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

Running head: Depression, anxiety, and hypertension

The study was performed at the Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

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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, 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, among other things, 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, SES, smoking, alcohol consumption, antidepressive medication (in the case of HADS depression), anxiolytic medication (in the case of HADS anxiety), 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, although the association between anxiety caseness and hypertension was not statistically significant in the fully adjusted regression model.

Conclusion: Symptoms of depression and anxiety were associated with hypertension status assessed five years later, although the mechanisms underlying these associations remain to be determined.

Key words: anxiety, depression, hypertension

BMI = body mass index; **C** = coefficient of contingency; **CI** = confidence intervals; **HADS** =

Hospital Anxiety and Depression Scale; **ISEI** = International Socio-Economic Index; **OR** = odds

ratio; **SES** = socio-economic status

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]. However, evidence of an association between questionnaire assessed symptoms of depression and anxiety and hypertension comes from older studies and is not wholly consistent. 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. Accordingly, we judged it timely to re-visit this issue and data collected as part of the Dutch Famine Birth Cohort Study [7] 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 Dutch Famine Birth Cohort Study was designed to investigate the potential consequences of prenatal exposure to famine on health in later life. One can therefore suggest

that population characteristics may hamper generalization of the present study results. However,

this is very unlikely as health differences have mainly been found in the group of people exposed

to famine in early gestation which only comprises 8% of the total study sample. The selection

procedures and subsequent loss to follow up have been described in detail elsewhere [8,9]. 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

[10]. 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 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. 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.

Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) [11]. 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 [12,13], performs well as a psychiatric screening device [13,14], and boasts acceptable psychometric properties; for example, a Cronbach's α of .90 for the depression items and .93 for the anxiety items has been reported [15] and test-retest reliability coefficients as high as .85 for depression and .84 for anxiety have been found [13]. 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 ANOVA. 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, alcohol consumption, antidepressive medication (in the case of HADS depression), anxiolytic medication (in the case of HADS anxiety), 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 I. Two hundred and nineteen (48%) of the participants reported a diagnosis of hypertension. HADS depression and anxiety scores were highly correlated, r (433) = .68, p <.001, as were 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 = 1.12, 95%CI 1.04 – 1.21, *p* =.004, and for symptoms of anxiety,

OR = 1.09, 95%CI 1.02 – 1.17, *p* =.01. The covariates significantly associated with

hypertension in these models were BMI and smoking; smokers, *p* =.03 and *p* == .04 respectively,

and those who were leaner, *p* < .001 in both cases, were less likely to be hypertensive. 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 = 2.45, 95%CI 1.02 – 4.95, *p* =.04. However, the

association between anxiety caseness and hypertension was attenuated to non-significance, OR =

1.50, 95%CI 0.89 – 2.52, *p* =.13. As before, the outcomes remained unchanged when we

additionally adjusted for whether or not participants had been exposed to the Dutch famine.

Again, of the covariates entered in these models, only BMI and smoking status were significantly

related to hypertension.

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 at the earlier

assessment, although the association between anxiety caseness and hypertension was not

statistically significant in the fully adjusted regression model. Overall, then 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. 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 two

of the more prominent unhealthy behaviours, smoking and high levels of alcohol consumption.

Indeed, smoking in the current study was negatively associated with hypertension, a not

uncommon finding [1,16]. With regard to physiological dysregulation, altered activity of the

hypothalamic-pituitary-adrenal axis has been observed in approximately 50% of depressed

patients [17], and this, in turn, may increase the risk of hypertension. However, cortisol was

measured in the present study during the clinic assessment and the addition of basal cortisol to

our regression models left the outcomes unaltered. 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; the majority of the sample

(71%) was diagnosed hypertensive prior to the clinic visit. However, HADS depression, 3.60

versus 3.30, $p = .57$, and anxiety, 5.98 versus 5.73, $p = .66$, scores were similar for those who

had been diagnosed before the clinic visit and those who had been diagnosed subsequently.

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 [18]. Although we did adjust statistically for a broad range

of potential confounders, including whether or not participants were exposed to the Dutch

famine, residual confounding as a consequence of poorly measured or un-measured variables

cannot be wholly discounted. Second, we relied on a questionnaire measure of symptoms rather

than formal diagnoses of major depressive and anxiety disorders. 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 regarding 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. Finally, 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].

In conclusion, the present analyses indicated that symptoms of depression and anxiety were

associated with hypertension status 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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Competing Interest Statement

All authors have completed the Unified Competing Interest form. The authors have no

competing interests to report.

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Table I. 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
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)	
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