10-year trajectories of depressive symptoms and risk of dementia: a population-based study

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Summary
Background Late-life depressive symptoms have been extensively studied for their relationship with incident dementia, but have been typically assessed at a single timepoint. Such an approach neglects the course of depression, which, given its remitting and relapsing nature, might provide further insights into the complex association of depression with dementia. We therefore repeatedly measured depressive symptoms in a population of adults over a decade to study the subsequent risk of dementia.

Methods Our study was embedded in the Rotterdam Study, a population-based study of adults aged 55 years or older in Rotterdam (Netherlands), ongoing since 1990. The cohort is monitored continuously for major events by data linkage between the study database and general practitioners. We examined a cohort of participants who were free from dementia, but had data for depressive symptoms from at least one examination round in 1993–95, 1997–99, or 2002–04. We assessed depressive symptoms with the validated Dutch version of the Center for Epidemiology Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale-Depression. We used these data to identify 11-year trajectories of depressive symptoms by latent class trajectory modelling. We screened participants for dementia at each examination round and followed up participants for 10 years for incident dementia by latent trajectory from the third examination round to 2014. We calculated hazard ratios (HR) for dementia by assigned trajectory using two Cox proportional hazards models (model 1 adjusted for age and sex only, and model 2 adjusted additionally for APOEε4 carrier status, educational level, body-mass index, smoking, alcohol consumption, cognitive score, use of antidepressants, and prevalent disease status at baseline). We repeated the analyses censoring for incident stroke, restricting to Alzheimer’s disease as an outcome, and accounting for mortality as a competing risk for dementia.

Findings From 1993–2004, we obtained data for depressive symptoms from at least one examination round for 3325 participants (median age: 74·88 years [IQR 70·62–80·06], 1995 [60%] women). We identified five trajectories of depressive symptoms in these 3325 individuals, characterised by maintained low CES-D scores (low; 2441 [73%]); moderately high starting scores but then remitting (decreasing; 369 [11%]); low starting scores, increasing, then remitting (remitting; 170 [5%]); low starting scores that steadily increased (increasing; 255 [8%]); and maintained high scores (high; 90 [3%]). During 26 330 person-years, 434 participants developed incident dementia. Only the trajectory with increasing depressive symptoms was associated with a higher risk of dementia compared with the low depressive symptom trajectory, using model 2 (HR 1·42, 95% CI 1·05–1·94; p=0·024). Additionally, only the increasing trajectory was associated with a higher risk of dementia compared with the low trajectory after censoring for incident stroke (1·58, 1·15–2·16; p=0·0041), restricting to Alzheimer’s disease as an outcome (1·44, 1·03–2·02; p=0·034), and accounting for mortality as a competing risk (1·45, 1·06–1·97; p=0·019).

Interpretation Risk of dementia differed with different courses of depression, which could not be captured by a single assessment of depressive symptoms. The higher risk of dementia only in the increasing trajectory suggests depression might be a prodrome of dementia.

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Introduction Clinical depression, particularly clinically relevant depressive symptoms, are not only highly prevalent in dementia but also highly predictive of incident dementia.1 The course of depression and depressive symptoms over a lifetime varies across individuals;2 some might have clinically relevant depressive symptoms only transiently, followed by full remission, others might have remitting and relapsing depression, and some might be chronically depressed. Such different courses might reflect different causes, and might predict dementia risk differently. For instance, remitting depressive symptoms as a physiological response to an adverse life event might have a different effect on the risk of dementia compared with depression with a more biological basis, such as pathological changes in the brain, or dysregulation of neurotransmitters. Studies assessing depressive symptoms at several timepoints are scarce,3,4 but show how repeated measures of depression can be useful to disentangle the complex association between depression and dementia. Nevertheless, most existing studies of the association of depression and dementia have assessed depression only once, which...
Research in context

Evidence before this study
Previous research has typically examined the association of depression assessed at a single timepoint in relation to the risk of dementia. However, depression has a remitting and relapsing course, therefore this approach is not suited to study long-term health outcomes. We undertook a systematic search on Dec 10, 2014, with the MEDLINE database and the search terms (“depressive symptoms”, “depression”, “trajectories of depression”, or “trajectories of depressive symptoms”), and (“dementia” and “trajectories”). We identified additional publications from citations in the identified articles. We did not find any articles that studied the course of depression in relation to the risk of dementia. The relevant literature largely focused on depression or clinically relevant depressive symptoms assessed only once.

Added value of this study
By leveraging repeated measures of depressive symptoms over an 11-year period, our study is the first to our knowledge to assess the course of depression in relation to risk of dementia. In this population-based study we showed differential risks of dementia associated with different trajectories of depressive symptoms, which could not be captured by a single assessment of depression. Furthermore, by repeatedly measuring depressive symptoms we noted the appearance and steady increase of depressive symptoms several years before the clinical diagnosis of dementia, probably as part of the dementia prodrome. Importantly, high depressive symptoms at a single timepoint followed by remission did not seem to have any lasting influence, but depressive symptoms that kept on increasing were significantly associated with the risk of developing dementia. Findings were consistent after adjusting for pertinent covariates, including sociodemographic characteristics, general health, cognition, APOEε4 carrier status, comorbidities, and use of antidepressants.

Implications of all the available evidence
Depressive symptoms that increase over time are predictive of dementia. By contrast, high depressive symptoms at a single timepoint are less likely to be linked to dementia. Trajectories of depression therefore provide better information about individuals with a higher risk of developing dementia.

Methods

Study design and participants
Our study was embedded in the Rotterdam Study, a population-based study of adults aged 55 years or older in the Netherlands, ongoing since 1990. Follow-up examinations including home interviews and physical examinations at a research centre take place every 3–4 years. Additionally, the cohort is continuously monitored for all major events by data linkage between the study database and participants’ general practitioners.9 The Rotterdam Study is approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Netherlands Ministry of Health, Welfare and Sports. Written informed consent was obtained from all participants.

Our study included participants who did not have dementia but had data for depressive symptoms at one or more of three examination rounds in 1993–95, 1997–99, and 2002–04 (appendix). We used these data to identify 11-year trajectories of depressive symptoms. We followed up participants for incident dementia from the third examination round to Jan 1, 2014. This study design enabled leveraging three assessments of depressive symptoms for a reliable trajectory classification, while ensuring a sufficient number of dementia cases during follow-up to calculate hazard ratios (HRs) for incident dementia. Although dementia follow-up data were available from 1993 onward in the Rotterdam Study, survival analyses were not done from this year, because the concomitant events of incident dementia and deaths occurring during the same period when depression assessments were made could have biased the trajectory classification and complicated the interpretation of risks associated with each trajectory.

Assessment of depressive symptoms
In the first examination round, we measured depressive symptoms using the validated Dutch version of the Center for Epidemiology Depression Scale (CES-D)10 for half of the participants invited at random, and the Hospital Anxiety and Depression Scale-Depression (HADS-D)11 for the other randomly invited half. For all subsequent rounds, CES-D was used. The CES-D comprises 20 items, each with a possible score of 0–3, and the score ranges from 0–60.12 HADS-D comprises seven items each with a possible score of 0–3, and the score ranges from 0–21.13 Both scales have been validated for assessment of depression and can indicate clinically relevant depressive symptoms. We checked for evidence of whether this introduces information bias but we noted...
the same percentage of screen positives (10%) using validated, predefined cutoffs. Depressive symptom scores were weighted for missing items if these did not exceed 25%; scores with missing values exceeding 25% were excluded. We then used the scores as a standardised continuous variable for analyses.

Assessment of dementia
We screened participants for dementia at each examination round with a three-step protocol. First, screening was done with the Mini Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level. Second, participants who screened as positive (ie, 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). Participants who were suspected of having dementia had further neuropsychological testing if necessary. Third, a consensus panel led by a neurologist (PKJ) decided on the final diagnosis in accordance with the standard criteria used in the DSM-III-revised criteria for dementia and criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association for Alzheimer’s disease. Additionally, the total cohort was continuously monitored for dementia through computerised linkage between the study database and digital medical records from participants’ general practitioners (GPs) and the Regional Institute for Outpatient Mental Health Care. This data-linkage system is highly efficient, and the possibility of underestimation of cases is low because the GPs receive all medical information about their patients if they contact any medical caregiver or professional, including specialists. We calculated the potential and observed person-years to determine the completeness of dementia follow-up, which was 93·5% complete until Jan 1, 2014.

Assessment of covariates
We assessed covariates between 2002 and 2004. The following measures were considered pertinent covariates because they are associated with depression and are independent risk factors for dementia: age; sex; APOEε4 carrier status (non-carriers of the ε4 allele, or carriers of one or two ε4 alleles); educational level (primary only [ie, 8 years of education] or higher than primary education); body-mass index (BMI; weight in kg/height in m²); smoking habits (never, past, or currently smoking); alcohol consumption (calculated as amount of alcohol in g/day); general cognition (MMSE score); use of antidepressants (Anatomical Therapeutic Chemical Classification System code N06, information obtained by interview); prevalent hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensives assessed by interview and pharmacy records); type 2 diabetes (diagnosed as fasting blood glucose ≥7·0 mmol/L, or use of antidiabetic medicines assessed by interview and pharmacy records); and previous myocardial infarction and stroke (determined by reported events on interview and confirmed by medical records).

Statistical analysis
We used latent class trajectory models to identify trajectories of depressive symptoms over time. This is a specialised form of finite mixture modelling, and is designed to identify latent classes of individuals following similar progressions of a determinant over time or with age. Our models used second-order polynomials. For every participant, we calculated the posterior probabilities for each trajectory taking into account their age (at the first round of depressive symptoms assessment from 1993 to 1995), sex, and educational level, and we assigned participants post hoc to the trajectory with the highest probability. We estimated the best-fitting number of trajectories based on a minimum Bayesian Information Criterion, while maintaining the posterior probabilities by class (≥0·70) and class size (≥2% of the population). To facilitate interpretability, we assigned labels to the trajectories on the basis of their modelled graphic patterns. As a check of how the observed trajectories of depressive symptoms of individual participants aligned with the identified trajectories in our final model, and to visually assess missing data patterns, we plotted the individual depressive symptoms values by the most likely trajectory, age, and visit. To compare covariates across identified trajectories, we used ANOVA for continuous and logistic regression for categorical variables.

To assess the risk of dementia, for the survival model time zero was the examination date of the third examination round (2002–04; appendix). Time to event (dementia) was defined as follows: participants were followed up from the date of start of the survival analyses (2002–04) and censored on the date of dementia, death, or being lost to follow-up. If participants were lost to follow-up, they were censored on the date that they were last seen or contacted.

We computed HR for dementia by assigned trajectory using Cox proportional hazards models. We assessed adherence to proportional hazards assumption by plotting smoothed Schoenfeld residuals against time; no violations of the assumption were identified. Given the strongly increased risk of dementia after stroke (25% to 33%), we also investigated the risk of dementia across trajectories after censoring for incident strokes occurring during follow-up (excluding all participants with prevalent stroke). Additionally, we investigated the risk of Alzheimer’s disease across trajectories. For these analyses, the outcome was Alzheimer’s disease instead of all-cause dementia (or non-Alzheimer’s dementia). Follow-up time was the time from third examination round (2002–04) until development of Alzheimer’s disease, death, or being lost to follow-up. Non-Alzheimer’s dementias were treated as censored.
We also stratified the follow-up time into a short-term stratum of 0–3 years and a long-term stratum of more than 3 years, to explore the possibility of reverse causality and the role of timing in any estimated associations. Finally, we assessed the influence of death as a competing risk for dementia in our interpretations by doing competing risk analyses. Because chronic high depression is associated with excess mortality, if individuals with most severe depression die before developing dementia, the incidence of dementia will appear higher in participants who are less or not depressed. The competing risk analysis modelled the cumulative incidence of dementia in the presence of mortality—ie, death events were not censored. For these analyses, the subdistribution hazard model was considered.

For all analyses, we fitted two models: model 1 that was adjusted for age and sex only; and model 2 that was additionally adjusted for APOEε4 carrier status, educational level, BMI, smoking, alcohol consumption, cognitive score, use of antidepressants, and prevalent disease status at baseline including hypertension, type 2 diabetes, myocardial infarction, and stroke (where applicable). To assess the specific influence of antidepressants on these associations, we also created a subsequent model that included all covariates except antidepressant use.

Although latent class modelling served as a useful data-reduction tool for understanding the general patterns of depressive symptoms in our population, individual membership in a class or trajectory is probabilistic. To assess the robustness of trajectory classification and the associated risk of dementia across trajectories, we did the following sensitivity analysis: we recalculated trajectories in a larger dataset of all participants with depressive symptom data available at the three examination rounds (prevalent dementia cases excluded 1993–95). We used these trajectory classifications to investigate the subsequent 12-year risk of dementia by trajectory in the participants who attended the examination round in 2002–04, as for the main analysis. We did all analyses with Stata software version 13 and R version 3.1.2.

**Role of the funding source**

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Table 1: Baseline characteristics of the study population**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Low trajectory (n=2441)</th>
<th>Decreasing trajectory (n=359)</th>
<th>Remitting trajectory (n=170)</th>
<th>Increasing trajectory (n=255)</th>
<th>High trajectory (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Women</td>
<td>74.1 (70.2–79.0)</td>
<td>76.1 (71.6–82.1)*</td>
<td>77.7 (73.5–82.3)*</td>
<td>76.5 (71.2–81.6)*</td>
<td>79.0 (73.3–83.2)*</td>
</tr>
<tr>
<td>Men</td>
<td>74.6 (70.2–79.0)</td>
<td>76.1 (71.6–82.1)*</td>
<td>77.7 (73.5–82.3)*</td>
<td>76.5 (71.2–81.6)*</td>
<td>79.0 (73.3–83.2)*</td>
</tr>
<tr>
<td>APOEε4 carrier status</td>
<td>640/2341 (27%)</td>
<td>93/355 (26%)</td>
<td>38/165 (23%)</td>
<td>62/240 (26%)</td>
<td>22/84 (26%)</td>
</tr>
<tr>
<td>Primary education</td>
<td>317/2421 (13%)</td>
<td>74/362 (20%)*</td>
<td>33/169 (20%)</td>
<td>55/249 (22%)</td>
<td>26/88 (29%)*</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>27.4 (4.0)</td>
<td>27.9 (4.5)</td>
<td>27.9 (4.3)</td>
<td>27.3 (4.3)</td>
<td>27.5 (4.7)</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>330/2377 (14%)</td>
<td>50/355 (14%)</td>
<td>28/166 (12%)</td>
<td>47/255 (18%)*</td>
<td>20/89 (22%)*</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.7 (2.0)</td>
<td>27.3 (2.2)*</td>
<td>27.3 (2.1)</td>
<td>27.3 (2.2)*</td>
<td>26.6 (2.5)*</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>12.4 (15.4)</td>
<td>10.2 (15.0)</td>
<td>9.1 (12.2)</td>
<td>8.7 (12.6)*</td>
<td>7.5 (19.8)*</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>62/2124 (3%)</td>
<td>17/135 (5%)</td>
<td>20/147 (14%)</td>
<td>30/244 (13%)</td>
<td>15/81 (18%)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2076/2393 (85%)</td>
<td>320/360 (87%)</td>
<td>150/269 (89%)</td>
<td>226/249 (91%)</td>
<td>79/84 (94%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>401 (16%)</td>
<td>71 (39%)</td>
<td>31 (18%)</td>
<td>51 (20%)</td>
<td>15 (17%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>128 (5%)</td>
<td>23 (6%)*</td>
<td>6 (4%)*</td>
<td>14 (5%)</td>
<td>6 (7%)*</td>
</tr>
<tr>
<td>Stroke</td>
<td>115 (5%)</td>
<td>12 (3%)</td>
<td>5 (3%)</td>
<td>17 (7%)</td>
<td>8 (9%)</td>
</tr>
</tbody>
</table>

Data for participants between 2002 and 2004 stratified by trajectory of depression. Values are median (IQR), counts (%), or means (SD). Denominators are given if they differ from the totals at the top. MMSE=Mini Mental State Examination. *Different from the low trajectory. †Different from the decreasing trajectory. ‡Different from the remitting trajectory.
Results

During the three examination rounds in 1993–95, 1997–99, and 2002–04, data for depressive symptoms were available for 2821, 3136, and 3234 dementia-free participants, respectively. 3325 had depressive symptoms in at least one examination round, 3254 at more than one examination round, and 2612 at all three examination rounds. Of the 3325 participants who had symptoms in at least one examination round, the median age was 74-88 years (IQR 70-62–80-06) and 1995 (60%) were women. The following variables had missing values that were dealt with using multiple imputations with all covariates of interest as predictors: APOEε4 carrier status (4·3%), education (1·1%), BMI (16·4%), smoking (2·5%), alcohol (11·3%), MMSE score (9·7%), antidepressant use (12·7%), hypertension (2·1%), and type 2 diabetes (0·2%).

We identified five distinct trajectories of depressive symptoms in these 3325 individuals (figure 1) characterised by maintaining a low CES-D score throughout the follow-up (low; 2441 [73%]); moderately high starting scores but then remitting (decreasing; 369 [11%]), low starting scores, increasing, then remitting (remitting; 170 [5%]); low starting scores that steadily increased throughout follow-up (increasing; 255 [8%]); and maintained high scores throughout (high; 2441 [73%]). Mean CES-D scores of participants, and numbers of participants with clinically relevant depressive symptoms and DSM-depressive disorders by trajectory, per visit, are in the appendix. Compared with individuals in the other trajectories, the low trajectory was more balanced between the sexes, and participants were likely to be younger and more educated (table 1).

Mean probabilities per trajectory ranged from 0·80 (SD 0·18) to 0·94 (0·12; appendix). Visual assessment of likely to be younger and more educated (table 1).

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Mean probabilities per trajectory ranged from 0·80 (SD 0·18) to 0·94 (0·12; appendix). Visual assessment of individual patterns of observed depressive symptoms, based on the most likely class membership, visit, and age, generally matched the model-based descriptions (appendix). This finding suggested that the model-based patterns of trajectories were unlikely to be influenced by missing data.

During 26 330 person-years, 434 participants developed incident dementia, including 348 Alzheimer’s disease cases, 26 vascular dementia cases, and 60 other dementias (Lewy body, frontotemporal, and Parkinson’s disease dementia). Using the low trajectory as the reference trajectory, we showed that only individuals within the increasing trajectory had a higher risk of dementia using model 2 (HR 1·45, 95% CI 1·02–2·04; p=0·036). Compared with models with inclusion of antidepressant use, we showed that models without inclusion of antidepressant use as a covariate yielded higher effect estimates: decreasing trajectory HR 1·04 (95% CI 0·77–1·40); remitting trajectory 1·24 (0·83–1·85); increasing trajectory 1·52 (1·12–2·06); and high trajectory 1·28 (0·80–2·07)—ie, adjustment for antidepressant use had an attenuating effect on the associations.

When trajectories of depressive symptoms were calculated in the sensitivity analysis including all short-term follow-up of 0–3 years, none of the trajectories showed a significant risk of dementia (table 5). However, after exclusion of the first 3 years of follow-up, only the increasing trajectory was associated with a higher risk of dementia compared with the low trajectory after exclusion of the first 3 years of follow-up, only the increasing trajectory was associated with a higher risk of dementia (HR 1·45, 95% CI 1·02–2·04; p=0·036).

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participants with depressive symptom data available for the three examination rounds, the identified trajectories were largely similar to those in the main analyses. The subsequent risks of dementia by trajectory with this classification also yielded similar pattern of results as the main analyses (data not shown). For this analysis, the numbers of incident dementia cases and number of deaths per trajectory that occurred before the survival analyses (ie, before 2002–04) are in the appendix.

**Discussion**

In our study of community-dwelling older adults, we identified five distinct trajectories of depressive symptoms, characterised by low, decreasing, remitting, increasing, and high depressive symptoms. The trajectory characterised by increasing depressive symptoms (ie, low CES-D scores that steadily increased throughout follow-up) was consistently associated with a higher risk of developing dementia. The trajectory typical of remitting depression (ie, low starting CES-D scores that increased, then remitted through follow-up) was not associated with a higher risk of dementia.

Compared with individuals in the low depressive symptoms trajectory, individuals in all other trajectories were older and more often women, whereas current smoking, alcohol consumption, and hypertension were more prevalent in the increasing and the high depressive symptoms trajectories. This finding is in line with those from previous studies. In our analyses, adjustment for age, APOE4, baseline cognitive score, prevalent stroke, and antidepressant use affected the associations between trajectories of depressive symptoms and dementia. For instance, adjustment for antidepressant use reduced the observed risk by approximately 10% in the high, increasing, and decreasing depressive symptoms trajectories with higher use of antidepressants. This finding agrees with those from previous studies, although the exact underlying mechanisms are still to be identified. Possible mechanisms include impairment of the cognitive-reserve capacity by long-term use of antidepressants, and reduced cholinergic activity due to long-term use, which has been shown to increase β-amyloid concentrations in animal models. Understanding of the relationships between depression, antidepressant use, and dementia is complex and requires other modelling approaches because antidepressants might be prescribed to treat prodromal emotional symptoms of dementia, and the treatment strategies and disease states for both depression and dementia vary over time.

Our study of different trajectories of depressive symptoms over more than a decade predicted the differential risks of dementia associated with each trajectory. This strategy can be useful to distinguish people at risk for dementia more accurately than from a single observation of depression. We noted that individuals with steadily increasing symptoms of depression had a significantly higher incidence of dementia. This finding is consistent with the prodromal hypothesis, which suggests that depressive symptoms in older age possibly represent a prodrome or an early stage of dementia. Indeed, depressive symptoms might appear as a reaction to underlying subclinical cognitive...
impairment, and lie in a continuum between subclinical cognitive impairment and overt dementia. By describing patterns in the course of depressive symptoms in our study, we could show the gradual escalation of depressive symptoms, which started several years before dementia was diagnosed. A study using latent growth curves showed similar depression trajectories to our study and a similar pattern of associations with dementia.

Our findings also augment previous suggestions that depression and dementia might be manifestations of a common cause, where symptoms of depression occur before the onset of clinical dementia. On a molecular level, the biological underpinnings of depression and neurodegenerative diseases overlap considerably, including insufficient defences against antioxidants and neurogenesis, increased apoptosis, and immune system dysregulation. Several potential biological mechanisms or their interplay might account for the observed association. First, vascular disease is implicated in the development of depression, which led to the formulation of the so-called vascular depression hypothesis, and in the development of dementia, including Alzheimer’s disease. Second, findings from some studies suggest that hippocampal atrophy might also give rise to symptoms of depression, besides resulting in cognitive dysfunction. Third, findings from other studies suggest that low serum folate concentrations might be associated with both depression and dementia syndromes. Finally, inflammation has also been suggested as a possible link between depression and cognitive decline.

In our study, although the remitting trajectory had substantially high depressive symptoms over the course of the first few years of follow-up, individuals in this trajectory did not have a higher risk of dementia than those with no depressive symptoms. This finding might suggest that having severe symptoms of depression at one point in time does not have any lasting influence or predict dementia, although we also observed that the estimates for the remitting trajectory suggested a higher risk of dementia during the short term (0–3 years). The remitting trajectory might reflect the causes of heterogeneous depression, including symptoms that represent a normal reaction to adverse life events, as well as a pattern akin to the increasing trajectory except for the time lag between their peaks.

The main strength of our study was to identify the risks of different courses of depression with respect to the development of dementia. By identifying high-risk groups from a population-based perspective, this approach might facilitate effective prevention and early treatment targeted to those at a higher risk. Additionally, the use of depressive symptoms as a continuum enabled the measurement of subtle increases in the depression score—ie, subclinical depression. Other strengths of our study included a population-based setting, large sample size, long follow-up, and robust dementia follow-up. The limitations of our study included that our analyses were fitted on the basis of assigned trajectories, and did not take into account the uncertainty in class membership of each individual, which might mean that the variance estimates from our models are underestimated. However, given the observed symptom patterns in the lasagna plot (figure 1), and that the posterior probabilities of class membership were universally high, and the robustness of our findings for the increasing symptoms trajectory across several analyses, it is unlikely that this would affect the general conclusions. Additionally, since depression is related to a higher risk of mortality, participants with most severe depression might not have been included in our analyses. This selection is probably strongest for the high trajectory. At the same time, results from the sensitivity analyses showed that the incidence of dementia before the start of the at-risk period for dementia was highest in the remitting trajectory, followed by the decreasing and high trajectories, possibly leading to an underestimation of risks in all these groups because of selection. Moreover, since the high depressive symptoms trajectory had fewer participants, inadequate power might explain why the estimates did not reach statistical significance. Finally, some relevant characteristics, such as physical activity and social networking, were not measured in our study; future research trying to understand or account for the observed trajectories and their relationship to dementia will benefit from investigating such characteristics.

In conclusion, different trajectories of depression identified by repeated measures of depressive symptoms were associated with different risks of dementia, with depressive symptoms increasing over an 11-year period associated with the highest subsequent risk of dementia. Future studies are warranted to unravel the biological underpinnings of these associations, and potential for using depression trajectories (as opposed to single assessments) as a screening method to identify older adults at risk of dementia.

Contributors
SSM, MAI, and HT conceived the research question and designed the study. SSM, MAI, HT, FJW, PJK, and AH oversaw the data acquisition. SSM, SAS, and MAI oversaw the analyses and analysed the data. SSM, MAI, HT, SAS, FJW, AH, and PJK interpreted the data. SSM, MAI, SAS, and FJW drafted the report. All authors contributed to the intellectual content, provided critical revisions to the report, and approved the final draft.

Declaration of interests
We declare no competing interests.

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