Severity of depression and risk for subsequent dementia: cohort studies in China and the UK*

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Background
Depression and dementia often exist concurrently. The associations of depressive syndromes and severity of depression with incident dementia have been little studied.

Aims
To determine the effects of depressive syndromes and cases of depression on the risk of incident dementia.

Method
Participants in China and the UK aged ≥65 years without dementia were interviewed using the Geriatric Mental State interview and re-interviewed 1 year later in 1254 Chinese, and 2 and 4 years later in 3341 and 2157 British participants respectively (Ageing in Liverpool Project Health Aspects: part of the Medical Research Council – Cognitive Function and Ageing study).

Results
Incident dementia was associated with only the most severe depressive syndromes in both Chinese and British participants. The risk of dementia increased, not in the least severe cases of depression but in the most severe cases. The multiple adjusted hazard ratio (HR)=5.44 (95% CI 1.67–17.8) for Chinese participants at 1-year follow-up, and HR=2.47 (95% CI 1.25–4.89) and HR=2.62 (95% CI 1.18–5.80) for British participants at 2- and 4-year follow-up respectively. The effect was greater in younger participants.

Conclusions
Only the most severe syndromes and cases of depression are a risk factor for dementia.

Declaration of interest
None. Funding detailed in Acknowledgements.

Depression and dementia are the most prevalent and disabling mental disorders among older populations. It has been predicted that the number of people with dementia in the world will double every 20 years to 42 million by 2020 as the aged population grows. Evidence that depression and dementia often exist concurrently has stimulated speculation that there are complex associations between these two conditions. Many studies, but not all, have reported that a history of depression is a risk factor for dementia. However, recent data have shown that depressive symptoms are cross-sectionally associated with cognitive impairment but not with subsequent cognitive decline, suggesting that the presence of depression alone does not increase the risk of cognitive decline. This may raise questions about the risk of dementia in relation to depression. Particularly, we could find no investigation linking depressive syndromes, as opposed to depressive symptoms with increased risk of dementia.

Previous studies on the association of depression with dementia have mainly been carried out in the Western world. Also, few investigators have examined the effects of the severity of depression on dementia. In many Western populations, low socio-economic status, low social support, high cardiovascular risk factors and depression tend to co-occur, making a relationship between depression and dementia difficult to unravel. By contrast with Western populations, older people in China exhibit different patterns of risk factors with extremes of absolute deprivation combined with high levels of social supports, low levels of depression and low levels of some cardiovascular risk factors (e.g. serum cholesterol, body mass index). Studying such a population may therefore, offer internationally applicable insights into the aetiological role of depression in dementia.

Method
Participants
Chinese participants were those from our Hefei cohort study in Anhui Province, China. The methods used in the study have been fully described elsewhere. Briefly, in 2001 we randomly selected 1810 people aged ≥65 years from the residency committee lists who had lived for at least 5 years in Yiming district of Hefei city, Anhui. Permission for interview and informed consent were obtained from each person but if that was not possible, from the closest responsible adult. Refusals were respected. Ethical approval was obtained from Anhui Medical University and the district government.

There were 1736 people who agreed to participate in the study (a response rate of 95.9%). Participants were interviewed at home by a trained survey team from the School of Health Administration, Anhui Medical University. The main interview materials were the GMS – a comprehensive semi-structured mental state interview and a general health record that included risk factors. Blood pressure and physical measurements...
were taken. The validation study of depression cases was carried out by two consultant psychiatrists. A year after the baseline interview, 1293 participants (74.5%) were successfully re-investigated, using the same protocol.

British participants were those from the MRC–ALPHA study, part of the MRC Cognitive Function and Ageing Study (www.cfas.ac.uk). The study methods have been fully described elsewhere. In brief, a sample of 6035 older people aged 65 years were randomly selected using the Liverpool Family Practitioner Committee central computerised list of general practice patients in 1989. Of these, 5222 participants were interviewed with a response rate of 86.5%. The main interview materials included the GMS and the Minimum Data Set. Two years later, 3519 (67.4%) participants were successfully re-interviewed, and 4 years later 2238 (42.9%) participants were re-investigated. Ethical approval was obtained from the multicentre and local ethical committee.

Assessment of syndromes and cases of depression and dementia

A computer program assisted diagnosis – the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) – was used to analyse the information from the GMS to identify the principal mental disorders in participants. It was developed using a theoretical model and tested against its success at replicating diagnoses on samples diagnosed by psychiatrists. It attempts to replicate the process by which a psychiatrist achieves a syndromal diagnosis followed by a differential diagnosis. Geriatric Mental State symptoms are coalesced into a 150 ‘symptoms components’. In stage I the symptom components are brought together into groups which typify the major symptom areas of each diagnostic syndrome. The scores on these individual groups determine the final syndromal level of ‘confidence of diagnosis’. Thus, the system uses both quantitative and qualitative measures when allocating participants to the levels of confidence; required for its construction are many hundreds of clinical decisions on the placement of groups of symptom components on the syndrome levels. Individual participants are allocated to levels of confidence of diagnosis (0–5) on each of the eight diagnostic syndromes: organic disorder, depression, mania, schizophrenia and paranoid, obsessive, phobic, hypochondriacal, and general anxiety. In stage II the various syndrome levels are compared to derive a final differential diagnosis, a level of confidence of diagnosis from 0–5. A level of 3 in most circumstances designates a ‘case level’ that has been shown to correspond with those at level 4 (nor cases) in our community-based samples. The risk of dementia was not associated with level 1–3 depressive syndromes, but significantly increased with level 4. Differences in the increased hazard ratio (HR) between Chinese and British participants were not significant (P > 0.20). This relationship was further observed with baseline depression cases at level 4 only, but not with less severe cases at level 3 and sub-cases at levels 1–2. These findings remained significant even after further consideration of baseline dementia subcases, which were associated with incident dementia (Fig. 1).

We investigated differences in baseline covariables between MRC–ALPHA participants with depression at level 4 (n=108) and those at level 3 (n=375). There were no significant differences with age (77.9 v. 77.6 years, P=0.20). Gender (male 40.7% v. 38.9%), education years (9.0 v. 9.2), Townsend score – an index for socio-economic deprivation (26.9% v. 30.7%), heart attack (9.3% v. 13.6%), angina/chest pain (15.7% v. 17.9%), and stroke/parts of body paralysed (11.1% v. 11.7%). However, individuals with level 4 depression had more organic syndromes at level ≥3 (8.3% v. 0.8%, P<0.001), more depressive neurosis (62.0% v. 21.9%, P<0.001) and more antidepressant drug use (benzodiazepines 37.0% v. 21.6%, P=0.001; tricyclic antidepressants, selective serotonin reuptake inhibitors, loperamide and others 17.6% v. 8.0%, P=0.004). After further adjustment for these medications, the results were not substantially changed; multiple adjusted HR for incident dementia was 2.41 (95% CI 1.20–4.85) and 2.54 (1.13–5.69) in the 2- and 4-year follow-up respectively.

We examined differences in the effects of level 4 depression on incident dementia between the subgroups in the MRC–ALPHA combined data of incident dementia in the 4-year follow-up with a 2-year follow-up (i.e. adding the Wave III incident dementia into Wave II). There were no significant differences in the adjusted HRs between men (HR=1.73, 95% CI 0.61–4.91) v. women (HR=2.07, 95% CI 1.03–4.15) (P=0.78); people with CVD

Table 1 shows number and incidence of dementia across baseline depressive syndromes. There were no level 5 depressive syndromes (nor cases) in our community-based samples. The risk of dementia was not associated with level 1–3 depressive syndromes, but significantly increased with level 4. Differences in the increased hazard ratio (HR) between Chinese and British participants were not significant (P > 0.20). This relationship was further observed with baseline depression cases at level 4 only, but not with less severe cases at level 3 and sub-cases at levels 1–2. These findings remained significant even after further consideration of baseline dementia subcases, which were associated with incident dementia (Fig. 1).

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Statistical analysis

Data were analysed for those who did not have dementia at baseline and were followed up (1294 Chinese and 3341 British). The associations of baseline depressive syndromes with subsequent dementia at follow-up were explored using a Cox regression model with adjustment for age, gender, educational level and CVD. In examining the risk of dementia in relation to depression, baseline sub-cases of dementia were further allowed in the multiple regression model for analysis. Differences in the relationship between subgroups of age, gender, ethnicity, CVD comorbidity and type of depression were tested. All analyses were performed in SPSS version 13.0 for Windows.

Results
Depressive syndromes, depression and dementia

comorbidities (HR=1.47, 95% CI 0.44–4.86) v. without CVD (HR=2.17, 95% CI 1.12–4.22) (P=0.58); and depressive neurosis (HR=2.77, 95% CI 1.22–6.26) v. depressive psychosis (HR=1.66, 95% CI 0.78–3.53) (P=0.37). However, the effect increased with younger age; adjusted HRs in those aged 65–74, 75–84 and 85+ years were 6.10 (95% CI 1.92–19.4), 2.16 (95% CI 0.92–5.08) and 1.05 (95% CI 0.45–1.94) respectively; P=0.012 in the youngest v. the oldest.

We carried out two sensitivity analyses to investigate further the effects of baseline depression on incident dementia using the above combined data. First, after excluding all participants with baseline organic syndrome at level 5, adjusted HRs in level 4 depression (n=10, 15.4% incident dementia) was 1.89 (95% CI 1.00–3.57), while those for depression at levels 1, 2 and 3 were 1.36 (95% CI 0.84–2.21), 0.85 (95% CI 0.52–1.40) and 0.88 (95% CI 0.53–1.44) respectively. Second, excluding 73 participants with incident dementia who at the same time had depressive syndrome at level 5 from 330 individuals with incident dementia, the matched figures were 1.46 (95% CI 0.68–3.10), 0.53 (95% CI 0.26–1.08), 0.55 (95% CI 0.28–1.07) and 1.18 (95% CI 0.66–2.13).

Discussion

In two large population-based cohorts in China and the UK, we found that an increased risk of dementia was associated with only the most severe syndromes and cases of depression, but not with less severe syndromes and cases. The increased risk was not statistically different with ethnicity, gender, cardiovascular disease comorbidity or type of depression, but was higher in younger participants.

Our findings may weigh more towards particular causal pathways. Depression may be associated with increased risk of dementia because depression is a reaction to perceived cognitive deficits, because depression is an early symptom of dementia (occurring before the syndrome becomes clinically definable), or because depression is actually a risk factor for dementia. The fact that subcase and less severe case syndrome levels were not associated with dementia in this study may support the third explanation more than the first two (which would be less likely to show specificity to a particular syndrome level).
Strengths and limitations
The strengths of the study were that we employed two markedly different populations in terms of levels of socio-economic status, social support, CVD and depression; the two cohorts had high response rates and the number of participants was relatively large, which gave sufficient power to test the relationship, including that in the subgroups; and the GMS–AGECAT, potentially measuring syndrome and diagnosis at 5 levels, offered a unique opportunity to examine dementia in relation to depression severity (rather than simply as a dichotomous variable of depression).

The limitations of the study were that in the Chinese cohort, the incident dementia may be over-diagnosed because it included some illiterate participants, although the GMS–AGECAT was satisfactory for high-income countries with literate populations. The follow-up in the Chinese cohort was relatively short (1 year), and the numbers with depression and dementia were small (and thus it was not possible to examine differences in the baseline covariables between people with depression levels 3 and 4, and differences in the effect of level 4 depression on dementia between the subgroups of participants). However, the findings were consistent and supported by the large British data with the long-term 4-year follow-up. Another limitation was that we could not separate dementia into Alzheimer’s disease, vascular dementia, or both in order to examine their associations with depression. Thus, we could not directly link level 4 depression cases to Alzheimer’s disease or vascular dementia. However, our data showed that depression at level 4 increased the risk of dementia in both participants with and without CVD, suggesting that the most severe cases of depression may be related to both vascular dementia and Alzheimer’s disease. The finding that depression increased the risk of Alzheimer’s disease has been shown in a recent meta-analysis paper, which did not examine the effects of the severity of depression on Alzheimer’s disease.

Effects of depression on incident dementia
To our knowledge, our study is the first to examine the relationship between depressive syndromes and the risk of dementia, and report that within clinical depressions, the less severe cases of depression did not increase any risk for developing dementia, but the most severe cases did so significantly. The MRC–ALPHA data showed that individuals with level 4 depression at baseline were more likely to have level 4 depression within 2 years than those with baseline level 3 (data on request), suggesting depression lasted longer at level 4 (although we cannot exclude some participants who may have recovered and then relapsed in the meantime). This longer duration may be a reflection of the level of depression severity. Several epidemiological studies have examined depression as a risk factor for dementia with conflicting results. In a meta-analysis, Jorm concluded that a history of depression increased the risk for developing dementia by 87%. Our data suggest that the most severe level of depression increased the incidence of dementia to a greater degree than those in previous studies. We believe this is because we separated severe from less severe depression. This may explain the variable conclusions in those studies which grouped severity levels of depression together. Failure to confirm this finding may have been partly due to a lower proportion of severe depression in their samples.

Why does the GMS–AGECAT level 4, not case level 3 depression appear to increase the risk of incident dementia? Such a pattern even existed in our sensitivity analyses. It seems not to arise from differences in those covariables at baseline. It could not be entirely explained by the lower proportion of depressive neurosis (or higher depressive psychosis) in participants with level 3 depression at baseline compared with those with level 4, since level 4 depressive psychosis itself increased the risk of dementia. We considered that some symptoms or other unmeasured variables might have been included in level 4, but not in level 3, depression and/or simply the severity of depression could play a role. Perturbations of the hypothalamic–pituitary–adrenal axis in depression can lead to hypercortisolemia-associated hippocampal atrophy which may also explain why the most severe cases of depression are those more likely to increase the risk of dementia. Nevertheless, the GMS–AGECAT diagnosis, adapted for clinical use, could be used to help identify those at higher risk in older populations in an attempt to prevent dementia. The strong effect found in younger elderly people and the long-term effect may imply that depression at a younger age is more important for developing dementia, suggesting that early treatment of depression and prevention of depression in the younger population may effectively reduce dementia in later life.

The increased risk of incident dementia in relation to only the most severe syndromes or cases of depression is unlikely to result from chance or bias. Our study urges that the aetiological roles of the severity of depressive syndromes, syndromes and clinical cases on dementia need to be addressed. Early treatment and prevention of depression and relieving its severity could reduce the burden of dementia in both high-income and low- and middle-income countries.
Attachment theory and the psychiatrist–patient relationship

Jeremy Holmes

When subject to stress, threat or illness, humans seek an older wiser figure or ‘secure base’. The patient comes to the psychiatrist in a state of arousal. An empathic response on the part of the doctor, with accurate verbal identification of emotion, produces assuagement of attachment arousal. An empathic response on the part of the doctor, with accurate verbal identification of emotion, produces assuagement of attachment

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