

Association Between Metabolic Syndrome and Depressive Symptoms in Middle-Aged Adults

Results from the Whitehall II study

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OBJECTIVE — Although it is possible that the association between depression and the metabolic syndrome is a “two-way street,” the metabolic syndrome as a predictor of depression has been little investigated. We examined whether the metabolic syndrome is associated with the onset of depressive symptoms in a cohort of middle-aged British civil servants.

RESEARCH DESIGN AND METHODS — Analyses included 5,232 participants (41–61 years of age) from the Whitehall II prospective cohort study. Depressive symptoms were assessed in 1991–1993 and again 6 years later using the depression subscale from the 30-item General Health Questionnaire. Metabolic syndrome was assessed in 1991–1993, according to National Cholesterol Education Program criteria.

RESULTS — Presence of the metabolic syndrome was associated with an increased risk of future depressive symptoms, odds ratio 1.38 (95% CI 1.02–1.96) after adjustment for potential confounders. Of the five components, only central obesity, high triglyceride levels, and low HDL cholesterol levels predicted depressive symptoms. These components explained most of the association between the metabolic syndrome and the onset of depressive symptoms.

CONCLUSIONS — Our results suggest that the metabolic syndrome, in particular the obesity and dyslipidemia components, is predictive of depressive symptoms.

Diabetes Care 32:499–504, 2009

Evidence of an association between depression and cardiovascular disease (CVD) (1,2) has led some studies to investigate whether the metabolic syndrome may constitute an explanatory mechanism. The metabolic syndrome is defined as a clustering of risk factors that predispose an individual to cardiovascular morbidity and mortality (3,4). It is characterized by elevated abdominal obesity, high triglycerides, high blood pressure, and high fasting blood glucose (FBG), and low HDL cholesterol and represents an important risk factor for CVD

(5). Cross-sectional studies have shown an association between depression and the metabolic syndrome in young adults (6) and in middle-aged populations (7–9). Cross-sectional associations between depressive symptoms and individual components of the metabolic syndrome have been observed in a North American study of elderly male twins (10) but were not evident in a middle-aged cohort from northern Finland (11). The focus of longitudinal studies essentially has been to investigate whether depression predicts the metabolic syndrome; some have

shown that, in middle aged populations, depressive symptoms appear to be associated with an increased risk of the metabolic syndrome in women but not in men (12,13).

Although in most existing research the assumption has been that depression predicts the metabolic syndrome, depression could also be a consequence of the metabolic syndrome. To date, this reverse association has been little investigated. However, a “two-way street” between depression and the metabolic syndrome was suggested by findings from a population-based prospective cohort study in which women with the metabolic syndrome in childhood and adulthood had the highest level of depressive symptoms in adulthood (14). This finding was not observed for men. Further evidence was provided from a cohort of middle-aged women in which Raikkonen et al. (12) showed that anger and anxiety increased in response to the metabolic syndrome. Only one recently published report has investigated the metabolic syndrome as a risk factor for depressive symptoms in middle-aged adults. It showed that the metabolic syndrome may be an important factor for the development of depression in women but not in men (15).

Our objective is to investigate prospectively whether the metabolic syndrome is associated with the onset of depressive symptoms in a cohort of middle-aged British adults free of such symptoms at baseline, after taking into account potential confounders.

RESEARCH DESIGN AND METHODS

The target population for the Whitehall II study was all London-based office staff aged 35–55 years and working in 20 civil service departments (16). Baseline screening (phase 1) took place during 1985–1988 ($N = 10,308$) and involved a clinical examination and a self-administered questionnaire containing sections on demographic characteristics, health, lifestyle factors, work characteristics, social support, and life

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Received 22 July 2008 and accepted 12 December 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 23 December 2008. DOI: 10.2337/dc08-1358.

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events. The clinical examination included measures of blood pressure, anthropometry, biochemical measurements, neuroendocrine function, and subclinical markers of CVD. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 [1988–1990], 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]).

Assessment of metabolic syndrome at phases 3 and 5

The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program (NCEP) (17) based on the presence of three or more of the following: waist circumference >102 cm in men and >88 cm in women, serum triglycerides ≥ 1.7 mmol/l, HDL cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women, systolic/diastolic blood pressure $\geq 130/\geq 85$ mmHg, and fasting glucose ≥ 6.1 mmol/l. Waist circumference was taken as the smallest circumference below the costal margin. Resting blood pressure was measured using the Hawksley Random Zero Sphygmomanometer. Serum triglycerides, HDL cholesterol, and FBG were analyzed as previously described (18).

Assessment of depressive symptoms at phases 3 and 5

We assessed depressive symptoms using the 4-item depression subscale of the 30-item General Health Questionnaire (GHQ) (19). The items, obtained on the basis of factor analysis and comparison with the items of the depression subscale of the 28-item GHQ (20), are “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.” All items were scored on a Likert scale from 0–3 and then summed (range 0–12). Respondents were categorized as free of depressive symptoms if they scored 0–3 or as having depressive symptoms if they scored 4 or more. New-onset depressive symptoms refer to participants who developed symptoms of depression between phases 3 and 5, after excluding participants with depressive symptoms at phase 3. Depressive symptoms assessed with GHQ cannot be equated with clinically diagnosed depression (21).

Assessment of covariates at phase 3

Sociodemographic variables consisted of age, sex, ethnicity (white/South Asian/black), marital status, employment grade, and education. Employment grade, defined on the basis of salary, ranges from 1 to 3, with grade 1 representing the highest level and grade 3 the lowest. Educational attainment was grouped into five levels (no academic qualification, lower secondary, higher secondary, university degree, and higher university degree). Health behaviors measured were current smoker (yes/no), alcohol consumption (grams/day), and intensity of physical activity (based on frequency and duration of physical activity and categorized as high, medium, and low). Prevalent coronary heart disease (CHD) identified using clinically verified events included nonfatal myocardial infarction and definite angina as described previously (22).

Statistical methods

Logistic regression was used to model the association between the metabolic syndrome and each of its components at phase 3 and the onset of depressive symptoms between phases 3 and 5. In model 1, the analyses were adjusted for age, sex, and ethnicity; in model 2, they were additionally adjusted for employment grade, educational level, marital status, smoking habit, alcohol consumption, physical activity, and CHD. Interactions among the metabolic syndrome and the covariates (including sex) were tested and were not found to be statistically significant at $P < 0.05$.

To assess the extent to which components of the metabolic syndrome drive the association with depressive symptoms, we calculated the percent attenuation in the metabolic syndrome–depressive symptoms association after the components separately associated with depressive symptoms were added to the model. The percent attenuation in the association between the metabolic syndrome and depressive symptoms was determined using the formula $\% = \{[(\beta_x - \beta_x \text{ adjusted for } w)/\beta_x]\} \times 100$, where β is the coefficient estimated from the logistic regression model.

To further understand the role of the metabolic syndrome as a risk factor for the onset of depressive symptoms, we performed analyses to explore whether its components act synergistically by testing interactions among them. We used a backward elimination approach that removed all of the 5-, 4-, 3-, and 2-way

interaction terms with $P > 0.05$ from a saturated model that included all of the metabolic syndrome components and their interaction terms. A new variable combining obesity, high triglyceride, and low HDL cholesterol components (seven modalities: 0 = none of the component, 1 = only obesity, 2 = only high triglyceride, 3 = only low HDL cholesterol, 4 = obesity and high triglyceride, 5 = obesity and low HDL cholesterol, 6 = high triglyceride and low HDL cholesterol, 7 = all three components) was constructed to test specifically the combined effects of these three components on onset of depressive symptoms.

In sensitivity analyses, we excluded participants with CHD at phase 3 to explore the contribution of CHD to the association between the metabolic syndrome and onset of depressive symptoms. To assess potential bidirectional effects, we excluded participants free of the metabolic syndrome at phase 3 and performed logistic regression analyses examining associations between depressive symptoms at phase 3 and onset of the metabolic syndrome between phases 3 and 5. All analyses were conducted using SAS software, version 9 (SAS Institute).

RESULTS— Overall, 7,263 individuals participated in phase 5. However, complete data on depressive symptoms at phases 3 and 5, the metabolic syndrome, and all the covariates were available for 5,562 participants (1,604 women and 3,958 men) aged 49.5 ± 6.1 years at phase 3. Of these participants, 330 had depressive symptoms at phase 3 and were excluded in order to identify new-onset depressive symptoms between phases 3 and 5. Compared with those who were excluded, participants included in the analysis ($n = 5,232$) were more likely to be men (71.5 vs. 66.2%, respectively) and younger (49.6 ± 6.08 vs. 49.9 ± 6.06 years, respectively). However, those included versus those excluded did not differ on educational level (participants with no academic qualification: 13.1 vs. 13.7%, respectively) or prevalence of the metabolic syndrome (10.4 vs. 11.4%, respectively). Prevalence of the metabolic syndrome in participants who already had depressive symptoms at phase 3 was 9.7% and was not significantly different from that in participants free from depressive symptoms at both phases 3 and 5 (10.2%).

Characteristics of the participants as a function of the presence of metabolic syn-

Table 1—Characteristics of Whitehall participants according to presence of the metabolic syndrome at phase 3 (1991–1993)

	Metabolic syndrome*		P
	No	Yes	
n	4,685	547	
Women	29.5	20.1	<10 ⁻⁴
Age (year)	49.4 ± 6.1	50.7 ± 6.0	<10 ⁻⁴
White participants	93.7	91.6	0.002
Single or divorced	19.8	21.0	0.85
Low employment grade	12.5	16.4	0.03
No academic level or lower secondary	45.2	49.3	0.06
Current smoker	11.5	12.2	0.62
Alcohol consumption (ml/day)	12.5 ± 14.1	13.0 ± 15.7	0.48
Low level of physical activity	23.8	27.8	0.002
Waist circumference (cm)	84.2 ± 10.5	98.6 ± 10.0	<10 ⁻⁴
Systolic blood pressure	119.2 ± 12.9	131.2 ± 11.6	<10 ⁻⁴
Diastolic blood pressure	78.8 ± 8.9	87.8 ± 7.7	<10 ⁻⁴
HDL cholesterol	1.48 ± 0.40	1.03 ± 0.25	<10 ⁻⁴
Triglycerides	1.26 ± 0.83	2.91 ± 1.52	<10 ⁻⁴
FBG	5.18 ± 0.53	5.77 ± 1.31	<10 ⁻⁴
CHD	2.3	5.1	<10 ⁻⁴

Data are means ± SD for continuous variables or percent. *Diagnosis of the metabolic syndrome was based on the NCEP definition (ref. 17).

drome are shown in Table 1. Prevalence of the metabolic syndrome was 10.4% ($n = 547$). Compared with participants without the metabolic syndrome, the proportion of participants with the metabolic syndrome was lower in women and white participants but was higher in those with a low education level and among those who had low physical activity levels. As expected, participants with the metabolic syndrome had higher waist circumference, triglycerides, blood pressure, and FBG levels and a lower HDL cholesterol concentration than those without the metabolic syndrome.

After phase 3, 428 participants (8.2%) developed depressive symptoms, 7.8% of the men and 9.2% of the women. New-onset depressive symptoms were more common among participants who had the metabolic syndrome at phase 3 (13.5 vs. 10.2%, respectively). Furthermore, a higher rate of new-onset depressive symptoms was observed in participants with the central obesity (14.3 vs. 10.4%), high triglycerides (29.4 vs. 24.9%), and low HDL cholesterol (22.7 vs. 17.8%) components of the metabolic syndrome.

Table 2 shows multivariate models of the association between the metabolic syndrome at phase 3 and onset of depressive symptoms between phases 3 and 5. In analyses adjusted for sex, ethnicity, and age, the odds ratio (OR) (95% CI) of

new-onset depressive symptoms was 1.47 (1.09–1.99) times higher for participants with the metabolic syndrome than for those without. This association remained statistically significant after further adjustment for other sociodemographic factors, health behavior, and CHD: 1.38

(1.02–1.87). Multivariate analyses of the association between each component of the metabolic syndrome and onset of depressive symptoms showed that of the five components only central obesity, high triglyceride levels, and low HDL cholesterol levels were related to greater odds of onset of depressive symptoms between phases 3 and 5, while there was no evidence of an association between hypertension and new-onset depressive symptoms. Unexpectedly, participants with elevated FBG levels were less likely to develop depressive symptoms during the 6-year follow-up. To examine whether the components of the metabolic syndrome had an independent effect, we included all components simultaneously in a model that included only participants with no missing data for any of the metabolic syndrome components ($n = 4,983$ participants; $n = 401$ with new-onset depressive symptoms). None of the components remained significantly associated with the onset of depressive symptoms (obesity 1.28 [0.92–1.77], high triglycerides 1.20 [0.93–1.56], low HDL cholesterol 1.19 [0.90–1.56], hypertension 0.97 [0.77–1.21], high FBG 0.57 [0.32–1.02]).

That nearly half the participants with metabolic syndrome were obese (49.8%) raises the possibility that the association we observed between the metabolic syn-

Table 2—Association of the metabolic syndrome at phase 3 with the onset of depressive symptoms between phases 3 (1991–1993) and 5 (1997–1999)

	n; n with new-onset depressive symptoms	OR (95% CI)	P
Metabolic syndrome	5,232; 428		
Model 1		1.47 (1.09–1.99)	0.01
Model 2		1.38 (1.02–1.87)	0.04
Central obesity	5,182; 424		
Model 1		1.50 (1.11–2.01)	0.007
Model 2		1.42 (1.06–1.91)	0.02
High triglycerides	5,232; 428		
Model 1		1.36 (1.09–1.71)	0.007
Model 2		1.30 (1.03–1.63)	0.02
Low HDL cholesterol	5,232; 428		
Model 1		1.33 (1.04–1.69)	0.02
Model 2		1.26 (0.98–1.61)	0.07
Hypertension	5,232; 428		
Model 1		1.06 (0.86–1.31)	0.57
Model 2		1.05 (0.85–1.30)	0.66
High FBG	5,049; 406		
Model 1		0.58 (0.33–1.04)	0.07
Model 2		0.57 (0.32–1.02)	0.06

Results of logistic regression analyses expressed as OR (95% CI). Model 1 is adjusted for sex, age at phase 3, and ethnicity. Model 2 reflects model 1 additionally adjusted for education, employment grade, marital status, smoking habits, alcohol consumption, physical activity, and CHD.

Table 3—Contribution of the obesity, high triglycerides, and low HDL cholesterol components of the metabolic syndrome to the association between the metabolic syndrome and onset of depressive symptoms

	β	SE	Reduction in effect (%)*
Each component alone			
Obesity	0.409	0.150	—
High triglycerides	0.294	0.116	—
Low HDL cholesterol	0.263	0.125	—
High triglycerides adjusted for obesity	0.234	0.120	20.4
HDL cholesterol adjusted for obesity	0.216	0.127	17.9
All three components included simultaneously in the model			
Obesity	0.322	0.156	21.3
High triglycerides	0.184	0.130	37.4
Low HDL cholesterol	0.143	0.137	45.6
Metabolic syndrome alone	0.389	0.153	—
Metabolic syndrome adjusted for obesity	0.250	0.175	35.7
Metabolic syndrome adjusted for triglycerides	0.241	0.186	38.0
Metabolic syndrome adjusted for HDL cholesterol	0.298	0.178	23.4

Analyses performed on 5,169 participants (423 with new-onset depressive symptoms). *Compared with a model not adjusted for any of the factors. β , logistic regression coefficient.

drome and depressive symptoms is driven mainly by obesity. The percent attenuation of the association between the metabolic syndrome and depressive symptoms by its individual components was as follows: 37.5% for obesity, 38.0% for triglycerides, and 23.4% for low HDL cholesterol. All three components together explained 93% of the association. Obesity explained only 20.4% of the relationship between high triglycerides and depressive symptoms and 17.8% of the association between low HDL cholesterol and depressive symptoms (Table 3). These findings provide support for the hypothesis that the association between the metabolic syndrome and depressive symptoms is partly driven by central obesity but that dyslipidemia is also a major driver.

To test for synergistic effects between each of the components of metabolic syndrome on depressive symptoms, we examined multiple interaction terms, but none were statistically significant (results not shown, data available upon request). However, using a unique variable with all possible combinations of obesity, high triglycerides, and low HDL cholesterol, we found that participants with all three components were at the greatest risk of new-onset depressive symptoms, OR 2.71 (95% CI 1.73–4.24).

Sensitivity analyses

Exclusion of participants with CHD at phase 3 ($n = 136$) had little effect on the

results. After adjusting for sex, ethnicity, and age, the OR (95% CI) for new-onset depressive symptoms was 1.37 (1.00–1.87) times higher for participants with the metabolic syndrome than for those without. No support was found for the hypothesis that depressive symptoms were a consequence rather than a cause of the metabolic syndrome, as there was no association between presence of depressive symptoms at phase 3 and new-onset cases of the metabolic syndrome in participants free of the metabolic syndrome at phase 3: 0.89 (0.60–1.33), $P = 0.57$ after controlling for sex, age, and ethnicity, and 0.81 (0.54–1.22) after adjusting for sociodemographic factors, health behaviors, and CHD (results not shown, but data available upon request).

CONCLUSIONS — We examined associations between presence of the metabolic syndrome and the onset of depressive symptoms in a middle-aged population free of symptoms at baseline. After adjusting for demographic measures, socioeconomic factors, health behaviors, and prevalent CHD, participants with the metabolic syndrome had a higher risk of developing depressive symptoms 6 years later. Of the components of the metabolic syndrome, central obesity, high triglycerides, and low HDL cholesterol were the main contributing factors to this association. There was no evidence to support bidirectional associ-

ations between the metabolic syndrome and depressive symptoms.

Among the 5,562 participants in this study in 1993, prevalence of the metabolic syndrome according to NCEP criteria was 10.4%. Similar levels of prevalence were found in a cohort of healthy middle-aged women in the Healthy Women Study (9.3% in 1988) (13) and in a cohort of middle-aged men participating in the Kuopio Ischemic Heart Disease Risk Factor Study (11% in 1989) (23). Prevalent CHD is a potential source of depression, but in the present study the association between the metabolic syndrome and new-onset depressive symptoms remained significant after controlling for prevalent CHD and in a sub-cohort that excluded participants with this disease. This suggests that the association between the metabolic syndrome and depressive symptoms is not driven by depressive symptoms generated by manifest CHD.

Our findings are consistent with the hypothesis that depressive symptoms may be a consequence rather than a cause of the metabolic syndrome. Prevalence of the metabolic syndrome was no higher in participants with depressive symptoms at baseline than among participants who did not have such symptoms at baseline or at follow-up. This lack of evidence was confirmed in further analyses showing no association between presence of depressive symptoms at baseline and development of the metabolic syndrome during follow-up. A corresponding finding was observed in the Northern Finland 1966 Birth Cohort Study in which the metabolic syndrome defined according to NCEP criteria was not associated with depressiveness and anxiousness in 31-year-old adults (11).

In a middle-aged population-based sample, Koponen et al. (15) found that the metabolic syndrome, assessed using NCEP criteria, was associated with a higher probability of depressive symptoms (measured using the Beck Depression Inventory) after a 7-year follow-up in women but not in men. In another Finnish population-based study, women with the metabolic syndrome in childhood had a higher mean depressive symptom score (Beck Depression Inventory) in adulthood, but again no association was found in men (14). The reasons why these associations should be sex-specific remain unclear and are in contrast to our findings of an association between the metabolic syn-

drome and onset of depressive symptoms 6 years later in both sexes.

An important aspect of our study is the exploration of the relationship between each component of the metabolic syndrome and subsequent onset of depressive symptoms. We found good evidence that central obesity and abnormal lipids were associated with the onset of depressive symptoms. However, the hypertension component was not associated with subsequent depressive symptoms; unexpectedly, high levels of FBG were associated with a lower rather than a higher probability of depressive symptoms. The results for central obesity are in concordance with the Alameda County Study, which showed that obesity was associated with an increased risk of depression 5 years later (24). According to Ross et al. (25), one explanation of the obesity-depression relationship could be devaluation and stigma that may cause overweight and obese individuals to suffer from lower self-esteem and a higher level of depression. Another potential explanation involves unsuccessful weight control by dieting among obese and overweight people that could be more stressful than the obesity per se (25).

It has been argued that the metabolic syndrome is driven almost entirely by central obesity. Our results do not support this position in relation to either the basic association between the metabolic syndrome and depressive symptoms or the associations between the high triglycerides and low HDL cholesterol components of the metabolic syndrome with the onset of depressive symptoms. Thus, the metabolic syndrome–depressive symptoms association does not appear to be simply an artifact of the preponderance of obesity in individuals with the syndrome. While we found no evidence of synergy among the metabolic syndrome components in predicting depressive symptoms, our results showed that central obesity, high triglycerides, and low HDL cholesterol components had a cumulative effect on onset. These findings suggest that a combination of central obesity and abnormal lipids constitutes a risk factor for the onset of depressive symptoms. Further research on prospective associations between components of the metabolic syndrome and the development of depression is needed to confirm our findings and to explore the mechanisms that underlie the association.

Our study has several potential limitations. First, depressive symptoms were

measured using a short scale that is not a measure of a clinically recognized psychiatric disorder. Although the symptom scale is reliable, it does not indicate the severity or the chronicity of the depression. A second limitation concerns the limited generalizability of our findings. Whitehall II study participants are mainly white, office-based civil servants who are not fully representative of the British population (16). Third, despite the extensive level of adjustment in our analyses, with observational data the possibility remains that unmeasured confounders may explain part of the association between the metabolic syndrome and depressive symptoms.

In conclusion, this is apparently the first study to show that the probability of new-onset depressive symptoms 6 years later is higher among men and women with the metabolic syndrome, an association that remains after taking into account a large range of potential confounders. Further research is needed to examine whether prevention of the metabolic syndrome, in particular the obesity and dyslipidemia components, might reduce the onset of depressive symptoms.

Acknowledgments—M.K. is supported by the Academy of Finland (projects 117604, 124322, and 124271). A.S.-M. is supported by a European Young Investigator Award from the European Science Foundation. M.M. is supported by a Medical Research Council (MRC) research professorship. J.E.F. is supported by the MRC (grant G8802774). The Whitehall II study has been supported by grants from the British MRC; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute (Grant HL36310); the National Institute on Aging (Grant AG13196); the Agency for Health Care Policy and Research (Grant HS06516); and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health.

No potential conflicts of interest relevant to this article were reported.

We thank all of the participating civil service departments and their welfare, personnel, and establishment officers; the British Occupational Health and Safety Agency; the British Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team.

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