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Generalised Anxiety Disorder is Associated with Metabolic Syndrome in the Vietnam Experience Study

Douglas Carroll, PhD[a], Anna C. Phillips, PhD[a], G.Neil Thomas, PhD[b], Catharine R. Gale, PhD[c], Ian Deary,PhD[d], G.David Batty, PhD[d,e]

[a]School of Sport & Exercise Sciences, University of Birmingham, UK

[b]Epidemiology, Public Health and Biostatistics, School of Medical and Dental Sciences, University of Birmingham, UK

[c]MRC Epidemiology Resource Centre, University of Southampton, UK

[d]MRC Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK

[e]MRC Social & Public Health Sciences Unit, University of Glasgow, UK

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Address correspondence to: Douglas Carroll, PhD, School of Sport and Exercise Sciences, University of Birmingham, Birmingham B15 2TT, England. E-mail:carrolld@bham.ac.uk

Abstract

Background: Few studies have explored the relationship between major mental health disorders and metabolic syndrome (MetS), although both have been linked to cardiovascular disease. The present study examined the cross-sectional associations of major depressive disorder (MDD) and generalized anxiety disorder (GAD) with MetS in a large study of male US veterans. Methods: The analyses were cross-sectional. Participants (N = 4256) were drawn from the Vietnam Experience Study. From military service files, telephone interviews, and a medical examination, occupational, socio-demographic, and health data were collected. One-year prevalence of MDD and GAD was determined using DSM-III criteria. MetS was ascertained from data on: body mass index; fasting blood glucose or a diagnosis of diabetes; blood pressure; HDL cholesterol; and triglyceride levels. Results: In models that adjusted for age, $p = .01$, and additionally for place of service, ethnicity, marital status, smoking, alcohol consumption, IQ at enlistment, household income in midlife, and education grade achieved, $p = .02$, GAD was positively associated with MetS. MDD was not related to MetS. Conclusions: Depression has very much been the focal condition for studies on mental health and physical health outcomes. The current data suggest that future research should perhaps pay equal attention to GAD.

Key words: generalised anxiety disorder, major depressive disorder, metabolic syndrome, veterans.

Metabolic syndrome (MetS) is a prevalent cluster of symptoms (obesity, high triglyceride levels, low levels of HDL cholesterol, raised blood pressure, and high levels of fasting blood glucose or a diagnosis of diabetes), that increases risk for cardiovascular and all-cause mortality (1). Recently, there has been interest in the relationship between affective disorders and MetS. The bulk of this research has focused on depression and although contrary indications exists (2), there is evidence of a positive association between depression and MetS (3-10). However, the vast majority of these studies were concerned with depressive symptoms; a recent review (11) identified only two studies examining major depressive disorder (MDD) in this context. In a small study of outpatients, those who still had a diagnosis at 6-year follow-up showed a higher prevalence of MetS (7). In a larger scale study, a history of MDD was associated with MetS in women but not men (5). Much less attention has been paid to anxiety and MetS and the three most recent studies reported null findings (2, 9, 12). However, an earlier study of women found an association between MetS and increased anxiety seven years later (3). These studies have all been concerned with anxiety symptoms; no study has tested the association with generalised anxiety disorder (GAD). The present analyses examined the associations between MDD and GAD and MetS in a cohort of male US veterans from the Vietnam Experience Study.

Methods and Materials

The effective sample size was 4256. Ethical approval for the study was given by various bodies, including the US Centers for Disease Control. Details of sampling at each stage of data collection are shown in Figure 1. Inclusion criteria were: entered military service between January 1, 1965 and December 31, 1971; served only one term of enlistment; served at least 16 weeks of active duty; earned a military specialty other than "trainee" or "duty soldier"; had a military pay grade at discharge no higher than sergeant. Information on place of service, ethnicity, and cognitive ability from the Army General Technical Test (referred to as "IQ") was extracted from the military archives. From the subsequent telephone survey, socio-economic position was measured using household income in midlife and the grade from which participants left school. Frequency of alcohol consumption was classified as number of units per week. Smoking habits and marital status were ascertained using standard questions. Participants were asked whether they had a range of physician-diagnosed diseases including hypertension, cancer, coronary heart disease (CHD), and diabetes (13).

Mean age at medical examination was 38.3 yr. (range: 31.1 to 49.0). From a fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer (13). Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-

coupled system (13). Blood pressure was measured twice in the right arm using a sphygmomanometer and an average computed. Height and weight were measured to calculate body mass index (BMI, kg/m^2). MetS was defined as having at least three of: BMI > 30 kg/m^2 (in the absence of waist circumference data, BMI at this threshold is regarded by World Health Organization as an acceptable substitute in defining MetS); triglycerides ≥ 1.7 mmol/l (150 mg/dl); HDL cholesterol < 1.036 mmol/l (40 mg/dl); blood pressure ≥ 130/85 mmHg or taking antihypertensive medication; fasting glucose ≥ 6.1 mmol/l (110 mg/dl) or taking diabetes medication. Psychological morbidity was assessed using the Diagnostic Interview Schedule (version 3A) as administered by a trained psychological technician. Study participants were considered positive for GAD and MDD if they reported a pattern of symptoms in the previous 12 months that satisfied DSM III criteria.

Demographic, service, health behaviour, metabolic, and haemodynamic variables were compared between those with and without MetS using χ^2 and ANOVAs. Logistic regression was used to examine the relationships between MDD, GAD, and MetS, first in age-adjusted analyses and then in analyses additionally adjusting for place of service, ethnicity, marital status, alcohol consumption, smoking, IQ, household income, and education grade.

Results

Seven hundred and seventy-three (18%) of the men were identified as having MetS. The demographic, health behaviour, service-related, metabolic, and haemodynamic characteristics of those with and without MetS are presented in Table 1. Aside from differing on all the components of MetS, participants with MetS were slightly older, had lower IQ scores and a briefer education, were less likely to be divorced, widowed or separated and more likely to come from ethnic groups other than white or black. Two hundred and seventy-seven (7%) participants had MDD and 411 (10%) GAD. MDD was not significantly associated with MetS in age-adjusted or fully adjusted models. However, there was a positive association between GAD and MetS in the age-adjusted model, OR = 1.38, 95%CI 1.07 – 1.77, $p = .01$. The descriptive statistics are presented in Table 1. Full adjustment did not attenuate this association, OR = 1.36, 95%CI 1.05 – 1.76, $p = .02$. Since depression and anxiety have been associated with CHD, the analyses were repeated excluding those participants who reported a diagnosis of CHD (N = 56). The results were virtually identical to those reported above. Depression and anxiety are highly co-morbid conditions. In the present sample, MDD and GAD were significantly correlated, $C(1) = .38$, $p < .001$, and 153 (4%) were diagnosed with both conditions. In competitive models, entering MMD alone, GAD alone, and their co-morbidity simultaneously, only GAD was

associated with MetS: OR = 1.45, 95%CI 1.07 – 1.96, p = .02, for age-adjusted and, OR = 1.39, 95%CI 1.02 – 1.89, p = .04, for fully adjusted models, respectively.

Discussion

Contrary to expectation, MDD was not associated with MetS. There was, however, a positive association between GAD and MetS that was not attenuated following adjustment for a range of covariates. This again contrasts with the results of previous studies. However, these have been concerned with symptoms of anxiety and this study is the first we know of to examine GAD in this context. Further, only two studies, to date, have explored the links between MDD and MetS (5,7). The much larger of these two studies reported an association between MDD and MetS in women, but not men (5). Thus, the apparent discrepancy between the present findings and those of others may be more illusory than real. Of the components of MetS, it was hypertension, obesity, and triglycerides that differentiated those with and without GAD. There was no association with diabetes.

With cross-sectional analyses it is impossible to determine the direction of the association and whether it is causal. If anxiety precedes MetS, there are at least two pathways through which it might contribute to the aetiology of MetS. First, anxiety has been associated with unhealthy behaviour, such as smoking, binge drinking, physical inactivity, and unhealthy diet (14, 15). However, despite the fact that participants with GAD consumed more units of alcohol per week and were more likely to be current smokers, p <.001 in both cases, the present association between GAD and MetS was unaffected by adjustment for smoking and alcohol consumption. Second, it has been postulated that hypothalamic-pituitary-adrenocortical dysregulation associated with affective disorders, including anxiety, may contribute over time to MetS (3). There is evidence linking anxiety with altered cortisol activity; high levels of anxiety symptoms were found to be associated with a less pronounced cortisol awakening response (16). However, it remains possible that the causal pathway is from MetS to GAD. MetS has been shown to predict symptoms of anxiety seven years later (3), whereas the reverse was not found (3, 12). Further, it is reasonable to presume that diagnosis of some of the components of MetS may be anxiolytic. For example, irrespective of actual blood pressure levels, perceived hypertensive status was positively associated with anxiety (17).

The present study may have other limitations. As the sample was exclusively male, there is the issue of generalisation. A recent review concluded that evidence relating depression to MetS was stronger for women than men (11). Our failure to find an association for depression might also reflect lower power, since there were fewer participants with MDD than GAD. Severely depressed veterans

may also have been less likely to participate in the medical, which may have accounted for the attenuated associations for MDD. This seems unlikely, though, given that only 10 (<0.2%) veterans were unable to attend because of physical/mental disability, and only 372 (<6%) refused to attend: the main reasons being lack of interest or unwillingness to travel. Moreover, underestimation in the present study would make the association between GAD and MetS even more compelling. Finally, although we adjusted for several possible confounders, residual confounding as a consequence of poorly measured or unmeasured variables cannot be wholly discounted. For example, both GAD and MetS are associated with poor sleep quality (18, 19).

In conclusion, this analysis showed that GAD was positively associated with MetS in Vietnam veterans. Depression has been the main focus for studies of mental health and physical health outcomes. The current data suggest that future research should perhaps pay equal attention to GAD.

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Disclosure

None of the authors have a conflict of interest.

References

1. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al (2002): The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709-2716.
2. Herva A, Rasanen P, Miettunen J, Timonen M, Laksy K, Veijola J, et al (2006): Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med* 68:213-216.
3. Raikkonen K, Matthews KA, Kuller LH (2002): The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism:* 51:1573-1577.
4. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D (2003): Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosom Med* 65:490-497.
5. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP (2004): Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med* 66:316-322.
6. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M (2008): Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatr* 69:178-182.
7. Heiskanen TH, Niskanen LK, Hintikka JJ, Koivumaa-Honkanen HT, Honkalampi KM, Haatainen KM, et al (2006): Metabolic syndrome and depression: a cross-sectional analysis. *J Clin Psychiatr* 67:1422-1427.
8. Dunbar JA, Reddy P, Davis-Lameloise N, Philpot B, Laatikainen T, Kilkkinen A, et al (2008): Depression: an important co morbidity with metabolic syndrome in a general population. *Diabetes Care*.
9. Skilton MR, Moulin P, Terra JL, Bonnet F (2007): Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatr* 62:1251-1257.
10. Vaccarino V, McClure C, Johnson BD, Sheps DS, Bittner V, Rutledge T, et al (2008): Depression, the metabolic syndrome and cardiovascular risk. *Psychosom Med* 70:40-48
11. Goldbacher EM, Matthews KA (2007): Are psychological characteristics related to risk of the metabolic syndrome? A review of the literature. *Ann Behav Med* 34:240-252.

12. Raikkonen K, Matthews KA, Kuller LH (2007): Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. *Diabetes Care* 30:872-877.
13. The Centers for Disease Control Vietnam Experience Study (1988): Health status of Vietnam veterans. II. Physical Health. *JAMA* 259:2708-2714.
14. Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, et al (2008): The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatr* 30:127-137.
15. Bonnet F, Irving K, Terra JL, Nony P, Berthezene F, Moulin P (2005): Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis* 178: 149-152.
16. Therrien F, Drapeau V, Lupien SJ, Beaulieu S, Dore J, Tremblay A, et al (2008): Awakening cortisol response in relation to psychosocial profiles and eating behaviors. *Physiol Behav* 93:282-288.
17. Spruill TM, Pickering TG, Schwartz JE, Mostofsky E, Ogedegbe G, Clemow L, et al (2007): The impact of perceived hypertension status on anxiety and the white coat effect. *Ann Behav Med* 34:1-9.
18. Tyrer P, Baldwin D (2006): Generalised anxiety disorder. *Lancet* 368:2156-2166.
19. Jennings JR, Muldoon MF, Hall M, Buysse DJ, Manuck SB (2007): Self-reported sleep quality is associated with the metabolic syndrome. *Sleep* 30:219-223.

Table 1. Descriptive characteristics of those with and without metabolic syndrome.

		Metabolic syndrome (N = 773)		No metabolic syndrome (N = 3483)		*p*
		Mean	SD	Mean	SD	
Metabolic Syndrome Markers:						
BMI (kg/m^2)		30.00	4.16	25.03	2.96	<.001
Triglycerides (mg/dL)		214.20	151.22	91.97	56.70	<.001
HDL cholesterol (mg/dL)		34.85	7.78	46.85	12.24	<.001
SBP (mmHg)		131.46	11.87	121.13	11.25	<.001
DBP (mmHg)		91.16	8.64	82.56	8.88	<.001
Blood glucose (mg/dL)		104.57	28.06	92.04	12.35	<.001
Covariates:						
Age at medical examination (years)		38.67	2.51	38.25	2.51	<.001
Units of alcohol per week		6.69	15.46	7.17	14.18	.40
Standardised IQ score from enlistment		99.63	15.03	101.75	15.20	<.001
Grade achieved in education		13.04	2.26	13.35	2.31	.001
		N (%)		N (%)		*p*
Metabolic Syndrome Markers:						
Obese		396 (51)		154 (4)		<.001
Hypertension Diagnosis		189 (24)		252 (7)		<.001
Diabetes Diagnosis		27 (4)		22 (1)		<.001
Predictor variables:						
MDD		57 (7)		220 (6)		.28
GAD		94 (12)		317 (9)		.009
Covariates:						
Place of service	Ever in Vietnam	444 (63)		1905 (55)		.29
	Other overseas	195 (21)		900 (26)		
	US only	134 (17)		678 (19)		
Ethnicity:	White	633 (82)		2857 (82)		.005
	Black	74 (10)		422 (12)		
	Other	66 (8)		204 (6)		
Household income in midlife	<$20,000	234 (30)		968 (28)		.35
	-$40,000	380 (49)		1749 (50)		
	>$40,000	159 (21)		766 (22)		
Smoking Status:	Non smoker	194 (25)		891 (26)		.85
	Ex smoker	226 (29)		983 (28)		
	Current smoker	353 (46)		1609 (46)		
Marital Status:	Married	612 (79)		2519 (72)		< .001
	Divorced/separated/widowed	99 (13)		668 (19)		
	Never married	62 (8)		296 (9)		

Figure 1: Sampling in the Vietnam Experience Study