Metabolic Syndrome and Symptom Resolution in Depression: A 5-Year Follow-Up of Older Adults

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ABSTRACT

Objective: Although metabolic syndrome is associated with the incidence of depression, little is known about its contribution to the course of depression. We examined whether metabolic syndrome and its components are associated with long-term symptom resolution in older adults with depressive symptoms.

Methods: Data from 965 participants in the Whitehall II cohort study (mean age = 62 years at baseline) were used to generate 1,172 person-observations of metabolic syndrome and its components (abdominal obesity, low level of high-density lipoprotein [HDL] cholesterol, high level of triglycerides, hypertension, and elevated fasting glucose or diabetes). All participants were depression cases at the beginning of 2 consecutive follow-up cycles: from 2002–2004 to 2007–2009 and from 2007–2009 to 2012–2013 (mean follow-up = 4.6 years). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale caseness at the beginning and the end of the 2 cycles.

Results: In multivariable adjusted analyses, metabolic syndrome per se was not associated with symptom resolution. Of its components, low HDL cholesterol (risk ratio [RR] = 0.82; 95% CI, 0.68–1.00; $P = .045$) and high triglyceride levels (RR = 0.81; 95% CI, 0.70–0.95; $P = .007$) were associated with a lower likelihood of symptom resolution. These findings were replicated in a subpopulation without coronary heart disease and stroke (RR = 0.77 [95% CI, 0.63–0.95; $P = .015$] for low HDL cholesterol; RR = 0.79 [95% CI, 0.67–0.94; $P = .006$] for high triglycerides).

Conclusions: Low HDL cholesterol and high triglyceride levels are associated with lower likelihood of long-term symptom resolution in depression. These data suggest that an adverse lipid profile, but not other components of metabolic syndrome, may delay recovery from depression.

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Depressive symptoms are common at older ages, affecting up to 20% of adults over 65 years.[1,2] The adverse impact of depression on people and society is considerable in terms of human suffering, reduced quality of life, increased health care costs, and premature mortality.[3–6] Depression tends to have an episodic course characterized by the reversal of symptoms leading to full recovery.[7] However, recurrent episodes are common,[8] and the risk of chronicity is high.[9]

Metabolic syndrome, a cluster of risk factors thought to predispose an individual to cardiovascular disease,[10] is characterized by elevated abdominal obesity, high level of triglycerides, low level of high-density lipoprotein (HDL) cholesterol, high blood pressure, and elevated fasting glucose or diabetes. There is some evidence to suggest that metabolic syndrome is associated with an increased risk of depression,[11,12] although the relationship between components of metabolic syndrome and the onset of depression is inconsistent.[13–15]

Research on the biological risk factors of depression has tended to focus on first episodes, not distinguishing between episodes.[8] Few previous studies have examined the contribution of metabolic syndrome or its components to the course of disease in depression.[7] Small-scale studies of patient populations have analyzed lipid components of metabolic syndrome and found high HDL cholesterol[16,17] and low triglyceride levels[16] to be associated with better prognosis of depression, whereas low HDL cholesterol was associated with longer symptom duration[18] and high triglycerides with deliberate self-harm among acute psychiatric patients.[19] In 1 study[20] of 168 participants with depression, metabolic syndrome was associated with chronic or repeated depressive symptoms over time.

To gain further insight into the potential prognostic role of cardiovascular and metabolic risk factors in depression, we examined the associations of metabolic syndrome and its components with symptom resolution in a large cohort of older adults.

METHODS

Participants and Procedure

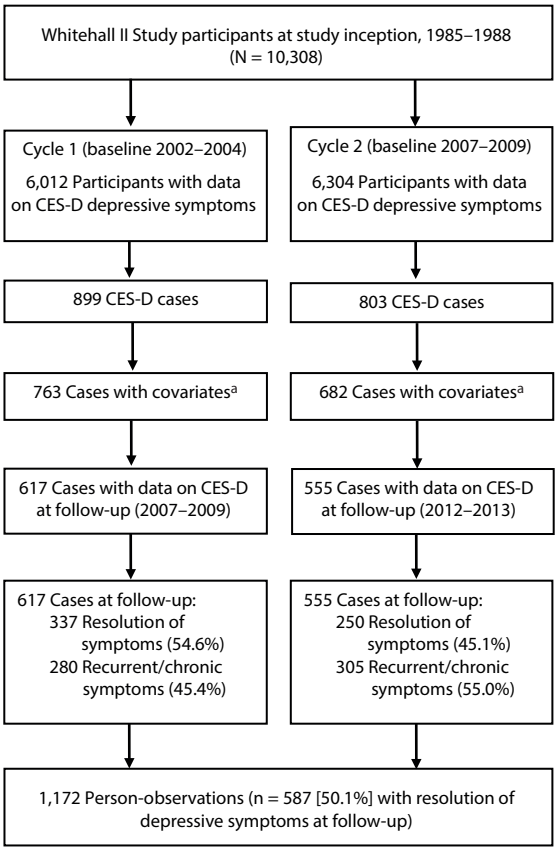
Data were drawn from the Whitehall II study,[21] which was established in 1985 and included all London-based civil servants, aged 35–55 years, working in 20

Clinical Points

- The contribution of metabolic syndrome and its components to the course of depression is not well known.
- An adverse lipid profile, but not other components of metabolic syndrome, may be associated with delayed recovery from depression.

departments. Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committee on the Ethics of Human Research; all participants provided written informed consent. The Center for Epidemiologic Studies Depression scale (CES-D)[22] was first introduced to the study at phase 7 (2002–2004), which forms the baseline of the first cycle of the present study (see the sample selection procedure in Figure 1). The data were structured into 2 separate longitudinal data cycles so that the first data cycle spanned from 2002–2004 to 2007–2009 and the second data cycle spanned from 2007–2009 to 2012–2013. Data were based on a total of 965 individuals (590 men, 375 women), all of whom had depressive symptoms at the cycle baseline. Of these 965 individuals, 410 contributed only to cycle 1, 348 only to cycle 2, and 207 to both cycles. Altogether they produced 1,172 person-observations (Figure 1), among which 587 (50.1%) reported symptom resolution and 585 (49.9%) reported recurrent or chronic depressive symptoms at follow-up. Mean (SD) follow-up time was 4.63 years (0.59): 5.08 (0.33) in cycle 1 and 4.12 (0.35) in cycle 2.

Figure 1. Flowchart of the Sample Selection Procedure for the Main Analysis



[a]Age, sex, socioeconomic status, long-standing illness, and antidepressant use.
Abbreviation: CES-D = Center for Epidemiologic Studies Depression scale.

Depressive Symptoms

The CES-D[22] is a 20-item self-administered scale designed to measure depressive symptoms in the general population. Participants score the frequency with which specific symptoms occurred during the previous week on a 4-point scale (0 = less than 1 day, 1 = 1–2 days, 2 = 3–4 days, and 3 = 5–7 days). These were summed to yield a total score between 0 and 60. Participants scoring 16 or higher are defined as cases of CES-D depressive symptoms. Symptom resolution is denoted as being a case at baseline but not at follow-up. Recurrent or chronic cases were those who reported depressive symptoms at both baseline and follow-up. Severity of depressive symptoms at baseline was defined according to tertiles of the CES-D symptom score distribution: mild = 16–18 points, moderate = 19–23 points, and severe = greater than 23 points.

Metabolic Syndrome

Metabolic syndrome was assessed at the baseline clinical examination of the study cycle and was defined according to the American Heart Association/National Heart, Lung, and Blood Institute 2009 Joint Scientific Statement[23,24] as the presence of 3 or more of the following components: (1) large waist circumference (measured at the study clinic visit): ≥ 102 cm for men (≥ 90 cm for Asian men), ≥ 88 cm for women (≥ 80 cm for Asian women); (2) high triglyceride level: ≥ 150 mg/dL (≥ 1.69 mmol/L); (3) low HDL cholesterol level: < 40 mg/dL (< 1.03 mmol/L) for men, < 50 mg/dL (< 1.29 mmol/L) for women; (4) high blood pressure: ≥ 130 mm Hg systolic blood pressure, ≥ 85 mm Hg diastolic blood pressure, or receipt of antihypertensive medication; and (5) high fasting glucose (≥ 100 mg/dL [≥ 5.56 mmol/L]) or diabetes diagnosis.

Diabetes was defined as a fasting glucose ≥ 7.0 mmol/L or a 2-hour postload glucose ≥ 11.1 mmol/L on the oral glucose tolerance test performed during the Whitehall II study clinical screening or as physician-diagnosed diabetes or use of diabetes medication.[25]

Covariates

Age, sex, socioeconomic status (based on occupational grade categorized as high, intermediate, and low),[21] and ethnicity (white, nonwhite [South Asian, black, other]) were based on survey responses.

Information on comorbid long-standing illnesses was obtained from several data sources: prevalent coronary heart disease was based on data collected at the baseline clinical screening for each study cycle and included definite angina and nonfatal myocardial infarction. Definite angina

was identified via a questionnaire and was corroborated with medical records, abnormalities in a resting electrocardiogram (ECG), an exercise ECG, or a coronary angiogram. Nonfatal myocardial infarction was defined following the World Health Organization MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) criteria[26] and confirmed using data from medical examinations, hospital records of ECGs, and use of cardiac enzymes. Stroke was based on self-reported, doctor-diagnosed stroke, which was further validated by information from the National Health Service (NHS) Hospital Episode Statistics database in England, by manual searches of hospital records, and by letters from general practitioners.[27] Data on prevalent long-standing illnesses other than those described above were based on a list of treated long-standing illnesses during the past 12 months reported in the survey questionnaire and transformed into *ICD-10* diagnostic codes (A15–A28, A80–A99, B15–B24, B50–B60, B64, C, D00–D09, D37–D48, D50–D53, D55–D59, D60–D77, D80–D84, D86, D89, E00–E07, E20–E32, E34–E35, E40–E46, F00–F29, F30–F31, F38–F99, G, H53–H54, H90–H91, I00–I02, I05–I09, I26–I28, I30–I52, I70–I74, I77–I79, I95–I99, J30–J32, J37, J40–J47, J60–J70, J80–J81, J90–J99, K20–K21, K25–K29, K31, K50–K52, K55–K63, K65–K67, K70–K77, K80–K83, K85–K87, L10–L14, L20–L22, L24–L30, L40–L45, L50–L54, M00–M99, N00–N29, N41, N45–N46, N70–N77, Q00–Q07, Q20–Q28, R51–R52, S, T). Prevalence of these comorbidities and prevalence of diabetes (as described previously) were combined to form the variable prevalent comorbid long-standing illness (yes/no). For participants with diabetes or metabolic syndrome, comorbid long-standing illness did not include diabetes.

Body mass index was calculated from measurements of weight and height as kg/m^2 and categorized as normal (< 25.0), overweight (25.0–29.9), and obese (≥ 30.0). Smoking (yes/no) and alcohol use (derived from the number of alcoholic drinks [spirits, wine, and beer] consumed in the last 7 days and classified as none; within the recommended limits [moderate and intermediate drinking], defined as up to 14/21 units for women/men; and above the recommended limits, defined as > 14/21 units)[28] were based on survey responses. Antidepressant, antihypertensive, and lipid-lowering drug use (yes/no) were based on survey responses.

To examine whether the association between lipid levels and recurrent depressive symptoms was nonlinear,[29] we further classified the lipid variables into 3 categories so the lower and higher cut points were the same as that used in the assessment of metabolic syndrome and the other cut point was set to the upper and lower tertiles of the distribution. Thus, the cut points were < 1.03, 1.03–1.60, and > 1.60 for HDL cholesterol among men; < 1.29, 1.29–2.0, and > 2.0 for HDL cholesterol among women; and ≤ 0.90, 0.91–1.68, and ≥ 1.69 for triglycerides in both sexes.

To examine robustness of the findings between high glucose level, diabetes, and resolution of depressive symptoms, we used an alternative formulation of prediabetes in a sensitivity analysis. This was defined as impaired fasting glucose (a fasting glucose between 6.1 and < 7.0 mmol/L and 2-hour glucose < 7.8 mmol/L), impaired glucose tolerance (a fasting glucose < 7 mmol/L and a 2-hour postload glucose between 7.8 and < 11.1 mmol/L), or both.[30]

Statistical Analyses

We used a repeated-measures Poisson regression analysis using generalized estimating equations (GEEs) with exchangeable correlation structure.[31] The GEE takes into account the intraindividual correlation between measurements. Among persons with depressive symptoms at baseline, we first examined associations of metabolic syndrome and its components with the probability of having severe depressive symptoms or antidepressant use at baseline and then with the probability of resolution of depressive symptoms at follow-up. The GEE takes into account the nonindependence of the multiple observations from the same participants when estimating standard errors. Because the analyzed outcomes were common (probability ranging from 12% to 50%), we used log-binomial regression analysis to calculate relative risks (risk ratios) and their 95% confidence intervals (CIs). All models were adjusted for age, sex, socioeconomic status, severity of depressive symptoms, antidepressant use, and comorbid long-standing illness. Models examining metabolic syndrome, HDL cholesterol, and triglycerides were additionally adjusted for lipid-lowering drug use.

A sensitivity analysis was carried out in which participants with coronary heart disease or stroke were excluded from the analyses. In a second sensitivity analysis, we compared participants with metabolic syndrome to those without any long-standing illness to better control for the impact of other comorbid long-standing illness. In a third sensitivity analysis, we used 3-category variables of HDL cholesterol and triglycerides and tested for linearity by entering the 3-category variable into the model as a continuous variable. SAS version 9.4 (SAS, Cary, North Carolina) was used for all analyses.

RESULTS

Altogether, this study included 1,172 person-observations: 723 from men and 449 from women with depressive symptoms, with a mean ± SD age of 62.4 ± 6.6 years at cycle baselines (see Supplementary eTable 1). As expected, as participants aged, the prevalence of comorbid long-standing illness and hypertension increased from the cycle 1 baseline to the cycle 2 baseline, although a more favorable lipid profile was seen in cycle 2 than in cycle 1. Distribution of body mass index expressed as normal weight, overweight, and obese did not differ between cycles, whereas abdominal obesity tended to increase from cycle 1 to cycle 2. The prevalence of smoking was lower and the prevalence of antidepressant use was higher at the baseline for cycle 2 compared to the baseline for cycle 1.

Cross-sectional associations of metabolic syndrome and its components with severe depressive symptoms, as indexed by a CES-D symptom score > 23, and antidepressant use

Table 1. Association of Severity of Depressive Symptoms and Antidepressant Use With Metabolic Syndrome and Its Components at Baseline

Variable	Severe Depressive Symptoms (CES-D depressive symptom score > 23)			Antidepressant Use		
	No. of Person-Observations With Severe Depressive Symptoms	No. of Person-Observations	Risk Ratio (95% CI)[a]	No. of Person-Observations With Antidepressant Use	No. of Person-Observations	Risk Ratio (95% CI)[a]
All	397	1,172		143	1,172	
Metabolic syndrome						
No	289	846	1.00	96	846	1.00
Yes	77	252	0.91 (0.73–1.13)	31	252	1.13 (0.80–1.61)
Components of metabolic syndrome						
IFG or diabetes						
No	266	776	1.00	91	776	1.00
Yes	107	333	0.99 (0.81–1.20)	40	333	1.12 (0.77–1.63)
Abdominal obesity						
No	243	735	1.00	89	735	1.00
Yes	149	429	1.05 (0.87–1.28)	51	429	1.12 (0.77–1.63)
Low HDL cholesterol						
No	345	1,028	1.00	118	1,028	1.00
Yes	46	136	0.99 (0.76–1.27)	21	136	1.37 (0.74–2.51)
High triglycerides						
No	274	790	1.00	82	790	1.00
Yes	68	231	0.84 (0.67–1.05)	33	231	1.35 (0.89–2.04)
Hypertension						
No	177	520	1.00	57	520	1.00
Yes	219	650	1.05 (0.88–1.26)	86	650	1.19 (0.80–1.75)

[a]Adjusted for age, sex, socioeconomic status, and long-standing illness (metabolic syndrome, HDL cholesterol, and triglycerides also adjusted for use of lipid-lowering drugs).
Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale, HDL = high-density lipoprotein, IFG = impaired fasting glucose.

Table 2. Association of Resolution of Depressive Symptoms at Follow-Up With Metabolic Syndrome and Its Components at Baseline

Variable	No. of Person-Observations With Depressive Symptom Resolution	No. of Person-Observations	Model 1, Risk Ratio (95% CI)[a]	Model 2, Risk Ratio (95% CI)[b]	Model 3, Risk Ratio (95% CI)[c]
All	587	1,172			
Metabolic syndrome					
No	430	846	1.00	1.00	1.00
Yes	125	252	0.98 (0.85–1.13)	1.02 (0.87–1.21)	0.98 (0.85–1.13)
Components of metabolic syndrome					
IFG or diabetes					
No	383	776	1.00	1.00	1.00
Yes	177	333	1.04 (0.93–1.16)	1.05 (0.94–1.17)	1.05 (0.94–1.18)
Abdominal obesity					
No	387	735	1.00	1.00	1.00
Yes	195	429	0.90 (0.80–1.01)	0.91 (0.81–1.02)	0.91 (0.81–1.02)
Low HDL cholesterol					
No	527	1,028	1.00	1.00	1.00
Yes	57	136	0.82 (0.67–1.00)[d]	0.81 (0.67–0.98)	0.82 (0.68–1.00)[e]
High triglycerides					
No	408	790	1.00	1.00	1.00
Yes	111	231	0.79 (0.68–0.93)	0.82 (0.70–0.95)	0.81 (0.70–0.95)
Hypertension					
No	273	520	1.00	1.00	1.00
Yes	313	650	0.94 (0.85–1.05)	0.96 (0.86–1.07)	0.97 (0.87–1.09)

[a]Adjusted for age, sex, and socioeconomic status.
[b]Adjusted for all variables in model 1 and additionally adjusted for severity of depressive symptoms and antidepressant use.
[c]Adjusted for all variables in model 2 and additionally adjusted for long-standing illness (metabolic syndrome, HDL cholesterol, and triglycerides; also adjusted for use of lipid-lowering drugs).
[d]*P* value = .049.
[e]*P* value = .045.
Abbreviations: HDL = high-density lipoprotein, IFG = impaired fasting glucose.

among participants with depression at baseline are shown in Table 1. Neither metabolic syndrome nor its components were significantly associated with severe depressive symptoms or antidepressant medication.

In the longitudinal analysis, metabolic syndrome was not associated with depressive symptom resolution at follow-up (Table 2). Of the components of metabolic syndrome, impaired fasting glucose or diabetes, abdominal obesity, and hypertension were not associated with symptom resolution. However, low HDL cholesterol (RR = 0.82 [95% CI, 0.68–1.00; *P* = .045] in the fully adjusted model) and high triglycerides (RR = 0.81 [95% CI, 0.70–0.95; *P* = .007]) were

Table 3. Association of Resolution of Depressive Symptoms at Follow-Up With Metabolic Syndrome and Its Components at Baseline Among Participants Free of Coronary Heart Disease and Stroke

Variable	No. of Person-Observations With Depressive Symptom Resolution	No. of Person-Observations	Model 1, Risk Ratio (95% CI)[a]	Model 2, Risk Ratio (95% CI)[b]	Model 3, Risk Ratio (95% CI)[c]
All	512	1,006			
Metabolic syndrome					
No	377	742	1.00	1.00	1.00
Yes	104	201	1.02 (0.87–1.19)	1.03 (0.89–1.19)	1.03 (0.89–1.19)
Components of metabolic syndrome					
IFG or diabetes					
No	335	677	1.00	1.00	1.00
Yes	150	272	1.09 (0.98–1.21)	1.09 (0.97–1.21)	1.09 (0.98–1.21)
Abdominal obesity					
No	347	656	1.00	1.00	1.00
Yes	161	344	0.92 (0.81–1.05)	0.93 (0.82–1.06)	0.93 (0.82–1.06)
Low HDL cholesterol					
No	464	890	1.00	1.00	1.00
Yes	46	112	0.74 (0.60–0.92)	0.77 (0.62–0.94)	0.77 (0.63–0.95)
High triglycerides					
No	352	678	1.00	1.00	1.00
Yes	100	204	0.75 (0.63–0.89)	0.80 (0.68–0.94)	0.79 (0.67–0.94)
Hypertension					
No	258	494	1.00	1.00	1.00
Yes	253	511	0.97 (0.87–1.09)	0.99 (0.89–1.11)	1.00 (0.89–1.12)

[a]Adjusted for age, sex, and socioeconomic status.
[b]Adjusted for all variables in model 1 and additionally adjusted for severity of depressive symptoms and antidepressant use.
[c]Adjusted for all variables in model 2 and additionally adjusted for long-standing illness (metabolic syndrome, HDL cholesterol, and triglycerides; also adjusted for use of lipid-lowering drugs).
Abbreviations: HDL = high-density lipoprotein, IFG = impaired fasting glucose.

associated with a lower likelihood of symptom resolution at follow-up.

In a sensitivity analysis excluding participants with coronary heart disease or stroke (Table 3), again metabolic syndrome was not associated with symptom resolution after adjustment for all covariates. Also as before, low HDL cholesterol (RR = 0.77 [95% CI, 0.63–0.95; $P = .015$] after all adjustments) and high triglycerides (RR = 0.79; 95% CI, 0.67–0.94; $P = .006$) were associated with lower likelihood of symptom resolution at follow-up.

We also examined the association between metabolic syndrome and depressive symptom resolution after excluding participants with all other long-standing illnesses (n = 593 for the analytic sample). In this healthy subsample, again metabolic syndrome was not associated with symptom resolution at follow-up (RR = 0.93; 95% CI, 0.80–1.09; data not shown).

Supplementary eTable 2 shows that low HDL cholesterol (RR = 0.76 [95% CI, 0.62–0.94] for the lowest vs highest HDL group in the fully adjusted model) and high triglycerides (RR = 0.79 [95% CI, 0.67–0.92] for the highest vs lowest triglycerides group) were associated with lower probability of symptom resolution, and a hypothesized linear rather than nonlinear association was supported (for linear term, $P = .004$ [HDL cholesterol] and $P = .003$ [triglycerides]). These findings were replicated in a subgroup free of coronary heart disease and stroke (1,002 and 882 person-observations, respectively); the RR for the lowest versus highest HDL group was 0.73; 95% CI, 0.59–0.91; the RR for the highest versus lowest triglyceride group was 0.76; 95% CI, 0.64–0.91 (data not shown). Supplementary eTable 2 also shows that when prediabetes and diabetes were analyzed separately in comparison to those without either condition, neither was associated with symptom resolution. Of the covariates assessed at baseline, more severe depressive symptoms, antidepressant use, and age > 65 versus ≤ 65 years at baseline were associated with lower likelihood of symptom resolution.

DISCUSSION

In this large cohort of older adults, we examined the contribution of metabolic syndrome and its components to the course of depression over 5 years among participants who had depressive symptoms at baseline. We found no overall association between metabolic syndrome and resolution of depressive symptoms at follow-up. Of the components of metabolic syndrome, low levels of HDL cholesterol and high levels of triglycerides were associated with an 18% to 19% lower probability of being symptom-free at follow-up, while we found no evidence supporting an association with diabetes, elevated glucose levels, abdominal obesity, or hypertension. These findings were robust to adjustment for several confounding factors and they were replicated in a subgroup of participants free of coronary heart disease and stroke.

Previous studies on the etiology of depression have shown an association between metabolic syndrome and the onset of depression in initially nondepressed individuals.[11,12] High HDL cholesterol (the favorable cholesterol)[16,17] and low triglyceride levels[16] were associated with better prognosis of depression, whereas low HDL cholesterol was associated with longer symptom duration[18] and high triglycerides with deliberate self-harm[19] in small-scale patient populations. One study[20] of a nonclinical sample of 168 cases with

depressive symptoms found that metabolic syndrome predicted chronic or repeated depressive symptoms over time. In general, low rather than high cholesterol levels have been associated with depression and suicide, but these finding are still inconclusive and most studies assessed only total cholesterol levels,[32] although there is some evidence showing associations between low HDL cholesterol levels and suicide.[32] A clear advantage of our study was the large number of observations that enabled a more accurate estimate of the association between metabolic syndrome and symptom resolution in depression. Our detailed analysis of the components of metabolic syndrome revealed that the null association was attributable to the lack of associations with glycemic status, abdominal obesity, and hypertension.

Although there is considerable evidence showing bidirectional associations between diabetes and depression, recent evidence suggests that depression-related biological changes, such as those related to the hypothalamic-pituitary-adrenal cortex and sympathetic nervous system as well as low-grade chronic inflammation, may not be consistently associated with type 2 diabetes.[33] This raises the possibility that the co-occurrence of diabetes and depression is not due to a causal association. Our null finding on the prognostic role of hypertension is in line with a previous meta-analysis[34] of etiologic studies showing no association between hypertension and the onset of depression in old age. However, it is noteworthy that, unlike our study, previous research on the relationship between metabolic syndrome, diabetes, hypertension, and depression has focused on the onset rather than the resolution of depressive symptoms.

Previous etiologic research has produced mixed evidence on the relationship between total cholesterol and mental disorders, with associations observed for both low and high cholesterol levels.[15,29,32] Similarly, a recent meta-analysis[34] found no significant association between dyslipidemia and the onset of depression. However, the meta-analysis used a composite index of dyslipidemia, which precludes direct comparison with our study. Our findings regarding the associations of HDL cholesterol and triglycerides with symptom resolution are consistent with previous prognostic studies[16–19] conducted among small-scale patient populations, suggesting an association between adverse lipid levels and poor prognosis of depression. Our analyses were based on older adults within a community cohort, and the results were replicated in a subpopulation free of coronary heart disease and stroke. Our findings suggest that adverse levels of HDL cholesterol and triglycerides seem to slow recovery from depressive symptoms, even among a "healthy population," suggesting an independent association of these risk factors.

The potential pathways linking adverse lipid levels to poorer recovery from depression include cerebral arteriosclerosis through subcortical small-vessel brain lesions, endothelial dysfunction, homocysteine regulation, inflammation, and white-matter abnormalities in the brain.[34–40] A specific role of HDL cholesterol is its anti-inflammatory effects in the body; it also reduces inflammation in the vascular epithelium and regresses the formation of atherosclerotic plaques.[41] It is probably no coincidence that both low HDL cholesterol and high triglyceride levels were associated with reduced symptom resolution because they are highly correlated (in the present data, Pearson $r = -0.39$, $P < .0001$). Indeed, recent evidence from Mendelian randomization studies suggests that low HDL cholesterol might be a marker of raised triglyceride levels and that high triglyceride levels are causally linked to cardiovascular diseases through raised concentrations of remnant cholesterol and increased low-grade inflammation, foam-cell formation, and atherosclerotic plaques.[42] Consistent with our findings, some evidence is suggestive of an association between high cholesterol levels and depression resistant to antidepressant treatment.[29]

There are a number of limitations to this study. As in all observational studies, causality cannot be established. More randomized controlled trials are needed to examine, for example, whether antidepressant medication augmented by lipid-lowering drugs reduces treatment-resistant depression. Second, as some unmeasured or imprecisely measured factors may lie behind the observed associations, mechanisms underlying these associations need further investigation. Third, we used the self-administered CES-D instrument to assess depressive symptoms instead of using the gold standard, structured interview–based method for the clinical diagnosis of depression. However, the CES-D has been proved to have good validity as a measure of depressive symptoms.[43] In addition, we had no data on past history of depressive episodes. Finally, our participants were from white-collar occupations, which restricts the generalizability of the findings. Replication in large general population–based cohorts is needed.

Specific strengths of our study are a relatively large sample derived from a nonpatient population, coronary heart disease and diabetes measured using gold standard methods, inclusion of a large variety of confounding and mediating factors, and sensitivity analyses that tested the robustness of the findings.

In conclusion, this study adds evidence on the contribution of cardiovascular risk factors to prognosis of depressive symptoms among older adults. Individuals with low HDL cholesterol and high triglyceride levels are less likely to experience symptom resolution than individuals free of these risk factors and are therefore at an increased risk of developing recurrent or chronic depression. These data suggest that an adverse lipid profile rather than other components of metabolic syndrome may delay recovery from depression.

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Potential conflicts of interest: None.

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Additional information: 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. Whitehall II data, protocols, and other metadata are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Metabolic Syndrome and Symptom Resolution in Depression: A 5-Year Follow-Up of Older Adults

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List of Supplementary Material for the article

1. eTable 1 — Characteristics of Participants Based on Observations at the Baseline of Study Cycles Combined and Separately for Each Cycle

2. eTable 2 — Association of Comorbid Longstanding Illness, Cardiovascular and Metabolic Risk Factors, Health Behaviors, Severity of Depressive Symptoms, Antidepressant Use, and Sociodemographic Characteristics at Baseline with Resolution of Depressive Symptoms at Follow-Up

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Supplementary eTable 1. Characteristics of Participants Based on Observations at the Baseline of Study Cycles Combined and Separately for Each Cycle

	All		Cycle 1 (2002-4 to 2007-9)		Cycle 2 (2007-9 to 2012-3)	
Characteristic	No. of Person-Observations	Mean (SD) or %	No. of Person-Observations	Mean (SD) or %	No. of Person-Observations	Mean (SD) or %
Age (years)	1,172	62.4 (6.6)	617	59.8 (6.0)	555	65.2 (6.1)
Sex: men	723	61.7	395	64.0	328	59.1
women	449	38.3	222	36.0	227	40.9
Ethnicity: white	1,014	86.6	532	86.2	482	87.0
South Asian	105	9.0	60	9.7	45	8.1
black	29	2.5	14	2.3	15	2.7
other	23	2.0	11	1.8	12	2.2
SES: high	424	36.2	223	36.1	201	36.2
intermediate	585	49.9	315	51.1	270	48.7
low	163	13.9	79	12.8	84	15.1
Metabolic syndrome: no	846	77.1	457	76.3	389	78.0
yes	252	23.0	142	23.7	110	22.0
IFG or diabetes: no	776	70.0	411	68.5	365	71.7
yes	333	30.0	189	31.5	144	28.3
Abdominal obesity: no	735	63.1	407	66.1	328	59.9
yes	429	36.9	209	33.9	220	40.2
Low HDL cholesterol: no	1,028	88.3	540	87.5	488	89.2
yes	136	11.7	77	12.5	59	10.8
High triglycerides: no	790	77.4	406	73.8	384	81.5
yes	231	22.6	144	26.2	87	18.5
Hypertension: no	520	44.4	287	46.5	233	42.1
yes	650	55.6	330	53.5	320	57.9
Comorbid longstanding illness: no	436	37.2	257	41.7	179	32.3
yes	736	62.8	360	58.4	376	67.8
Body mass index: normal	418	35.9	217	35.2	201	36.8
overweight	486	41.8	260	42.2	226	41.3
obese	259	22.3	139	22.6	120	21.9
Smoking: no	1,066	91.3	558	90.6	508	92.0
yes	102	8.7	58	9.4	44	8.0
Alcohol use: no	271	23.5	134	22.0	137	25.1
within recommended limits	677	58.7	365	59.9	312	57.3
above recommended limits	206	17.9	110	18.1	96	17.6
Severe depressive symptoms: no	775	66.1	411	66.6	364	65.6
yes	397	33.9	206	33.4	191	34.4
Antidepressant use: no	1,029	87.8	548	88.8	481	86.7
yes	143	12.2	69	11.2	74	13.3

Supplementary eTable 2. Association of Comorbid Longstanding Illness, Cardiovascular and Metabolic Risk Factors, Health Behaviors, Severity of Depressive Symptoms, Antidepressant Use, and Sociodemographic Characteristics at Baseline with Resolution of Depressive Symptoms at Follow-Up

	No. of Person-Observations with Symptom Resolution	No. of Person-Observations	Risk Ratio (95% CI)[a]	Risk Ratio (95% CI)[b]
All	587	1,172		
HDL cholesterol: >1.60 (men) >2.00 (women)	184	331	1.00	1.00
1.03-1.60 (men) 1.29-2.00 (women)	343	697	0.90 (0.80-1.00)	0.90 (0.81-1.00)
<1.03 (men) <1.29 (women)	57	136	0.76 (0.61-0.93)	0.76 (0.62-0.94)
P for trend			0.003	0.004
Triglycerides: ≤0.90	205	379	1.00	1.00
0.91-1.68	203	411	0.95 (0.86-1.05)	0.95 (0.86-1.06)
≥1.69	111	231	0.77 (0.65-0.91)	0.79 (0.67-0.92)
P for trend			0.002	0.003
Comorbid longstanding illness: no	242	436	1.00	1.00
yes	345	736	0.88 (0.80-0.98)	0.91 (0.82-1.00)
Prediabetes or diabetes: no	444	880	1.00	1.00
prediabetes (IFG and/or IGT)	77	152	1.00 (0.85-1.16)	1.01 (0.86-1.17)
diabetes	66	140	1.02 (0.87-1.19)	0.99 (0.85-1.16)
Body mass index: normal	213	418	1.00	1.00
overweight	245	486	0.95 (0.85-1.07)	0.97 (0.86-1.08)
obese	125	259	0.95 (0.82-1.09)	0.97 (0.84-1.11)
P for trend			0.40	0.58
Smoking: no	538	1,066	1.00	1.00
yes	47	102	0.95 (0.77-1.17)	0.93 (0.76-1.13)
Alcohol use: within recommended limits	349	677	1.00	1.00
no	121	271	0.94 (0.81-1.09)	0.95 (0.83-1.10)
above recommended limits	108	206	1.00 (0.86-1.17)	1.02 (0.89-1.18)
Severity of depressive symptoms (CES-D score): 16-18	258	394	1.00	1.00
19-23	197	381	0.86 (0.77-0.96)	0.86 (0.77-0.97)
>23	132	397	0.60 (0.52-0.69)	0.62 (0.54-0.71)
P for trend			<0.001	<0.001
Antidepressant use: no	538	1,029	1.00	1.00
yes	49	143	0.72 (0.59-0.88)	0.77 (0.62-0.94)
Age (years): ≤65	400	765	1.00	1.00
>65	187	407	0.93 (0.84-1.03)	0.90 (0.81-1.00)
Sex: men	377	723	1.00	1.00
Women	210	449	0.92 (0.81-1.04)	0.97 (0.86-1.09)
Socioeconomic status: high	237	424	1.00	1.00
Intermediate	279	585	0.87 (0.78-0.98)	0.90 (0.81-1.01)
Low	71	163	0.84 (0.69-1.03)	0.85 (0.70-1.03)
P for trend			0.029	0.038
Ethnicity: white	516	1,014	1.00	1.00
non-white	71	157	0.94 (0.79-1.13)	0.92 (0.77-1.10)

[a]Model 1: adjusted for age, sex, and socioeconomic status.
[b]Model 2: as model 1 and additionally adjusted for severity of depressive symptoms, antidepressant use and longstanding illness (HDL cholesterol and triglycerides also adjusted for use of lipid lowering drugs).
CI, Confidence interval; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.