RESEARCH REPORT

Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study

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Background: Low blood pressure has mainly been regarded as ideal, but recent studies have indicated an association with depression in elderly people.

Objective: To investigate whether low blood pressure is associated with anxiety and depression in the general population.

Design: Cross-sectional study.

Setting: Participants in the population-based Nord-Trøndelag Health Study (HUNT-2, 1995–7), Norway.

Participants: 60 799 men and women aged 20–89 years filled in the Hospital Anxiety and Depression Scale as part of a general health study. Systolic and diastolic blood pressure was classified in age-stratified and sex-stratified centile groups.

Main results: Compared with participants with systolic blood pressure within the 41–60 centile (reference) group, the odds ratio for anxiety was 1.31 (95% confidence intervals (CI) 1.16 to 1.49), for depression 1.22 (95% CI 1.03 to 1.46), and for comorbid anxiety and depression 1.44 (95% CI 1.24 to 1.68) in the group with ≤ 5 centile systolic blood pressure. Slightly weaker associations were found of low diastolic blood pressure with anxiety and depression. These associations were similar across sex and age groups. Physical impairment, smoking and angina pectoris influenced the associations only marginally, whereas stroke, myocardial infarction, use of drugs for hypertension, body mass index and several other covariates had no influence.

Conclusions: This study represents epidemiological evidence for an association of low blood pressure with anxiety and depression, which is not caused by cardiovascular disease.

The global burden of hypertension as a leading risk factor for cardiovascular and kidney disease, and for mortality,¹ has overshadowed possible health problems associated with chronic low blood pressure. Through decades, medicine has viewed hypotension as an ideal blood pressure level,² and as an example of a non-disease.³ Earlier, however, low blood pressure was associated with neurasthenic symptoms such as tiredness, weakness, dizziness and headache,⁴ and with sleep disturbances, anxiety and depression.⁵ Although chronic low blood pressure can still be used in some continental European countries to explain a variety of constitutional symptoms, the prevailing attitude in English-speaking countries has been that low blood pressure does not produce symptoms.^{5 6}

Psychosomatic research on blood pressure has mainly focused on hypertension.^{7–9} Several studies have indicated an association between hypertension and psychological factors. However, the psychometric properties of the scales used have often been less well established,⁹ and most previous studies have not explored the lower range of blood pressure. By contrast, some studies have indicated that low blood pressure is associated with various somatic and psychological symptoms.^{5 10–12} Four of six geriatric studies, using standardised screening inventories for depression, found an association between low blood pressure and depression,^{6 13–15} one study found no association,¹⁶ whereas a recent study found an association between hypertension and depression.¹⁷ However, the design and findings in some of the studies have been contested.¹⁸ In the absence of a commonly accepted definition of low blood pressure, various boundaries have been used. Four geriatric studies defined blood pressure $<120/75$ mm Hg as hypotensive, 120–139/75–84 mm Hg as normal and $\geq 140/85$ mm Hg as hypertensive.^{6 13 15 16}

As most previous studies have limitations, and as their results are inconsistent, we wanted to examine the association

of blood pressure with anxiety and depression in the general population using a standardised screening inventory. Our large sample size and broad age range gave an opportunity to explore both tails of the blood pressure distribution, and to control for body weight, cigarette smoking, cardiovascular disease and other relevant covariates.

PARTICIPANTS AND METHODS

Study design and participants

This study is part of the Nord-Trøndelag Health Study (HUNT Study), Norway, which is described in detail elsewhere (www.hunt.ntnu.no).¹⁹ All inhabitants aged ≥ 20 years in the county were invited to a general health study. They received an invitation letter with a questionnaire and an appointed date for physical tests and blood samples. The questionnaire covered demographic characteristics, somatic illnesses, somatic and mental symptoms, physical impairments, drugs, lifestyle and health-related behaviour. This study concerned 65 648 (71.3%) of a total of 92 100 people aged 20–89 years who participated, and 60 799 had valid scores of data relevant to this study. Participation in the HUNT Study was voluntary, and all participants gave written informed consent. The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved the study.

Measures of anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is recognised as a good screening instrument for epidemiological studies. The HADS is a self-report questionnaire

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; GAM, generalised additive model; HADS, Hospital Anxiety and Depression Scale; HUNT Study, Nord-Trøndelag Health Study

comprising 14 four-point Likert-scaled items, seven for anxiety (HADS-A) and seven for depression (HADS-D). No items relating to somatic or sleep issues are included. Earlier papers on the HADS in HUNT have shown a shared variance between HADS-A and HADS-D of 30%,²⁰ and presented data relating to depression in sex and age groups.²¹ According to a recent literature review covering 31 studies, the HADS has shown good case-finding properties for anxiety and depression defined by Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV in primary care and hospital settings.²² A cut-off score of 8 on both subscales was found to give an optimal balance between sensitivity and specificity, both at about 0.80 for depression (major depressive disorder and dysthymia) and anxiety (generalised anxiety disorder, specific phobias and adjustment disorders) according to DSM-III-R and DSM-IV. By using these cut-offs, four groups were identified for this study: anxiety only (HADS-A $\geq$ 8, HADS-D <8), depression only (HADS-D $\geq$ 8, HADS-A <8), comorbid anxiety and depression (both HADS-A and HADS-D $\geq$ 8) and a reference group (both HADS-A and HADS-D <8).

Measure of blood pressure

Standardised blood pressure was measured by specially trained nurses at the beginning of the screening procedure using a Dinamap 845XT (Criticon, Florida, USA) based on oscillometry. Cuff size was adjusted after measuring the arm circumference. The Dinamap was started after the participant had been seated for 2 min with the cuff on the arm, and the arm resting on a table. Blood pressure was measured automatically three times at 1-min intervals. The mean of the second and third readings was used in this study.

Statistical analyses

We assessed if blood pressure was associated with mental disorders by multinomial logistic regression analyses (blood pressure in categories) and by generalised additive logistic regression analyses (blood pressure continuous), with adjustments for sex, 10-year age groups and education. In the logistic regression analyses, the dependent variables were cases of anxiety, depression, or comorbid anxiety and depression, as defined earlier. Systolic and diastolic blood pressure was classified into age-stratified and sex-stratified centile groups, because: (a) there were marked differences in blood pressure between sex and age groups; (b) blood pressure categories in textbooks are clinically derived on the basis of prevention of cardiovascular disease, with no generally accepted definition of hypotension; and (c) centiles enabled us to explore the tails of the blood pressure distributions. Previous studies with a wide age distribution have used 10 mm Hg blood pressure groups in the analysis.^{5–10} Other studies with a more narrow age span have used gender stratified quartiles,^{11–14} quintiles¹² or normative values separating the participants into hypo-, normo- or hypertensive people.^{6–13–15–16}

With generalised additive logistic regression analyses, on the basis of the generalised additive model (GAM),²³ we made graphs of the association between continuous systolic and diastolic blood pressure, and anxiety, depression, or comorbid anxiety and depression. The outcome measure of such an analysis is a plot of odds ratios (ORs) on a log scale where the reference value (OR = 1.00) corresponds to the mean value of the explanatory variable (x axis). Point-to-point 95% confidence interval (CI) merely shows the relative precision of the point-to-point estimates along the plot.

The multivariable models were adjusted for the following covariates: age, sex, education, stroke, myocardial infarction, angina pectoris, use of drugs for hypertension, cancer, diabetes

mellitus, fibromyalgia, headache (migraine or non-migraines), hypothyroidism, physical impairment (due to movement or somatic disease), smoking status, physical activity (light or heavy leisure activity), body mass index, triglycerides and total cholesterol. In successive multinomial logistic regression analyses, we excluded people using drugs for hypertension and for depression, with physical impairment and people with a history of cardiovascular disease (angina pectoris, myocardial infarction or stroke). In additional analyses, we tested for effect modification by sex and age (age groups 20–39, 40–59, 60–75, 76–89 years) by incorporating interaction terms (blood pressure $\times$ covariate) in the models.

Two-tailed p values <0.05 were considered significant. SPSS software V.11.5 was used for statistical analyses.

RESULTS

Characteristics of the participants

Table 1 lists the characteristics of the participants: 9.6% reported anxiety (without depressive) symptoms above the predefined cut-off level, 4.9% reported depressive (without anxiety) symptoms and 5.9% reported the presence of both anxiety and depression symptoms. Mean age was 45.9 years for participants with anxiety only, 59.4 years for those with depression only and 52.4 years for those with comorbid anxiety and depression. Blood pressure increased with age, especially in women (table 2).

Main outcome

We found associations of low blood pressure with anxiety, depression, and comorbid anxiety and depression in all analyses. By multinomial logistic regression analyses, there were higher odds for these disorders in the 0–5 centile systolic and diastolic blood pressure than in the reference (41–60 centile) group (basic covariate model, table 3). The ORs were gradually reduced up to the 30-centile blood pressure. Using higher cut-offs for anxiety and depression did not change these patterns considerably. We found no significant differences in the associations by further subdivision of the lowest five centiles of blood pressure.

Three GAM plots, where systolic blood pressure was included as a continuous variable, show similar shapes of the associations of systolic blood pressure with anxiety, depression, and comorbid anxiety and depression (fig 1). The GAM curves for the associations between diastolic blood pressure and these disorders were comparable, but with weaker effects.

Multivariable analyses

In multivariable models, adjustment for cardiovascular disease and other covariates hardly weakened the associations (table 3). In the 0–5 centile systolic blood pressure group, OR for comorbid anxiety and depression was reduced from 1.44 (95% CI 1.24 to 1.68) to 1.35 (95% CI 1.16 to 1.58), compared with the reference group, when adjusted for all covariates. Adjustment for all covariates gave similar results for both anxiety and depression (table 3). Corresponding adjustments gave only smaller changes in the associations between diastolic blood pressure and mental disorders. In the 6–30 centile systolic and diastolic blood pressure range, adjustments for all covariates yielded minimal change in ORs.

In fig 2, adjustment for each covariate is shown for the association of low systolic blood pressure with comorbid anxiety and depression. Similar patterns of adjustments were found for anxiety and for depression separately. Physical impairment and smoking contributed most to explain the association between systolic blood pressure and mental disorders. Among the cardiovascular variables, angina pectoris

Table 1 Characteristics of the 60 799 participants by scores on the Hospital Anxiety and Depression Scale

Characteristic	Reference group (n = 48 398)	Anxiety (n = 5818)	Depression (n = 2982)	Comorbid anxiety and depression (n = 3601)
Sex, %				
Men	48.5	35.7	57.4	41.7
Women	51.5	64.3	42.6	58.3
Age (years), %				
20–29	14.8	16.7	3.6	6.8
30–39	19.3	21.3	8.4	14.9
40–49	21.8	24.2	15.8	23.3
50–59	17.3	17.3	20.1	22.6
60–69	13.4	11.0	20.7	16.1
70–79	10.5	7.3	22.9	12.4
80–89	2.9	2.3	8.6	3.9
Education (years),* %				
≤9	35.1	36.5	56.4	51.8
10–12	43.7	44.9	32.6	35.9
≥13	21.1	18.6	11.0	12.3
Cardiovascular conditions,* %				
Stroke	1.4	1.7	5.2	3.0
Myocardial infarction	2.7	1.9	7.1	4.2
Angina pectoris	4.0	3.8	9.5	7.8
Drugs for hypertension	9.8	8.8	17.8	12.7
Other medical conditions,* %				
Cancer	3.4	3.9	4.8	4.5
Diabetes	2.5	2.3	4.9	3.8
Fibromyalgia	2.4	6.4	4.1	9.8
Headache	29.3	45.8	29.4	46.5
Hypothyroidism	2.6	3.8	3.7	4.8
Physical impairment,* %				
Low	8.2	10.1	12.8	13.3
Moderate	5.5	8.6	11.3	12.6
High	4.0	7.5	12.8	14.9
Current smoker,* %	26.7	35.4	26.2	38.5
Physical activity,*† %				
None	6.4	7.2	13.6	12.8
<1 h/week	14.4	15.6	18.5	19.7
1–2 h/week	35.5	34.0	29.3	30.2
>2 h/week	36.4	34.8	14.4	26.6
Physical measures				
BMI, kg/m ²	26.3	26.0	27.0	26.7
Cholesterol, mmol/l	5.84	5.78	6.18	6.05
Triglycerides, mmol/l	1.74	1.67	1.98	1.90

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale.

Scores on the anxiety (HADS-A) and depression (HADS-D) subscales defined the four groups: anxiety only (HADS-A ≥8, HADS-D <8); depression only (HADS-A <8, HADS-D ≥8); comorbid anxiety and depression (≥8 on both subscales); and reference group (<8 on both subscales).

*Data were obtained by questionnaire.

†Data on physical activity were missing for 4877 (8%) of the participants.

was the only one that influenced the association, and the effect was marginal.

Stratified analyses

The considerable associations of systolic blood pressure (0–5 v 41–60 centiles) with comorbid anxiety and depression were maintained in stratified analyses. The OR for the total population was 1.44 (95% CI 1.24 to 1.68), which compares to 1.46 (95% CI 1.24 to 1.71) when excluding people taking drugs for hypertension, 1.33 (95% CI 1.13 to 1.57) when excluding those taking drugs for depression, 1.47 (95% CI 1.22 to 1.79) when excluding those reporting physical impairment and 1.41 (95% CI 1.19 to 1.66) when excluding those with cardiovascular disease. The associations did not

vary significantly with sex or age groups ($p > 0.15$ for all interactions).

Supplementary analyses

Supplementary multinomial logistic regression analyses using blood pressure cut-offs (systolic <120, 120–139 (reference) and ≥140, diastolic <75, 75–84 (reference) and ≥85 mm Hg), as used in four geriatric studies,^{6 13 15 16} confirmed the direction of the associations described above. However, the ORs were smaller than those estimated using age-stratified and sex-stratified centiles of blood pressure (data not shown). Similarly, in models using the combination of systolic and diastolic blood pressure, hypotension (<120/75 mm Hg) was associated with anxiety (OR 1.13, 95% CI 1.03 to 1.24) and depression (OR 1.23,

Table 2 Blood pressure centiles across sex and age groups

	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)		
	5th centile	50th centile	95th centile	5th centile	50th centile	95th centile
Men (years)						
20–29	114	132	153	58	72	87
30–39	113	132	154	63	77	93
40–49	113	134	161	67	82	101
50–59	114	139	173	70	85	105
60–69	115	147	185	69	86	107
70–79	117	152	191	66	85	108
80–89	117	153	196	63	83	109
Women (years)						
20–29	103	120	140	57	70	85
30–39	103	119	143	59	73	89
40–49	105	125	158	63	77	96
50–59	109	135	175	65	81	102
60–69	115	147	188	66	82	105
70–79	122	158	201	65	83	109
80–89	127	164	209	64	84	116

95% CI 1.06 to 1.43). Hypertension ($\geq 140/95$ mm Hg) was inversely associated with anxiety (OR 0.90, 95% CI 0.82 to 0.99) and depression (OR 0.93, 95% CI 0.82 to 1.05).

DISCUSSION

In this large epidemiological study, we found that low blood pressure was associated with increased prevalence of anxiety and depression. The associations were independent of age, sex or cardiovascular disease, and our sample size makes it likely that any effect modification by these factors would have been discovered. This is the first time that these common mental disorders have been clearly linked to low systolic and diastolic blood pressure in a large, community-based population. The large sample size gave us an opportunity to examine the whole blood pressure distribution, and showed that the lowest centiles were associated with the highest prevalence of anxiety and depression.

Four of six geriatric studies reported an association of low diastolic blood pressure with depression,^{13–15} or of both diastolic and systolic blood pressure with depression.^{6–14} In one of these studies, no association was found; however, high diastolic blood pressure seemed to predict fewer cases of depression 3 years later.¹⁶ Increased “negative affect”, which

was recognised as a common feature of both anxiety and depression in one of the geriatric studies, was not found to be associated with low blood pressure.¹⁵ Compared with these studies, our study is the first to report an association also with anxiety, and to show that these associations are not only seen in old age. Other studies have reported positive associations between hypertension and anger, anxiety and depression. However, psychometric properties of the scales used in these studies have often been less well established.⁹ In our study, hypertension was not associated with anxiety or depression, except for the upper five centiles of systolic blood pressure, which had significant lower OR for comorbid anxiety and depression compared with the reference group (table 3). Our results are in contrast with a recent study among poor, elderly people from rural China, where an association between undetected hypertension and depression was found.¹⁷

In the multivariable analyses, the most important finding was that adjustment for several covariates reduced the effect sizes only moderately. Physical impairment, owing to somatic disease or movement restriction, had the strongest effect on the associations. Low blood pressure might partly be a result of immobility due to physical impairment, but the variable “physical activity” had no adjusting effect. In addition,

Table 3 Associations of blood pressure with anxiety and depression estimated with multinomial logistic regression models

	Anxiety*		Depression*		Comorbid anxiety and depression*	
	Basic covariate model† OR (95% CI)	Multivariable-model OR‡ (95% CI)	Basic covariate model† OR (95% CI)	Multivariable-model OR‡ (95% CI)	Basic covariate model† OR (95% CI)	Multivariable-model OR‡ (95% CI)
Systolic blood pressure (centile)						
0–5	1.31 (1.16 to 1.49)	1.26 (1.12 to 1.44)	1.22 (1.03 to 1.46)	1.19 (1.00 to 1.42)	1.44 (1.24 to 1.68)	1.35 (1.16 to 1.58)
41–60	1.00	1.00	1.00	1.00	1.00	1.00
96–100	0.96 (0.84 to 1.11)	0.98 (0.85 to 1.13)	0.89 (0.73 to 1.08)	0.88 (0.73 to 1.07)	0.76 (0.63 to 0.91)	0.77 (0.63 to 0.93)
Diastolic blood pressure (centile)						
0–5	1.13 (1.00 to 1.29)	1.13 (0.99 to 1.28)	1.31 (1.10 to 1.56)	1.29 (1.09 to 1.54)	1.24 (1.06 to 1.46)	1.21 (1.03 to 1.43)
41–60	1.00	1.00	1.00	1.00	1.00	1.00
96–100	0.93 (0.80 to 1.07)	0.92 (0.80 to 1.07)	1.06 (0.88 to 1.29)	1.05 (0.86 to 1.27)	0.97 (0.81 to 1.16)	0.95 (0.79 to 1.14)

The 41–60th centile was the reference blood pressure group.

*Defined by scores on subscales of the Hospital Anxiety and Depression Scale: anxiety (HADS-A ≥ 8 , HADS-D < 8); depression (HADS-A < 8 , HADS-D ≥ 8); comorbid anxiety and depression (≥ 8 on both subscales).

†Included terms for age, sex and education.

‡Included terms for age, sex, education, use of drugs for hypertension, body mass index, cholesterol, triglycerides, physical activity, cigarette smoking, physical impairment, and a history of stroke, myocardial infarction, angina pectoris, cancer, diabetes, fibromyalgia, headache and hypothyroidism.

Figure 1 Association of systolic blood pressure with anxiety, depression, and comorbid anxiety and depression. These generalised additive model (GAM) plots represent the relationships of continuous systolic blood pressure with cases of anxiety, depression, and comorbid anxiety and depression, respectively, with adjustment for age, sex and education. The bold lines give the odds ratios (ORs) on a log scale, where OR = 1.00 corresponds to the mean value of the systolic blood pressure. The dotted lines represent 95% confidence interval (CI).

depression, and possibly also anxiety, could result in over-estimation of somatic health problems. Therefore, it is difficult to assess if physical impairment had a mediating effect on the associations or represented some type of information bias. Smoking was the second most influential covariate. Activation of cerebral nicotinic receptors is reported to have effects on anxiety and depression,²⁴ and adverse haemodynamic effects.²⁵ However, the influence of nicotine on the relationship of low blood pressure with anxiety and depression is probably quite complex.

In our study, use of drugs for hypertension did not influence the association of low blood pressure with anxiety and depression. This is in line with geriatric studies finding no effect of drugs against hypertension on the association between low blood pressure and depression.^{13–15} Similarly, previous studies also found that antidepressants did not influence this association.^{6–13} In our sample, 2.9% of participants reported using drugs for depression during some part of the year before the survey; at the time of the blood pressure measurement, about half of these were currently using drugs for depression. As the use of drugs for depression is an alternative measure of depression besides the HADS, we did not include the use of antidepressants due to the risk of over-adjustment. However, the association was maintained, although weakened, when

people using drugs for depression were excluded from the analyses.

The strengths of this study are the examination of the whole adult population within a geographical area that is fairly representative of Norway, and with a high participation rate¹⁹; the standardised assessment of blood pressure, and symptoms of anxiety and depression; the exploration of the whole blood pressure range; and the multivariable analyses with adjustment for several factors, of whom many are known to influence blood pressure, and anxiety and depression.

It might be argued that in this study, the blood pressure measurement, and to a lesser degree the HADS, give only a “snap-shot” of the participants’ situation. In epidemiological studies, however, screening measurements, and not clinical diagnosis, are the standard. Statistically, slightly reduced validity of measuring either blood pressure or mental symptoms would weaken rather than strengthen any association between them. Clinically, anxiety often increases blood pressure at measurement,²⁶ making it unlikely that this “white coat effect” could strengthen the association with low blood pressure. Therefore, measurement bias may probably not explain the observed associations.

Previously, medicine regarded the association between low blood pressure and mental symptoms as part of a “constitutional hypotension” or a “hypotensive syndrome”. A “hypotoner symptomkomplex” is still mentioned in a new German textbook.²⁷ In English-speaking countries, from 1940² until now, the dominant attitude has been far more unanimous: chronic low blood pressure does not produce symptoms. Several papers have reflected this controversy: a study in 1997 found no link between low blood pressure and psychological dysfunction or fatigue, and questioned the findings in earlier studies.¹⁸ In the same year, however, other authors asked if hypotension was a forgotten illness.²⁸ Since then, studies have linked low blood pressure to depression,^{6–14–15} sleep-disordered breathing,²⁹ higher risk of dementia in elderly people³⁰ and the development of chronic fatigue.³¹

What mechanisms could be involved in the relationship of low blood pressure with anxiety and depression? Neurons that control blood pressure are reported to express neuropeptide Y; this peptide seems to reduce both blood pressure and anxiety, and lowers the sympathetic outflow.³² Neuropeptide Y is only one of a large number of neurotransmitters or neuromodulators that are involved in different stress responses. Two main systems play a pivotal part: the hypothalamic–pituitary–adrenocortical axis and the renin–angiotensin system.³³ The neuroendocrine mechanisms involved are most likely very complicated and only partly understood at present.

Our data give epidemiological evidence for an association of low blood pressure with anxiety and depression in adults, independent of age and sex. We want to underline that: (1) our findings could not be ascribed to lowering of blood pressure by

Figure 2 Effect of adjustments for covariates on the association of 0–5 centile systolic blood pressure with comorbid anxiety and depression. All effects (odds ratios (ORs) compared with the 41–60 centile systolic blood pressure) were adjusted for age, sex and education. Bars show 95% confidence interval (CI). The basic covariate model included terms for age, sex and education. Antihypert.med., drugs for hypertension; phys. impairment, physical impairment.

Key points

- Low blood pressure was found to be associated with anxiety and depression in the general population.
- The associations were independent of sex or age groups.
- Cardiovascular disease or the use of drugs for hypertension did not explain the associations.
- Neuroendocrine studies are needed to explore the mechanisms that might be involved in the associations.

the use of drugs for hypertension. In fact, people taking drugs for hypertension had higher blood pressure than the rest of the study participants, and the use of such drugs had no effect on the blood-pressure-mental disorder relationship. Thus, the results provide no argument for not treating hypertension adequately. (2) Neuroendocrine studies are needed to explore the mechanisms that might be involved in the association between low blood pressure and mental disorders, and further epidemiological studies are needed to clarify whether a more extensive hypotensive syndrome really exists.

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