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A Cross-National Study of Depression in Pre-clinical Dementia: a COSMIC Collaboration Study

Sophie Carles[1], **Isabelle Carrière**[1,*], **Simone Reppermund**[2], **Annalisa Davin**[3], **Antonio Guaita**[3], **Roberta Vaccaro**[3], **Mary Ganguli**[4,5,6], **Erin P Jacobsen**[7], **Joanne C Beer**[8], **Steffi G Riedel-Heller**[9], **Susanne Roehr**[9], **Alexander Pabst**[9], **Mary N Haan**[10], **Henry Brodaty**[11], **Nicole A Kochan**[2], **Julian N Trollor**[2,12], **Ki Woong Kim**[13,14], **Ji Won Han**[15], **Seung Wan Suh**[16], **Antonio Lobo**[17,18], **Concepción De la Camara**[18,19,20], **Elena Lobo**[18,20,21], **Darren M Lipnicki**[2], **Perminder S Sachdev**[2,22], **Marie-Laure Ancelin**[1], **Karen Ritchie**[1,23], **for Cohort Studies of Memory in an International Consortium (COSMIC)**[†]

[1.] INSERM, Montpellier University, Neuropsychiatry: Epidemiological and Clinical Research,, Montpellier, France

[2.] Centre for Healthy Brain Ageing, University of New South Wales, Sydney, New South Wales, Australia.

[3.] Golgi Cenci Foundation, c. San Martino 10, 20081 Abbiategrasso (Milan), Italy

[4.] Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

[5.] Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

[6.] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

[†] Individuals associated with the management of COSMIC are listed in the Acknowledgments.

Invece.Ab: Annalisa Davin, Antonio Guaita, Roberta Vaccaro

- Golgi Cenci Foundation, c. San Martino 10, 20081 Abbiategrasso (Milan), Italy

SALSA: Mary N Haan (UCSF), Allison E Aiello (UNC) Kristina Dang (UCSF)

- MNH and KD: Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, California, United States of America
- AEA: Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America; Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America

LEILA75+: Steffi G. Riedel-Heller, Susanne Roehr, Alexander Pabst

- Institute of Social Medicine, Occupational Health and Public Health (ISAP), Medical Faculty, University of Leipzig, Leipzig, Germany

Corresponding author Karen Ritchie, Inserm Unit1061: Neuropsychiatry, La Colombière Hospital, 39 Ave Charles Flahault, 34093 Montpellier Cedex 5.

* Joint first authors

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[7.] Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

[8.] Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America.

[9.] Institute of Social Medicine, Occupational Health and Public Health, Medical Faculty, University of Leipzig, Leipzig, Germany.

[10.] Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, California, United States of America

[11.] Dementia Collaborative Research Centre, University of New South Wales, Sydney, New South Wales, Australia

[12.] Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia.

[13.] Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea

[14.] Department of Psychiatry, Seoul National University, College of Medicine, Seoul, Korea

[15.] Department of Brain and Cognitive Sciences, Seoul National University, College of Natural Sciences, Seoul, Korea

[16.] Department of Psychiatry, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul

[17.] Department of Medicine and Psychiatry, Universidad de Zaragoza, Zaragoza, Spain

[18.] Centro de Investigación Biomédica en Red de Salud Mental, Ministry of Science and Innovation, Madrid, Spain

[19.] Hospital Clínico Universitario, Zaragoza, Spain. Department of Medicine and Psychiatry, Universidad de Zaragoza, Zaragoza, Spain

[20.] Instituto de Investigación Sanitaria Aragón, Zaragoza, Spain

[21.] Department of Microbiology, Preventive Medicine and Public Health, Universidad de Zaragoza, Zaragoza, Spain

[22.] Dementia Collaborative Research Centre, University of New South Wales, Sydney, New South Wales, Australia

[23.] Centre for Clinical Brain Sciences, University of Edinburgh

Abstract

INTRODUCTION: Depression commonly accompanies Alzheimer's disease, but the nature of this association remains uncertain.

METHODS: Longitudinal data from the COSMIC consortium were harmonized for 8 population-based cohorts from 4 continents. Incident dementia was diagnosed in 646 participants, with a median follow-up time of 5.6 years to diagnosis. The association between years to dementia

diagnosis and successive depressive states was assessed using a mixed effect logistic regression model. A generic inverse variance method was used to group study results, construct forest plots, and generate heterogeneity statistics.

RESULTS: A common trajectory was observed showing an increase in the incidence of depression as the time to dementia diagnosis decreased despite cross-national variability in depression rates.

DISCUSSION: The results support the hypothesis that depression occurring in the pre-clinical phases of dementia is more likely to be attributable to dementia-related brain changes than environment or reverse causality.

Keywords

depression; dementia; incidence

BACKGROUND

Depression is closely associated with Alzheimer's disease (AD), with depression prevalence being estimated at around 50% in clinically diagnosed cases (1, 2). However, the underlying mechanism which links the two pathologies is still uncertain, with the chief debate being whether depression in later life is an independent risk factor for dementia, a prodromal symptom (a state preceding clinical signs) or a reaction to loss of competence (3–7).

Overall little is known about the natural course of depression in AD because of fluctuations in depressive symptoms over time and differences in research methodology (8), notably how depression is measured (screening scales, clinical diagnosis, application of diagnostic algorithms, medical records). While data from the Chicago Health and Aging Project have shown depressive symptoms to remain relatively stable during the prodromal period and after the diagnosis of AD (9, 10), longer term prospective studies reaching back into the pre-clinical phases of AD are sparse. Several epidemiological studies assert that depression onset occurs mostly within a few years preceding the diagnosis of AD dementia, and is therefore prodromal (5), whereas a 10 year retrospective study of clinical and biomarker changes in persons with incident AD observed that depressive symptomatology was significantly higher ten years before dementia diagnosis, with no change in the strength of the association over the time period, independently of changes in other AD markers (11). This relative stability of depression symptom severity across time contrasted with the sigmoidal trajectory associated with established biomarkers, thus suggesting depression to be a risk or accelerating factor rather than a feature of the disease process. A population-based study that examined associations between depression and dementia over 17 years found that, after controlling for age and sex, depression almost doubled the risk of dementia and AD (12). Different trajectories of depression may also be associated with different risks of developing AD. It has been shown that depressive symptoms increasing over a period of 10 years were associated with a higher risk of subsequent AD compared to stable or fluctuating depressive symptoms, suggesting that depression and AD could be manifestations of a common cause, with depressive symptoms preceding the onset of AD (13).

Cross-national differences in AD-related depression trajectories may help resolve the question of the direction of causality. Depression prevalence, patterns of depressive symptomatology (affective versus somatic), risk factors for depression and social stigma in relation to dementia are known to vary widely across ethnic groups (14–16) whereas the underlying brain changes may be expected to be similar.

This study is designed to test the hypothesis that trajectories of increasing depression incidence in the pre-clinical and prodromal phases of dementia will be comparable across geographic regions, countries, and cultures. If so, we could conclude that depression may be more likely related to the same underlying brain changes that cause dementia. Alternatively, if we found significant variation among the trajectories, we could conclude that depression might be an independent risk factor for, or a reaction to loss of cognitive competence, lack of social support, or pre-existing depressive states. Being principally descriptive, this study is not designed to establish causality or improve previous methodologies, but rather introduces an alternative approach (trajectory description) to complement current knowledge.

The present study used eight prospective epidemiological data sets from the COSMIC collaboration to examine trajectories of depression in the pre-clinical phase of AD and their heterogeneity across countries. As few population studies have differentiated AD from other dementias and mixed states we have included all persons diagnosed with dementia as these will be predominantly AD or mixed dementias.

METHODS

Contributing studies and participants

We included participants diagnosed with dementia from eight longitudinal population-based studies involved in the COSMIC consortium (17) in which measures of depression and dementia were performed over time. In all studies AD was the principal diagnosis, however, the distinction between AD and other causes of dementia could not be reliably made across studies. Table 1 describes the eligible studies; Invece.Ab (18), LEILA75+ (20), SALSA (21), ZARADEMP (22), MAS (23), KLOSCAD (24), ESPRIT (25) and MYHAT (19).

Depression over time in the pre-clinical phases.

For each study the depression status of subjects diagnosed with dementia at any point in time during their follow-up was defined as a binary outcome (clinically depressed versus non-depressed) by reference to clinically validated cut-off points except in the case of MYHAT which used the 90^{th} percentile on a modified screening scale (see Table 1 for a description of the scales used). The estimated years from dementia diagnosis were calculated as the date of each follow-up minus the date at dementia diagnosis (time origin). Estimated years from dementia are consequently expressed with negative signs in the pre-dementia phase.

Statistical Analysis

For each study, the incidence rate of depression and its confidence limits were calculated on the time interval between the inclusion and the last examination before dementia diagnosis

on participants free of depression at inclusion. For this calculation only the first post-inclusion occurrence of depression was considered.

Individuals were pooled from all studies and the association between years from dementia diagnosis and successive depressive states was assessed using a mixed effect logistic regression model including an interaction term between years from dementia and study and a subject-specific random intercept to take the correlation between individual measures of depression over time into account. The model was fitted using the "lme4" package from the R version 3.5.0. The mean effect and associated 95% confidence interval (CI) of an increase in one year from dementia (i.e. for each year closest to the diagnosis of dementia) and the probability of being depressed was derived by reference to odds ratios (OR) for each study included in the model. The generic inverse variance method was used to group study results, construct forest plots and generate heterogeneity statistics. Analyses were performed using the "meta" package from the R version 3.5.0.

Analysis of longitudinal depression scores over time

Subject-specific trajectories of depression scores as a function of years from dementia diagnosis were modeled using Smoothing-Splines Mixed Effects (SME) models with the use of the 'sme' package in R software version 3.5.1.. Cubic spline models were fitted considering the method described by Ruppert et al (26), using k knots ($k = 2, \ldots, 5$) setting at quantiles $100/(k+1),\ 2 \times 100/(k+1), \ldots, k \times 100/(k+1)$ for $k = 2, \ldots, 5$ of years from dementia diagnosis. The model minimizing the Akaike Information Criteria (AIC) while not overfitting the data was selected according to the number and position of knots that best fit the data while minimizing the number of model parameters.

RESULTS

Characteristics of the included studies and subjects

The eight contributing studies provided a total of 646 subjects with incident dementia. The median follow-up time ranged from 5.6 years pre-dementia diagnosis to 1.7 years post-dementia diagnosis. The number of depression measures available for the analyses by study in the pre-dementia phase are described in Table 1. The majority of studies used the Center for Epidemiologic Studies- Depression scale (CES-D) (27), followed by the Geriatric Depression Scale (GDS) (28).

Table 2 summarizes the main characteristics of the included subjects by study. Among the enrolled subjects, the median age by study at inclusion ranged from 73.1 to 83.5 years and the median age at dementia diagnosis ranged from 77.4 to 88.2 years. The percentage of *APOE*4* carriers varied noticeably between 10.8% and 35.06% across the studies.

Table 3 shows the depression incidence rate per 1000 person years across studies considering only the first occurrence. Incidence rates varied from 35 per 1000 person years in an Australian cohort to 154.6 per 1000 person years in a cohort from the USA.

Effect of years from dementia on depressive state

Figure 1 shows the forest plots of the years from dementia effect estimate for when all studies were included, and for two analyses where some studies were excluded. Considering all the selected studies (see Figure 1A), the pooled estimated odds ratio was 1.03 (95%CI: [0.99–1.08]), that corresponds to a 3% odds increase for each year closer to dementia. Given the substantial heterogeneity (I^2=52.4%, P=0.04) of the estimates between studies, we explored the potential impact of two studies that used substantially different methodology to assess dementia than the other studies (LEILA75+ and ZARADEMP).

In LEILA75+, dementia diagnosis was an algorithmic diagnosis largely based on a structured interview (SIDAM, (29)). Consequently, a subject can be classified as having dementia at one point in time and later classified as a non-case. In our main analysis (on all studies), we considered a subject once diagnosed with dementia to retain the diagnosis across follow-up. In ZARADEMP, the first screening of individuals with dementia was also based on an algorithmic classification using the Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy package (GMS-AGECAT, (30)).

Excluding LEILA75+ and ZARADEMP from our analyses, the pooled estimated odds ratio remained significant at 1.06 (95%CI: [1.01–1.11]) (see Figure 1B). However, the inter-studies heterogeneity was reduced and no longer significant (I^2=40.8%, P=0.133). In an additional analysis we further excluded KLOSCAD because of its relatively short follow-up period, but the results were unchanged (Figure 1C).

Evolution of depression scores over time to dementia

Figure 2 describes, using SME models, the mean evolution and associated 95% CI of depression scores over time to dementia for the 7 studies providing continuous scores (all except ZARADEMP). The fitted curves confirm the above results for binary depression state. Depression scores increased with diminishing time to dementia diagnosis most clearly for Invece.Ab , but also for MYHAT, SALSA, Sydney MAS and ESPRIT. Conversely, decreasing scores were found for LEILA75+ and KLOSCAD with a large CI near the dementia time for LEILA75+ and over all the time period for Kloscad, denoting small numbers of depression measures at each time for these two cohorts.

DISCUSSION

Previous clinical and population studies have given conflicting conclusions as to the relationship between depression and dementia. A meta-analysis (3) of 23 prospective population studies concluded that late-life depression significantly increased the future risk of AD incidence 1.65 fold, suggesting it to be a significant risk factor even after adjustment for multiple confounders. On the other hand, the observed associations between depression and smaller hippocampal volume, neurotransmitter imbalance, tau accumulation and amyloid metabolism in persons with diagnosed AD (4–7) have supported the alternative hypothesis that depression is linked to the underlying pathological brain changes and therefore constitutes a prodrome of the disease rather than a risk factor. Other studies have

suggested it to be a reaction to loss of competence which could be culturally determined (14–16).

Few studies have investigated the incidence and clinical course of depression longitudinally within the pre-clinical phase of dementia, and as far as we are aware this is the first to examine cross-national differences. This study has thus been able to examine the hypothesis that if depression is prodromal, that is an early feature of the disease itself, then risk of depression would be seen to rise as pre-clinical persons approached diagnosis despite population variability in depression prevalence and cultural factors.

The incidence of depression or depressive symptoms in dementia has been shown to vary greatly across studies from 2% per year (31, 32) to 20% per year (33, 34) with differences in these studies being largely attributable to differences in method of case identification. Considerable heterogeneity was also found in this study, with the incidence of depression ranging from 35 to 15.4 per 1000 person-years, but with rates being closer when similar scales were used.

This meta-analysis highlights the great variability in observations of the association between depressive state and time from dementia. Among 5 of the 8 studies considered in the first assessment, the odds of depression tend to increase as the time from dementia decreases. In the remaining 3 studies, the odds of depression tend to decrease as the time from dementia decreases, but the associations are not significant. When combined across studies, the odds of depression increased as the time from dementia decreases, but not significantly, and in the presence of statistical heterogeneity.

Our principal hypothesis was that cohort differences in depression rates would be expressed as heterogeneity in incidence and trajectories over time, whereas depression related to degenerative brain pathology would give similar trajectories. We did not observe positive and negative associations attributable to any particular geographic grouping. In the 3 studies with negative associations, two were European (Germany for LEILA75+ and Spain for Zarademp) and one Korean. Studies with positive associations were conducted in European and American countries.

Previous population studies of depression incidence have attributed inconsistency in results principally to case detection methods. We assessed this by excluding LEILA75+ and Zarademp; diagnoses in these two studies being by automatic algorithm rather than standardized clinical scales. Heterogeneity in the sample estimates was subsequently seen to decrease significantly and the pooled results show a significant increase in the odds of depression as the time from dementia diagnosis decreases. We cannot however exclude that other factors specific to these two studies may explain the observed heterogeneity.

Overall the results suggest that differences in the trajectories between countries appear largely attributable to methodological differences rather than cultural groups. Taking the methodologically most similar studies, an increase in the incidence of depression is seen to occur over time across countries and, despite inter-cultural variability in depression rates. Rates increase with increasing proximity to the diagnosis of dementia, suggesting it to be more a prodrome than a risk factor, although the present study design cannot preclude the

possibility of an interactive effect with depression due to external causes accelerating silent brain changes. Our findings are, however, in agreement with a previous ten year prospective study of depression and dementia trajectories which also concluded that depression was an early symptom of progressive disease (13). There is also the possibility that increasing depression rates due to increasing loss of competence may be common to all cases and explain the similarity in trajectories, although given that this is a preclinical trajectory with little overt evidence of cognitive loss, this seems unlikely.

Given the similarities across countries in dementia pathology, we are still left with the question as to why not all persons developing dementia manifest depression in the years preceding diagnosis. Future studies could take a closer look at the continuum from mild cognitive impairment (MCI) to dementia and the association with depression. A recent study reported that the risk of progression from MCI to AD was significantly elevated in people with depression in the last two years, compared to those with a more remote history of depression suggesting that the presence of depression in closer proximity to AD could be considered a marker of even greater risk (35).

This meta-analysis has several strengths. First, data was obtained from American, Asian and European countries allowing observations from a wide range of ethnicities with different attitudes, rates of depression, clinical care and exposure to different risk factors associated with both depression and dementia. Second, studies with long follow-up were included in the analysis, with a maximal follow-up time before the dementia diagnosis of almost 15 years in ESPRIT.

There are limitations to our analyses. Firstly we were not able to differentiate AD from other forms of dementia, which may have weakened the observed associations. For four studies (Invece, Mas, Kloscad and Zarademp) the number of depression measures before the dementia diagnosis was low at only 2, and their follow-up time was relatively short (3 to 5 years). The studies included did not all use the same measures of depressive symptomatology (main ones being the GDS and CESD-D). However, a bias in our analysis linked to the use of different scales is unlikely. Estimates varied identically in the two main sub-groups of depression scales used and no systematic differences between sub-groups were observed. Additionally, only eight studies were maintained to assess a pooled estimate of the association between depression state and time from dementia.

Parallel observations of depression trajectories and brain changes would have greatly reinforced aetiological hypotheses, but unfortunately these were available for very few studies. Finally, if depression were a risk factor for dementia, it would be expected that younger age at first onset of depression and greater number and severity of previous episodes would be linked to dementia incidence. However, we were unable given the limits of the data set to consider previous history or prior medication use in our analyses. Considerable methodological heterogeneity of the observations included in the COSMIC consortium and high variability in the risk factors precluded use of these data to more closely examine interaction effects of depression with other risk factors in the pre-clinical phase of dementia. However, it has been able to show a common pattern of increasing

incidence as the underlying pathology progresses which appears relatively independent of environmental factors.

In conclusion it is important to see this study in terms of its overall contribution to knowledge of AD and other neurodegenerative disorders. It is above all a methodological contribution in relation to theory validation. There has already been ample research on the relationship of depression to biomarkers which has given evidence of statistically significant associations, while population studies going back to before the prodromal period suggest depression to precede brain changes thus constituting a risk factor. Our usual approach to validation is to repeat previous research procedures with some improvements, for example in depression measures or population sampling, which does not take our thinking outside of current cause-effect models. The starting point for this study has been Karl Popper's [36] notion that good scientific practice is characterized by testing constructs against experience in the real world in an attempt to refute them. In this case we were not trying to generate a new theory but rather take an alternative descriptive approach to validation by ascertaining which hypothesis best fits empirical observations of disease occurrence and is universal across cultures. Our conclusion is that the theory that depression is part of the disease process shows evidence of coherence with population incidence rates in the pre-clinical and prodromal phases of disease. However, it does not explain why many persons with dementia do not develop depression. Our observations do not therefore permit us to construct an alternative etiological model.

This study of data bases from a variety of cultures has led us to speculate above all on the limits of pre-conceived nosological entities such as depression in constructing causative models. Each study provided the number of persons corresponding to a clinical cut-off point for depression, but we do not know which symptoms have contributed to this diagnosis, whether there were other notable co-occuring behavioural symptoms not included in the depression measure, and more importantly whether these signs and symptoms were 'depression' or expressions of brain changes which overlap with those seen in depression but of different etiology. Similar symptoms may be the clinical expression of quite different underlying disease processes. This approach aligns with a trend in psychiatric research towards 'trans-diagnostic' classifications rather than diagnostic categories in an attempt to better determine the biological bases of behavioural and mood disorders.

Thus in terms of future research we may better understand behavioural correlates of neurodegenerative disease if we return to observations of phenomenology from the pre-clinical period, recording signs and symptoms and their changes in relation to biomarkers and brain changes as the disease progresses rather than converting them *apriori* into diagnostic categories such as depression, anxiety, apathy. In this sense the frequently asked question of whether anti-depressants may reduce dementia risk is premature, and in the spirit of a recent editorial on revising our approach to dementia research, attempting to change the world without trying to understand it [37].

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COSMIC NIH grant investigators: Perminder Sachdev: Scientia Professor of Neuropsychiatry; Co-Director, Centre for Healthy Brain Ageing (CHeBA), UNSW Sydney; Director, Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia. Mary Ganguli: Professor of Psychiatry, Neurology, and Epidemiology, University of Pittsburgh. Ronald Petersen: Professor of Neurology; Director, Mayo Clinic Alzheimer's Disease Research Center and the Mayo Clinic Study of Aging. Richard Lipton: Edwin S. Lowe Professor and Vice Chair of Neurology, Albert Einstein College of Medicine. Karen Ritchie: Professor and Director of the Neuropsychiatry Research Unit of the French National Institute of Research (INSERM U1061). Ki-Woong Kim: Professor of Brain and Cognitive Sciences, Director of National Institute of Dementia of Korea. Louisa Jorm: Director, Centre for Big Data Research in Health and Professor, Faculty of Medicine, UNSW Sydney, Australia. Henry Brodaty: Scientia Professor of Ageing & Mental Health; Co-Director, Centre for Healthy Brain Ageing (CHeBA), UNSW Sydney; Director, Dementia Collaborative Research Centre (DCRC); Senior Consultant, Old Age Psychiatry, Prince of Wales Hospital.

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REFERENCES

1. Engedal K, Barca ML, Laks J, Selbaek G. Depression in Alzheimer's disease: specificity of depressive symptoms using three different clinical criteria. Int J Geriatr Psychiatry. 2011;26(9):944–51. [PubMed: 21845597]
2. Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry. 2002;52(3):243–52. [PubMed: 12182930]
3. 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):329–35. [PubMed: 23637108]
4. Campbell S, Macqueen G. The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci. 2004;29(6):417–26. [PubMed: 15644983]

5. Chi S, Yu JT, Tan MS, Tan L. Depression in Alzheimer's disease: epidemiology, mechanisms, and management. J Alzheimers Dis. 2014;42(3):739–55. [PubMed: 24946876]
6. Namekawa Y, Baba H, Maeshima H, Nakano Y, Satomura E, Takebayashi N, et al. Heterogeneity of elderly depression: increased risk of Alzheimer's disease and Abeta protein metabolism. Prog Neuropsychopharmacol Biol Psychiatry. 2013;43:203–8. [PubMed: 23276885]
7. Sun X, Steffens DC, Au R, Folstein M, Summergrad P, Yee J, et al. Amyloid-associated depression: a prodromal depression of Alzheimer disease? Arch Gen Psychiatry. 2008;65(5):542–50. [PubMed: 18458206]
8. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. Biol Psychiatry. 2003;54(3):353–62. [PubMed: 12893110]
9. Wilson RS, Arnold SE, Beck TL, Bienias JL, Bennett DA. Change in depressive symptoms during the prodromal phase of Alzheimer disease. Arch Gen Psychiatry. 2008;65(4):439–45. [PubMed: 18391132]
10. Wilson RS, Hoganson GM, Rajan KB, Barnes LL, Mendes de Leon CF, Evans DA. Temporal course of depressive symptoms during the development of Alzheimer disease. Neurology. 2010;75(1):21–6. [PubMed: 20603481]
11. Ritchie K, Carriere I, Berr C, Amieva H, Dartigues JF, Ancelin ML, et al. The clinical picture of Alzheimer's disease in the decade before diagnosis: clinical and biomarker trajectories. J Clin Psychiatry. 2016;77(3):e305–11. [PubMed: 26891108]
12. 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. [PubMed: 20603483]
13. Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, et al. 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. Lancet Psychiatry. 2016;3(7):628–35. [PubMed: 27138970]
14. Calia C, Johnson H, Cristea M. Cross-cultural representations of dementia: an exploratory study. J Glob Health. 2019;9(1):011001.
15. Dixit S. Meaning and Explanations of Mental Illness: A Social Representations Approach. . Psychol Dev Soc. 2005;17(1):1–18.
16. Kohrt BA, Rasmussen A, Kaiser BN, Haroz EE, Maharjan SM, Mutamba BB, et al. Cultural concepts of distress and psychiatric disorders: literature review and research recommendations for global mental health epidemiology. Int J Epidemiol. 2014;43(2):365–406. [PubMed: 24366490]
17. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Rockwood K, Xiao S, et al. COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. BMC Neurol. 2013;13:165. [PubMed: 24195705]
18. Guaita A, Colombo M, Vaccaro R, Fossi S, Vitali SF, Forloni G, et al. Brain aging and dementia during the transition from late adulthood to old age: design and methodology of the "Invece.Ab" population-based study. BMC Geriatr. 2013;13:98. [PubMed: 24063518]
19. Ganguli M, Snitz B, Vander Bilt J, Chang CC. How much do depressive symptoms affect cognition at the population level? The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) study. Int J Geriatr Psychiatry. 2009;24(11):1277–84. [PubMed: 19340894]
20. Riedel-Heller SG, Busse A, Aurich C, Matschinger H, Angermeyer MC. Prevalence of dementia according to DSM-III-R and ICD-10: results of the Leipzig Longitudinal Study of the Aged (LEILA75+) Part 1. Br J Psychiatry. 2001;179:250–4. [PubMed: 11532803]
21. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc. 2003;51(2):169–77. [PubMed: 12558712]
22. Lobo A, Saz P, Marcos G, Dia J, De-La-Camara C, Ventura T, et al. The ZARADEMP Project on the incidence, prevalence and risk factors of dementia (and depression) in the elderly community: I. The context and the objectives. Eur J Psychiat. 2005;19(1):31–9.
23. Sachdev PS, Brodaty H, Reppermund S, Kochan NA, Trollor JN, Draper B, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. Int Psychogeriatr. 2010;22(8):1248–64. [PubMed: 20637138]

24. Han JW, Kim TH, Kwak KP, Kim K, Kim BJ, Kim SG, et al. Overview of the Korean Longitudinal Study on Cognitive Aging and Dementia. Psychiatry Investig. 2018;15(8):767–74.
25. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ. 2010;341:c3885.
26. Ruppert D Semiparametric Regression. . New York: Cambridge University Press; 2003.
27. Radloff L. The CES–D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.
28. Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F. The criterion validity of the Geriatric Depression Scale: a systematic review. Acta Psychiatr Scand. 2006;114(6):398–410. [PubMed: 17087788]
29. Zaudig M, Mittelhammer J, Hiller W, Pauls A, Thora C, Morinigo A, et al. SIDAM--A structured interview for the diagnosis of dementia of the Alzheimer type, multi-infarct dementia and dementias of other aetiology according to ICD-10 and DSM-III-R. Psychol Med. 1991;21(1):225–36. [PubMed: 2047500]
30. Copeland JR, Dewey ME, Davidson IA, Saunders PA, Scott A. Geriatric Mental State-AGECAT: prevalence, incidence and long-term outcome of dementia and organic disorders in the Liverpool study of continuing health in the community. Neuroepidemiology. 1992;11 Suppl 1:84–7. [PubMed: 1603256]
31. Weiner MF, Doody RS, Sairam R, Foster B, Liao TY. Prevalence and incidence of major depressive disorder in Alzheimer's disease: findings from two databases. Dement Geriatr Cogn Disord. 2002;13(1):8–12. [PubMed: 11731709]
32. Weiner MF, Edland SD, Luszczynska H. Prevalence and incidence of major depression in Alzheimer's disease. Am J Psychiatry. 1994;151(7):1006–9. [PubMed: 8010355]
33. Arbus C, Gardette V, Cantet CE, Andrieu S, Nourhashemi F, Schmitt L, et al. Incidence and predictive factors of depressive symptoms in Alzheimer's disease: the REAL.FR study. J Nutr Health Aging. 2011;15(8):609–17. [PubMed: 21968854]
34. Ballard CG, Patel A, Solis M, Lowe K, Wilcock G. A one-year follow-up study of depression in dementia sufferers. Br J Psychiatry. 1996;168(3):287–91. [PubMed: 8833681]
35. Gallagher D, Kiss A, Lanctot K, Herrmann N. Depression and Risk of Alzheimer Dementia: A Longitudinal Analysis to Determine Predictors of Increased Risk among Older Adults with Depression. Am J Geriatr Psychiatry. 2018;26(8):819–27. [PubMed: 29960668]
36. Popper K. Conjectures and Refutations: The Growth of Scientific Knowledge. London, Routledge: Fifthe Edition 1989
37. Khachaturian AS, Hayden KM, Mielke MM, Tang Y, Lutz MW, Gold M, Kukull WA, Mohs R, Gauthier S, Molinuevo JL, Zetterberg H, Khachaturian ZS. New thinking about thinking, part two. Theoretical articles for Alzheimler's and Dementia. Alz Dem 2018; 14 703–706

RESEARCH IN CONTEXT

Systematic Review.

Depression commonly accompanies Alzheimer's disease, but the nature of this association is unknown.

Interpretation.

An increase in the incidence of depression as the time to dementia diagnosis decreases despite cross-national variability in depression rates support the hypothesis that depression is more likely to be attributable to dementia-related brain changes than a risk factor or reaction to the disease. The studies have made the assumption that the symptoms experienced in the pre-clinical phase are the same as clinical depression rather than depression-like symptoms linked to brain changes.

Future directions.

The results underline the importance of studies of symptomatology trajectories in relation to AD biomarkers in the pre-clinical phase.

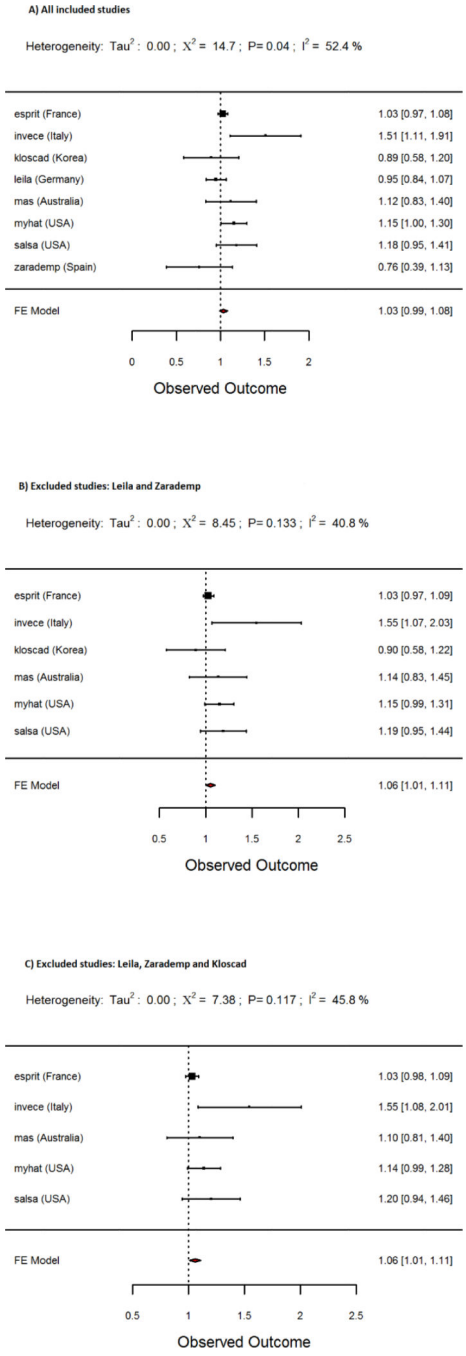

Figure 1.
Forest plots of years from dementia effects on depressive state

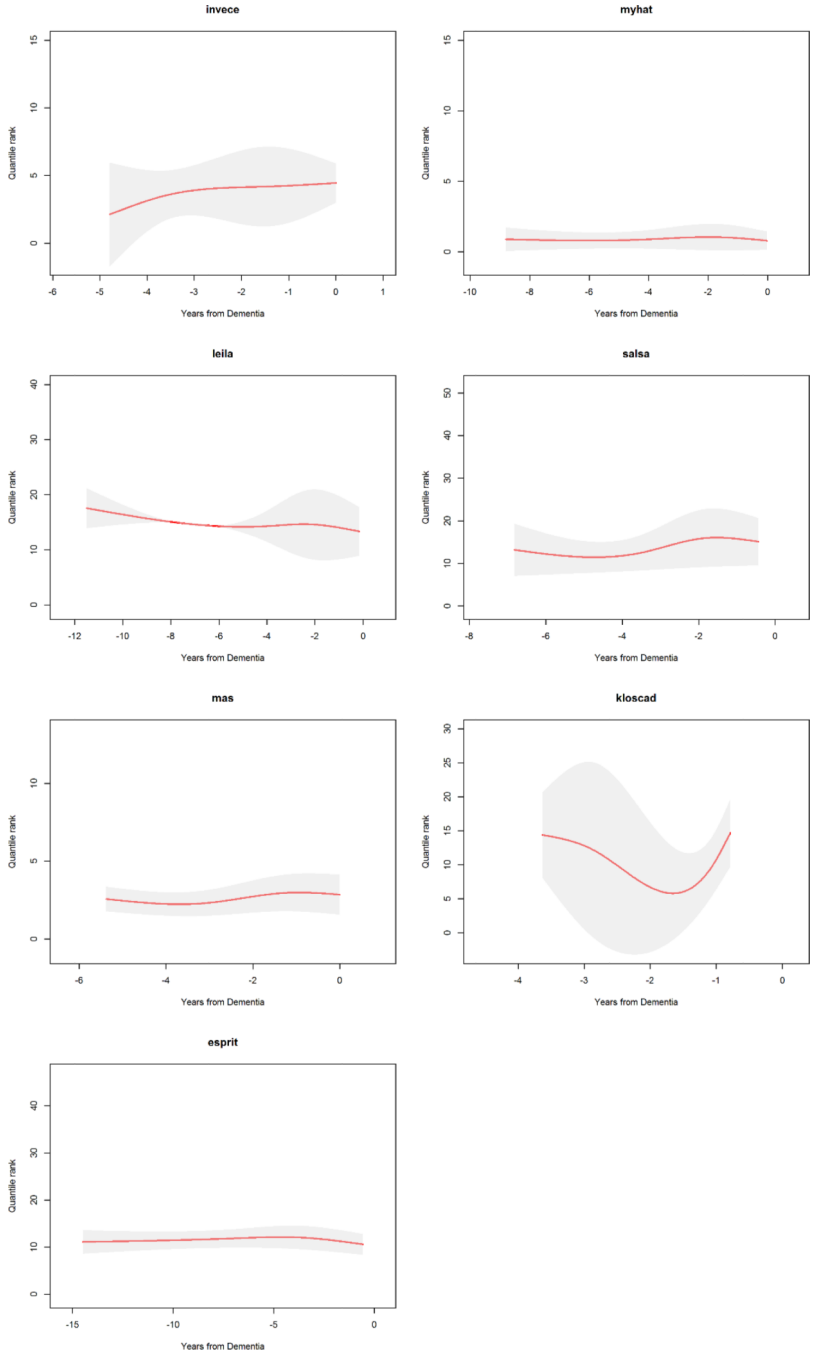

Figure 2.
Mean and associated 95%CI of depression score over time from dementia by study (Smoothing Splines Mixed curves)

Table 1.

Characteristics of the eligible studies

Study	Country	No. of Subjects with dementia	No. of Subjects with at least 2 depression measures pre-dementia	No. of Measures per Subjects		Years from dementia		Depression Scale Used	Continuous depression score available
				Median	[Min - Max]	Median	[Min - Max]		
Invece (18)	Italy	99	31	2	[2 – 2]	−3.37	[−4.79 – 0.00]	GDS	Y
MYHAT(19)	USA	128	94	6	[2 – 9]	−2.53	[−8.80 – −0.02]	Modified CES-D	Y
Leila (20)	Germany	400	101	3	[2 – 6]	−3.00	[−11.50 – −0.01]	CES-D	Y
SALSA (21)	USA	158	62	3	[2 – 5]	−3.06	[−8.03 – −0.44]	CES-D	Y
Zarademp (22)	Spain	136	46	2	[2 – 2]	−2.55	[−4.15 – −1.04]	GMS AGECAT	N
MAS (23)	Australia	105	77	2	[2 – 3]	−2.89	[−5.38 – −0.01]	GDS	Y
Kloscad (24)	Korea	526	67	2	[2 – 2]	−1.70	[−3.63 – −0.79]	GDS	Y
Esprit (25)	France	280	168	5	[2 – 6]	−5.61	[−14.49 – −0.49]	CES-D	Y

Abbreviations: CES-D: Center for Epidemiological Studies-Depression; GDS: Geriatric Depression Scale; GMS AGECAT: Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy

Table 2.

Characteristics of the study population

Study	Country	Female sex (%)	ApoE E4 carriers (%)	Education level (years)		Age at inclusion (years)		Age at dementia diagnosis (years)	
				Median	[Min-Max]	Median	[Min-Max]	Median	[Min-Max]
Invece	Italy	48.39	29.03	5	[2 – 13]	73.08	[70.69 – 75.24]	77.41	[74.68 – 79.39]
MYHAT	USA	69.15	31.82	12	[4 – 18]	83.48	[67.40 – 96.32]	88.25	[72.33 – 100.80]
LEILA75+	Germany	87.13	NA	12	[9 – 16]	82.32	[75.31 – 91.46]	87.77	[78.46 – 96.88]
SALSA	USA	74.19	27.87	6	[0 – 18]	74.14	[63.81 – 92.52]	79.96	[69.53 – 98.41]
Zarademp	Spain	54.35	NA	8	[1 – 18]	80.76	[62.70 – 93.99]	84.35	[66.86 – 97.33]
MAS	Australia	49.35	35.06	11	[4 – 21]	81.12	[71.90 – 89.58]	85.39	[75.03 – 94.64]
Kloscad	Korea	67.16	NA	6	[0 – 18]	76.00	[61.00 – 90.00]	79.09	[64.00 – 93.27]
Esprit	France	66.07	30.25	-	- – -	73.63	[65.01 – 91.22]	82.47	[67.85 – 99.87]

Table 3.

Depression incidence rates

Study	Incidence per 1000 person-years	95% confidence interval
Invece (Italy)	127.57	(120.13 ; 135.01)
MYHAT (USA)	49.33	(47.9 ; 50.76)
LEILA75+ (Germany)	107.12	(103.85 ; 110.39)
SALSA (USA)	154.59	(147.14 ; 162.04)
Zarademp (Spain)	36.31	(31.79 ; 40.83)
MAS (Australia)	35.12	(33.28 ; 36.96)
Kloscad (Korea)	67.40	(61.68 ; 73.12)
Esprit (France)	50.01	(49.37 ; 50.65)