Cardiovascular and cortisol reactions to acute psychological stress and cognitive ability in the Dutch Famine Birth Cohort Study

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Generalised Anxiety Disorder is Associated with Reduced Lung Function in the Vietnam Experience Study

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Abstract

Background: There is no clear consensus in the few studies to have explored the relationship between major mental health disorders and lung function. The present study examined the cross-sectional associations of generalized anxiety disorder (GAD) and major depressive disorder (MDD) with lung function in a large study of male US veterans. Methods: Participants (N = 4256) were drawn from the Vietnam Experience Study. From military files, telephone interview, and a medical examination, anthropometric, socio-demographic, and health data were collected. One-year prevalence of GAD and MDD was determined using DSM-III criteria. Forced expiratory volume in one second (FEV$_1$) was measured by spirometry. Results: In models that adjusted for age and height, both GAD, $p < .001$, and MDD, $p = .004$, were associated with lower FEV$_1$. In models additionally adjusting for weight, place of service, ethnicity, marriage, smoking, alcohol consumption, income, education, and major illness, GAD was still associated with poorer lung function, $p = .01$, whereas MDD was not, $p = .18$. Conclusions: Depression has very much been the focus of studies on mental health and physical health status. The current findings suggest that future research should perhaps pay equal attention to GAD.

Key words: forced expiratory volume; generalised anxiety disorder; lung function; major depressive disorder

INTRODUCTION

Poor lung function, typically indexed by low forced expiratory volume (FEV_1), has been shown to predict all-cause and cause specific mortality (1-3), even in non-smokers (4, 5). Mental health problems, most noticeably MDD and GAD, are prominent contributors to overall societal disease burden (6, 7). Further, both depression and anxiety have been implicated in diseases such as asthma (8, 9) and chronic obstructive pulmonary disease (10, 11), both of which are characterized by impaired FEV_1. However, there is a distinct shortage of studies examining the relationship between objectively measured lung function and psychiatric morbidity particularly in non-clinical samples. Lower lung function was related to increased prevalence of symptoms of depression, but not anxiety, in analysis of 5,544 US adults (12). In contrast, in a study of 2,443 young Australians, MDD and GAD were not associated with FEV_1, although both were related to an increased prevalence of asthma and greater asthma medication use (8). Given the paucity of available evidence, as well as its inconsistency, we examined the relationship between MDD and GAD, measured by standard psychiatric assessment, and lung function in a large, well characterized cohort of US army veterans. It is worth noting that in this cohort GAD has proved to be as strong, if not stronger, a predictor than MDD of health outcomes such as all-cause and cardiovascular disease mortality (13), metabolic syndrome (14) and hypertension (15). However, in general, GAD has received far less attention in the context of physical health outcomes than MDD.

MATERIALS AND METHODS

Participants

The sample size was 4,256; the participants were all male. 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 have been described elsewhere (13). In brief, 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.

Data Collection

Information on place of service, and ethnicity 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, and
diabetes.

   Mean age at medical examination was 38.3 years (range: 31.1 to 49.0) and the average
length of time between demobilization and the medical examination was 15.8 years (range 9.1
to 20.5). This time lag was highly correlated with age at the medical examination, r (4254) =
.73, *p* <.001. Height and weight were measured. FEV_1 was determined by spirometry. Flow
volume loops were recorded by a MedScience 570 Wedge Spirometer and a Digital DEC
Writer 111 used to transmit the analogue data from the spirometer to a pulmonary function
computer. The spirometer was calibrated daily; at the beginning of each day, atmospheric
pressure and temperature were entered into the computer. For quality control, on each day one
participant was randomly selected for repeat testing by a different examiner. Reproducibility
was good and the coefficient of variation was 4.4%. 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
(16). The diagnosis of GAD requires persistent anxious mood, as indicated by the presence of
three of four group of symptoms: motor tension; autonomic hyperactivity (sweating, heart
pounding); apprehensive expectation; vigilance and scanning. The diagnosis of MDD requires
persistent dysphoria or loss of interest in all or almost all usual activities and pastimes. At least
four of the following symptoms have to be present: poor appetite or significant weight loss;
insomnia or hypersomnia; psychomotor agitation or retardation; loss of pleasure in usual
activities; loss of energy; feelings of worthlessness; diminished ability to concentrate; thoughts
of death or suicidal ideation. For the supplementary analysis, a diagnosis of PTSD and panic
disorder was also examined, based on the DSM III criteria. The diagnosis of PTSD was given

when symptoms were suffered following exceptional and traumatic events experienced or
witnessed. The diagnosis requires re-experiencing the event in dreams or through recollections
and numbing of responsiveness. Two of six other symptoms must be present: hyper-alertness;
guilt about survival; sleep disturbance; cognitive problems; avoidance of recollection;
intensification of symptoms when exposed to similar events. The diagnosis of a panic disorder
requires recurrent panic attacks manifested by the sudden onset of intense apprehension, fear,
or terror, often associated with feelings of impending doom. The most common symptoms
experienced during an attack are: breathing difficulty; heart pounding; chest pain or
discomfort; choking or smothering sensations; dizziness; feelings of unreality; tingling in the
hands or feet; hot and cold flushes; sweating; faintness; trembling or shaking; and fear of
dying.

Statistical Analysis

Demographic, service, health behaviour and status variables were compared between those
with and without GAD and MDD using χ^2 and ANOVAs. Correlation and ANOVA were used
to examine the association between FEV_1 and the various covariates. ANCOVA was used to
examine the relationships between MDD, GAD, and FEV_1, first in age and height adjusted
analyses, and then in analyses additionally adjusting for weight, place of service, ethnicity,
marital status, alcohol consumption, smoking, household income, education grade, and
diagnosed major illness (cancer, coronary heart disease, diabetes, hypertension). Partial η^2 is
reported as a measure of effect size.

RESULTS

Main Analyses

Table 1 presents the summary statistics for those with and without GAD and MDD. Those
with GAD or MDD were younger, consumed more alcohol, had a shorter education and a
lower income, were more likely to smoke, to have served in Vietnam, have a serious illness,
and were less likely to be married. FEV_1 was positively associated with height, weight, the
absence of a major diagnosed illness, a longer education, and being white ($p < .001$). Those

who were widowed, separated, or divorced and those with a lower income had poorer lung function ($p < .01$). In ANCOVA models adjusting for age and height, both GAD (mean = 3.9 versus 4.1L) and MDD (mean = 3.9 versus 4.0L) were associated with lower FEV_1 values, $F(1,4252) = 19.70$, $p < .001$, $\eta^2 = .005$ and $F(1,4252) = 8.18$, $p = .004$, $\eta^2 = .002$, respectively. In a model that additionally adjusted for all the other covariates, GAD was still negatively associated with FEV_1, $F(1,4243) = 6.40$, $p = .01$, $\eta^2 = .002$. However, the association between MDD and FEV_1 was no longer statistically significant, $F(1,4243) = 1.83$, $p = .18$, $\eta^2 = .000$. One hundred and fifty three (4%) of the veterans had co-morbid GAD and MDD. ANCOVA, adjusting for age and height, comparing those who were co-morbid, those with GAD alone, MDD alone, and neither condition, yielded a significant group effect, $F(3,4250) = 7.02$, $p < .001$, $\eta^2 = .005$; post hoc analyses indicated that those who had co-morbidity and those with GAD alone had poorer lung function than those with neither condition ($p < .05$ in each case). This effect is illustrated in Figure 1. However, it is important to note the overall groups effect was no longer statistically significant in the fully adjusted model, $F(3,4241) = 2.15$, $p = .09$, $\eta^2 = .002$. In order to explore the impact of utilizing alternative computations of lung function, FEV_1 was also computed as $FEV_1/height^2$ (17) and as percentage of predicted FEV_1 using a standard algorithm to calculate predicted FEV_1 (18). In these analyses, the results were almost identical to those previously reported; GAD was more strongly and robustly associated with lung function than was MDD.

[Insert Table 1 and Figure 1 about here]

Supplementary Analyses

Supplementary analyses were conducted to examine the relationship between FEV_1 and other psychological measures. In all of these, fully adjusted models were tested. The associations with lifetime GAD, $F(1,4243) = 1.87$, $p = .17$, $\eta^2 = .001$, and MDD, $F(1,4243) = 2.61$, $p = .11$, $\eta^2 = .001$, were not statistically significant, nor were the associations with one-year, $F(1,4241) = 2.79$, $p = .10$, $\eta^2 = .001$, and lifetime, $F(1,4242) = 2.08$, $p = .13$, $\eta^2 = .001$, post-traumatic stress disorder and one-year, $F(1,4243) = 1.37$, $p = .24$, $\eta^2 < .001$, and lifetime, $F(1,4243) = 1.44$, $p = .23$, $\eta^2 = .001$, panic disorder.

DISCUSSION

In analyses that adjusted only for age and height, GAD and, to a lesser extent, MDD were associated with lower FEV_1. With additional adjustment for circumstantial, socio-demographic, and health behaviour variables, MDD was no longer significantly related to lung function. However, the negative association between GAD and FEV_1 was still evident in the fully adjusted model. Neither post-traumatic stress disorder nor panic disorder was related to FEV_1 in the fully adjusted model. The same associations with GAD emerged when FEV_1 was characterized as $FEV_1/height^2$ and $FEV_1/predicted$ FEV_1. Although the effect sizes are small, they may still be of clinical significance, given that as lung function deteriorates life expectancy declines (1-5). In addition, it is worth noting, in this context, that the prevalence of GAD and MDD is higher in populations, such as war veterans, that have been exposed to traumatic events than in the general population (19-21).

The present results apparently contrast with those reported from the two previous studies. However, the first of these was concerned with symptoms of anxiety and depression, measured on a general well-being scale, and not with psychiatric status (12). The second, although focusing on MDD and GAD, examined a much younger sample; average age 20 years with a narrow range (8). Although a modest association between MDD and lung function was evident for males, there was no association for females, and no association for the sample as a whole. Thus, the fact that the present study included only men is unlikely to account for discrepancies in the findings. It is possible that associations between psychiatric morbidity and lung function only appear later in middle age when lung function might be expected to start to decline. However, the similarity in average FEV_1 between the two studies argues against this. The present findings also resonate with those from experimental studies showing that induced negative emotions elicit bronchoconstriction, particularly in asthma patients (22-24). However, it is not clear whether such increased airway resistance effects are specific to negative affect, as they have also been observed with pleasant affective stimuli (25).

The present results for GAD, though, are certainly in accord with those from other analyses of this dataset which showed it to be as strong, if not stronger, a predictor than MDD of all-cause and cardiovascular mortality (13), metabolic syndrome (14), and hypertension (15). More recently, we have also shown in this cohort that another psychological factor, low

cognitive ability in early adulthood, predicts poor lung function in middle age (26). Other analyses of the Vietnam Experience Study by members of our group have shown that low cognitive ability is also associated with metabolic syndrome (27) and greater all-cause mortality (28). In this context, it is worth noting that the present association between GAD and FEV_1 remained statistically significant when cognitive ability was added as a covariate in the fully adjusted model, $p = .02$. Accordingly, GAD and low cognitive ability would seem to be largely independent correlates of poorer lung function and other health outcomes.

With cross-sectional analyses it is impossible to determine the direction or causality of the association. If anxiety precedes poor lung function, there is at least one pathway through which it might contribute to impaired FEV_1. Anxiety has been associated with unhealthy behaviour, such as smoking, binge drinking, physical inactivity, and unhealthy diet which could compromise lung function (29). However, despite the fact that participants with GAD consumed more units of alcohol per week and were more likely to be current smokers, the present association between GAD and FEV_1 remained significant after adjustment for smoking and alcohol consumption. It is likely, however, that we have not captured lifetime exposure to such behaviours. Alternatively, it is possible that the causal pathway is from low FEV_1 to GAD. Clinically, it has been observed that conditions associated with impaired lung function elicit distress, which is a salient presentation in GAD (8). Finally, it is possible that low FEV_1 and GAD have common antecedents. Poor lung function has been regarded as a marker of early life adversity including exposure to suboptimal nutrition, poverty, chronic childhood illness and psychosocial stress (4). The extent of earlier stress exposure has also been linked to GAD (30).

The present study may have other limitations. First, as the sample was exclusively male, it is unknown to what extent the same relationships would have been seen in women. Second, there was a relatively narrow age range. Nevertheless, the range was sufficient to afford a significant association between age and FEV_1, r = - .14, $p < .001$. Third, that we did not find an association between FEV_1 and MDD in the fully adjusted analyses might also reflect lower power, since there were a fewer number of participants with MDD. Fourth, spirometry is an effort-dependent technique and this may pose particular problems when testing individuals with serious mental health problems. Accordingly, replication with effort-independent lung function

assessments is advisable. Finally, it should be conceded that the current study would have be strengthened by the inclusion of an analyses of GAD and other psychological factors and morbid asthma.

The present analysis showed that GAD was negatively associated with lung function in Vietnam veterans. Depression has been the main focus for studies of mental health and physical health outcomes. The present findings, added to those from our earlier analyses of this cohort (13-15), suggest that future research should perhaps pay equal attention to GAD.

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Table 1: Descriptive statistics and frequencies for each variable by MDD and GAD status

		MDD N = 277, 7%		No MDD N = 3979		*p*	GAD N = 411, 10%		No GAD N = 3845		*p*
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age at medical exam (yrs)		37.8	2.67	38.4	2.50	.001	38.0	2.65	38.4	2.50	.003
Units of alcohol per week		10.7	24.8	6.8	13.4	<.001	10.6	22.87	6.7	13.15	<.001
Height (metres)		1.78	0.07	1.78	0.07	.97	1.78	0.07	1.78	0.07	.40
Weight (kgs)		82.2	13.5	82.2	14.3	.73	82.2	15.2	82.5	13.4	.67
		N (%)		N (%)		*p*	N (%)		N (%)		*P*
Place of service	Vietnam	186 (68)		2163 (54)		<.001	267 (65)		2082 (54)		<.001
	Other overseas	51 (18)		1044 (26)			85 (21)		1010 (26)		
	US only	40 (14)		772 (20)			59 (14)		753 (20)		
Ethnicity	White	218 (79)		3272 (82)		.31	311 (76)		3179 (83)		.001
	Black	37 (13)		459 (12)			61 (15)		435 (11)		
	Other	22 (8)		248 (6)			39 (9)		231 (6)		
Education grade	<12	47 (17)		486 (12)		.03	77 (19)		436 (11)		<.001
	12	99 (36)		1465 (37)			169 (41)		1396 (36)		
	>12	131 (47)		2048 (51)			166 (40)		2013 (52)		
Household income	<$20,000	130 (47)		1072 (27)		<.001	184 (45)		1018 (26)		<.001
	-$40,000	110 (40)		2019 (51)			171 (42)		1958 (51)		
	>$40,000	37 (13)		888 (22)			56 (13)		869 (23)		
Smoking status:	Non smoker	50 (18)		1035 (26)		<.001	79 (19)		1006 (26)		<.001
	Ex smoker	57 (21)		1152 (29)			90 (22)		1119 (29)		
	Current smoker	170 (61)		1792 (45)			242 (59)		1720 (45)		
Marital status:	Married	151 (55)		2980 (75)		<.001	244 (59)		2887 (75)		<.001
	Divorced/separated/widowed	94 (34)		673 (17)			116 (28)		651 (17)		
	Never married	32 (11)		326 (8)			51 (12)		307 (8)		
Physical illness:	Yes	57 (21)		515 (13)		<.001	76 (18)		496 (13)		.002
	No	220 (79)		3463 (87)			335 (82)		3349 (87)		

Figure Caption FEV_1 (L) as a function of psychiatric status