Depression: An Important Comorbidity With Metabolic Syndrome in a General Population

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OBJECTIVE — There is a recognized association among depression, diabetes, and cardiovascular disease. The aim of this study was to examine in a sample representative of the general population whether depression, anxiety, and psychological distress are associated with metabolic syndrome and its components.

RESEARCH DESIGN AND METHODS — Three cross-sectional surveys including clinical health measures were completed in rural regions of Australia during 2004–2006. A stratified random sample (n = 1,690, response rate 48%) of men and women aged 25–84 years was selected from the electoral roll. Metabolic syndrome was defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (NCEP ATP III), and International Diabetes Federation (IDF) criteria. Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale and psychological distress by the Kessler 10 measure.

RESULTS — Metabolic syndrome was associated with depression but not psychological distress or anxiety. Participants with the metabolic syndrome had higher scores for depression (n = 409, mean score 3.41, 95% CI 3.12–3.70) than individuals without the metabolic syndrome (n = 936, mean 2.95, 95% CI 2.76–3.13). This association was also present in 338 participants with the metabolic syndrome and without diabetes (mean score 3.37, 95% CI 3.06–3.68). Large waist circumference and low HDL cholesterol showed significant and independent associations with depression.

CONCLUSIONS — Our results show an association between metabolic syndrome and depression in a heterogeneous sample. The presence of depression in individuals with the metabolic syndrome has implications for clinical management.

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Recent definitions of metabolic syndrome (1,2) specify the following quantitative criteria: large waist circumference, high blood pressure, dyslipidemia (high triglycerides and low HDL cholesterol), and fasting hyperglycemia with underlying insulin resistance as the likely mechanism. The combination of these components is a strong predictor of cardiovascular disease and type 2 diabetes. Understanding the mechanisms involved and factors associated with the metabolic syndrome is of great interest given the pandemic of obesity and increasing prevalence of the metabolic syndrome (32% in the U.S. adult population in 1999–2000 [3] using the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III [NCEP ATP III] [1], criteria and 28% in our region [4]).

There is an increasing interest in the association between metabolic syndrome and depression and whether causal relationships are involved. The proposed link is consistent with reports that depression is associated with development of diabetes and with poor glycemic control in established diabetes (5). For instance, Björntorp (6) has hypothesized that psychological problems are associated with metabolic disorders via visceral fat accumulation. The postulated role of the hypothalamic-pituitary-adrenal (HPA) axis in the pathogenesis of central adiposity and metabolic syndrome has led to the conceptualization of the metabolic syndrome as a neuroendocrine disorder (7).

To investigate the link between metabolic syndrome and depression, several studies have been conducted with results generally supporting an association of metabolic syndrome with depression. However, the groups studied were not representative samples from the general population with metabolic syndrome, being either relatively young (8,9), men only (10), premenopausal women only (11,12), or a clinically targeted population (13) (Table 1). Other important variations such as study design, psychological measures used, and definition of metabolic syndrome used have led to inconsistent results.

To the best of our knowledge, this is the first study to assess evidence from a randomized sample of a heterogeneous population with a high prevalence of metabolic syndrome (4) to determine whether depression has an important association with metabolic syndrome.

RESEARCH DESIGN AND METHODS

— Three cross-sectional surveys of cardiovascular disease risk factors and related health behavior were carried out in southeastern Australia (14) to obtain rural data for comparison with the

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Table 1—*Studies of depression and metabolic syndrome*

	n	Sex	Age range (years)	Depression measure	Metabolic syndrome measure	Main outcomes
Herva et al. (9)	5,698	Men and women	31 mean	HSCL-25	ATP III	No clear association between metabolic syndrome and psychological distress
Kinder et al. (8)	6,189	Men and women	17–39	SCID	ATP III	Association between metabolic syndrome and depression in women only; high blood pressure and high triglycerides associated with depression
McCaffery et al. (10)	173 pairs	Twin men	≥45	CES-D	*	Small association between metabolic syndrome and depression (participants with self-reported diabetes excluded)
Miller et al. (25)	100	Men and women	18–45	HAM-D; BDI	*	Evidence linking depressive symptoms with inflammatory processes as part of the mechanism for cardiovascular morbidity and mortality
Raikkonen et al. (11)†	425	Women	42–50 (at study entry)	BDI	ATP III	Depression, anxiety, tension, and anger are associated concurrently with and/or predict the risk for developing metabolic syndrome
Raikkonen et al. (12)†	432	Women	Middle-aged	BDI	WHO, ATP III, IDF	Depressive symptoms associated with the cumulative prevalence and risk for developing metabolic syndrome for all criteria used
Vogelzangs et al. (17)	867	Men and women	≥65	CES-D	ATP III	Synergistic relationship between depression, cortisol, and metabolic syndrome
Skilton et al. (13)	1,598	Men and women	30–80	HADS-D	ATP III; IDF	Association between metabolic syndrome and depression in a cohort of subjects at an increased risk of cardiovascular disease

*Authors were not using any of the defined criteria of metabolic syndrome but were analyzing clusters of metabolic factors. †Longitudinal in design. BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies–Depression Scale; HAM-D, Hamilton Rating Scale for Depression; HSCL, Hopkins Symptom Checklist; SCID, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; WHO, World Health Organization.

existing urban data. The first survey was conducted from August to October 2004 in Limestone Coast (LC, South Australia), the second in February to March 2005 in Corangamite Shire (CO, Victoria), and the third in May to October 2006 in the Wimmera region (WI, Victoria). These regions are predominantly rural farming areas.

Each survey used a stratified random sample of the population aged 25–74 years drawn from the electoral roll. Stratification was by sex and 10-year age-groups, with the exception of the combined 25- to 44-year age-group considered as one stratum. The original samples consisted of 1,120 individuals in LC, 1,000 in CO, and 1,500 in WI. After excluding individuals who had died or had left the region, a total of 552 people in LC (participation rate 51%), 415 people in CO (42%), and 596 people in WI (53%) participated in the study. The WI sample included an additional 127 subjects (participation rate 44%) from the age-group 75–84 years.

The survey methodology, as previously described (4), comprised self-administered questionnaires, physical measurements, and laboratory tests. A comparison of the socioeconomic background with population statistics available indicated that the participants closely

resembled the true populations of the areas surveyed (4).

Measures

The questionnaire, which included questions on health behavior, symptoms and diseases, medical history, socioeconomic background, and psychosocial factors, together with the invitation to attend the health check, was sent by mail to all selected participants. Health checks were carried out in local health centers or other survey sites by specially trained nurses.

In the health check, weight, height, waist and hip circumference, systolic and diastolic blood pressure, as well as fasting lipids and glucose were ascertained, and BMI was computed as described in more detail elsewhere (4). The venous blood samples were drawn after an overnight fast of at least 10 h and analyzed at the Flinders Medical Centre Clinical Trials Laboratory, which is internationally accredited for lipid measurement under the Centres for Disease Control Lipid Standardization Program (Atlanta, GA) (4).

Metabolic syndrome definition

The following definitions of metabolic syndrome were used. First, the most recent NCEP ATP III (1) criteria require three or more of the following: waist circumference ≥102 cm for men and ≥88 cm for women; fasting glucose ≥5.6 mmol/l or medication for high blood glucose; systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or antihypertensive medication; triglycerides ≥1.7 mmol/l; and HDL cholesterol <1.03 mmol/l for men and <1.30 mmol/l for women.

Second, the International Diabetes Federation (IDF) (2) criteria specify central obesity with a waist circumference ≥94 cm for men and ≥80 cm for women of Europid origin, plus two or more of the following: fasting plasma glucose ≥5.6 mmol/l or previously diagnosed type 2 diabetes; systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, antihypertensive medication; plasma triglycerides ≥1.7 mmol/l; and plasma HDL cholesterol <1.03 mmol/l for men and <1.29 mmol/l for women.

Psychological measures

Depression and anxiety were measured by the Hospital Anxiety and Depression Scale (HADS) (15). The instrument consists of seven items for anxiety (HADS-A) and seven for depression (HADS-D), reported by respondents over the last week. Responses are scored on items from 0 to 3: separate summed scores for anxiety and depression range from 0 to 21, where normal is 0–7, mild is 8–10, moderate is 11–14, and severe is 15–21. In the present study, we defined anxiety and depression as having a score in the mild to severe range (≥8).

Psychological distress was assessed by the Kessler 10 measure (K10) (16), a 10-item measure of the anxiety and depression symptoms experienced in the most recent 4-week period. Responses are recorded on a five-point scale, and the score is the sum of the responses. Total scores are categorized into two levels of psychological distress: low (10–15) and moderate–high (16–50). The internal consistency coefficients for the HADS-A, HADS-D, and K10 in this study were $\alpha =$ 0.82, 0.79, and 0.87, respectively.

Ethics approval for this study was obtained from the Flinders University Clinical Research Ethics Committee. Informed consent in writing was obtained from participants when they attended the health check component of the survey.

Statistical analysis

Statistical analyses were undertaken using SPSS version 14.0. Internal consistency was determined by using Cronbach's α. Pearson correlation coefficients were used to assess the intercorrelations between depression, anxiety, and psychological distress. Pearson χ^2 test was used to test the associations of depression, anxiety, and psychological distress with the presence of metabolic syndrome. Independent *t* tests were used to compare mean age and alcohol consumption for patients with metabolic syndrome and for healthy subjects. Multivariate analysis of covariance was used to test differences between individuals with the metabolic syndrome and individuals without the metabolic syndrome for psychological distress, anxiety, and depression. ANCOVA was used to examine the association between depression and the five components of metabolic syndrome simultaneously. Analyses were adjusted for age, sex, smoking status, alcohol intake, physical activity, marital status, and education. Nonsignificant covariates were not included in the final models.

RESULTS — For 1,345 men and women aged 25–84 years, information was available for the metabolic syndrome, HADS-D, HADS-A, K10, smoking status, alcohol intake, and physical activity (Table 2). A total of 409 (30.4%) participants met the NCEP ATPIII criteria (1) for metabolic syndrome. A total of 90 participants (6.7%) had diabetes (based on self-reported diabetes or fasting glucose ≥7.0 mmol/l): 71 (5.3%) with and 19 (1.4%) without the metabolic syndrome.

The characteristics of the 409 participants with and 936 without the metabolic syndrome are presented in Table 2, which also shows the characteristics of the 338 subjects without diabetes who had the metabolic syndrome.

When comparing all 409 metabolic syndrome participants with those without the metabolic syndrome, no sex-based prevalence differences were found. Participants with metabolic syndrome were older (mean 60.5 vs. 55.0 years, $P < 0.001$). The correlations between depression (HADS-D) and anxiety (HADS-A), depression and psychological distress (K-10), and anxiety and psychological distress were 0.59 (95% CI 0.56–0.63), 0.66 (0.63–0.69), and 0.72 (0.69–0.74), respectively, and were all significant ($P < 0.001$). Participants with the metabolic syndrome were more likely to have moderate to severe depression (10 vs. 6.9%, $P = 0.069$); but the two groups were not significantly different in psychological distress (30.1 vs. 25.7%, $P = 0.115$) or anxiety (9.8 vs. 10.4%, $P =$ 0.820).

Multivariate analysis showed that participants with metabolic syndrome by NCEP ATP III criteria (1) had higher scores for depression compared with individuals without the metabolic syndrome (mean scores 3.41 vs. 2.95, $P =$ 0.013 [Table 3]) after adjusting for sex, smoking status, alcohol intake, and physical activity.

When each of the components of the metabolic syndrome was considered for all participants, both the HDL cholesterol and waist circumference components were independently associated with depression (Table 3). Participants with lower HDL cholesterol had higher scores for depression compared with individuals with higher HDL cholesterol (mean scores 3.75 vs. 2.93, $P = 0.003$). Participants with a larger waist circumference had higher scores for depression than individuals with smaller waist circumference (mean scores 3.38 vs. 2.86, $P =$ 0.002).

The 338 participants with the metabolic syndrome but without diabetes were similarly more likely to have moderate to severe depression (10.1 vs. 6.9%,

Table 2—*Sample characteristics of participants aged 25–84 years*

	n (%)	*n* (%)	*P*†	*n* (%)	*P*†
	A	B	A vs. B	C	A vs. C
Overall metabolic syndrome	No	Yes (diabetes included)		Yes (diabetes excluded)	
n	936 (100)	409 (100)		338 (100)	
Sex			0.306		0.338
Men	446 (47.6)	208 (50.9)		172 (50.9)	
Women	490 (52.4)	201 (49.1)		166 (49.1)	
Diabetes (self-reported or fasting glucose ≥7.0 mmol/l)	19 (2.0)	71 (17.4)	<0.001	NA	NA
Age (years)	55.0 ± 13.1	60.5 ± 10.8	<0.001	59.8 ± 10.9	<0.001
Smoking			0.250		0.488
Current	132 (14.1)	49 (12.0)		34 (10.1)	
Ex-smoker	303 (32.4)	150 (36.7)		111 (32.8)	
Nonsmoker	501 (53.5)	210 (51.3)		193 (57.1)	
Alcohol (g/week)	7.4 ± 11.6	6.6 ± 10.6	0.196	6.9 ± 10.9	0.442
Daily physical activity (>30 min)	767 (81.9)	314 (76.8)	0.034	261 (77.2)	0.071
Depression	65 (6.9)	41 (10.0)	0.069	34 (10.1)	0.086
Anxiety	97 (10.4)	40 (9.8)	0.820	31 (9.2)	0.604
Psychological distress	241 (25.7)	123 (30.1)	0.115	103 (30.5)	0.108
Metabolic syndrome components*					
Elevated fasting glucose	112 (12.1)	247 (60.1)	<0.001	176 (52.7)	<0.001
Hypertension	441 (47.1)	374 (91.4)	<0.001	306 (40.5)	<0.001
Elevated triglycerides	129 (13.9)	281 (71.1)	<0.001	239 (72.2)	<0.001
Low HDL cholesterol	67 (7.2)	194 (47.8)	<0.001	158 (46.7)	<0.001
Central obesity	226 (24.3)	351 (86.2)	<0.001	288 (85.5)	<0.001

Data are *n* (%) or means ± SD. *Cutoffs are for NCEP ATP III criteria as defined in RESEARCH DESIGN AND METHODS. †*P* values were obtained by χ^2 or independent *t* test, as appropriate. *A*: Participants without metabolic syndrome. *B*: Participants with metabolic syndrome including those with type 2 diabetes. *C*: Participants with the metabolic syndrome, excluding those with type 2 diabetes. NA, not available.

P = 0.086 [Table 2]). Again, no significant differences between groups were found in psychological distress (30.5 vs. 25.7%, *P* = 0.108) or anxiety (9.2 vs. 10.4%, *P* = 0.604). Association of low HDL cholesterol (mean depression scores 3.68 vs. 2.92, *P* = 0.004) and large waist circumference (mean depression scores 3.36 vs. 2.86, *P* = 0.003) with depression were also found (Table 3).

Similar results were obtained when using IDF criteria (2). Participants (*n* = 409) with the metabolic syndrome had higher scores for depression than individuals without the metabolic syndrome (mean scores 3.30 vs. 2.95, *P* = 0.035, data not shown) after controlling for covariates. In the group of 338 participants with the metabolic syndrome but without diabetes, we obtained the same association when using the IDF criteria (mean scores 3.27 vs. 2.95, *P* = 0.070, data not shown). Metabolic syndrome was associated with depression, anxiety, and psychological distress in the 409 participants with metabolic syndrome (*P* = 0.009) as well as the 338 participants without diabetes (*P* = 0.032) when combined in multivariate analyses and adjusted for the same covariates.

CONCLUSIONS — In the present study, we have demonstrated an association between metabolic syndrome and depression. Although the association is modest, it is important because of the increasing prevalence of metabolic syndrome and the effect that depression can have on the ability of patients to success-

Table 3—*Results of ANOVA for mean HADS-Depression scores by metabolic syndrome (NCEP ATP III) and its components for participants aged 25–84 years*

	Including participants with both metabolic syndrome and diabetes (*n* = 1,345)			Excluding participants with both metabolic syndrome and diabetes (*n* = 1,274)		
	Mean (95% CI)	Mean (95% CI)	*P*	Mean (95% CI)	Mean (95% CI)	*P*
Overall metabolic syndrome	Yes	No		Yes	No	
	3.41 (3.12–3.70)	2.95 (2.76–3.13)	0.013	3.37 (3.06–3.68)	2.95 (2.76–3.13)	0.030
Components	Abnormal	Normal		Abnormal	Normal	
Fasting glucose	3.14 (2.84–3.44)	3.06 (2.88–3.24)	0.198	3.03 (2.71–3.35)	3.06 (2.88–3.24)	0.190
Blood pressure	3.18 (2.98–3.38)	2.94 (2.70–3.19)	0.395	3.14 (2.93–3.35)	2.95 (2.70–3.19)	0.414
Triglycerides	3.17 (2.89–3.45)	3.04 (2.85–3.22)	0.281	3.13 (2.84–3.41)	3.02 (2.83–3.21)	0.238
HDL cholesterol	3.75 (3.37–4.13)	2.93 (2.76–3.10)	0.003	3.68 (3.28–4.09)	2.92 (2.75–3.10)	0.004
Waist circumference	3.38 (3.14–3.63)	2.86 (2.66–3.06)	0.002	3.36 (3.10–3.62)	2.86 (2.66–3.06)	0.003

fully make lifestyle changes and comply with medication required for hypertension and dyslipidemia.

The association is demonstrated here in a general population to our knowledge for the first time, whereas earlier studies (Table 1) used subgroups of populations (8–13,17). This association between metabolic syndrome and depression was present regardless of diabetes status. This distinction is important because many individuals with metabolic syndrome have diabetes, which itself is known to be associated with depression (5).

Metabolic syndrome has been defined in several ways that involve quantitative anthropometric, clinical, and laboratory measurements (1,2). For the primary assessment, we chose NCEP ATP III (1) criteria, since these criteria were used in most of the previously reported studies (8,9,11–13,17). In addition, we used the more recently described IDF criteria (2), with a lower cutoff point for waist circumference, and showed that the association was consistent across both definitions.

Of the components of metabolic syndrome, increased waist circumference was associated with depression, as reported in another study using a restricted population sample (9). This association is present regardless of the diabetes status and remained even when adjusted for significant covariates. We also found a significant independent relationship between low HDL cholesterol level and depression (Table 3). This finding appears to be consistent with other recent research (17), but the underlying mechanism remains unknown.

There has been little consistency in the psychological tests used in previous studies to measure depression (Table 1). Assessment varies from individual interview instruments (e.g., The Structured Clinical Interview for DSM Disorders or the Hopkins Symptom Checklist) to self-reported epidemiological measures (e.g., Centre for Epidemiological Studies–Depression Scale) (Table 1). Most measures include somatic components of depression, and the length of recall ranges from present symptoms to past months. Symptoms are recorded in either intensity or presence. In this study, we used the HADS, which has been designed for and validated in medical patients. It measures the presence of cognitive and affective components of depression and, unlike other instruments, excludes many of the somatic symptoms of depression (fatigue, loss of appetite and weight, sleep disturbance, psychomotor changes) that may overlap with physical problems. In addition, the length of recall is limited to the past week. The HADS is widely used in population health studies and screening in primary care, although it has only been used in one reported study (13) linking metabolic syndrome and depression.

The pathophysiological basis for the association between metabolic syndrome and depression is likely to be complex and to involve the inflammatory state that has been described as a consequence of central obesity (18). Björntorp (7) postulated that psychosocial factors, including depression, can activate the HPA axis, producing hypersecretion of corticotrophin-releasing hormone, adrenocorticotropic hormone, and cortisol. This dysregulation of the HPA axis promotes deposition of visceral adipose tissue (6), which secretes inflammatory cytokines such as interleukin (IL)-1 and IL-6 and tumor necrosis factor (TNF)-α (19,20). Both IL-6 and TNF-α have been implicated in insulin resistance, which is considered to be the key factor in the metabolic abnormalities (21) of the metabolic syndrome. The proinflammatory response associated with depression may also have a direct effect on dyslipidemia (22). An alternative construct of the link between metabolic syndrome and depression places development of central obesity and activation of inflammatory processes as the initiating step. Depression is seen as being a consequence of this immune activation (23). In this model, development of depression is analogous to "sickness behavior," which can be associated with viral infection or other causes of immune activation. Dysregulation of the HPA axis can occur via cytokine-induced stimulation of the central noradrenergic stress system (24).

The main limitation of our study is the cross-sectional design, which does not allow for the demonstration of the existence of HPA axis activation and an inflammatory state in participants with central obesity. Establishment of this link requires both longitudinal investigation and further analysis of blood samples, which would allow direct examination of the link between depression, inflammatory state, and metabolic syndrome. Another limitation of this study is the rural population; the association still needs to be demonstrated in urban groups as well as those who have greater cultural and socioeconomic diversity. While the characteristics of participants in our study closely resembled those of the local populations surveyed (4), it is possible that depressed individuals may have been less likely to participate. If this is the case, the present findings could over- or understate the association.

In summary, our data show an association between the metabolic syndrome and the cognitive and affective components of depression in a general population, where the prevalence of depression in individuals with the metabolic syndrome is 50% higher. The importance of our study lies in the heterogeneity of the sample used. Contrasting other studies, conclusions we have made are unlikely to be attributed to idiosyncrasies of the sample. Based on the findings in this study, awareness of depressive symptoms as part of metabolic syndrome could be important in clinical management as in other chronic diseases. Acknowledgment of depressive symptoms by the practitioner and the patient should improve ability to undertake lifestyle changes with adjustment of physical activity and food intake, as well as adherence to medications that are likely to be compromised by depression. Identification and management of depression should therefore precede or accompany other measures in the management of metabolic syndrome. It is also possible that treatment of metabolic syndrome with lifestyle changes will ameliorate depression through reduction of visceral adiposity and inflammation. Intervention studies to address this hypothesis could provide further insight into the relationship between depression, central obesity, and inflammation.

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