

Symptoms of anxiety and depression across adulthood and blood pressure in late middle age: the 1946 British birth cohort

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Objective: Previous studies testing the hypothesis that symptoms of anxiety and depression increase blood pressure (BP) levels show inconsistent and limited findings. We examined the association between those symptoms across adult life and BP in late middle age.

Methods: Using data from 1683 participants from the MRC NSHD, we investigated associations between affective symptoms at ages 36, 43, 53 and 60–64 years and SBP and DBP at age 60–64. Multivariable linear regression was used to examine the effect on BP of affective symptoms at each age separately and as a categorical cumulative score based on the number of times an individual was classified as a 'case'. Models were adjusted for sex, BMI, educational attainment, socio-economic position, heart rate, lifestyle factors and antihypertensive treatment.

Results: In fully adjusted models, we observed lower SBP in study members with case-level symptoms at one to two time-points [−1.83 mmHg; 95% confidence interval (CI) −3.74 to 0.01] and at three to four time-points (−3.93 mmHg; 95% CI −7.19 to −0.68) compared with those never meeting case criteria suggesting a cumulative inverse impact of affective symptoms on SBP across adulthood (*P* value for trend 0.022). Sex and BMI had a large impact on the estimates while not other confounders. Potential mediators such as heart rate and lifestyle behaviours had a little impact on the association. SBP at age 36 and behavioural changes across adulthood, as additional covariates, had a little impact on the association. A similar but weaker trend was observed for DBP.

Conclusion: A cumulative effect of symptoms of anxiety and depression across adulthood results in lower SBP in late middle age that is not explained by lifestyle factors and antihypertensive treatment. Mechanisms by which mood may impact BP should be investigated.

Keywords: blood pressure, epidemiology, longitudinal studies, population, repeated measures, symptoms of anxiety and depression

Abbreviations: ACTH, adrenocorticotrophic hormone; BNF, British National Formulary; BP, blood pressure; CI, confidence interval; CRH, corticotrophin-releasing-factor;

GHQ, General Health Questionnaire; HPA, hypothalamic-pituitary-adrenal; MRC NSHD, Medical Research Council National Survey of Health and Development; PSE, Present State Examination; PSE-ID, index of definition; PSF, Psychiatric Symptom Frequency scale

INTRODUCTION

The hypothesis that symptoms of anxiety and depression affect long-term blood pressure (BP) regulation was postulated in the early 20th Century [1]. This association has been investigated in several cross-sectional studies, but conflicting evidence emerged [2–7]. The lack of appropriate prospective data has long been perceived as a critical flaw. However, in the last decade, findings from longitudinal studies became available [8–13], although conflicting results remained. As summarized in a recent meta-analysis [14], the methodological protocols across studies vary tremendously with regard to the length of follow-up, sample size, age, sex and ethnic composition, psychological measures, definition of hypertension (e.g. $\geq 140/90$, $\geq 165/95$ mmHg or self-reported hypertension) and appropriate control for potential mediators and confounders. Although some longitudinal studies found a positive association between depressive symptoms and hypertension [10–13,15], others reported no such association [16–19] or found an inverse association [8,9,20]. Most

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of these reports have typically focused on incident hypertension as an outcome [10–13,15,17–20] rather than on BP as continuous trait [8,9,16,21]. To date, few studies have examined the longitudinal association between symptoms of anxiety and depression and BP levels.

In the present study, we investigated the effect of repeated measures of symptoms of anxiety and depression collected through 24 years on BP levels at age 60–64 within a British community-based population. We also tested whether there were cumulative effects of those symptoms on BP levels while accounting for a large number of potential confounders and mediators.

MATERIALS AND METHODS

Study members

The Medical Research Council National Survey of Health and Development (NSHD) is a socially stratified sample of 5362 singleton births that took place in 1 week of March 1946 in England, Scotland and Wales [22]. This cohort has been followed up prospectively 23 times, from birth onwards. The main data collections in adult life were at 26, 36, 43 and 53 years. Between 2006 and 2010 (at 60–64 years), 2856 eligible study members (those known to be alive and with a known address in England, Scotland or Wales) were invited for an assessment at one of six clinical research facilities or to be visited by a research nurse at home. Invitations were not sent to those who had died ($n=778$), who were living abroad ($n=584$), had previously withdrawn from the study ($n=594$) or had been lost to follow-up ($n=550$) [23]. Of those invited, 2229 (78%) were assessed: 1690 (59.2%) attended a clinical research facility and the remaining 539 were seen at home. A total of 2216 study members had at least one valid outcome measured. Of those 627 not assessed, 31 had died, 356 refused to participate and 240 completed only a postal questionnaire. Ethical approval for the study was obtained from the Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics Committee. Written, informed consent was obtained from study members for each component of the data collection. From the current respondents, a total of 1683 study members had nonmissing data for all variables incorporated in these analyses.

Assessments of symptoms of depression and anxiety

Symptoms of anxiety and depression were assessed at age 36 by a short version of the Present State Examination (PSE) [24], a clinically validated interview administered by trained nurses assessing the frequency and severity of neurotic and affective symptoms in the preceding month. For case-level anxiety and depression symptoms, the index of definition (PSE-ID) provides a scale of severity ranging from 1 to 7, with a threshold for caseness of 5 or more [25]. At age 43 years, the Psychiatric Symptom Frequency scale (PSF) [26], an interview-based 20-item scale that rates the frequency and severity of neurotic and affective symptoms in the 12 preceding months was administered. The total score on the PSF scale was calculated by adding the scores of the first 18 items of the instrument, with a threshold for potential caseness between 22 and 23 [26]. At ages 53 and 60–64

years, study members completed the 28-item General Health Questionnaire (GHQ) [27], a self-administered questionnaire focusing on the experience and psychosocial impact of symptoms of anxiety and depression in the preceding month. This questionnaire correlates highly with the PSE [28]. Each item was coded according to Likert scoring (0–1–2–3) and further coded as 0 for response choices 0 and 1 and as 1 for response choices 2 and 3. Caseness was defined as a total score equal to or greater than 5 when these items were recoded to 0–0–1–1 [29].

Assessment of blood pressure and hypertension

At each assessment, BP was measured twice by a trained nurse in the participant's home or at one of the clinical research facilities, while the survey member was seated and after 5 min rest. An average of two consecutive readings was calculated, unless only one reading was available, in which case this was used instead (<1% of all observations). At ages 36 and 43 years, a Hawksley random zero sphygmomanometer was used, and at ages 53 and 60–64 years, an automated digital oscillometric sphygmomanometer (Omron HEM-705; Omron Corp., Tokyo, Japan) was used. Corrections for the machine switch in the last wave using published conversion equations [30,31] made no difference to the results, and so we present the results using the uncorrected values. All readings were taken using an appropriate cuff size for arm circumference. We defined hypertension as the mean SBP of 140 mmHg or higher, or as the mean DBP of 90 mmHg or higher, or current use of antihypertensive medications. At each assessment, study members were asked whether they had taken any prescribed medication or tablets for high BP in the last year. Antihypertensive medications included drug listed in the British National Formulary (BNF) in section 2.2 (diuretics), 2.4 (β blockers), 2.5 (Hypertension and heart failure) and 2.6.2 (calcium channel blockers) [32].

Covariates

Factors that could confound or mediate the main associations were identified *a priori*. The highest educational qualification achieved by age 26 years was dichotomized into those with advanced ('A level', taken during the final year of secondary/high school) or higher (university or equivalent) qualifications, versus those below this level. Socio-economic position at age 53 was used as an indicator of main occupation in adulthood and categorized using the Registrar General's Social Classification into two groups: nonmanual skill (I or II or IIINM) and manual skill (IIIM or IV or V). In addition, the following covariates at age 36, 43, 53 and 60–64 years were used as potential mediators. Data on lifestyle behaviours were extracted from questionnaires, interview-based prospective information and diet diaries. At each interview waves, study members who provided an affirmative response to being current cigarette smokers, regardless of the quantity of cigarettes smoked per day, were classified as 'smokers', whereas those who provided a negative response were classified as 'nonsmoker'. From the type and number of alcoholic drinks, we calculated alcohol consumption in grams per day. To exclude occasional drinkers, we distinguished drinkers from nondrinkers on

consumption of at least 5 g of ethanol per day. Physical activity levels were ascertained at ages 36, 43 and 53 years during interviews with nurses at the study participants' homes. Different measures for leisure-time physical activity were included in the surveys administered at the respective ages. Full description of those specific ascertainment was extensively described elsewhere [33,34]. At each age, participants were categorized as physically inactive (no participation or participation in relevant activities one to four times in the previous 4 weeks) or active (participated in relevant activities five or more times in the previous 4 week).

Lifetime behaviour status was constructed from the four interview waves for smoking, drinking and physical activity for participants with information on at least three of the four data collections. For lifetime smoking status, the study members were classified into one of four trajectories: 'Never smoker' (a nonsmoker at all available data collections), 'Predominantly nonsmoker' (a nonsmoker for at least two data collections), 'Predominantly smoker' (a smoker for at least three data collections), 'Lifelong smoker' (a smoker at all available data collections). In cases wherein data were missing from one waves, classification was based on the status at the majority of data collections. Thus, if at two of three data collections the cohort members reported being a smoker, then they were classified as predominantly smokers. This behaviour was then categorized into two trajectories: never smoker (i.e. a never smoker or predominantly nonsmoker) and ever smoker (i.e. a predominantly smoker or lifelong smoker). The same approach in coding was used for lifetime drinking status (never drinker and ever drinker) and for physically active status (never active and ever active).

BMI was calculated as weight in kilograms divided by height in meters squared, derived from height and weight measured at ages 36 and 60–64 years without shoes with study members wearing light indoor clothing by research nurses during the home visit. Change in mean BMI was calculated as the difference between BMI at age 60–64 and BMI at age 36.

While the study member was seated and after 5 min rest, at age 36, resting heart rate at the wrist (beats/min) was counted for 1 min. At age 60–64, heart rate was measured by the automated digital oscillometric sphygmomanometer. Change in mean heart rate was calculated as the difference between heart rate at age 60–64 and heart rate at age 36.

Diabetes mellitus at age 60–64, coded as a binary variable, was a self-reported diagnosis, or a fasting blood glucose concentration of at least 7.0 mmol/l, or glycated haemoglobin of at least 6.5%, or use of insulin or oral antidiabetic agents. History of cardiovascular disease (CVD) self-reported at age 60–64, coded as a binary variable, included nonfatal myocardial infarction, acute coronary syndrome, surgical and percutaneous coronary revascularization, angina pectoris, chronic ischemic heart disease, stroke and heart failure.

Treatment with antidepressant medications was coded at ages 36, 43, 53 and 60–64. Antidepressant medications included any drug listed in the BNF section 4.3 (tricyclic antidepressants, monoamine-oxidase inhibitors, selective

serotonin reuptake inhibitors and other antidepressant drugs) [32].

Statistical methods

We used χ^2 and one-way analysis of variance (ANOVA) to examine differences in characteristics across groups of lifetime symptoms of anxiety and depression status.

Multivariable linear regression models were used to test the association between symptoms of anxiety and depression (case versus noncase) at each age and BP levels (systolic and diastolic in separate models) at age 60–64 years, initially unadjusted (model 1) then adjusted for the two confounders sex and BMI at 60–64 years (model 2). Formal tests of gender by symptoms of anxiety and depression interaction were performed in model 2 and no evidence of this was found. Further adjustments were then made for the confounders educational attainment and socio-economic position (model 3). Potential mediators such as heart rate, smoking status, drinking status and physical activity at age 60–64 and confounder such as antihypertensive treatment at age 60–64 were also added (model 4). Finally, the two confounders' history of CVD and diabetes mellitus status at age 60–64 were included (model 5).

We then tested whether there was evidence of a cumulative effect of symptoms of anxiety and depression across adulthood by creating a lifetime anxiety and depression caseness variable based on the number of times an individual was classified as a 'case' during the follow-up: never meeting affective symptom case criteria, case-level symptoms at one to two time-points and case-level symptoms at three to four time-points. Associations between lifetime affective caseness (categorized into three groups) and each BP outcome (SBP and DBP) were tested with adjustments for the same covariates as above. The analyses presented are based on the sample with complete data on symptoms of anxiety and depression at all four ages, all covariates and at least one of the outcome measures ($n = 1683$).

Logistic regression analysis with adjustments for the same covariates as above was conducted to determine whether the lifetime symptoms of anxiety and depression status was a potential predictor for hypertension at age 60–64.

Linear regression analyses were also rerun with adjustments for SBP at age 36 years (starting from model 3); with adjustments for behavioural changes across adulthood (including in model 2 change in mean BMI between ages 36 and 60–64 years and in model 4 change in mean heart rate between age 60–64 and 36 years, lifetime smoking status, lifetime drinking status, lifetime physical activity status); with adjustments for antidepressant medications at age 60–64; incorporating the use of antidepressant medications into the definition of symptoms of anxiety and depression; excluding participants using antihypertensive medications; and introducing a correction of BP value for study members on hypertensive medication by adding 10 mmHg to SBP and 5 mmHg to DBP in accordance with Cui *et al.* [35] and based on the efficacy of antihypertensive drugs in randomized trials [36]. Antihypertensive treatment was excluded as a covariate from Models 4 and 5. There were no differences in findings.

For statistical analysis, we used SAS software, version 9.3 (SAS Institute, Cary, North Carolina, USA). *P* value less than 0.05 (two-tailed) was considered statistically significant.

RESULTS

Characteristics of participants

Table 1 presents the general characteristics of the 1683 study members (52.4% women) at age 60–64 by lifetime symptoms of anxiety and depression status. The number of study members never meeting affective symptom case criteria over the course of the study was 1080 (64.2%); the number who reported case-level symptoms at one to two time-points was 474 (28.1%); and at three to four time-points, this was 129 (7.7%). There were significant between-group differences. Study members who reported case-level symptoms at three to four time-points compared with those never meeting case criteria were more likely to be female, to have lower SBP and DBP, to have higher BMI and lower education level, to be smokers, nondrinkers and physically inactive, to be treated for hypertension, to be diabetic, to have a prevalent history of CVD and to be treated with antidepressant drugs. No between-group differences at the 5% level were observed for heart rate, socio-economic position and prevalence of hypertension.

Symptoms of anxiety and depression across follow-up time points

In unadjusted models, caseness affective symptoms at ages 43, 53 and 60–64 were inversely associated with SBP at age 60–64 (supplementary Table 1, <http://links.lww.com/HJH/A361>). There was no evidence at ages 43, 53 and 60–64 that these associations differed by sex (*P*=0.47, 0.49 and 0.64 from tests of sex interaction, respectively). However, adjustment for the confounders sex and BMI at age

60–64 (model 2) attenuated those associations. The other confounders (education at age 26, socio-economic position at age 53 and antihypertensive treatment, history of CVD and diabetes at age 60–64) and potential mediators (heart rate, smoking, drinking and physical inactive status at age 60–64) had a little impact. In fully adjusted models, a borderline inverse association between caseness of symptoms of anxiety and depression at age 43 and SBP remained [−2.71 mmHg; 95% confidence interval (CI) −5.47 to 0.06], whereas at ages 53 and 60–64, the inverse associations were not statistically significant (−1.97 mmHg; 95% CI −4.14 to 0.18; and −1.72 mmHg; 95% CI −3.94 to 0.49, respectively). No association between caseness of symptoms of anxiety and depression at age 36 and SBP at age 60–64 was found.

For DBP at age 60–64, in unadjusted models, we observed inverse associations with caseness affective symptoms at ages 53 and 60–64 years (data not shown). However, adjustment for the confounders sex and BMI at age 60–64 strongly attenuated those associations. No associations between caseness of anxiety and depression at ages 36 and 43 years and DBP at age 60–64 were found.

Lifetime anxiety and depression caseness

Across follow-up, there were differences in SBP means by lifetime anxiety and depression caseness (Fig. 1). The differences in means between age 53 and age 36 were 16.4 mmHg for SBP (*P*<0.0001) and 7.8 mmHg for DBP (*P*<0.0001). No difference in mean was observed between age 53 and age 60–64 for SBP (*P*=0.63), whereas mean DBP at age 53 was lower by 6.3 mmHg than at age 60–64 (*P*<0.0001).

In Table 2, the unadjusted model (model 1) showed that study members reporting case-level affective symptoms at one to two time-points had lower SBP at age 60–64 than

TABLE 1. Characteristics of the study participants at age 60–64 by lifetime anxiety and depression caseness (n = 1683)

| Characteristics at 60–64 years | All individuals (n = 1683) | Never meeting case-criteria (n = 1080) | Case-level symptoms at 1–2 time-points (n = 474) | Case-level symptoms at 3 to 4 time-points (n = 129) | <i>P</i> trend |
|---|----------------------------|--|--|---|----------------|
| Sex (women), n % | 883 (52.4) | 499 (46.2) | 286 (60.3) | 98 (76.0) | <0.0001 |
| Clinical features | | | | | |
| SBP (mmHg) ^a | 136.2 ± 18.0 | 137.3 ± 18.3 | 134.8 ± 17.8 | 132.0 ± 16.0 | 0.001 |
| DBP (mmHg) ^a | 77.8 ± 9.8 | 78.3 ± 9.7 | 76.9 ± 9.9 | 76.4 ± 9.2 | 0.009 |
| Heart rate (bpm) | 68.6 ± 11.0 | 68.6 ± 11.2 | 68.5 ± 10.7 | 68.7 ± 10.4 | 0.97 |
| BMI (kg/m ²) ^b | 28.0 ± 4.9 | 27.8 ± 4.6 | 28.2 ± 5.3 | 28.9 ± 5.7 | 0.04 |
| Questionnaire data | | | | | |
| Educational attainment by age 26 (higher level), n (%) | 682 (40.5) | 445 (41.2) | 202 (42.6) | 35 (27.1) | 0.005 |
| Socioeconomic position at age 53 (nonmanual skill), n (%) | 1134 (67.4) | 726 (67.2) | 327 (69.0) | 81 (62.8) | 0.40 |
| Smokers (current), n (%) | 190 (11.3) | 96 (8.9) | 71 (15.0) | 23 (17.8) | 0.0001 |
| Drinkers (≥5 g/day), n (%) | 1067 (63.4) | 882 (76.1) | 346 (73.0) | 76 (58.9) | 0.0001 |
| Leisure-time physical activity (inactive), n (%) | 1059 (63.0) | 653 (60.5) | 305 (64.3) | 101 (78.3) | 0.0003 |
| Hypertension, n (%) | 982 (58.4) | 629 (58.2) | 275 (58.0) | 78 (60.5) | 0.87 |
| Antihypertensive treatment, n (%) | 562 (33.4) | 331 (30.6) | 181 (38.2) | 50 (38.8) | 0.006 |
| Diabetes mellitus, n (%) | 164 (9.7) | 100 (9.3) | 43 (9.1) | 21 (16.3) | 0.03 |
| History of cardiovascular disease, n (%) | 131 (7.8) | 110 (10.2) | 77 (16.2) | 25 (19.4) | 0.002 |
| Antidepressant treatment, n (%) | 130 (7.7) | 44 (4.1) | 58 (12.2) | 28 (21.7) | <0.0001 |

Values are arithmetic means ± SD or number of individuals (%).

^aAverage of two blood pressure readings obtained at clinic or at home visit.

^bThe BMI is weight in kilograms divided by the square of the height in meters.

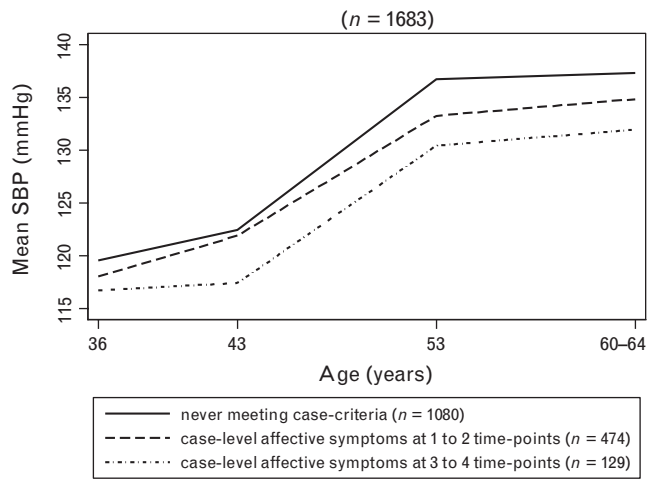


FIGURE 1 Mean SBP by lifetime anxiety and depression caseness across four follow-up time points ($n = 1683$). The solid line represents study members never meeting affective symptoms case criteria; the dash line represents study members with case-level affective symptoms at 1–2 time-points; the short dash dot line represents study members with case-level affective symptoms at 3–4 time-points.

those never meeting case criteria (-2.46 mmHg; 95% CI -4.39 to -0.52), as well as study members meeting criteria at three to four time-points (-5.36 mmHg; 95% CI: -8.62 to -2.07) (P -value for trend 0.001). In model 2, sex and BMI at age 60–64 acted as strong confounders and partially attenuated those associations. Models 3, 4 and 5 showed that the other confounders (education at age 26, socioeconomic position at age 53 and antihypertensive treatment, history of CVD and diabetes at age 60–64) and potential mediators (heart rate, smoking, drinking and physical inactive status at age 60–64) had a little impact. Therefore, after full covariate adjustment, we observed a clear inverse dose–response for lower SBP in relation to frequency of affective caseness [case-level symptoms at one to two time-points: -1.83 mmHg (95% CI -3.74 to 0.01); and at three to four time-points: -3.93 mmHg (95% CI -7.19 to -0.68) compared to those never meeting case-criteria] suggesting a cumulative impact of anxiety and depression on SBP across adulthood (P value for trend 0.022).

A similar but weaker negative association was observed for DBP (supplementary Table 2, <http://links.lww.com/HJH/A361>). In the unadjusted model, study members with case-level symptoms at one to two time-points had lower DBP than those never meeting case-criteria (-1.40 mmHg; 95% CI -2.46 to -0.35); for case-level at three to four time-points, this was -1.93 mmHg (95% CI -3.71 to -0.15) (P -value for trend 0.01). These associations were significantly attenuated after adjustment for sex and BMI and less attenuated after adjustment for the other confounders and mediators (-0.88 and -0.75 mmHg, respectively; P value for trend 0.22).

Lifetime anxiety and depression caseness and hypertension risk

In unadjusted logistic regression analysis, study members with case-level affective symptoms at one to two time-points and at three to four time-points were not more likely

TABLE 2. Multivariable adjusted associations of lifetime anxiety and depression caseness and SBP at age 60–64 ($n = 1683$)

| Lifetime affective caseness ^a | n (%) | Difference in mean systolic BP (mmHg) | | | | |
|--|-------------|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| | | Model 1 β (95% CI) | Model 2 β (95% CI) | Model 3 β (95% CI) | Model 4 β (95% CI) | Model 5 β (95% CI) |
| Never meeting case criteria | 1080 (64.2) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Case-level symptoms at 1–2 time-points | 474 (28.1) | -2.46 (-4.39 to -0.52) | -1.75 (-3.65 to 0.15) | -1.74 (-3.64 to 0.16) | -1.89 (-3.80 to 0.01) | -1.83 (-3.74 to 0.01) |
| Case-level symptoms at 3–4 time-points | 129 (7.7) | -5.36 (-8.62 to -2.07) | -4.10 (-7.35 to -0.87) | -4.11 (-7.35 to -0.87) | -4.03 (-7.27 to -0.79) | -3.93 (-7.19 to -0.68) |
| P | | 0.001 | 0.019 | 0.019 | 0.017 | 0.022 |

Model 1: unadjusted effect estimates. Model 2: effect estimates adjusted for sex and BMI at age 60–64. Model 3: Model 2 additionally adjusted for educational attainment by age 26 and socioeconomic position at age 53. Model 4: Model 3 additionally adjusted for covariates at age 60–64: heart rate, current smoking, alcohol consumption, physical activity and antihypertensive treatment. Model 5: Model 4 additionally adjusted for history of cardiovascular disease and diabetes mellitus status at age 60–64. BP, blood pressure; CI, confidence interval.
^aAffective caseness assessed at each time point as follow: PSE-ID ≥ 5 at age 36, total PSF score ≥ 23 at age 43 and total GHQ-28 score ≥ 5 at ages 53 and 60–64 years.
^b P value for the effect size versus never.

to be hypertensive than those never meeting case criteria [odds ratio (OR) 0.96; 95% CI 0.77–1.20 and OR 1.10; 95% CI 0.75–1.60, respectively] (*P* value for trend 0.83). This was confirmed in a fully adjusted model considering all covariates except antihypertensive treatment (OR 0.98; 95% CI 0.77–1.24 and OR 0.96; 95% CI 0.63–1.45, respectively) (*P* value for trend 0.97).

Sensitivity analysis

To test the robustness of our findings, we undertook several sensitivity analyses.

First, in our main analysis, we considered SBP at age 36 years as an additional covariate in order to evaluate the potential confounding effect of baseline BP value. In supplementary Table 3, <http://links.lww.com/HJH/A361>, Model 3 shows that SBP at age 36 had a little impact. In the fully adjusted model, the inverse association between lifetime anxiety and depression caseness and SBP at age 60–64 years [–3.34 mmHg (95% CI –6.53 to –0.16)] was only slightly attenuated (*P*=0.07).

Second, we considered adjustments for behavioural changes across adulthood. The sample for this analysis comprised those who provided data for at least three of the four data collections (*n*=1660). Study members with case-level symptoms at three to four time-points (*n*=123) than those never meeting case criteria (*n*=1070) were more likely to be smokers overtime (22.8 versus 12.5%, *P*=0.003), nondrinkers overtime (58.5 versus 44.9%, *P*=0.01), to be physically inactive overtime (69.9 versus 54.0%, *P*=0.0003) and to have higher BMI change overtime (+4.80 versus +3.87 kg/m², *P*=0.003). No between-group differences at the 5% level were observed for change in heart rate. In study members with case-level symptoms at three to four time-points, the unadjusted inverse association between lifetime anxiety and depression caseness and SBP [–5.02 mmHg (95% CI –8.34 to –1.69)] was attenuated once adjusted by sex and change in BMI between ages 60–64 and 36 years [–3.47 (95% CI –6.76 to –0.17)] (Table 3). The additional adjustments for change in heart rate between ages 60–64 and 36, lifetime smoking, drinking and physical activity status had little impact on the association (Table 3, Model 4). A similar pattern was observed for DBP (data not shown), with the inverse association largely attenuated by change in BMI between ages 60–64 and 36 years and marginally by the other behavioural changes across adulthood.

Third, we additionally adjusted our main analyses by antidepressant medications at age 60–64 and found the associations to be close to those reported in the main analyses in Model 5: lower SBP in study members with case-level affective symptoms at one to two time-points (–1.65 mmHg; 95% CI –3.57 to 0.28) and at three to four time-points (–3.57 mmHg; 95% CI –6.85 to –0.28), compared with those never meeting case criteria (*P* value for trend 0.048).

Fourth, we expanded our definition of caseness of anxiety and depression by including any participant who reported use of antidepressant medications at each time point, thus increasing the frequency of affective caseness. In analyses adjusted for all covariates, as in Model 5, we found a similar pattern of associations to that reported in the

TABLE 3. Multivariable adjusted associations of lifetime anxiety and depression caseness and SBP at age 60–64 considering behavioural changes across adulthood (*n* = 1660)

| Lifetime affective caseness ^a | <i>n</i> (%) | Difference in mean SBP (mmHg) | | | | |
|--|--------------|-------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | | Model 1 β (95% CI) | Model 2 β (95% CI) | Model 3 β (95% CI) | Model 4 β (95% CI) | Model 5 β (95% CI) |
| Never meeting case-criteria | 1070 (64.5) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Case-level symptoms at 1–2 time-points | 467 (28.1) | –2.44 (–4.38 to –0.50) | –1.75 (–3.66 to 0.16) | –1.72 (–3.63 to –0.19) | –1.95 (–3.86 to –0.03) | –1.88 (–3.80 to 0.04) |
| Case-level symptoms at 3–4 time-points | 123 (7.4) | –5.02 (–8.34 to –1.69) | –3.47 (–6.76 to –0.17) | –3.54 (–6.84 to –0.24) | –3.69 (–6.98 to –0.39) | –3.71 (–7.02 to –0.40) |
| <i>p</i> -value ^b | | 0.002 | 0.043 | 0.042 | 0.026 | 0.029 |

Model 1: unadjusted effect estimates. Model 2: effect estimates adjusted for sex and change in BMI between ages 60–64 and 36. Model 3: Model 2 additionally adjusted for educational attainment by age 26 and socioeconomic position at age 53. Model 4: Model 3 additionally adjusted change in heart rate between ages 60–64 and 36, lifetime smoking status, lifetime drinking status, lifetime physical activity status and antihypertensive treatment at age 60–64. Model 5: Model 4 additionally adjusted for history of cardiovascular disease and diabetes mellitus status at age 60–64. BP, blood pressure; CI, confidence interval.
^aAffective caseness assessed at each time point as follow: PSE-ID ≥ 5 at age 36, total PSF score ≥ 23 at age 43, and total GHQ-28 score ≥ 5 at ages 53 and 60–64.
^b*P* value for the effect size versus never.

main analysis: lower SBP in study members with affective caseness at one to two time-points ($n = 476$) (-1.54 mmHg; 95% CI -3.47 to 0.39) and at three to four time-points ($n = 179$) (-3.63 mmHg; 95% CI -6.46 to -0.79), compared with those never meeting case criteria ($n = 1028$) (P value for trend 0.027).

Fifth, we excluded study members using antihypertensive medications from the analyses (remained $n = 1121$) and found the associations to be close to those reported in the main analysis in Model 5: lower systolic BP in study members with case-level affective symptoms at one to two time-points ($n = 293$) (-2.28 mmHg; 95% CI -4.58 to 0.02) and at three to four time-points ($n = 79$) (-3.32 mmHg; 95% CI -7.32 to 0.67), compared with those never meeting case criteria ($n = 749$) (P value for trend 0.06).

Finally, when we added 10 mmHg to SBP for individuals who used antihypertensive medications, we found the associations to be close to those reported in the main analysis in Model 5: lower SBP in study members with case-level affective symptoms at one to two time-points (-1.11 mmHg; 95% CI -3.12 to 0.90) and at three to four time-points (-3.84 mmHg; 95% CI -7.27 to -0.41), compared with those never meeting case criteria (P value for trend 0.07).

DISCUSSION

In a nationally representative British population, evidence was found of a cumulative inverse effect of anxiety and depression across adulthood on SBP in early old age, although no association was found between caseness of anxiety and depression and hypertension. These associations were robust to adjustment for a range of potential confounding factors and mediators and were not explained by use of antidepressant or antihypertensive medication.

Together, these findings contradict the hypothesis that the well established association between depression and CVD might be explained by elevated BP [37]. However, the results of low SBP with respect to symptoms of anxiety and depression support other large population-based studies findings [8,9,20] and extend the existing literature by providing evidence of the cumulative effect of anxiety and depression on BP levels across four follow-up examinations.

Recently, Hildrum *et al.* [9] reported changes in mean SBP from baseline to year 22 and from year 11 to year 22 with a stronger decrease in SBP in individuals with a high affective symptom level at all three examinations compared with individuals with a lower symptom level in a fully adjusted model. This is in line with our fully adjusted findings even though our outcome (BP level at age 60–64 compared with change in BP value) and our statistical approach were different. Indeed, we were able to demonstrate a cumulative effect of anxiety and depression across adulthood on SBP level.

In another recent study based on the British Whitehall II study, Nabi *et al.* [12] observed an increased risk of hypertension in later life in men with repeated experience of symptoms of anxiety and depression over time. This at first appears to be the opposite of our own findings. However, they observed a lower risk of hypertension before 55 years in both men and women in the increasing depression group

compared with those in the low/transient group (24% lower risk at ages 35–39).

In a recent article by Shah *et al.* [21], sex and age differences were observed in the association between depressive symptoms and BP as a continuous trait. Women and older adults with greater depressive symptoms were at an increased risk of elevated SBP compared with those with fewer depressive symptoms. However, opposite results were observed in men, in line with our findings even though we did not observe sex differences.

Other studies with contradictory or nonsignificant findings are hard to interpret and to compare due to the use of self-reported hypertension instead of direct measurement of BP [11,15,16], a short period of follow-up [16] and a possible mediating role of tricyclic antidepressants [16]. It is unlikely that our results were biased by the use of antihypertensive medications or antidepressants. Antidepressant medications might, in fact, be expected to increase SBP [6], and in our analysis, the association persisted after adjustment for these. Furthermore, it may be argued that study members with case-level affective symptoms at three to four time-points had lower SBP due to better antihypertensive treatment. Indeed, we observed that at age 60–64, those with affective symptoms were more likely to be treated (38.8 versus 30.6%) and had a better BP control (24.8 versus 15.2% controlled hypertensive) than the study members never meeting case criteria. However, our sensitivity analyses showed that the inverse association persisted after excluding individuals using antihypertensive medications.

The potential mechanism between symptoms of anxiety and depression and lower SBP is a matter of speculation. The neuropeptide Y and related peptides might be involved. Cerebrospinal fluid levels of those neuropeptides have been found to be inversely associated with anxiety scores in depressed patients [38]. These peptides seem to be associated with several mental symptoms and disorders, to suppress sympathetic activity and to decrease BP [39]. Another possible explanation for the association of chronic elevated symptom levels of anxiety/depression with lower BP might be the dysregulation of cortisol secretion [40]. Cortisol plays a major role on the regulation of vascular tone. In recent studies, lower cortisol levels have been observed in depressed patients, possibly indicating a sign of exhaustion of the hypothalamic-pituitary-adrenal (HPA) axis, after chronic and recurrent depressive episodes [41–43]. A possible mechanism for hypocortisolism is downregulation of corticotrophin-releasing factor (CRH) receptors in the pituitary, following a longer period of stress-induced hypothalamic CRH secretion, resulting in lower adrenocorticotrophic hormone (ACTH) and reduced cortisol levels [44]. Alternatively, reduced biosynthesis or depletion of CRH, ACTH and/or cortisol or increased sensitivity of the HPA-axis to negative feedback [44,45] could play a role in hypocortisolism.

The main strength of the present study is the prospective collection of information on symptoms of anxiety and depression at multiple times across adulthood. Indeed, in a recent meta-analysis, Meng *et al.* [14] showed that the association of depression with hypertension risk depends on the follow-up duration. In the cohorts with

short follow-up duration, depression contributed a little to hypertension risk, whereas in the cohorts with longer follow-up duration, depression had a positive association with hypertension risk. Therefore, the authors recommended a minimum of 5-year follow-up to show whether there is any effect of psychological factors on hypertension [14]. Moreover, other authors emphasized the importance of repeated assessments when evaluating the effect of mental distress on BP due to the fluctuation of symptoms of anxiety and depression over time [12,13,21]. The increasing number of assessments provides a more precise exposure measure. It seems reasonable that ongoing symptoms of anxiety and depression have stronger long-term physiological effects than a shorter period of mental distress.

Another strength is that the association between case-level affective symptoms across adulthood and lower SBP remained after the adjustment for most of the potential confounders and mediators. Two confounders, sex and BMI, had a large impact on the estimates, whereas other confounders such as educational attainment, socioeconomic position, history of CVD and diabetes mellitus did not. The potential mediators such as heart rate and lifestyle behaviours had a little impact on the association, even taking into account their changes across adulthood.

Study limitations include potential residual confounding due to the information bias in the collection of risk behaviours or to their use as a binary variable (although that was necessary to define longitudinal health behaviour due to small numbers in certain categories), the use of different measures of caseness of anxiety and depression over time, and the difficulty of assessing the independent effects of anxiety and depression on BP because of the different assessment of symptoms of anxiety and depression at different time points. However, several authors have observed notable neurobiological, psychological and psychometric overlap between anxiety and depression [46,47] and Hildrum *et al.* [9] found that anxiety and depression each contributed to the lowering of BP.

The NSHD cohort was established using a sampling frame that ensured that it was nationally representative of the population born in England, Scotland and Wales in 1946. Since then, losses to follow-up due to death, emigration, loss of contact and permanent refusal have occurred. Despite this, at age 60–64 years, the sample remained representative of the national population born at a similar time [23]. Our frequency of affective symptom caseness (17.7%) was in-between that reported for common mental disorder in the UK Psychiatric Morbidity Survey [48] for age 55–64 years (14.1%) and that reported in a recent meta-analysis based on the GHQ used at UK population level [49]. Moreover, Stafford *et al.* [23] have shown that in NSHD, psychological distress at the prior sweep and mental health profiles across several previous sweeps were not associated with response rates at age 60–64.

From the 2216 people with at least one valid outcome measure, 533 were excluded from analyses because of missing data on covariates. When the characteristics of those excluded were compared with those included, there were no differences in the distributions of most

key characteristics (supplementary Table 4, <http://links.lww.com/HJH/A361>). However, those excluded were more likely to have lower educational level and lower socioeconomic position, to be current smokers and nondrinkers, and to have higher prevalence of CVD than those included. It is not expected that these differences would introduce a substantial bias, as the adjustment by those covariates had a little impact on the association between case-level affective symptoms and BP. In the sample under investigation, the frequency of hypertension was slightly underestimated compared with those excluded. However, comparing excluded and included study members, there was no difference in the frequency of hypertension across lifetime affective caseness groups.

In conclusion, our results suggest that there is a cumulative inverse effect of case-level affective symptoms across adulthood on SBP in early old age, and that this association remains after controlling for potential confounders and mediators. Mechanisms by which mood may impact BP are poorly understood and population research should now focus on teasing out potential causal pathways.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Referee 1

The authors carried out a longitudinal study in a large sample ($n=1683$) of participants in the British Cohort Study. The study aimed at evaluating the impact of symptoms of anxiety and depression, recorded across adult life, on BP at age 60–64 years.

The longitudinal design is undoubtedly a point of strength of the study. Among the possible weaknesses, it should be noted that BP values (the outcome measure) were significantly different already at baseline between participants with personal history of anxiety/depression symptoms and those without; statistical analysis, however, clarified the impact of these baseline differences on BP values measured at the follow-up.