Persistent Depressive Symptoms and Cognitive Function in Late Midlife: The Whitehall II Study

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Objective: Depression has been widely linked to poor cognition and dementia in the elderly. However, comorbidity at older ages does not allow an assessment of the role of mental health as a risk factor for cognitive outcomes. We examined the association between depressive symptoms, measured 6 times over an 18-year period, and cognitive deficits in late midlife.

Method: Of the 10,308 participants in the Whitehall II study, 4,271 men and women (aged 35–55 years at baseline) were followed up for 18 years, during which depressive symptoms were assessed 6 times using the General Health Questionnaire depression subscale. The follow-up was from 1985–1988 to 2002–2004. Cognition was assessed at the most recent wave (2002–2004, mean age 61 years, range 50–74 years) using 6 tests: memory, reasoning, vocabulary, 2 tests of verbal fluency, and the MMSE (Mini Mental State Examination). Cognitive deficit was defined as MMSE score < 28 and performance in the worst sex-specific quintile for the other tests.

Results: History of depressive symptoms, once or more in the 6 times assessed, had a weak association with some of the cognitive tests. However, in analysis adjusted for sociodemographic variables, diabetes, coronary heart disease, hypertension, stroke, and antidepressant use, persistent depressive symptoms (4–6 times) were associated with cognitive deficits on all tests: memory (OR = 1.91; 95% CI, 1.36–2.67), reasoning (OR = 1.60; 95% CI, 1.15–2.20), vocabulary (OR = 1.75; 95% CI, 1.27–2.41), phonemic fluency (OR = 1.40; 95% CI, 1.00–1.94), semantic fluency (OR = 1.68; 95% CI, 1.20–2.35), and the MMSE (OR = 1.76; 95% CI, 1.25–2.50).

Conclusions: Our data show that depressive episodes tend to persist in some individuals, and these individuals are at a greater risk of cognitive deficits in late midlife.

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Depression[1] and impaired cognition[2] are common conditions in the elderly, and their comorbid prevalence doubles every 5 years after the age of 70, leading to both conditions being present in 25% of those over 85 years of age.[3] Depression has been shown to be associated with poor cognitive performance,[4–9] cognitive decline,[10–15] and dementia.[11,16–32] Three explanations of these associations have been put forward. The first is that depressive symptoms themselves are a psychological reaction to the awareness of declining cognitive capacities.[9,29,33] Another implicates a common cause, like vascular disease,[10,11,19,23,25,30,31] while the third view is that depression is a risk factor for cognitive decline.[12,14,15,18,32,34,35] This debate on depression as a cause or consequence of cognitive decline is further confused by the presence of cross-sectional associations, but lack of longitudinal associations, in the same studies.[6,7]

Most of the research in this domain has been carried out on the elderly,* where incipient dementia is more likely to introduce some recall bias in the results. Thus, it is possible that depression is both a remote risk factor and a proximal prodromal feature of Alzheimer's Disease.[36] It is now widely accepted that dementia develops over many years, perhaps 20–30 years,[37] but much research on the identification of risk factors for dementia is undertaken in elderly populations. There is considerable evidence to link poor adult cognition to late-life dementia[38,39]; but few studies have looked at the association between depression and cognition at earlier ages. One exception, a small case control study on individuals aged 20 to 64 years, found major depression to be associated with deficits in memory and mental flexibility.[4] Another large study on middle aged adults, from a clinical population, used hospital admission data to show that the risk of dementia increased with the number of episodes of depressive disorders.[28]

The temporal dimension in the association between depression and cognitive impairment[40] is crucial in order to assess whether depression, amenable to treatment, is a risk factor for cognitive outcomes. However, most studies use one measure of depression and examine cognitive function either cross-sectionally or cognitive-decline prospectively. Thus, it remains unclear whether recurrent or multiple episodes of depression have a stronger affect on cognition. The primary objective of our study was to examine the association between history and frequency of depressive symptoms, measured 6 times over an 18-year period, and cognitive deficits using a range of cognitive tests in late midlife. We also examined cross-sectional associations and associations with proximal and distal measures of depressive symptoms.

METHOD

The target population for the Whitehall II study was all London-based office staff, aged 35–55 years, working in 20 civil service departments.[41] Baseline screening (Phase 1)

*References 5–10, 12, 14, 16–23, 26, 27, 29–31, 35.

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took place during 1985–1988 (N = 10,308; 67% men) and involved a clinical examination and a self-administered questionnaire containing sections on demographic characteristics, health, lifestyle factors, work characteristics, social support, and life events. The clinical examination included measures of blood pressure, anthropometry, biochemical measurements, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between postal questionnaire alone: Phases 2 (1989–1990), 4 (1995–1996), 6 (2001), and 8 (2006) and postal questionnaire accompanied by a clinical examination: Phases 3 (1991–1993), 5 (1997–1999), and 7 (2002–2004). All participants provided written consent, and the University College London Research Ethics Committee approved this study.

Depressive Symptoms

In the Whitehall II study, a 4-item depression subscale has been identified[42] from the 30-item General Health Questionnaire (GHQ)[43] on the basis of factor analysis and comparison with the 7-item depression subscale of the GHQ-28.[44] These items were as follows: "thinking of yourself as a worthless person," "felt life is entirely hopeless," "felt life isn't worth living," and "found at times you couldn't do anything because your nerves were too bad." Depressive symptoms were assessed by summing all items scored on a Likert scale from 0 to 3. Respondents scoring 0–3 were considered "non-cases," and those scoring 4 or more were considered "GHQ depression cases." GHQ depressive symptoms were assessed at Phases 1, 2, 3, 5, 6, and 7 of the study and used to construct a summary score, range 0 to 6, indicating the number of times a person is a case. Distal (to the measure of cognition) depressive symptoms were defined as GHQ depression in the first 3 assessments (phases 1, 2, and 3), over the first 6 years of follow-up. Proximal (to the measure of cognition) depressive symptoms were defined as GHQ depression in the last 3 assessments (phases 5, 6, and 7), over the last 6 of the total 18-year follow-up.

Cognitive Function

The cognitive test battery, administered at Phase 7 (2002–2004), consisted of 6 standard tasks chosen to provide a comprehensive assessment of cognitive function. The 6 tests are as follows:

Memory. Short-term verbal memory was assessed with a 20-word free-recall test. Participants were presented a list of 20 one- or two-syllable words at 2-second intervals and were then asked to recall in writing as many of the words as they could in any order and had 2 minutes to do so.

Reasoning. The Alice Heim 4-I (AH4-I) is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty.[45] It tests inductive reasoning, measuring the ability to identify patterns and infer principles and rules. Participants had 10 minutes to do this section.

Vocabulary. Vocabulary was assessed using the Mill Hill Vocabulary test,[46] used in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and 6 response choices for each word.

Verbal fluency. We used 2 measures of verbal fluency: phonemic and semantic.[47] Phonemic fluency was assessed via "s" words and semantic fluency via "animal" words. Subjects were asked to recall in writing as many words beginning with "s" and as many animal names as they could. One minute was allowed for each test.

Mini Mental State Examination. Finally, the 30-item Mini Mental State Examination (MMSE) was used to assess global cognitive status.[48]

Covariates

Covariates used were age, sex, highest qualification on leaving full-time education (primary school, lower secondary school, higher secondary school, university, and higher university degree), and marital status (married/cohabiting, single, widowed, and divorced/separated). As measures of health are associated with depression and cognition,[31,40] we adjusted for the effects of diabetes (self-report of doctor diagnosis), clinically validated coronary heart disease (CHD), stroke (self-report of doctor diagnosis), and hypertension (systolic and diastolic blood pressure > 140/90 mm Hg or treatment for hypertension). Antidepressant use was assessed using a questionnaire on medications.

Statistical Analysis

Scores in the lowest sex-specific quintile for all tests except the MMSE were seen to represent cognitive deficit. Among men (women), deficit was defined as scores below 5 (5) for memory, 39 (30) for the AH4-I, 24 (20) for the Mill Hill, 13 (12) for phonemic fluency, and 13 (12) for semantic fluency. For the MMSE, instead of applying the standard cutoff used in elderly populations, we used a higher cut-off of 28 in order to match the categorization for other cognitive tests, leading to 12.1% of men and 14.7% of women to be classified as having cognitive deficit.

We first examined the association between GHQ depression and cognitive deficit using the broad categorization of those with and without a history of depressive symptoms at Phase 7. Thus, depression "caseness" at any phase over the 18-year follow-up led the individual to be classified as having a history of GHQ depression. These associations were assessed using logistic regression, first adjusted for age, sex, marital status, and education in order to remove confounding effects of sociodemographic variables. The second level of adjustment includes measures of diabetes, CHD, hypertension, stroke, and antidepressant use in order to assess whether the association between depression and cognition was robust to adjustment for potential common causes[10,11,19,23,25,30,31] and confounding by antidepressant use. We repeated this analysis using data only from Phase 7 in order to assess the cross-sectional association between GHQ depression and cognitive deficit.

We then examined the association between frequency of depressive symptoms over the 18-year follow-up and cognitive deficit at Phase 7. For these analyses, we categorized the

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Table 1. Sample Characteristics at Phase 7 of Those With and Without a History of Depressive Symptoms[a]

	Men			Women		
	Ever Depressed,[b] n = 965 (31.4)	Never Depressed,[c] n = 2,111 (68.6)	*P*	Ever Depressed,[b] n = 454 (38.0)	Never Depressed,[c] n = 741 (62.0)	*P*
Age, mean (SD)	60.4 (5.9)	61.4 (6.0)	< .0001	61.1 (6.0)	61.5 (6.2)	.37
Married	757 (78.5)	1,820 (86.2)	< .0001	238 (52.4)	443 (59.8)	.01
University degree or higher	347 (36.0)	658 (31.2)	.009	121 (26.7)	141 (19.0)	.002
Coronary heart disease	94 (9.7)	204 (9.7)	.94	38 (8.4)	57 (7.7)	.67
Diabetes	221 (22.9)	529 (25.1)	.20	98 (21.6)	180 (24.3)	.28
Hypertension	365 (37.8)	809 (38.3)	.80	159 (35.0)	315 (42.5)	.01
Stroke	32 (3.3)	58 (2.8)	.38	10 (2.2)	15 (2.0)	.83
Antidepressant medication	58 (6.0)	26 (1.2)	< .0001	34 (7.5)	18 (2.4)	< .0001

[a]Values are expressed as n (%) unless stated otherwise.
[b]Depressed 1 or more times over the 6 waves of measurement.
[c]Not depressed at any of the 6 measures over the 18-year follow-up.

6 measures of GHQ depression as follows: never depressed, depressed once, depressed 2–3 times, and depressed 4–6 times. Subsequently, we examined the association between distal and proximal depressive symptoms and poor cognitive performance. For both of these measures, we categorized proximal and distal depressive symptoms as follows: never depressed, depressed once, and depressed 2–3 times. All analyses have the 2 levels of adjustment outlined above, the first for the sociodemographic variables and the second for potential common causes. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 10,308 participants at the start of the Whitehall II study, 6,967 were alive and involved in the study at Phase 7. Of these, 5,837 undertook cognitive testing, and, for 4,353 individuals, a full history of GHQ depression (measured 6 times over 18 years) was available. Data on covariates were missing for a further 82 individuals, leading to the analysis on 4,271 participants. Compared to baseline, more men (72% vs 67%) and more participants with a university degree or higher (30% vs 27%) were included in our analyses. Out of the 4,271 participants, a similar percentage reported experiencing depressive symptoms at all 6 measures: 11.9%, 13.8%, 12.1%, 11.4%, 9.6%, and 10.9%, respectively.

Table 1 compares those with a history of depressive symptoms, GHQ depression at 1 or more of the 6 phases, with those who did not report depressive symptoms at any of the 6 measures over the 18-year period. Those with a history of depression were more likely to be unmarried, highly educated, and on antidepressants. The interaction term between sex and the summary score of depressive symptoms showed no sex differences on the influence of depression on cognition (all $P > .13$); thus, men and women were combined in further analysis. Table 2 presents the results from the logistic regression showing the association between history of depressive symptoms, defined as GHQ depression at any of the 6 measures, and cognitive deficit on the left-hand side. On the right-hand side are shown the cross-sectional associations between depressive symptoms and cognitive deficit at Phase 7. In general terms, the associations between depressive symptoms and cognitive deficit are stronger in cross-sectional analyses.

The association between the frequency of GHQ depression, measured 6 times over 18 years, and poor cognitive performance are shown in Table 3. The categories depressed 2 (6.9%) and 3 times (3.9%) were combined in these analyses. Similarly, the categories depressed 4 (3.0%), 5 (1.7%), and 6 times (1.2%) were also combined. Frequent depressive symptoms (4 to 6 times) were associated with poor performances on the tests of memory (OR = 1.91; 95% CI, 1.36–2.67), reasoning (OR = 1.60; 95% CI, 1.15–2.20), vocabulary (OR = 1.75; 95% CI, 1.27–2.41), phonemic fluency (OR = 1.40; 95% CI, 1.00–1.94), semantic fluency (OR = 1.68; 95% CI, 1.20–2.35), and the MMSE (OR = 1.76; 95% CI, 1.25–2.50) compared to participants who reported no depressive symptoms at any of the 6 measures over the 18-year follow-up.

Table 4 presents the results on the association between distal depressive symptoms, GHQ depression in the 3 measures taken during the first 6 years of follow-up, and poor cognitive performance. Those with 2 (6.4%) and 3 episodes (3.3%) of GHQ depression have been combined in these analyses. There is some evidence of an association between frequent (2–3 times out of the 3 measured) distal depressive symptoms and poor memory (OR = 1.49; 95% CI, 1.14–1.95) and semantic fluency (OR = 1.35; 95% CI, 1.03–1.76). Table 5 presents the results for proximal depressive symptoms, depressive symptoms in the 6 years before the measure of cognition. Here again, 2 (4.3%) and 3 (3.6%) episodes of depression have been combined for the analyses. Frequent proximal depressive symptoms (2–3 times out of the 3 measured) were associated with poor performance on all tests (ORs 1.48 to 1.8 for the tests).

DISCUSSION

A quick look at our results would suggest that the association between depressive symptoms and cognitive deficit in late midlife is being driven by cross-sectional associations. However, this interpretation does not take into account the fact that depressive episodes tend to cluster in individuals. Of those with (distal) GHQ depression at Phases 1, 2, or 3, 49% also had (proximal) depressive symptoms at Phases 5, 6, or 7. Furthermore, 43% of those with 2–3 episodes of distal depressive symptoms also had 2–3 episodes of proximal depressive symptoms. The persistence effect is stronger

Table 2. The Association Between Depressive Symptoms (history and cross-sectionally) and Cognitive Deficit[a] at Phase 7

	History of Depressive Symptoms and Cognition		Cross-Sectional Association Between Depressive Symptoms and Cognition	
	Never Depressed,[b] n = 2,852 (66.8%), Reference	Ever (once or more) Depressed, n = 1,419 (33.2%), OR (95% CI)	Not Depressed at Phase 7, n = 3,805 (89.1%), Reference	Depressed at Phase 7, n = 466 (10.9%), OR (95% CI)
Memory				
Adjusted for age, sex, marital status, and education	1	1.20 (1.00–1.45)*	1	1.38 (1.06–1.80)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.19 (0.99–1.43)	1	1.36 (1.04–1.77)*
AH4-I (reasoning)				
Adjusted for age, sex, marital status, and education	1	1.26 (1.07–1.49)*	1	1.46 (1.14–1.86)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.28 (1.08–1.51)*	1	1.46 (1.14–1.87)*
Mill Hill (vocabulary)				
Adjusted for age, sex, marital status, and education	1	1.14 (0.96–1.34)	1	1.40 (1.10–1.78)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.14 (0.96–1.35)	1	1.39 (1.10–1.77)*
Phonemic fluency				
Adjusted for age, sex, marital status, and education	1	1.11 (0.94–1.32)	1	1.24 (0.97–1.60)
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.11 (0.94–1.32)	1	1.22 (0.94–1.58)
Semantic fluency				
Adjusted for age, sex, marital status, and education	1	1.19 (1.00–1.42)*	1	1.40 (1.10–1.80)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.19 (1.00–1.42)*	1	1.37 (1.05–1.77)*
MMSE				
Adjusted for age, sex, marital status, and education	1	1.08 (0.89–1.32)	1	1.24 (0.93–1.64)
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.05 (0.86–1.29)	1	1.17 (0.88–1.56)

[a]Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 7.
[b]Not depressed at any of the 6 measures over the 18-year follow-up.
*Denotes significance at $P < .05$.
Abbreviations: AH4-I = Alice Heim 4-I, CHD = coronary heart disease, MMSE = Mini Mental State Examination.

Table 3. The Association Between Frequency of Depressive Symptoms Over 18 Years and Cognitive Deficit[a] at Phase 7

	Never Depressed,[b] n = 2,852 (66.8%), Reference	Depressed 1 Time, n = 706 (16.5%), OR (95% CI)	Depressed 2 or 3 Times, n = 463 (10.8%), OR (95% CI)	Depressed 4, 5, or 6 Times, n = 250 (5.9%), OR (95% CI)
Memory				
Adjusted for age, sex, marital status, and education	1	0.95 (0.74–1.22)	1.27 (0.96–1.67)	1.92 (1.38–2.66)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	0.95 (0.74–1.22)	1.26 (0.96–1.66)	1.91 (1.36–2.67)*
AH4-I (reasoning)				
Adjusted for age, sex, marital status, and education	1	1.16 (0.93–1.44)	1.26 (0.98–1.63)	1.60 (1.16–2.20)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.18 (0.95–1.47)	1.28 (0.99–1.66)	1.60 (1.15–2.20)*
Mill Hill (vocabulary)				
Adjusted for age, sex, marital status, and education	1	1.08 (0.87–1.34)	0.93 (0.72–1.22)	1.75 (1.28–2.40)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.10 (0.88–1.36)	0.94 (0.72–1.23)	1.75 (1.27–2.41)*
Phonemic fluency				
Adjusted for age, sex, marital status, and education	1	1.06 (0.85–1.33)	1.04 (0.80–1.36)	1.43 (1.03–1.98)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.07 (0.86–1.34)	1.04 (0.80–1.37)	1.40 (1.00–1.94)*
Semantic fluency				
Adjusted for age, sex, marital status, and education	1	1.01 (0.80–1.28)	1.21 (0.93–1.60)	1.73 (1.25–2.40)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.03 (0.81–1.30)	1.22 (0.93–1.60)	1.68 (1.20–2.35)*
MMSE				
Adjusted for age, sex, marital status, and education	1	0.95 (0.73–1.23)	0.91 (0.66–1.25)	1.90 (1.35–2.65)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	0.95 (0.73–1.23)	0.89 (0.65–1.23)	1.76 (1.25–2.50)*

[a]Worst sex-specific quintile of cognitive function; covariates drawn from Phase 7.
[b]Not depressed at any of the 6 measures over the 18-year follow-up.
*Denotes significance at $P < .05$.
Abbreviations: AH4-I = Alice Heim 4-I, CHD = coronary heart disease, MMSE = Mini Mental State Examination.

when looking at all 6 measures of GHQ depression over the 18-year period. In all, 250 participants reported depressive episodes between 4 and 6 times over the total follow-up period; out of these, 210 (84%) had 2–3 episodes of distal, and 218 (87%) reported proximal depressive symptoms. Thus, clearly a subgroup of individuals reports persistent depressive symptoms, and our results suggest that it is this group that has greater risk of cognitive deficits in late midlife.

The association between depressive symptoms and cognition, impaired cognition, or dementia has been much examined in the research literature. There is a general consensus that it is important to examine the temporal aspect of this association in order to make sense of the 3 different explanations of this association: depression as a cause or a consequence of cognitive decline, plus the common cause hypothesis. Considerable attention has been paid to separating the cross-sectional from the longitudinal associations[6,7] and examining either multiple waves of data on cognition[10–14] or dementia.[16–31] Less attention has been paid to measuring depression over the adult lifecourse. The exceptions are studies

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Table 4. The Association Between Frequency of Distal Depressive Symptoms (Phases 1, 2, 3) and Cognitive Deficit[a] at Phase 7

	Not Depressed,[b] n = 3,208 (75.1%), Reference	Depressed 1 Time, n = 651 (15.2%), OR (95% CI)	Depressed 2 or 3 Times, n = 412 (9.7%), OR (95% CI)
Memory			
Adjusted for age, sex, marital status, and education	1	1.14 (0.90–1.45)	1.50 (1.14–1.97)*
+ Diabetes, CHD, and hypertension	1	1.14 (0.90–1.46)	1.49 (1.14–1.95)*
AH4-I (reasoning)			
Adjusted for age, sex, marital status, and education	1	1.13 (0.90–1.40)	1.22 (0.94–1.58)
+ Diabetes, CHD, and hypertension	1	1.14 (0.91–1.42)	1.20 (0.92–1.56)
Mill Hill (vocabulary)			
Adjusted for age, sex, marital status, and education	1	1.16 (0.93–1.45)	1.06 (0.81–1.39)
+ Diabetes, CHD, and hypertension	1	1.17 (0.94–1.46)	1.05 (0.80–1.37)
Phonemic fluency			
Adjusted for age, sex, marital status, and education	1	0.93 (0.74–1.17)	1.21 (0.93–1.57)
+ Diabetes, CHD, and hypertension	1	0.93 (0.74–1.18)	1.19 (0.92–1.56)
Semantic fluency			
Adjusted for age, sex, marital status, and education	1	1.20 (0.95–1.51)	1.36 (1.04–1.78)*
+ Diabetes, CHD, and hypertension	1	1.21 (0.96–1.52)	1.35 (1.03–1.76)*
MMSE			
Adjusted for age, sex, marital status, and education	1	0.97 (0.74–1.26)	1.31 (0.98–1.76)
+ Diabetes, CHD, and hypertension	1	0.98 (0.74–1.28)	1.29 (0.96–1.73)

[a]Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 3.
[b]Not depressed at the 3 distal measures of depressive symptoms.
*Denotes significance at $P < .05$.
Abbreviations: AH4-I = Alice Heim 4-I, CHD = coronary heart disease, MMSE = Mini Mental State Examination.

Table 5. The Association Between Frequency of Proximal Depressive Symptoms (Phases 5, 6, 7) and Cognitive Deficit[a] at Phase 7

	Not Depressed,[b] n = 3,399 (79.6%), Reference	Depressed 1 Time, n = 535 (12.5%), OR (95% CI)	Depressed 2 or 3 Times, n = 337 (7.9%), OR (95% CI)
Memory			
Adjusted for age, sex, marital status, and education	1	1.13 (0.87–1.48)	1.74 (1.30–2.34)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.12 (0.86–1.47)	1.70 (1.26–2.29)*
AH4-I (reasoning)			
Adjusted for age, sex, marital status, and education	1	1.30 (1.02–1.64)*	1.75 (1.33–2.30)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.30 (1.03–1.66)*	1.76 (1.32–2.33)*
Mill Hill (vocabulary)			
Adjusted for age, sex, marital status, and education	1	1.20 (0.95–1.52)	1.58 (1.20–2.09)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.20 (0.95–1.52)	1.57 (1.18–2.08)*
Phonemic fluency			
Adjusted for age, sex, marital status, and education	1	1.09 (0.85–1.39)	1.51 (1.14–2.00)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.08 (0.84–1.39)	1.48 (1.11–1.98)*
Semantic fluency			
Adjusted for age, sex, marital status, and education	1	0.95 (0.73–1.24)	1.80 (1.36–2.39)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	0.95 (0.73–1.24)	1.76 (1.32–2.36)*
MMSE			
Adjusted for age, sex, marital status, and education	1	1.03 (0.77–1.37)	1.70 (1.25–2.31)*
+ Diabetes, CHD, hypertension, stroke, and antidepressant use	1	1.00 (0.75–1.34)	1.59 (1.16–2.18)*

[a]Worst sex-specific quintile of cognitive function at Phase 7; covariates drawn from Phase 7.
[b]Not depressed at the 3 proximal measures of depressive symptoms.
*Denotes significance at $P < .05$.
Abbreviations: AH4-I = Alice Heim 4-I, CHD = coronary heart disease, MMSE = Mini Mental State Examination.

that assess history of depression.[20,27,28,49] However, 2 of these studies measure depression history retrospectively[24,27] and are more likely to suffer from some recall bias, particularly as they are based on the elderly. The other 2 studies use medical data to show increased risk of cognitive deficit with increases in the number of episodes of depressive disorders[28] or with recurrent depression.[49] One of these studies used data on hospital admissions for affective disorders,[28] and the other study was on an elderly sample and used data drawn from physician records.[49]

A recent meta-analysis examined the association between depression and Alzheimer's disease and reported an OR of 2.02 (95% CI, 1.80–2.26) for Alzheimer's disease among those with a history of depression.[36] The review also found a positive association between a longer interval between the diagnosis of depression and an increased risk of Alzheimer's disease, in the few studies where it was available. The conclusion reached by the review was that depression appears to be a risk factor rather than a prodrome of Alzheimer's disease. However, subsequent work continues to show inconsistent

results. Data from the Rush Religious Orders Study[50] and the Rotterdam Scan study[35] suggest no increase in depressive symptoms during the prodromal phase of dementia, but a Swedish Twin study found the contrary.[51] Finally, another study found only "severe" depression to be a risk factor for dementia.[32] However, in studies on the elderly, when the risk factor being examined is influenced by early subclinical stages of disease, protopathic bias is a real concern. Studies like ours that shift the observation window to midlife are more likely to be unbiased in this regard. Our results suggest that multiple or persistent episodes of depressive symptoms are associated with greater risk of cognitive deficits. The association of frequent proximal depressive episodes with cognition was somewhat more robust than that with frequent distal depressive episodes. However, in further analyses (not shown, but available on request), we excluded all individuals with distal episodes, and the associations for proximal episodes were much reduced. Thus, clearly it is persistent depressive symptoms that are either a risk factor or identify a group of individuals at risk of cognitive deficits.

Of the studies examining dementia as an outcome, a majority have focused on Alzheimer's disease,* which implicates deficits in memory.[38,39] Our results suggest a consistent effect of depressive symptoms (history, cross-sectional, distal, proximal, and overall frequency) on memory deficits. One study on the elderly reported recurrent depression or history of depression to be characterized by deficits in memory,[49] suggesting that memory might be a particularly vulnerable domain. However, another study in which depressive symptoms were associated with an increased risk of mild cognitive impairment showed stronger effects for the mild cognitive impairment subtype without memory impairment.[15] In general terms, the mechanisms behind the association between depression and cognition remain little understood. It has been suggested that the link between depression and cognition can be attributed to vascular disease,[10,11,19,23,25,30,31] reflecting the common cause hypothesis. In our data, as in other studies,[52] statistical adjustment for vascular disease did not much change the association between persistent depressive symptoms and cognitive deficit.

Our study has several strengths and limitations. The strengths lie in the size of the study; the 6 measures of depressive symptoms over 18 years and multiple measures of cognition. A further strength is the examination of the link between depression and cognition in an age group in which incipient dementia is less likely to be a confounding factor. The limitations are mostly to do with the scale used to assess depression. The GHQ depression scale used is only a part of the 7-item depression scale of the GHQ 28. GHQ depression is also best considered to be a measure of depressive symptoms and should not be equated with clinically diagnosed depression.[42] It is essentially a measure of self-reported depressive symptoms, and, although reliable, it does not indicate the severity of depression. There is some evidence to suggest that major depression has a stronger effect on cognitive impairment.[4,32] Nevertheless, our 6 measures of depressive symptoms are a good measure of persistent depression. A further limitation is that no data were available for cognition at baseline, and thus it remains unclear to what extent cognitive functioning at study entry determined subsequent trajectories of depression. Finally, the Whitehall II study is based on white-collar civil servants and is not representative of the general population, limiting the generalizability of our results.

In conclusion, our study of middle-aged adults from the Whitehall II cohort shows that persistent depressive symptoms are a risk factor for cognition in late midlife. This association is independent of vascular risk factors and appears to implicate memory in particular. Of the 3 hypotheses put forward to explain the association between depression and cognition—depression as a cause or a consequence and the common cause hypothesis—we did not examine the hypothesis that depression was a consequence of declining cognition. However, there was little evidence of vascular diseases explaining away the association between persistent depressive symptoms and cognition. Our results suggest an association between persistent depressive symptoms and poor cognitive function in late midlife. However, whether this association is causal remains unclear as the precise mechanisms linking depression to cognitive functioning remain to be elucidated.

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