Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study.

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Manuscript statistics: abstract: 343 words in abstract, 3000 words in text, 36 references, 3 tables and 1 figure, supplemental data (2 Tables, 3 Figures)

Key Points

Question: Does the course of depressive symptoms over adulthood in those who develop dementia differ from those who remain dementia-free?

Findings: Depressive symptoms in late- but not mid-life were associated with increased risk of dementia. Analysis of depressive symptoms spanning 28 years showed them to emerge approximately a decade prior to dementia diagnosis. No substantive differences in depressive symptoms were apparent between those who went on to develop dementia and dementia free persons 12 to 28 years prior to dementia diagnosis.

Meaning: The association between depressive symptoms and dementia in older adults may be primarily due to common causes or depressive symptoms being a feature of the preclinical phase of dementia.

ABSTRACT

Importance Neuropsychiatric symptoms, depressive symptoms in particular, are common in dementia patients but whether depressive symptoms in adulthood increases risk for dementia remains the subject of debate.

Objective To characterize the trajectory of depressive symptoms over 28 years prior to dementia diagnosis in order to determine whether depressive symptoms carry risk for dementia.

Design: Whitehall II cohort study, study recruitment in 1985 and end of follow-up 2015.

Setting General community, United Kingdom.

Participants Up to 10,189 persons (33% women), aged 35-55 years in 1985.

Exposures Depressive symptoms, assessed on 9 occasions between 1985 and 2012 using the General Health Questionnaire (GHQ-30).

Main Outcome(s) and Measure(s) Incidence of dementia, (N=322), between 1985 and 2015.

Results Those reporting depressive symptoms in 1985 (mean follow-up 27 years) did not have significantly increased risk of dementia (Hazard Ratio (HR)=1.21; 95% CI: 0.95, 1.54) in Cox regression adjusted for sociodemographic covariates, health behaviors, and chronic conditions. However, those with depressive symptoms in 2003 (mean follow-up 11 years) had an increased risk (HR=1.72; 95% CI: 1.21, 2.44). Those with chronic/recurring depressive symptoms (≥2 of 3 occasions) in the early study phase (mean follow-up 22 years) did not have excess risk (HR=1.02; 95% CI: 0.72, 1.44) but those with chronic/recurring symptoms in the late phase (mean follow-up 11 years) did have higher risk of dementia (HR=1.67; 95% CI: 1.11, 2.49). Analysis of retrospective depressive trajectories over 28 years, using mixed models and a backward time scale, shows that in those with dementia, differences in depressive symptoms compared to those without dementia became apparent 11 years (difference 0.61, p=0.02) before dementia diagnosis and became over nine times larger at the year of diagnosis (difference 5.81, p<0.001).

Conclusions Depressive symptoms in the early phase of the study corresponding to midlife, even when chronic/recurring, do not increase risk of dementia. Along with our analysis of depressive trajectories over 28 years, these results suggest that depressive symptoms are a prodromal feature of dementia or that the two share common causes. The findings do not support the hypothesis that depressive symptoms increase risk of dementia.

INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, is a progressive disorder. The histopathological hallmarks of AD begin decades prior to its clinical expression;[1,2] a recent study estimated that amyloid beta deposits over a period of more than two decades.[3] The long preclinical phase of dementia has implications for the timing of interventions. There is growing consensus that interventions ought to target the earliest possible phase, perhaps the asymptomatic stage,[4,5] to be effective. The other major implication, which has received less attention to date, is the analytic framework used to identify putative risk factors for dementia. When measured in the years immediately prior to dementia diagnosis, these factors are likely to reflect common causes, the effects of preclinical disease (reverse causation) or prodromal changes rather than risk factors for dementia.

There is considerable research on the association of depression or depressive symptoms with dementia. A meta-analysis published in 2006 suggested that depression is associated with a 2-fold increased risk of AD,[6] but studies covering the same period also conclude that depression may be a prodromal feature of dementia,[7-9] implying no causal effect of depression on dementia. Recent studies using repeat assessments of depressive symptoms have shown increasing symptoms to be associated with risk of dementia.[10,11] In these studies, depression trajectories were assessed over 5 years in one study[10] and over 11 years in the other study,[11] not long enough to cover the preclinical phase of dementia. Furthermore, the analytic strategy did not allow depressive symptoms in the follow-up period for dementia to be examined. Thus, whether depression is a risk factor for dementia or a symptom of an underlying neurodegenerative process could not be determined.

The objective of our study is to characterize trajectories of depressive symptoms starting at dementia diagnosis using a backward timescale over 28 years, and compare them with changes in

depressive symptoms over the same time period in those free from dementia. A secondary objective is to assess whether dementia risk is higher in those with chronic/recurring depressive symptoms in mid- and late-life.

METHODS

Study Design and participants

The Whitehall II study is an ongoing cohort study of 10,308 persons (6,895 men and 3,413 women), aged 35-55 years at study recruitment in 1985.[12] Participants responded to a questionnaire and underwent a structured clinical evaluation, consisting of measures of anthropometry, cardiovascular and metabolic risk factors and diseases. Follow-up assessment including postal questionnaire and clinical examinations have taken place approximately every 5 years. A postal questionnaire only wave was also undertaken in between these waves. Participant consent and research ethics approvals (University College London (UCL) ethics committee) are renewed at each contact; the latest approval was by the Joint UCL/UCLH Committee on the Ethics of Human Research (Committee Alpha), reference number 85/0938.

Depressive symptoms

Depressive symptoms were self-reported on 9 occasions (1985, 1989, 1991, 1997, 2001, 2003, 2006, 2007, 2012) using the 30-item General Health Questionnaire (GHQ-30),[13] a well-established screening questionnaire for non-psychotic psychological distress, largely depression, suitable for use in general population studies. Response options to 30 questions are: not at all, no more than usual, rather more than usual, and much more than usual. The binary scoring method was used (the two least symptomatic answers scoring 0 and the two most symptomatic answers scoring 1), and so the total score ranged from 0 to 30. Scores ≥5 defined caseness, or the presence of depressive symptoms.[14] Depressive symptoms were also assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D)[15] on 3 occasions (2003, 2007, 2012). The CES-D is a 20-item inventory of the National Institute of Mental Health Center for Epidemiological Studies, to

assess frequency and severity of depressive symptoms using a standard cut-off score ≥16. Relative performance within the cohort of GHQ-30 and CES-D against the interviewer-administered revised Clinical Interview Schedule as criterion for detecting a depressive episode were similar; sensitivity and specificity was 78 and 83% for the GHQ-30 and 89 and 86% for the CES-D.[16]

Chronic/recurring GHQ depressive symptoms were defined in two ways: during early phase of follow-up using data from 1985, 1989, and 1991, and late phase using data from 1997, 2001, and 2003.

Dementia

We used comprehensive tracing of electronic health records for dementia ascertainment using three databases: the national hospital episode statistics (HES) database, the Mental Health Services Data Set (MHSDS) and the mortality register. The National Health Service (NHS) in the UK uses in-house codes mapped on to ICD-10 codes for dementia. The NHS provides most of the health care; HES and MHSDS are national databases with information on both in- and out-patient care, with the latter also including data on care in the community. Record linkage until 31st of March 2015 identified 322 cases of dementia, 172 cases were first recorded in the hospitalization register, 142 in the mental health register, and 8 in the mortality register.

The validity of dementia cases in our study is supported by modelling changes in the global cognitive score, composed of tests of memory, reasoning, phonemic and semantic fluency administered to the participants in 1997, 2003, 2007, and 2012.[17] These results show accelerated decline in global cognitive score in the 8-10 years before dementia diagnosis (eFigure 1 in the Supplement), as has been shown in studies that use a “gold-standard” dementia ascertainment procedure.[18]

Covariates (1985, 1991, 1997, 2003)

Socio-demographic factors included age, sex, ethnicity (white, non-white), marital status (married/cohabiting vs. other), education (no formal education, lower secondary school, higher secondary school, university, higher degree), and occupational position, a three level variable related to salary, social status and level of responsibility at work.[12]

Health behaviors included smoking (current-, ex-, and never-smoker), alcohol consumption (categorized as no/occasional, moderate (1-21 (14) alcohol units/week in men (women)), and heavy alcohol consumption (≥21 (14) units/week in men (women)), physical activity (hours/week of moderate or vigorous physical activity) and frequency of fruit and vegetable consumption (once/day, once/day, more often).

Health status included diabetes (fasting glucose ≥ 7.0 mmol/l, a 2-h postload glucose ≥ 11.1 mmol/l, reported doctor-diagnosed diabetes, or use of diabetes medication), clinically assessed cardiovascular disease (CVD) including coronary heart disease (CHD; ICD codes: I20-I25) and stroke (ICD codes: I60-I64), CVD medication, and antidepressant use.

Statistical analysis

Associations between GHQ-30 caseness and participant characteristics in 1985 and 2003 were examined using Student's t-test and Chi-squared test. Two sets of analyses were performed, described below. As there were no sex differences in effect estimates (all p for interaction between 0.13 and 0.98), men and women were combined in the analyses.

Depressive symptoms & incidence of dementia

The association of GHQ-30 caseness and incidence of dementia was modelled using Cox regression; participants were censored at date of record of dementia, death (to account for competing risk of mortality), or March 31st 2015, whichever came first. These analyses were first

undertaken using GHQ-30 (and covariates) drawn from 1985 and repeated using data from 1991, 1997, and 2003, mean follow-up was 26.6, 21.7, 16.3, and 11.1 years, respectively. We also examined the association of CES-D caseness in 2003 and incidence of dementia. All analyses were first adjusted for sociodemographic measures (Model 1), then also for health behaviors (Model 2) and finally for health covariates (Model 3).

We then examined the association of chronic/recurring depressive symptoms (never, once, ≥2 times) over the "early" study period (1985, 1989, 1991) and late study period (1997, 2001, 2003) with incidence of dementia; covariates in these analyses were drawn from 1991 and 2003, respectively. Follow-up for dementia began in 1991 for early phase and 2003 for late phase depressive symptoms.

Retrospective analysis of 28-year depressive symptoms trajectory

Trajectories of GHQ-30 depressive scores (range 0 to 30) over 28 years were modelled using a backward timescale such that Year 0 (index date) was year of dementia for dementia cases, year of death for those who died during the follow-up, and March 31st 2015 (end of follow-up) for all others. GHQ-30 score in each of the 28 years (Year 0 to Year -28) was modelled using mixed effects models with the intercept and slope as random effects.[18] Dementia (coded as 1 or 0) and its interaction with slope terms (time, time^2, time^3, to allow for non-linear change) were added to the model in order to test for differences in GHQ-30 trajectories between those with dementia and all others. This modelling strategy implies that Year 0 (the index date) was the intercept in the analysis and the beta associated with the dementia term yielded the difference in GHQ-30 score between those with and without dementia diagnosis. We examined whether the terms dementia*time, dementia*time^2, and dementia*time^3 improved fit of the model using the Wald test. Analyses were adjusted for age at year 0, sex, ethnicity, education, year of birth (5-year categories), and time-dependent occupational position, and marital status. These analyses on

GHQ-30 trajectories were repeated using the CES-D score (range 0-60) within a 12-year time window prior to dementia diagnosis.

Analyses were undertaken using STATA 14 for analysis. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Of the 10,308 participants recruited to the study, data on GHQ-30 were available on 10,189 participants in 1985 and 6,728 participants in 2003; study design in flow chart eFigure 2. Of the 3,461 participants lost over this period, 15.3% had died and 0.4% had a dementia diagnosis before 2003. Those without data at the 2003 assessment were more likely to be older (44.9 vs. 44.7 years in 1985, p=0.04), to be women (41.1 vs. 29.4%, p<0.001), and not to have a university degree (79.6 vs. 70.9%, p<0.001). Cases of dementia accrued mainly between 1995 and 2015, with 73% of cases recorded in the last five years of follow-up. Increasing age (Hazard Ratio (HR) for 1 year greater age at study baseline associated with a 1.21; 95% Confidence Interval (CI): 1.19, 1.24), female sex (HR: 1.58; 1.27, 1.96), and education less than secondary school diploma (HR: 1.76; 1.41, 2.19) were associated with higher risk of dementia. Table 1 shows sample characteristics of participants in 1985 and 2003 as a function of GHQ-30 caseness.

Table 2 shows that the association of GHQ-30 caseness in 1985, 1991, 1997, and 2003 with incidence of dementia was only evident for the 2003 measure of depressive symptoms (HR=1.72; 95% CI: 1.21, 2.44, Model 3). These analyses are based on maximum available data although analysis on those with depressive symptoms data at all measures yielded similar results (HRs of 1.14 (0.79, 1.63), 0.93 (0.60, 1.44), 1.40 (0.93, 2.09), and 1.86 (1.27, 2.73) with GHQ-30 caseness measures in 1985, 1991, 1997, and 2003, respectively; N dementia=146, N total=5783). Table 2 also shows that in fully adjusted analyses, CES-D caseness was associated with higher risk of

dementia (HR=2.28; 95% CI: 1.53, 3.39), with the mean follow-up being 11.1 years. Further analysis showed associations of dementia with late-life (mean age 70 years) but not midlife (mean age 50 years) GHQ-30 depressive symptoms (e Table1).

Those with chronic/recurring GHQ-30 depressive symptoms (≥ 2 times) in the early phase of the study (1985, 1989, 1991) did not have higher risk of dementia (Model 3, HR=1.02; 95% CI: 0.72, 1.44), Table 3. However, those with chronic/recurring depressive symptoms (≥ 2 times) over the later waves of the study (1997, 2001, 2003) had higher risk of dementia (Model 3, HR=1.67; 95% CI 1.11, 2.49).

The trajectory of GHQ-30 depressive symptoms, modelled as a continuous variable, over 28 years was different ($p<0.001$) in those with dementia compared to all non-demented participants (Figure 1), the differences in GHQ-30 score between these two groups are shown in eTable 2. These results showed an accelerated increase in depressive symptoms in the decade prior to dementia diagnosis. CESD score trajectory, modelled up to 12 years before dementia diagnosis, also showed an increase in depressive symptoms in the years prior to dementia diagnosis (Figure 1, eTable 2). The robustness of the shape of the depressive symptoms trajectory was confirmed in analysis using cubic regression splines (eFigure 3).

DISCUSSION

In this study of up to 10,189 men and women, depressive symptoms in late- but not mid-life were associated with higher risk of dementia. In effect this association was evident only when depressive symptoms were measured in the decade preceding dementia diagnosis. Even chronic/recurring midlife depressive symptoms, assessed in the early years of the study, were not associated with increased risk of dementia. The retrospective trajectory of depressive symptoms over 28 years show the emergence of depressive symptoms a decade before dementia diagnosis,

differences that went on to amplify over nine times at dementia diagnosis. Taken together, these findings are consistent with the hypothesis that depressive symptoms are a prodromal feature of dementia or that the two share common causes. Thus, our findings do not support the hypothesis that depressive symptoms increase risk of dementia.

In up to 50% of people with AD or dementia, depression is comorbid.[19,20] At older ages, markers of AD pathology[21] and cognitive impairement[22] have been shown to be associated with subsequent depressive symptoms, and the presence of depressive symptoms with subsequent accelerated cognitive decline.[23] It has been hypothesized that depression increases risk of dementia through hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis,[24] prolonged exposure to glucocorticoids in depressed persons would lead to hippocampal atrophy and development of dementia.[25] However, there is limited support for this hypothesis in relation to hippocampal and amygdalar volume,[26] or other neuropathologic markers.[23]

Data from meta-analysis of prospective studies find depressive symptoms in late life to be associated with approximately a two-fold increase in risk of dementia.[6,27] Nonetheless, these findings are compatible with several alternative explanations: a causal effect of depressive symptoms, depression being a prodromal feature, and common causes. In order to test the first of these explanations, studies have used long follow-ups, 17[28] and 24.7[29] in recent years. It has been suggested that severe[30,31] or repeated depressive episodes[32] carry risk although our findings do not support this hypothesis. The analytical approach in these studies is time to event analysis, such as Cox regression where even in studies with very long “mean” follow-up, dementia occurring in the first few years of follow-up are likely to influence estimates of associations with depressive symptoms. Furthermore, the remitting, and relapsing nature of depressive symptoms is not accounted for in such analyses. Recent use of a two-step design where latent class trajectory models on repeat data on depression are used to categorize individuals and then time to event

analysis for assessment of risk of dementia shows higher risk of dementia in those with increasing levels of depression.[10,11] Even with this design depressive symptoms in the follow-up for dementia are not taken into account in Cox regression, a limitation addressed in our analysis of the 28-year trajectory of depressive symptoms which models them over the entire follow-up.

The need to assess risk of dementia associated with earlier-life depressive symptoms, before 60 years of age, was emphasized in a recent review.[20] The evidence from these studies is inconclusive as studies show no association with early-life depression,[33] and when they do the use of a one-item measure of depressive symptoms,[34] self-report of previous depression,[35] or associations seen only in men,[36] do not allow firm conclusions to be drawn. Our results with depressive symptoms assessed once (Table 2), 3 times before age 60 (Table 3), or at age 50 (eTable 1) provide no robust evidence of increased risk of dementia. A complementary analytic framework, reflected in our analysis of depressive trajectories over 28 years, up to the year of dementia diagnosis is novel and suggests that a rapid increase in depressive symptoms over ten years before dementia diagnosis may be the primary explanation for the association of depressive symptoms and dementia at older ages. One previous study has used a similar analytic approach in a cohort of adults 65 years and older followed for 14 years to assess prodromal changes in AD and showed the emergence of depressive symptoms 8 years before diagnosis.[18]

Besides the prodromal explanation, it is possible that risk factors common to both depression and dementia explain the observed association between these conditions. Impairment in memory, sleep disturbances, and impaired social functioning are common to both conditions and common pathophysiological pathways such as neurodegeneration, inflammation, vascular risk factors, the HPA axis dysregulation may well explain their association. Irrespective of the nature of the association, the co-morbidity of depressive symptoms and dementia is well established and needs to be taken into consideration in the care of patients with cognitive impairment or

dementia. For now, it is important to determine whether treatment for depression improves cognitive functioning.

Our findings need to be considered in light of the study strengths and limitations. The major strength of our study is the use of data on depressive symptoms covering a period of 28 years which allowed us to assess both the risk associated with symptoms early and late in life and to model their trajectories over 28 years prior to dementia diagnosis. Despite the limitations of GHQ-30, our association between late life depressive symptoms and dementia is similar to that reported in the literature.[6] Furthermore, the analysis of trajectories shows its ability to reflect changes in depressive symptoms over time. A limitation of the study is ascertainment of dementia being based on linkage to electronic health records. While the specificity of cases with this method is likely to be high, the sensitivity is undoubtedly low as only half of patients living with dementia have a documented diagnosis.[4] As dementia ascertainment in our study was independent from timing and report of depressive symptoms, major bias due to undetected dementia is unlikely. We were unable to examine the subcategories of dementia due to small numbers but previous reports show similar findings for the association of depression with dementia subtypes.[26,33]

Depression is common at older ages and often co-morbid with many chronic diseases, and is associated with greater risk for mortality, higher healthcare costs, and disability. However, our study provides no support for the hypothesis that depressive symptoms increase risk of dementia. The observed association between the two is likely to be due to common causes or the effects of preclinical dementia.

ACKNOWLEDGEMENTS

We thank all of the participating civil service departments and their welfare, personnel, and establishment officers; the British Occupational Health and Safety Agency; the British Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team. The Whitehall II Study team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants and data entry staff, who make the study possible.

Funding

The Whitehall II study is supported by grants from the US National Institutes on Aging (R01AG013196; R01AG034454), the UK Medical Research Council (MRC K013351), and British Heart Foundation (RG/13/2/30098). MK is supported by the MRC and NordForsk.

Role of Funder

The funding bodies did not play any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Interest

The authors have no conflicts of interest to declare.

Access to Data and Data Analysis

ASM & SS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. *J Neuropathol Exp Neurol.* 2009;68(1):1-14.

2. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013;12(2):207-216.

3. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol.* 2013;12(4):357-367.

4. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol.* 2016;15(5):455-532.

5. Sperling RA, Jack CR, Jr., Aisen PS. Testing the right target and right drug at the right stage. *Sci Transl Med.* 2011;3(111):111cm133.

6. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry.* 2006;63(5):530-538.

7. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. *Archives of General Psychiatry.* 1999;56(3):261-266.

8. Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang CC. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. *Archives of General Psychiatry.* 2006;63(2):153-160.

9. Geerlings MI, Schoevers RA, Beekman AT, et al. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry.* 2000;176:568-575.

10. Kaup AR, Byers AL, Falvey C, et al. Trajectories of Depressive Symptoms in Older Adults and Risk of Dementia. *JAMA Psychiatry.* 2016;73(5):525-531.

11. Mirza SS, Wolters FJ, Swanson SA, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry.* 2016;3(7):628-635.

12. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet.* 1991;337(8754):1387-1393.

13. Goldberg DP. The detection of psychiatric illness by questionnaire. London, UK: Oxford University Press; 1972.

14. Stansfeld SA, Marmot MG. Social class and minor psychiatric disorder in British Civil Servants: a validated screening survey using the General Health Questionnaire. *Psychological Medicine.* 1992;22(3):739-749.

15. Radloff L. The CES-D scale: a self report depression scale for research in the general population. *Applied Psychological Measurement.* 1997;1:385-401.

16. Head J, Stansfeld SA, Ebmeier KP, et al. Use of self-administered instruments to assess psychiatric disorders in older people: validity of the General Health Questionnaire, the Center for Epidemiologic Studies Depression Scale and the self-completion version of the revised Clinical Interview Schedule. *Psychol Med.* 2013;43(12):2649-2656.

17. Singh-Manoux A, Kivimaki M, Glymour MM, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ.* 2012;344:d7622.

18. Amieva H, Le GM, Millet X, et al. Prodromal Alzheimer's disease: Successive emergence of the clinical symptoms. *Annals of Neurology.* 2008;64(5):492-498.

19. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. *Am J Psychiatry.* 2005;162(11):2086-2093.

20. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol.* 2011;7(6):323-331.

21. Babulal GM, Ghoshal N, Head D, et al. Mood Changes in Cognitively Normal Older Adults are Linked to Alzheimer Disease Biomarker Levels. *Am J Geriatr Psychiatry.* 2016;24(11):1095-1104.

22. Snowden MB, Atkins DC, Steinman LE, et al. Longitudinal Association of Dementia and Depression. *Am J Geriatr Psychiatry.* 2015;23(9):897-905.

23. Wilson RS, Capuano AW, Boyle PA, et al. Clinical-pathologic study of depressive symptoms and cognitive decline in old age. *Neurology.* 2014;83(8):702-709.

24. Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. *Horm Behav.* 2003;43(1):60-66.

25. Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Rev.* 1991;12(2):118-134.

26. Geerlings MI, den HT, Koudstaal PJ, Hofman A, Breteler MM. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology.* 2008;70(15):1258-1264.

27. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry.* 2013;202(5):329-335.

28. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology.* 2010;75(1):35-41.

29. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology.* 2010;75(1):27-34.

30. Chen R, Hu Z, Wei L, Qin X, McCracken C, Copeland JR. Severity of depression and risk for subsequent dementia: cohort studies in China and the UK. *Br J Psychiatry.* 2008;193(5):373-377.

31. Wilson RS, Schneider JA, Bienias JL, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. *Neurology.* 2003;61(8):1102-1107.

32. Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology.* 2002;59(3):364-370.

33. Li G, Wang LY, Shofer JB, et al. Temporal relationship between depression and dementia: findings from a large community-based 15-year follow-up study. *Arch Gen Psychiatry.* 2011;68(9):970-977.

34. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry.* 2012;69(5):493-498.

35. Green RC, Cupples LA, Kurz A, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. *Arch Neurol.* 2003;60(5):753-759.

36. G. DF, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. *Annals of Neurology.* 2005;57(3):381-387.

Table 1: Characteristics of the study population as a function of GHQ-30 caseness in 1985 and 2003.[a]

	GHQ-30 caseness (1985)			GHQ-30 caseness (2003)		
	No N=7445	**Yes** N=2744	P	**No** N=5353	**Yes** N=1375	P
Female, N (%)	2334 (31.4)	1017 (37.1)	<0.001	1490 (27.8)	490 (35.6)	<0.001
Age, M(SD)	45.1 (6.0)	44.5 (6.0)	<0.001	61.5 (6.0)	60.0 (6.0)	<0.001
Non-white, N (%)	840 (11.3)	247 (9.0)	0.001	389 (7.3)	149 (10.8)	<0.001
Single, N (%)	1811 (24.3)	821 (29.9)	<0.001	1218 (22.8)	416 (30.3)	<0.001
Low education, N (%)	3601 (48.4)	1244 (45.3)	0.007	2373 (44.3)	581 (42.3)	0.17
Low occupational position, N (%)	1722 (23.1)	564 (20.6)	0.006	574 (10.7)	172 (12.5)	0.06
Physical activity (hours/week), M(SD)	3.8 (4.2)	3.6 (4.3)	0.05	3.9 (3.4)	2.9 (3.1)	<0.001
Poor diet[b], N (%)	3064 (41.2)	1199 (43.7)	0.02	1230 (23.0)	424 (30.8)	<0.001
Heavy alcohol consumption[c], N (%)	1227 (16.5)	512 (18.7)	0.01	1185 (22.1)	299 (21.8)	0.76
Current smokers, N (%)	1328 (17.8)	543 (19.8)	0.02	405 (7.6)	143 (10.4)	0.02
Diabetes, N (%)	73 (1,0)	23 (0.8)	0.51	401 (7.5)	125 (9.1)	0.05
Cardiovascular disease, N (%)	91 (1.22)	28 (1.02)	0.40	501 (9.4)	183 (13.3)	<0.001
CVD medication, N (%)	223 (3.0)	110 (4.0)	0.01	1603 (30.0)	446 (32.4)	0.07
Antidepressants, N (%)	72 (1.0)	91 (3.3)	<0.001	123 (2.3)	118 (8.6)	<0.001
Incident dementia, N (%)	226 (3.0)	96 (3.5)	0.24	130 (2.4)	47 (3.4)	0.04

[a] Overall, 32.9% of the sample was composed of women in 1985 and 29.4% in 2003.

[b]Corresponds to fruit and vegetable consumption <once a day.

[c]Heavy alcohol consumption was defined as >14 units/week in women and > 21 units/week in men.

Abbreviations: M: Mean, SD: Standard deviation, CVD: Cardiovascular Disease, including coronary heart disease and stroke, GHQ: General Health Questionnaire.

Table 2. Association of depressive symptoms (1985, 1991, 1997, 2003) and incidence of dementia.

	Depressive symptoms in 1985 Age: 35-55 years N dementia/N total = 322/10189 **Mean FU 26.6 (SD=4.5) years**		**Depressive symptoms in 1991** Age: 40-60 years N dementia/N total = 246/8307 **Mean FU 21.7 (SD=3.6) years**		**Depressive symptoms in 1997** Age: 45-69 years N dementia/N total = 201/7036 **Mean FU 16.3 (SD=2.7) years**		**Depressive symptoms in 2003** Age: 50-74 years N dementia/N total = 177/6728 **Mean FU 11.1 (SD=1.8) years**	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Model 1: Analysis adjusted for age (time-scale), sex, marital status, ethnicity, education, occupation								
GHQ-30	Ref.		Ref.		Ref.		Ref.	
caseness	1.24 (0.98, 1.58)	0.08	1.05 (0.76, 1.46)	0.76	1.38 (0.98, 1.94)	0.07	1.89 (1.34, 2.65)	<0.001
CES-D							Ref.	
≥16 caseness							2.37 (1.61, 3.47)	<0.001
Model 2: Model 1 + health behaviors[a]								
GHQ-30	Ref.		Ref.		Ref.		Ref.	
caseness	1.23 (0.97, 1.57)	0.09	1.05 (0.76, 1.46)	0.77	1.35 (0.96, 1.90)	0.09	1.82 (1.29, 2.56)	0.001
CES-D							Ref.	
≥16 caseness							2.35 (1.60, 3.46)	<0.001
Model 3: Model 2 + chronic conditions[b]								
GHQ-30	Ref.		Ref.		Ref.		Ref.	
caseness	1.21 (0.95, 1.54)	0.13	1.04 (0.75, 1.45)	0.80	1.39 (0.98, 1.97)	0.06	1.72 (1.21, 2.44)	0.002
CES-D							Ref.	
≥16 caseness							2.28 (1.53, 3.39)	<0.001

[a]Smoking, alcohol consumption, physical activity, fruit and vegetable consumption.

[b]Diabetes, coronary heart disease, stroke, use of medication for cardiovascular disease, antidepressants.

FU: Follow-up, GHQ-30 caseness: 27.0% in 1985, 22.1% in 1991, 21.8% in 1997, and 20.4% in 2003. CES-D≥16 caseness: 15.0% in 2003.

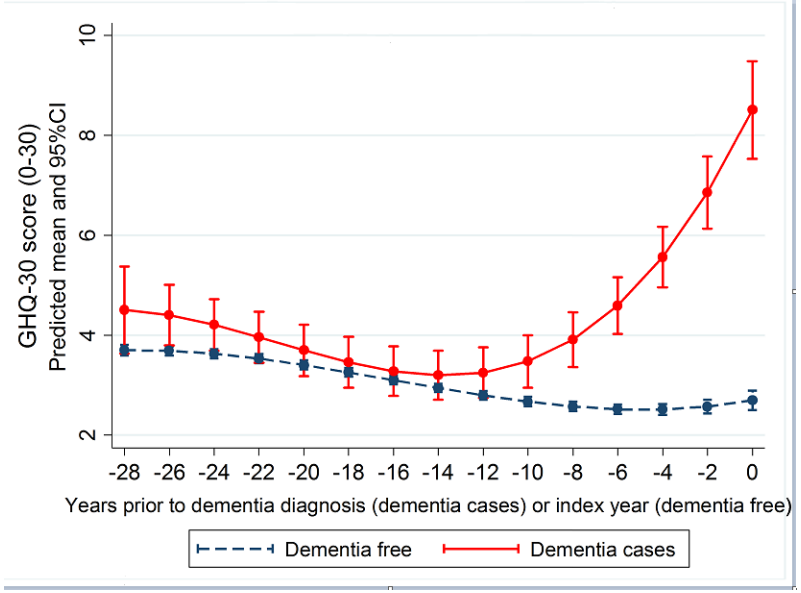
Table 3. Chronic/recurring GHQ-30 caseness in early and late study phase and incidence of dementia.

	Early study phase **Chronic/recurring GHQ-30 caseness** (1985, 1989, 1991) **Age 35-60 years** **Mean FU 21.7 (SD=3.6) years**		**Late study phase** **Chronic/recurring GHQ-30 caseness** (1997, 2001, 2003) **Age 45-74 years** **Mean FU 11.1 (SD=1.8) years**	
	N dementia/ N total = 277/9095		**N dementia/ N total[a] = 198/6948**	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Model 1: Analysis adjusted for age (time-sale), sex, marital status, ethnicity, education, occupation				
Never	Ref		Ref.	
Once	1.21 (0.92, 1.58)	0.18	1.54 (1.10, 2.17)	0.01
Twice or more	1.12 (0.81, 1.56)	0.48	1.89 (1.28, 2.78)	0.001
Model 2: Model 1 + health behaviors[b]				
Never	Ref.		Ref.	
Once	1.18 (0.90, 1.56)	0.23	1.51 (1.07, 2.13)	0.02
Twice or more	1.12 (0.81, 1.55)	0.49	1.78 (1.20, 2.62)	0.004
Model 3: Model 2 + chronic conditions[c]				
Never	Ref.		Ref.	
Once	1.16 (0.87, 1.54)	0.31	1.49 (1.06, 2.11)	0.02
Twice or more	1.02 (0.72, 1.44)	0.91	1.67 (1.11, 2.49)	0.01

For early chronic/recurring GHQ caseness: Never are 53.5%, Once are 26.6% and Twice or more are 19.9%.
For late chronic/recurring GHQ caseness: Never are 61.6%, Once are 22.4% and Twice or more are 16.0%.
FU: Follow-up
[a] The response rate in 2003 in GHQ-30 cases and non-cases in 1985 was 67.4% and 64.7%, respectively.
[b]Smoking, alcohol consumption, physical activity, fruit and vegetable consumption.
[c]Diabetes, coronary heart disease, stroke, use of medication for cardiovascular disease, antidepressants

Figure 1. Trajectories of depressive symptoms over 28 years (GHQ-30) and 12 years (CES-D) before dementia diagnosis.

A. GHQ-30 score
Difference in trajectories, P<0.001



B. CES-D score
Difference in trajectories, P<0.001