the baseline (i.e., 0–5 years, 0–10 years, and 0–13.7 years). Likewise, for the 100-case analysis, we examined the association of depression and dementia by increasing 100 incident cases in every subsequent step without changing our baseline (i.e., baseline to first 100 incident cases, baseline to first 200 cases, baseline to first 300 cases, etc.).

As secondary analyses, we explored effect modification by gender and age (median used as cutoff) using stratification and interaction terms. In addition, we analyzed our data using only Alzheimer's disease as an outcome. Finally, we repeated our analysis using depressive symptoms dichotomized at a cutoff of 16 points on the CES-D.

We ran an additional analysis to test the sensitivity of our findings. The analysis was repeated excluding persons with clinically relevant depressive symptoms occurring before baseline. Depressive symptoms were also assessed, 4 years before baseline either with the CES-D (cutoff $\geq$ 16) in 48% of participants or the Hospital Anxiety and Depression Scale (HADS; cutoff $\geq$ 9) in 52% of participants, as part of a pilot [25]. In this sensitivity analysis, the effect of more chronic depressive symptoms, which are less likely to be an indicator of a dementia prodrome, is reduced. If there were an effect of depression as part of a dementia prodrome only, then our HR for the short follow-up would be expected to increase slightly if chronic cases are excluded.

Because depressive symptoms in the Rotterdam Study were remeasured at a follow-up round in 2002 to 2004, we also repeated our analysis using depressive symptoms assessed at this follow-up round as our baseline.

Results are presented as HR with 95% confidence intervals (CIs). All analyses were adjusted for age and gender in the first model and additionally for education, smoking, hypertension, diabetes, prevalent stroke, MMSE score, and antidepressant use in the second model. Data were analyzed using the Stata Software Version 12 (StataCorp, College Station, TX).

3. Results

Baseline characteristics of the study population are summarized in Table 1. The study included 4393 individuals, 59% of which were females (n = 2599). Mean age at

Table 1
Baseline characteristics of the study population, RS-I-3 (N = 4393)

Characteristics	Descriptives
Females, *n* (%)	2599 (59.2)
Age, mean (SD), years	72.7 (7.3)
BMI, mean (SD)	26.86 (3.7)
Education	
Low level of education	1350 (31.2)
Intermediate to high	2980 (68.8)
Smoking status, *n* (%)	
Never	1520 (34.6)
Former	2157 (49.1)
Current	716 (16.3)
Diabetes, *n* (%)	534 (12.2)
Stroke, *n* (%)	338 (7.7)
Myocardial infarction, *n* (%)	427 (9.7)
Hypertension, *n* (%)	2990 (68.1)
Total cholesterol (mmol/L), mean (SD)	5.82 (0.9)
HDL (mmol/L), mean (SD)	1.39 (0.4)
Antipsychotic use, *n* (%)	642 (14.6)
Antidepressant use, *n* (%)	135 (3.1)
Clinically relevant depressive symptoms, *n* (%)	323 (7.4)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; RS-I-3, Rotterdam study cohort I examination round 3; SD, standard deviation.

baseline was 73 years (SD 7.3 years; range 61.1–105.8 years), and participants were followed for a maximum of 13.7 years (mean 8.7, SD 3.5 years). Applying the accepted cutoff of 16 or greater for CES-D, 7% (n = 323) of the study population had clinically relevant depressive symptoms at baseline; however, we used continuous depression scores for all analyses.

Of the 4393 individuals, 13% (n = 582) developed dementia (all cause); 84% of those were Alzheimer's disease cases (n = 489). The mean age of dementia diagnosis was 83 years (SD 6.3 years; range 65.5–102 years).

When investigating each time period with 100 subsequent cases separately, the risk of dementia decreased gradually from HR 1.24, 95% CI 1.06–1.44 in the first period, to HR 0.89, 95% CI 0.69–1.15 in the last period. A similar pattern was observed when we calculated hazards for cumulative time periods of 100 cases; HR 1.24, 95% CI 1.06–1.44 in the first period to HR 1.11, 95% CI 1.03–1.20 in the last period (Fig. 1).

In the overall follow-up of 13.7 years, depressive symptoms were associated with a moderately increased risk of incident dementia (Table 2). During a shorter follow-up time (i.e., 5 years from baseline), depressive symptoms were associated with a high risk of incident dementia (fully adjusted HR 1.13, 95% CI 1.01–1.27). The same was true for the period of 5 to 10 years follow-up (HR 1.14, 95% CI 1.01–1.29). In contrast, we did not find any relationship in the third follow-up period in the fully adjusted model (HR 0.83, 95% CI 0.66–1.04)

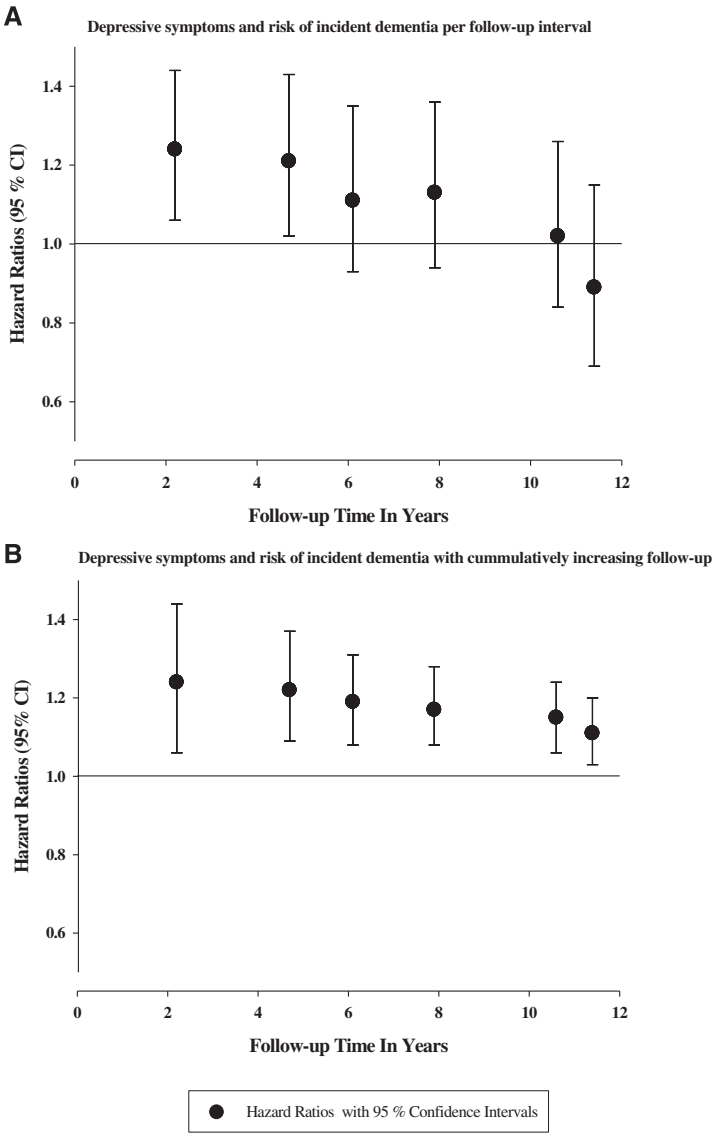

Fig. 1. Adjusted hazard ratios for risk of dementia at different time points in depressed individuals (N = 4393). Depressive symptoms and risk of incident dementia-effect estimates per 100 consecutive incident dementia cases. (A) Depressive symptoms and risk of incident dementia per follow-up interval. (B) Depressive symptoms and risk of incident dementia with cumulatively increasing follow-up. Total number of dementia cases (n = 582) were split in subgroups of 100 patients according to incidence of dementia. Hazard ratios for these 100 cases were calculated. Mean follow-up time for each subgroup of 100 additional cases is used to plot the graphs. The circles represent the hazard ratios and the lines represent the 95% confidence intervals. CI, confidence interval.

Table 2
Clinically relevant depressive symptoms and risk of incident dementia—overall and gender split analysis ($N = 4393$)

	Follow-up time in years			
Depressive symptoms	Overall follow-up	0–5 years	5–10 years	10–13.7 years
Cases/*n*	582/4393	222/4393	238/3529	122/2554
Depressive score, (per SD)*	1.11 (1.03–1.20)	1.19 (1.07–1.33)	1.15 (1.03–1.29)	0.84 (0.68–1.05)
Depressive score, (per SD)†	1.08 (1.00–1.17)	1.13 (1.01–1.27)	1.14 (1.01–1.29)	0.83 (0.66–1.04)
Males ($n = 1794$)				
Cases/*n*	176/1794	62/1794	71/1416	43/985
Depressive score, (per SD)*	1.20 (1.02–1.41)	1.51 (1.23–1.86)	1.20 (0.91–1.58)	0.40 (0.17–0.93)
Depressive score, (per SD)†	1.04 (0.88–1.24)	1.31 (1.04–1.66)	1.06 (0.79–1.41)	0.38 (0.16–0.93)
Females ($n = 2599$)				
Cases/*n*	406/2599	160/2599	167/2113	79/1569
Depressive score, (per SD)*	1.09 (1.01–1.19)	1.12 (0.99–1.27)	1.14 (1.01–1.30)	0.94 (0.75–1.18)
Depressive score, (per SD)†	1.09 (1.00–1.18)	1.10 (0.96–1.26)	1.15 (1.01–1.31)	0.92 (0.73–1.15)

Abbreviation: SD, standard deviation.

NOTE. Cases refer to incident dementia cases. Data are presented as hazard ratio (95% confidence interval). Depression is taken as a continuous standardized variable using the Center for Epidemiologic Studies Depression Scale scores.

*Age and gender adjusted.

†Additionally adjusted for smoking, education, hypertension, diabetes, prevalent stroke, Mini-Mental State Examination score, and antidepressant use.

(Table 2). After additional adjustments for marital status, *APOE*-ε4 carrier status (*APOE* ε2/ε4, *APOE* ε3/ε4 or *APOE* ε4/ε4), cognitive complaints at baseline, and use of psychotropic drug use, our results remained unchanged.

In a secondary gender split analysis, we found a more pronounced effect in men than in women, although the overall pattern in both sexes was similar to the main analysis (Table 2). However, in depressed men, the risk of dementia in the 10- to 13.7-year interval was reduced by 60% (HR 0.38, 95% CI 0.16–0.93). The interaction for gender was statistically significant ($P < .001$). Interaction for age was not significant; hence, it is not shown.

Repeating all analyses using Alzheimer's disease as the outcome yielded similar results and patterns (Supplementary Table 1). Results using depressive symptoms as a dichotomized variable also showed a similar pattern as our main analysis (Supplementary Table 2).

In the sensitivity analysis, after excluding individuals who had been screened positive for clinically relevant depressive symptoms 4 years before baseline, the presence of depressive symptoms showed a 16 % higher risk of incident dementia in the 0- to 5-year follow-up (HR 1.16, 95% CI 1.02–1.32). Using depressive symptoms assessed at the 2002 to 2004 examination round, we found a similar pattern of results as the main analysis (data not shown).

4. Discussion

We found that persons with depressive symptoms had a higher risk of incident dementia, including Alzheimer's disease. These associations were strongest for short follow-up time and they attenuated with incrementally longer follow-up periods. Furthermore, the association was more pronounced in men than in women.

Prevalence of depressive symptoms is relatively low in this cohort. However, it falls within the variable range of 2.8% to 35% reported in a review of depressive symptoms in the elderly [26]. In addition, the Survey of Health, Aging and Retirement in Europe (SHARE) study has reported the Netherlands to be one of the lower depression prevalence countries in Europe [27].

Strengths of the study include the large population-based cohort followed for over 13 years. However, certain methodological considerations need to be mentioned. First, we included clinically relevant depressive symptoms (assessed by CES-D) as the determinant rather than diagnosed depression. Therefore, we cannot be certain about the generalizability of our results to clinical depressive syndromes as well. Second, some residual confounding due to unknown or unmeasured confounders such as physical activity and diet cannot be completely ruled out.

Third, there is a possibility that some selection through depressive symptoms and/or cognitive function in the previous examination round may have influenced the results. Fourth, depressive symptoms were related to death of participants in the first 10 years of follow-up; therefore, there is a possibility of some selection by death in the 10- to 13.7-year interval.

There are a few possible explanations for our observation that the association of depression with incident dementia was strongest with short follow-up and attenuated with longer follow-up. First, late-onset depressive symptoms preceding dementia could be merely a reactive phenomenon. It is possible that depression is a psychological response to the ongoing cognitive decline [28]. Second, late-onset depressive symptoms may represent a prodrome of dementia. The prodrome can be defined as a predementia syndrome in which the underlying subclinical dementing process manifests itself by depression or altered behavior, thus marking the onset of clinical dementia in the near future. Whereas a depression in adult life or a lifetime history of depression would be considered a risk factor for dementia, a very recent history of late-onset depressive

symptoms may be an early clinical manifestation of the underlying neurodegenerative condition. This implies that depression and dementia are the result of a common underlying process or processes, but that symptoms of depression manifest earlier than dementia. It has been shown that patients experiencing cognitive decline together with late-onset depression develop dementia within a few years after the onset of depression [28]. This prodromal hypothesis is in line with recent findings from large cohort studies suggesting that late-onset depression is a prodrome of dementia onset [21,29]. Studies have reported a positive association between depression and dementia over a shorter follow-up period of at most 5 years [4–7]. In a subset of the Rotterdam Study, we previously reported a null association between depressive symptoms and dementia; however, differences in sample size, follow-up, age, and cognition at baseline could explain the difference in results [30].

Third, depression may only increase the risk of dementia over a short-term period. Some individuals with depressive symptoms may be more vulnerable for incident dementia because of certain genetic or environmental risk factors, although a shared etiology would typically convey a constant risk over time [3,31]. Several potential biological mechanisms could be a common intermediate between depression and dementia, such as hippocampal atrophy [2]. It has also been shown that depressed individuals have low levels of adrenaline [32] and serotonin [33], and deficits of these monoamines are also associated with increased severity of dementia.

The underlying neurodegenerative process might get accelerated because of depression by the activation of hippocampal pituitary axis leading to increased cortisol levels, hence precipitating dementia [28]. We also found that the association of depressive symptoms and dementia in the short-term period was stronger in men than in women. This finding concurs with two prospective cohort studies that reported a stronger association of depressive symptoms and risk of incident dementia in men compared with women [34,35]. There is limited literature available in this context, and further epidemiological and etiological studies are highly recommended to better understand the gender differences in the association between depression and dementia.

We observed a protective association between depression and dementia in the 10- to 13.7-year interval in men. However, because this period has a fewer number of cases ($n = 43$), the estimates may not be very precise. It is also possible that reduced effect estimates are a result of other competing risks in this period and deaths occurring due to other causes such as cardiovascular causes or cancers. In addition, we speculate that perhaps depressed persons who survive 10 years or more become resilient against subsequent dementia.

In conclusion, late-onset depressive symptoms represent a part of the prodromal stage of dementia rather than being a risk factor for dementia. Depressive symptoms posed a much higher risk of incident dementia in men compared with women in a short follow-up.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature using PubMed for articles describing depression and risk of dementia. We cite several studies showing a link between late-life depression and risk of incident dementia. In our study, we investigated the association of late-onset depression and dementia in short- and long-term follow-up to disentangle whether late-onset depression is a risk factor or a prodrome of dementia.
2. Interpretation: We found that depressive symptoms predict incident dementia in the short term, but not in the long term, especially in men. This suggests that late-onset depression is a prodrome of dementia rather than a risk factor.
3. Future directions: Future studies should unravel the biological mechanisms underlying this association. If depression is indeed a prodrome of dementia, then this may aid to identify, at an early stage, persons at high risk of clinical dementia. Another focus should be on unraveling the differences between males and females regarding the association of depression and dementia.

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Supplementary Table 1
Clinically relevant depressive symptoms and risk of Alzheimer's disease ($N = 4393$)

	Follow-up time in years			
Depressive symptoms	Overall follow–up	0–5 years	5–10 years	10–13.7 years
Cases/*n*	489/4393	194/4393	199/3529	96/2554
Depressive score, (per SD)*	1.08 (0.99–1.17)	1.16 (1.03–1.31)	1.11 (0.98–1.27)	0.79 (0.61–1.03)
Depressive score, (per SD)†	1.05 (0.96–1.15)	1.11 (0.98–1.26)	1.09 (0.95–1.25)	0.79 (0.60–1.04)
Males ($n = 1794$)				
Cases/*n*	131/1794	43/1794	55/1416	33/985
Depressive score, (per SD)*	1.16 (0.95–1.41)	1.38 (1.04–1.82)	1.30 (0.98–1.73)	0.43 (0.17–1.06)
Depressive score, (per SD)†	1.02 (0.83–1.25)	1.16 (0.83–1.60)	1.13 (0.83–1.53)	0.48 (0.19–1.22)
Females ($n = 2599$)				
Cases/*n*	358/2599	151/2599	144/2113	63/1569
Depressive score, (per SD)*	1.07 (0.97–1.17)	1.13 (0.99–1.28)	1.08 (0.93–1.24)	1.08 (0.93–1.24)
Depressive score, (per SD)†	1.06 (0.96–1.16)	1.11 (0.97–1.27)	1.07 (0.92–1.25)	1.07 (0.92–1.25)

Abbreviation: SD, standard deviation.

NOTE. Cases refer to incident dementia cases. Data are presented as hazard ratio (95% confidence interval). Depression is taken as a continuous standardized variable using the Center for Epidemiologic Studies Depression Scale scores.

*Age and gender adjusted.

†Additionally adjusted for smoking, education, hypertension, diabetes, prevalent stroke, Mini-Mental State Examination score, and antidepressant use.

Supplementary Table 2
Clinically relevant depressive symptoms and risk of incident dementia ($N = 4393$)

	Follow-up time in years			
Depressive symptoms	Overall follow-up	0–5 years	5–10 years	10–13.7 years
Cases/*n*	582/4393	222/4393	238/3529	122/2554
Depressive symptoms*	1.46 (1.13–1.89)	1.43 (0.96–2.15)	1.94 (1.33–2.82)	0.74 (0.34–1.59)
Depressive symptoms†	1.38 (1.06–1.80)	1.26 (0.83–1.91)	1.94 (1.31–2.87)	0.74 (0.34–1.60)

NOTE. Cases refer to incident dementia cases. Data are presented as hazard ratio (95% confidence interval). Depression is used as dichotomized variable (cutoff Center for Epidemiologic Studies Depression Scale score ≥ 16 taken as positive for depressive symptoms).

*Age and gender adjusted.

†Additionally adjusted for smoking, education, hypertension, diabetes, prevalent stroke, Mini-Mental State Examination score, and antidepressant use.