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Depression and anxiety are associated with a diagnosis of hypertension five years later in a cohort of late middle aged men and women.

Running head: Depression, anxiety, and hypertension

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ABSTRACT

Objective: To examine the association between symptoms of depression and anxiety and hypertension status. **Methods:** Participants (*n* = 455, 238 women) were drawn from the Dutch Famine Birth Cohort Study. In 2002-2004, they attended a clinic assessment during which socio-demographics, anthropometrics, resting systolic blood pressure, and health behaviours were measured. Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale. In 2008-2009, participants completed a questionnaire which asked whether they ever had a physician diagnosing them as suffering from hypertension. **Results:** In separate regression models that initially adjusted for age and then additionally for sex, socioeconomic status, smoking, sports participation, alcohol consumption, resting systolic blood pressure, antidepressive and anxiolytic medication, whether or not participants were exposed to the Dutch famine *in utero*, BMI, and waist:hip ratio, both depression and anxiety were positively associated with hypertension status. Those who met the criterion for possible clinical depression and anxiety were also more likely to be hypertensive, and these associations remained statistically significant in the fully adjusted regression model. **Conclusion:** Symptoms of depression and anxiety were associated with a diagnosis of hypertension assessed five years later, although the mechanisms underlying these associations remain to be determined.

Key words: anxiety, depression, hypertension

INTRODUCTION

A number of recent studies testify to positive cross-sectional and/or prospective associations between major depressive disorder and hypertension (1–3) and between generalised anxiety disorder and hypertension (1). In these studies, depression and anxiety were based on a diagnostic interview. However, evidence of an association between questionnaire assessed symptoms of depression and anxiety and hypertension comes from older studies and is not wholly consistent (4-9). The National Health and Nutrition Examination Survey (4) and the Framingham study (5) observed that high levels of symptoms of depression and anxiety were associated with an increased risk of developing hypertension, whereas the Coronary Artery Risk Development in Young Adults study (6) found no consistent relationship between symptoms of depression and anxiety and hypertension. Other studies have demonstrated associations between depression and anxiety symptomatology and lower blood pressure (7-9). Accordingly, we judged it timely to re-visit this issue and data collected as part of the Dutch Famine Birth Cohort Study (10) permitted re-examination of the association between symptoms of depression and anxiety and hypertension status. We hypothesised, on the balance of the previous evidence, that elevated depression and anxiety symptom levels would be associated with an increased risk for hypertension.

METHOD

Participants

Participants were selected from the Dutch Famine Birth Cohort, which comprises men and women who were born in Amsterdam, the Netherlands, between November 1943 and February 1947. The selection procedures and subsequent loss to follow up have been described in detail

elsewhere (11-13). In 2002-2004, 740 members of the cohort provided data at a clinic assessment, performed by a trained research nurse. In 2008-2009, 455 of those who had attended the clinic returned a completed questionnaire package, which among other things, asked about diagnosed illness. The study was approved by the local Medical Ethics Committee, carried out in accordance with the Declaration of Helsinki, and with the adequate understanding and written consent of the participants.

Measures

In 2002-2004, socio-demographics, life style, and anthropometrics were assessed. Socio-economic status (SES) was measured using the ISEI (International Socio-Economic Index)-92, which is based on the participant's or their partner's occupation, whichever has the higher status (14). Measured values in the ISEI-92 scale ranged from 16 (low status, for example a cleaning person) to 87 (high status, for example a lawyer). Participants were asked whether they were current smokers, ex-smokers, or had never smoked. They were also asked whether they participated in sports and how many alcoholic drinks of different types they consumed per week, and an overall units per week measure was derived. Participants had to indicate whether they were taking antidepressant and/or anxiolytic medication (NSRIs). Height was measured twice using a fixed or portable stadiometer and weight twice using Seca and portable Tefal scales. Body mass index (BMI) was computed in kg/m^2 from the averages of the two height and weight measurements. Waist and hip circumference was measured in duplicate with a flexible tape measure and an average taken. Waist was measured midway between the costal margin and the iliac crest and hip at the widest point over the buttocks to compute the waist:hip ratio. Systolic blood pressure (SBP) was measured twice in a row on two occasions (morning and afternoon)

using an automated device (Omron 705 CP/IT; Omron Healthcare UK, West Sussex, UK) and appropriate cuff sizes. Mean SBP was calculated using all available measurements.

Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) (15). The HADS is a well-recognised assessment instrument that comprises 14 items, seven measuring depression and seven measuring anxiety. The depression subscale emphasises anhedonia and excludes somatic items. Items are scored on a 4-point scale, 0 to 3; the higher the score, the greater the depression and anxiety. The HADS has good concurrent validity (16,17), performs well as a psychiatric screening device (17,18), and has been shown to have acceptable psychometric properties; for example, a Cronbach's α of .90 for the depression items and .93 for the anxiety items has been reported (19) and test-retest reliability coefficients as high as .85 for depression and .84 for anxiety have been found (17). Possible caseness for both depression and anxiety is defined by scores ≥ 8.

The 2008-2009 questionnaire asked participants whether or not they had ever received a diagnosis of hypertension from a physician. The mean (SD) temporal lag between this assessment and the measurement of depression and anxiety was 5.5 (0.6) years.

Statistical Analyses

Preliminary analyses of differences between participants with and without a diagnosis of hypertension were conducted using χ^2 and t-tests. The main analysis was by logistic regression, where depression and anxiety served as the independent variables in separate models with hypertension status as the dependent variable. The initial models adjusted only for age at clinic

assessment, whereas subsequent models additionally adjusted for sex, SES, smoking, sports participation, alcohol consumption, SBP, antidepressive and anxiolytic medication, whether or not participants were exposed to the Dutch famine *in utero*, BMI, and waist:hip ratio. These covariates were chosen because they have been implicated in depression, anxiety, and/or hypertension. Depression and anxiety were first tested as continuous variables, i.e. actual HADS scores, and subsequently as categorical variables, i.e. HADS caseness.

RESULTS

The summary characteristics of the cohort by hypertension status are presented in Table 1. Two hundred and nineteen (48%) of the participants reported a diagnosis of hypertension at the second time point of assessment. HADS depression and anxiety scores were highly correlated, r (433) = .68, p <.001, as was HADS depression and anxiety caseness, C (coefficient of contingency) (433) = .43, p <.001. In regression models adjusting only for age, both depression, OR = 1.13, 95%CI 1.05 – 1.21, p =.001, and anxiety scores, OR = 1.11, 95%CI 1.05 – 1.18, p =.001, were associated with future hypertension status; the greater the symptoms of depression and anxiety the greater the likelihood that the particular person would have been diagnosed with hypertension five years later. These associations remained statistically significant in the fully adjusted models: for symptoms of depression, OR = 1.19, 95%CI 1.09 – 1.30, p <.001, and for symptoms of anxiety, OR = 1.14, 95%CI 1.06 – 1.23, p =.001. In these models, hypertension was also associated with a higher BMI and a higher resting SBP at the clinic assessment, p = .001 in both cases. Men were also more likely to be hypertensive in the depression model, p = .05.

These analyses were repeated using cut-off scores of ≥ 8 to identify possible clinical depression and anxiety. In the age adjusted models, both depression caseness, OR = 2.34, 95%CI 1.14 – 4.79, p =.02, and anxiety caseness, OR = 1.73, 95%CI 1.08 – 2.77, p =.02, were positively associated with hypertension status. With full adjustment, the association between depression caseness and hypertension remained significant, OR = 3.44, 95%CI 1.44 – 8.23, p =.005, as did the association between anxiety caseness and hypertension, OR = 2.08, 95%CI 1.17 – 3.72, p =.01.

Sensitivity analyses

During the clinic assessment, 108 participants admitted to taking antihypertensive medication. Accordingly, it could be argued that the present prospective associations between symptoms of depression and anxiety, on the one hand, and hypertension, on the other, were largely reflecting cross-sectional associations. As a consequence we first repeated the analyses for the continuous depression and anxiety scores removing those individuals from the analyses. In the fully adjusted models, both symptoms of depression, OR = 1.18, 95%CI 1.06 – 1.31, p = .003, and anxiety, OR = 1.14, 95%CI 1.03 – 1.25, p = .008, continued to predict hypertensive status five years later. We also repeated the analyses of the whole sample with hypertensive medication status added as a further covariate to the fully adjusted models. Although the associations were slightly attenuated, symptoms of depression, OR = 1.16, 95%CI 1.06 – 1.28, p = .002, and symptoms of anxiety, OR = 1.11, 95%CI 1.02 – 1.21, p = .01, continued to predict future hypertension.

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DISCUSSION

Almost half the current sample reported that a physician had diagnosed them as hypertensive. This is a higher prevalence than that reported in other studies (1,3), but could reflect the age of the sample who were all over 60 at the time of the questionnaire assessment of hypertension status as well as the close medical attention paid to this cohort. It certainly suggests, though, that there was little undiagnosed hypertension, a concern when relying on self-reports of physician diagnosis (1). As hypothesised, participants with high levels of depression and anxiety symptoms were more likely to be hypertensive when questioned five years later. Hypertensive participants were also more likely to meet the criterion for possible clinical caseness for depression and anxiety at the earlier assessment. Overall, our results are in line with those from other studies comparing hypertension in those varying in symptoms of depression and anxiety (4,5) and those with and without Major Depressive Disorder (1-3) and with and without Generalised Anxiety Disorder (1).

There are several possible pathways through which depression and anxiety might contribute to the development of hypertension (20). The two most cited are unhealthy behaviours and physiological dysregulation. However, in the present analyses, the associations between symptoms of depression and anxiety and hypertension were still evident after adjustment for three of the more prominent unhealthy behaviours, smoking, non participation in sports and high levels of alcohol consumption. With regard to physiological dysregulation, altered activity of the hypothalamic-pituitary-adrenal axis has been observed in approximately 50% of depressed

patients (21), and this, in turn, may increase the risk of hypertension. Cortisol was measured in the present study during the clinic assessment, but the addition of basal cortisol to our regression models left the outcomes unaltered. Altered autonomic function have also been suggested as a possible psychophysiological mechanism (22). However, in a previous study in the same cohort we found that those with symptoms of depression and anxiety had decreased and not increased cardiovascular stress responses (23). In the present study, the addition of SBP and HR reactivity to our regression models left the outcomes unaltered (p <.001 and p = .001 for depression and anxiety, respectively). One other possibility is reverse causation, such that increased symptoms of depression and anxiety are reactions to a diagnosis of hypertension, a chronic and ultimately life-threatening condition. However, when we excluded participants who reported taking antihypertensive medication at the time of the assessment of depression and anxiety, symptoms of depression and anxiety continued to predict hypertension status at the subsequent assessment, making reverse causation an unlikely explanation.

The present study is not without limitations. First, from observational data it is impossible to determine causality and the direction of causality. However, as indicated above, reverse causation would seem to be an unlikely explanation. Nevertheless, the issue of confounding is ever present in observational studies (24). However, we did adjust statistically for a broad range of potential confounders, including whether or not participants were exposed to the Dutch famine and SBP during the clinic assessment, and, in sensitivity analyses, whether or not participants reported taking antihypertensive medication at the earlier assessment. That the links between depression and anxiety and future hypertension survived such adjustments suggest that these associations were not simply an artefact of cross-sectional relationships. Second, we relied on a

questionnaire measure of symptoms rather than formal diagnoses of major depressive and anxiety disorders. Further, use of the HADS may have lead to an underestimation of the association between depression and hypertension as it excludes somatic-affective symptoms of depression and anxiety and these may particularly increase the risk for hypertension. However, our findings are very much in accord with those from studies that did examine hypertension in the context of psychiatric diagnoses (1-3). Third, the relative seniority of our participants and the consequently high prevalence of diagnosed hypertension could be regarded as limiting the generalisability of our findings. However, given that similar associations have emerged in middle-aged cohorts (1-3), it would appear that the relationship between depression and anxiety and hypertension transcends the age of the sample studied. Fourth, this study relied on self-report of a physician diagnosis of hypertension. However, the high prevalence of hypertension suggests that there were unlikely to be many false negatives. Further, other studies in the field have also used self-report of hypertension (2,3). Finally, although the high prevalence of hypertension makes it unlikely, it cannot be ruled out that depressed and anxious subjects were more likely to be diagnosed with hypertension and non-depressed / anxious subjects remained undiagnosed, as hypertension is frequently asymptomatic and depressed / anxious subjects may have been checked more often. Another possibility would be that there were more false positives among depressed /anxious subjects due to panic-attack related high blood pressure being misinterpreted as hypertension.

In conclusion, the present analyses indicated that symptoms of depression and anxiety were associated with a diagnosis of hypertension assessed five years later. These associations would not seem to be accounted for by unhealthy behaviour, nor would they appear a function of

reverse causation, where increased symptoms of depression and anxiety are reactions to a diagnosis of hypertension. Further studies are needed to unravel the mechanisms underlying what appear to be fairly robust associations between psychological status and hypertension.

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Conflict of interest

The authors declare no conflict of interest.

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Table 1. Descriptive characteristics of those with and without a diagnosis of hypertension.

	Hypertensive (*n* = 219)		Normotensive (*n* = 236)		
	Mean	SD	Mean	SD	*P*
Age at clinic assessment (years)	58.16	0.88	58.28	0.94	.16
Socio-economic status (ISEI-92)	49.82	13.88	50.88	13.79	.42
Body mass index (kg/m^2)	30.42	5.04	27.08	3.94	<.001
Waist:hip ratio	93.69	9.00	91.89	8.58	.03
Systolic blood pressure (mmHg)	142.83	16.17	128.68	14.76	<.001
Alcohol consumption (units/week)	9.54	16.53	9.97	12.56	.76
HADS depression score	3.66	3.44	2.64	2.43	<.001
HADS anxiety score	5.99	3.55	4.85	2.97	<.001
	n (%)		*n* (%)		*P*

Sex			.23
Male	98 (45)	119 (55)	
Female	121 (51)	117 (49)	
Smoking			.13
Current smokers	44 (42)	61 (58)	
Ex-smokers	83 (46)	97 (54)	
Never smoker	91 (54)	78 (46)	
Sports participation	129 (59)	138 (58)	.93
Exposed to famine *in utero*	90 (41)	99 (42)	.22
Medication			
Antidepressive	14 (6)	12 (5)	.55
Anxiolytic	18 (8)	18 (8)	.90
Caseness			
Depression	25 (12)	12 (5)	.01
Anxiety	54 (26)	37 (16)	.02

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Table 2. Summary Table

What is known about this topic

- Recent studies consistently indicate that major depressive disorder and generalised anxiety disorder are positively related to hypertension.
- Evidence linking symptoms of depression and anxiety with hypertension is less compelling.

What this study adds

- Participants with high levels of depression and anxiety symptoms are more likely to be hypertensive five years later.
- These associations would not seem to be accounted for by unhealthy behaviours.
- They would also not appear to be a function of reverse causation, where increased symptoms of depression and anxiety are reactions to a diagnosis of hypertension.