Depression, anxiety and risk of hypertension in mid-aged women:

Depression, anxiety and risk of hypertension in mid-aged women: a prospective longitudinal study

Running title: Depression, anxiety and hypertension

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CONFLICTS OF INTERESTS

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ABSTRACT

Objectives The evidence for an association between depression and anxiety and increased hypertension risk is inconsistent. We aimed to investigate the association between each of depression and anxiety and incident hypertension.

Methods We included women born 1946-51 from the Australian Longitudinal Study on Women's Health, surveyed triennially from 1998-2013, without a history of hypertension at baseline. We defined depression using the CESD-10 scale and anxiety using self-reported doctor-diagnosis. We related depression and anxiety to incident hypertension, using generalised estimating equations, adjusting for time-varying covariates.

Results Among 9182 women, 2738 developed hypertension during 15 years follow-up. Depression was associated with a 30% increased odds of hypertension (age-adjusted OR 1.30, 95% CI 1.19 to 1.43). This attenuated and was no longer significant in fully adjusted analyses (1.07, 95% CI 0.96 to 1.20). Adjusting for BMI alone reduced the association markedly (OR 1.19, 95% CI 1.08 to 1.31). Anxiety was similarly associated with increased odds of hypertension, but this association became non-significant after adjusting for depression (OR 1.12, 95% CI 0.97 to 1.30).

Conclusions The frequently observed association between depression and hypertension may be explained by confounding, whilst co-morbid depression may account for the apparent effect of anxiety on hypertension risk. However, further research is needed to determine whether factors such as BMI play a mediating role on a causal pathway between depression and hypertension. Nevertheless, weight and weight gain among women with depression should be closely monitored to reduce potential effects on hypertension risk.

Key words: hypertension; depression; anxiety; women; BMI

INTRODUCTION

Cardiovascular and cerebrovascular disease (CVD) are the leading cause of mortality worldwide, whilst poor mental health is a major cause of morbidity. The Global Burden of Disease Study reported that mental and substance use disorders are the leading global cause of all non-fatal burden of disease, as measured by years lived with disability [1]. Depressive disorders contributed most to this burden of disease, followed by anxiety disorders [1]. Common mental disorders such as depression and anxiety appear to disproportionately affect women [2], whilst CVD outcomes are often poorer in women than men [3]. Furthermore, there is growing evidence that depression and anxiety are associated with increased risk of CVD [4, 5]. However, this complex relationship is far from understood and it remains unclear whether depression and anxiety are actually causally related to the development of CVD, with alternative potential explanations for the observed association yet to be disproved. On the other hand, plausible pathophysiologic mechanisms that may well underlie this association have been proposed. This includes the potential for psychological factors, such as depression and anxiety, to increase the risk of arterial hypertension, a major risk factor for CVD [6]. However, the observational evidence to support this is conflicting. Among the few prospective studies that have addressed this question, some found no association between depression and hypertension [7, 8], whereas others found depression to be associated with an increased [9, 10] or decreased risk of hypertension [11, 12]. Despite substantial heterogeneity between the methodology and results of existing prospective studies, a recent systematic review of these cohort studies concluded that depression is 'probably an independent risk factor for hypertension', but recommended that further studies are needed to exclude the role of a wider range of confounding factors [13]. The evidence for an association between anxiety and hypertension

risk is more convincing, although substantial cross-study heterogeneity in the magnitude of effect does exist [14]. Importantly, to date, most prospective studies of the association between depression and anxiety and hypertension collected information on exposures and confounders at baseline only, with very few having collected repeated measurements over time [15, 16].

Given the inconsistencies in the existing literature and shortcomings of existing studies, we sought to investigate whether depression and anxiety are associated with incident hypertension using data from the Australian Longitudinal Study on Women's Health (ALSWH).

METHODS

Study setting and population

We included participants from the ALSWH, a national population-based study of women born in 1921-26, 1946-51 and 1973-78. Women were randomly selected from the Medicare database, which covers all citizens and permanent residents of Australia, including refugees and immigrants. We included women from the 1946-51 cohort who were surveyed using self-administered questionnaires in 1996 (survey 1 [S1], N=13,715), 1998 (survey 2 [S2], N=12,338 [90% response rate]), and every three years thereafter until 2013 (survey 7 [S7], N= 9151). Full details of recruitment and response rates for all surveys are reported elsewhere [17, 18]. For the purposes of this study we included women from the 1946-51 cohort who did not report ever having a history of doctor-diagnosed hypertension at S2, thereby identifying a 'hypertension-free' cohort of women. We did not identify this cohort of women from S1 because information on depressive symptoms was collected from S2 onwards.

In accordance with the Declaration of Helsinki, ethical approval for the ALSWH was obtained from the Universities of Newcastle and Queensland Research Ethics Committees and all participants gave informed consent to be included in the study.

Hypertension

At each survey subsequent to S2, women were asked "In the past three years have you been diagnosed with or treated for hypertension?" (i.e. since the previous survey), to which they could respond "yes" or "no". We defined incident hypertension as first reported occurrence of hypertension during the entire follow-up period, with women who reached this end-point not contributing to analysis thereafter.

Depression and anxiety

Depressive symptoms experienced in the last week were identified using the Center for Epidemiological Studies Depression scale shortened version (CESD-10) [19], which is well-validated and has good test-retest reliability and predictive validity compared with the original 20-item format [19-21]. In primary analyses we defined depression at each time point as being present if women scored ≥10 on the CESD-10 scale.

Women were also asked at S2 if they had been diagnosed with or treated for anxiety in either "the past two years" (i.e. since S1) or "ever". In subsequent surveys women were asked about the diagnosis of or treatment for anxiety in the previous three years (i.e. since the last survey).

Covariates

Lifestyle, physiological and disease history variables were determined at each survey. Smoking was classified as never, ex-smoker or current smoker. Body mass index (kg/m^2) was computed as self-reported weight (kg)/height (m^2), and in descriptive tables presented as a

continuous and also a categorical variable using the following categories (underweight [<18.5 kg/m^2], normal weight [18.5-24.9 kg/m^2], overweight [25-29.9 kg/m^2] or obese [≥ 30 kg/m^2]). BMI was treated as a continuous variable in the regression models. At S2, physical activity was assessed using a modified (self-report) version of the Active Australia Physical Activity Survey [22, 23]. The women were asked to report frequency and total duration of walking, moderate, and vigorous intensity leisure time physical activity during the last week. A physical activity score in metabolic equivalent (MET) minutes per week was derived using the following formula: MET min/week = (walking minutes * 3.5 METs) + (moderate minutes * 4.0 METs) + (vigorous minutes * 7.5 METs). Physical activity was categorized as sedentary (0-39 MET min/week), low (40-599 MET min/week), moderate (600-1199 MET min/week) and high (≥ 1200 MET min/week). Alcohol intake was defined in light of the Australian National Health and Medical Research Council (NHMRC) guidelines with 'Risky drinkers' (15 to 28 drinks per week) and 'High risk drinkers' (more than 28 drinks per week) categorised accordingly [24]. Given the low frequency of high risk drinkers, the latter two groups were combined. For women identified as low risk by the NHMRC guidelines, we separately categorised women who reported that they drink only rarely (any alcohol consumption less than once a month) and non-drinkers, with the remainder classified as low-risk drinkers (up to 14 drinks per week).

Socioeconomic status (SES) was determined by two measures. Education level, collected at S1 only, was classified as high (university degree or diploma), middle (trade/apprenticeship or high school qualification(s)) or low (no formal qualifications). At all surveys women were also asked how well they managed on their income and could respond 'easy', 'not bad', 'difficult sometimes', 'difficult all of the time' or 'impossible'. We grouped this variable into three categories of: easy/not bad; difficult sometimes; and difficult all of the

time/impossible. Relationship status at each survey was categorised into: married/de-factor partner; divorced/separated/widowed; and single. Area of residence at S2, classified as urban or rural/remote, was included as a covariate in the statistical modelling since women from rural/remote areas were deliberately over-sampled to ensure sufficient representation of women from these less populated areas.

At S2, women were asked if they had ever been diagnosed with or treated for diabetes mellitus, heart disease or stroke. Subsequently, they were asked if they had been diagnosed with these conditions in the period since the previous survey. Menopausal status at each survey was determined from women's responses to questions on hysterectomy, oophorectomy, hormone replacement therapy use (HRT), oral contraceptive use (OCP) and menstrual bleeding and took into account responses at previous surveys. Menopausal status was defined as: pre-menopausal; surgical menopause; HRT use; OCP use; peri-menopausal; and post-menopausal.

Statistical analysis

All analyses were performed using Stata v14.0.

We compared baseline characteristics of women according to occurrence of incident hypertension during the entire follow-up period using the Pearson's chi-squared test and student's t-test. To account for multiple observations for each participant, we used generalised estimating equation (GEE) regression models for binary outcome data (using an unstructured correlation structure and a logit link function). We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for the relationship between each of depression and anxiety and hypertension, including depression and anxiety as time-varying covariates. In our analyses women who reported hypertension did not contribute to the analyses of time periods thereafter. Ability to manage on income and all physiological and lifestyle variables

were included as time-varying covariates. Once women reported diabetes, stroke or heart disease, they were considered to have it at each subsequent survey. Time lags were used so that exposures, including depression and anxiety, were associated with stroke occurring at the subsequent survey. For the association between depression and hypertension, we calculated age-adjusted ORs before additionally adjusting for groups of covariates: anxiety; history of heart disease, diabetes and stroke; menopausal status; SES; marital status; all lifestyle factors; individual lifestyle factors; SES and all lifestyle factors; all factors. Similarly, for the association between anxiety and hypertension, we adjusted for the same groups of confounders plus depression.

Sensitivity analyses

Additional information related to depression was collected in the surveys. Women were asked at each survey whether they had ever been diagnosed with or treated for depression. In S2-S4 women were also asked "During the past four weeks have you taken any medications for depression", and in S5 and S6 women were asked to list the medications they had taken in the previous four weeks. For the latter two surveys we ascertained anti-depressant use from the anatomical therapeutical chemical system, by identifying medications coded as N06A or N06B. In sensitivity analyses, we repeated the primary analyses using two alternative definitions of depression, to assess the impact of the definition of depression on the results: presence of depressive symptoms as defined by CESD-10 or medication for depression/anti-depressant use; and a combination of depressive symptoms as defined by CESD-10 or medication for depression/anti-depressant use or diagnosed with or treated for depression by a doctor. We also repeated our analysis after excluding all women who had ever reported use of medication for depression or anti-depressant medication.

RESULTS

Among 13,715 women who returned S1, 12,338 (90%) returned S2, 9966 of whom reported that they had never had hypertension. Follow-up data on hypertension occurrence was available in 9410 women, of whom 9149 women were included in the analyses, with 9024 included in the depression analyses and 9126 in the anxiety analyses (Figure 1). The mean age of the 9149 women at S2 was 49.5 (±1.4 SD).

Between 1998 and 2013, 2738 (30%) women reported having been diagnosed with hypertension. Incident hypertension during the follow-up period was significantly associated with alcohol intake, BMI, physical activity level, education level, history of diabetes, history of stroke and menopausal status at S2 (Table 1).

At S2, 1950 (22.1%) women were classified as depressed, whilst 1111 (12.2%) reported diagnosis of or treatment for anxiety. Similar frequencies of depression and anxiety were observed at S3-S6. Depression at S2 was significantly associated with all included characteristics, apart from area of residence, whilst anxiety was associated with all characteristics apart from age, area of residence, alcohol intake, BMI, physical activity and history of diabetes mellitus (Supplementary Table 1).

In GEE modelling, depression was associated with a 27% increased odds of incident hypertension (age-adjusted OR 1.27, 95% CI 1.15 to 1.40; Figure 2). Adjustment for each of: diabetes, heart disease or stroke; anxiety; marital status and menopausal status had little effect on this association, whereas adjustment for education level and ability to manage on income did attenuate the association (OR 1.18, 95% CI 1.06 to 1.30). Individual adjustment for smoking and alcohol intake did not attenuate the association, whilst adjustment for BMI, and to a much lesser extent, physical activity, did (adjusted ORs 1.16, 95% CI 1.04 to 1.28 and 1.21, 95% 1.09 to 1.34, respectively; Figure 2). After adjustment for all factors, the

association was no longer statistically significant (OR 1.02, 95% CI 0.91 to 1.15; Figure 2). The results of sensitivity analyses, where we defined depression according to: depressive symptoms or use of anti-depressants/medication for depression; and the presence of either depressive symptoms, use of anti-depressants/medication for depression or doctor-diagnosed depression gave similar associations between depression and incident hypertension as in the primary analysis (supplementary Tables 2 and 3). Interestingly, sensitivity analyses in which we excluded all women reporting any use of anti-depressants/medicine for depression showed similar findings, albeit ORs were slightly attenuated compared to the primary analysis findings (supplementary Table 4).

The association between anxiety and incident hypertension was slightly weaker than that observed for depression and hypertension. Anxiety was associated with a 24% increased odds of hypertension (age-adjusted OR 1.24, 95% CI 1.09 to 1.42; Figure 3). After adjusting for age and depression, this association attenuated and was no longer statistically significant (OR 1.15, 95% CI 0.99 to 1.32). Adjustment for all factors attenuated the OR further (OR 1.06, 95% CI 0.90 to 1.24).

DISCUSSION

In our study of mid-aged women, depression and anxiety were associated with a 30% and 24% increased odds of hypertension. However, the association for depression was markedly reduced after controlling for BMI and was no longer significant after full adjustment for confounding variables. The association between anxiety and hypertension was no longer significant after adjusting for depression.

Our finding that depression is associated, in unadjusted analyses, with a 30% increased odds of hypertension is in keeping with the unadjusted magnitude of effect reported in previous

prospective studies [10, 25, 26]. However, our findings suggest that lifestyle and socioeconomic factors may confound this association. Findings from previous studies are mixed in terms of whether the association persists after adjustment for potential confounders. As in our study, some found no significant association between depression and hypertension risk after adjusting for confounding factors [7, 27-29], whilst others found a positive association persisted [16, 25, 26, 30, 31]. Differential associations by age have been observed in some studies, with a positive association observed in mid-aged adults [9, 10], but not in younger adults [10] or older aged adults [9]. These mixed findings are likely partly explained by differences in study population, age-group, gender composition, definition of depression, adjustment for confounders, and other methodological factors. It is possible that effect estimates from prospective studies that did not adjust for time-varying covariates may be residually confounded, particularly where participants were followed up over a long period of time. However, our study, and the results of previous studies, cannot exclude the possibility that there is indeed a true causal association between depression and hypertension. It is feasible that lifestyle factors, particularly BMI, may partly mediate the association between the two, in which case adjustment for these factors may adjust out and obscure any true causal association. Few studies reported on effect estimates after sequential adjustment for confounders, but, as in our study, Tickhonoff *et al* also found that adjustment for BMI (as well as female gender) had a large impact on the effect estimate [16]. Ideally, we would have performed mediation analyses in the present study to test the hypothesis that weight gain may partly mediate a causal association between depression and hypertension. However, in this mid-aged cohort, almost half of the women were already overweight or obese at baseline. It would therefore be more powerful to test the hypothesis that BMI may partially mediate the association between depression and hypertension in a

slightly younger cohort, where the occurrence of depression prior to weight gain can be more reliable ascertained.

The lack of association between anxiety and hypertension in our study is in contrast to the findings from a recent meta-analysis of prospective studies [14]. Although we did find a positive association in unadjusted analyses, this did not persist after adjustment for depression (whereas the association between depression and hypertension was not affected by adjusting for anxiety). None of the previous studies included in the recent systematic review adjusted for depression in their analyses of anxiety and hypertension occurrence. Anxiety is known to increase the risk of developing depression [32]. Our findings suggest that depression, but not anxiety, is associated with increased risk of hypertension, and that the observed association between anxiety and hypertension in other studies may be due to the increased risk of depression among those with anxiety.

Our study has a number of strengths. It is based on a large, nationally representative study population. The long follow-up period meant that we identified a large number of cases of incident hypertension, enabling us to draw conclusions about the long-term associations between depression and anxiety and incident hypertension. Since women were surveyed multiple times during follow-up we were able to measure depression occurrence repeatedly over time and account for changes in lifestyle and other confounding variables in our analyses. Finally, we used an objective measurement of depressive symptoms, and also performed a series of sensitivity analyses examining the effects of different definitions of depression.

Limitations

Our study has some limitations. Anxiety, hypertension occurrence and covariates, including lifestyle behaviour and cardiovascular disease, were self-reported. We relied on self-report of doctor-diagnosed anxiety, which means that we may not have identified women with anxiety who have not sought medical help. Although hypertension occurrence was also based on self-report of doctor-diagnosis, validity studies do suggest that self-reported hypertension has good validity when compared to health records, with one study reporting that 86% of self-reported hypertension cases were verified by medical records and high agreement was associated with being female and aged <65 years[33]. In addition, the prevalence of self-reported hypertension is in line with age-specific estimates from other Australian health surveys [34]. Furthermore, to have impacted the key findings, misclassification would need to have been differential. It is possible that people with depression or anxiety may over-report chronic conditions such as hypertension. If so, this would have overestimated rather than underestimated the association with hypertension. Misclassification of covariates such as BMI and physical activity may have occurred. However, self-reported height and weight have been shown to be valid for calculating BMI in this cohort.[35] The physical activity questionnaire in this study has also been found to have measurement properties which compare favourably with those of other commonly used physical activity measures [36]. We were unable to adjust for the potential confounding effect of medication use in our analyses because the information collected on on medication use varied across surveys, with information on all medication use only collected in surveys 5 and 6. Weight gain and increased risk of hypertension are known to be side-effects of some anti-depressant drugs [12, 37]. However, reassuringly, our sensitivity analysis in which we examined the effect of depression on hypertension risk among women who did not report either use of medication for depression in surveys 3 and 4 or specific anti-depressant

medication use in surveys 5 and 6 gave very similar results to the primary analysis.Our measurement of depression did not measure depression status between surveys, which, given that depression and anxiety can be episodic and are known to fluctuate, is a limitation. However, sensitivity analyses using alternate measures of depression (including doctor-diagnosed depression), gave similar findings and our study improves on cohort studies that measured depression and/or anxiety at one time point. Finally, our study population included mid-aged women and thus we cannot necessarily extrapolate our results to women outside this age-group or to men.

CONCLUSIONS

In our study of mid-aged women, depression was associated with a substantial increased risk of hypertension. There are a number of practical implications for the care of women with depression. Our findings contribute to the growing evidence for a need for improved prevention and monitoring of hypertension in those with depression by mental health and primary care practitioners. Whilst the mechanism underlying the association between depression and hypertension remains unclear, our findings suggest that lifestyle, in particular BMI, may partially confound and/or mediate the association. Practitioners are therefore urged to monitor BMI in those with depression, to reduce excessive weight gain, especially in women. Further research, ideally in a slightly younger cohort, is needed to determine whether BMI confounds or mediates the association between depression and hypertension. This would further contribute to our understanding of whether depression has a direct physiological impact or whether the pathway to hypertension risk is explained by other factors, such as BMI. Our findings that the association between anxiety and hypertension may be explained by confounding by depression deserves further investigation, to confirm or refute these findings.

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AUTHOR CONTRIBUTIONS

CAJ devised the study, CAJ and TP performed the analyses, CAJ drafted the paper, all authors contributed to the interpretation of the findings, and TP and PG commented on a draft manuscript.

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Table 1 Characteristics at survey 2, according to whether or not women subsequently developed hypertension

Characteristic	Hypertension N = 2738 n (%)	No hypertension N = 6444 n (%)	P-value†
Age (years; mean ± SD)	49.6 (± 1.4)	49.5 (± 1.5)	<0.001
Area of residence			
Urban	934 (34.3)	2426 (37.9)	
Rural	1619 (59.5)	3624 (56.6)	0.005
Remote	170 (6.2)	358 (5.6)	
Marital status			
Married/de facto	2272 (83.5)	5344 (83.4)	
Separated/divorced/widowed	373 (13.7)	847 (13.2)	0.35
Single	77 (2.8)	216 (3.4)	
Smoking			
Never	1504 (57.0)	3543 (56.2)	
Ex-smoker	705 (26.7)	1634 (26.6)	0.57
Current	429 (16.3)	1055 (17.2)	
Alcohol intake			
Low risk	1358 (51.5)	3462 (56.4)	
Non /rarely	1121 (42.5)	2370 (38.6)	<0.001
Risky/ high risk	159 (6.0)	303 (4.9)	

BMI (kg/m^2)			
Normal (18.5-24.9)	926 (37.0)	3313 (57.3)	
Underweight (<18.5)	26 (1.0)	112 (1.9)	<0.001
Overweight (25.0-29.9)	878 (35.1)	1694 (29.3)	
Obese (≥30)	670 (26.8)	666 (11.5)	
BMI (kg/m2; mean ± SD)	27.4 (± 5.4)	24.9 (± 4.4)	<0.001
Physical activity			
High	704 (27.6)	1863 (31.1)	
Moderate	570 (22.3)	1370 (22.9)	0.003
Low	817 (32.0)	1762 (29.4)	
Nil/ Sedentary	464 (18.2)	993 (16.6)	
Education level			
High	814 (30.0)	2122 (33.2)	
Medium	1411 (52.0)	3287 (51.4)	0.002
low	491 (18.1)	988 (15.4)	
Ability to manage on income			
Easy/not too bad	1447 (55.1)	3598 (58.9)	
Difficult some of the time	779 (29.6)	1706 (27.9)	0.002
Difficult/Impossible	402 (15.3)	809 (13.2)	
Type I or Type II Diabetes Mellitus			
No	2671 (97.6)	6376 (98.9)	<0.001

Yes	67 (2.5)	68 (1.1)	
History of heart disease			
No	2693 (98.4)	6356 (98.6)	0.31
Yes	45 (1.6)	88 (1.4)	
History of stroke			
No	2714 (99.1)	6419 (99.6)	0.003
Yes	24 (0.9)	25 (0.4)	
Menopausal status			
Premenopausal	623 (22.9)	1579 (24.6)	<0.001
Surgical menopause	825 (30.3)	1445 (22.7)	
HRT use	321 (11.8)	683 (10.7)	
OCP use	95 (3.5)	273 (4.3)	
Peri menopausal	582 (21.4)	1676 (26.1)	
Post-menopausal	279 (10.2)	748 (11.7)	

†p-values of mantel-haenszel chi^2 test (for dichotomous or categorical variables) or student's t-test (for continuous variables)

BMI = body mass index; HRT = hormone replacement therapy; OCP = oral contraceptive use

Figure Legends

Figure 1 Flow diagram of included participants

Figure 2 Odds ratios for the association between depression and incident hypertension, with individual adjustment for confounding factors

Figure 3 Odds ratios for the association between anxiety and incident hypertension, with individual adjustment for confounding factors

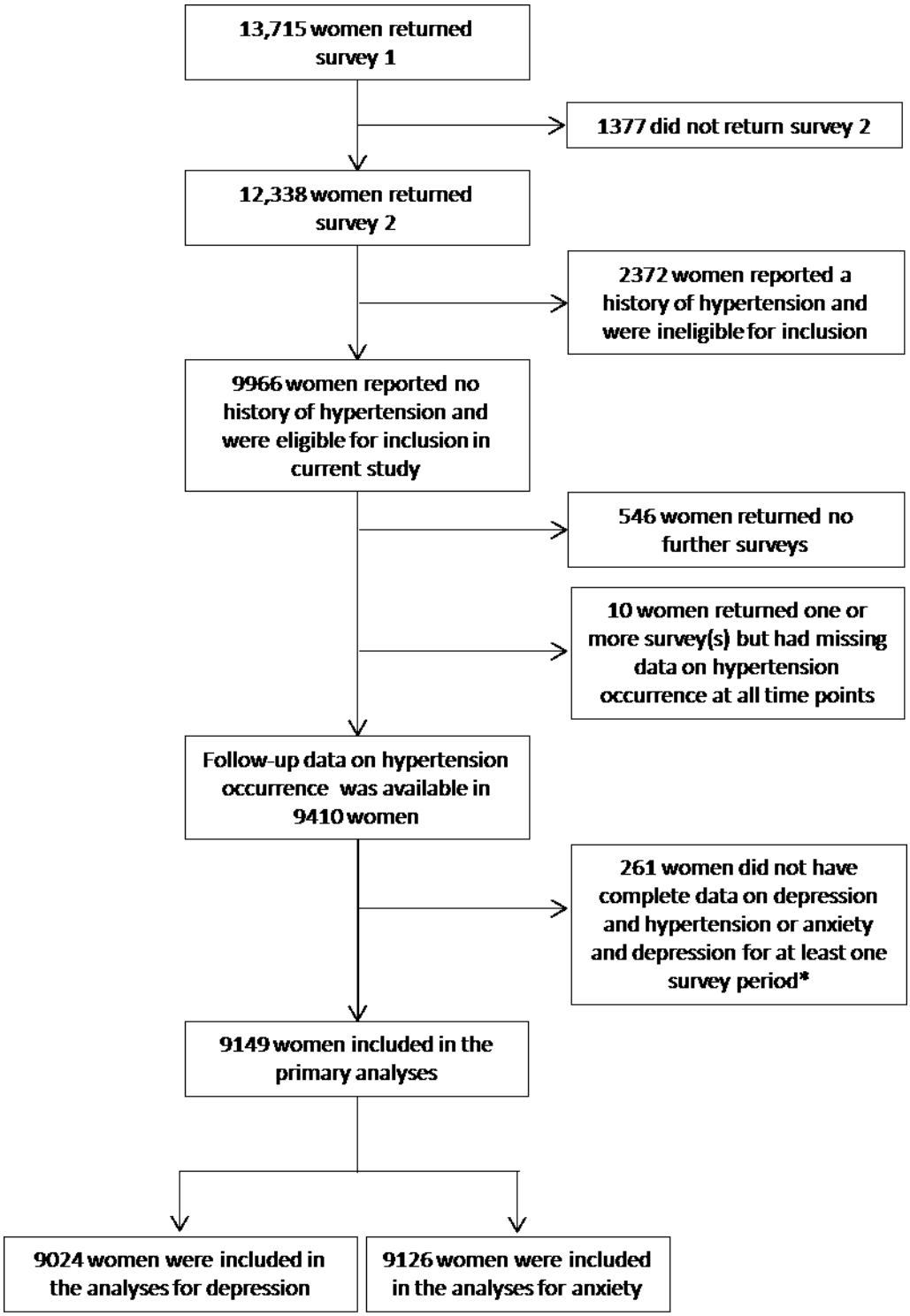

13,715 women returned survey 1
1377 did not return survey 2
12,338 women returned survey 2
2372 women reported a history of hypertension and were ineligible for inclusion
9966 women reported no history of hypertension and were eligible for inclusion in current study
546 women returned no further surveys
10 women returned one or more survey(s) but had missing data on hypertension occurrence at all time points
Follow-up data on hypertension occurrence was available in 9410 women
261 women did not have complete data on depression and hypertension or anxiety and depression for at least one survey period*
9149 women included in the primary analyses
9024 women were included in the analyses for depression
9126 women were included in the analyses for anxiety

Figure 2

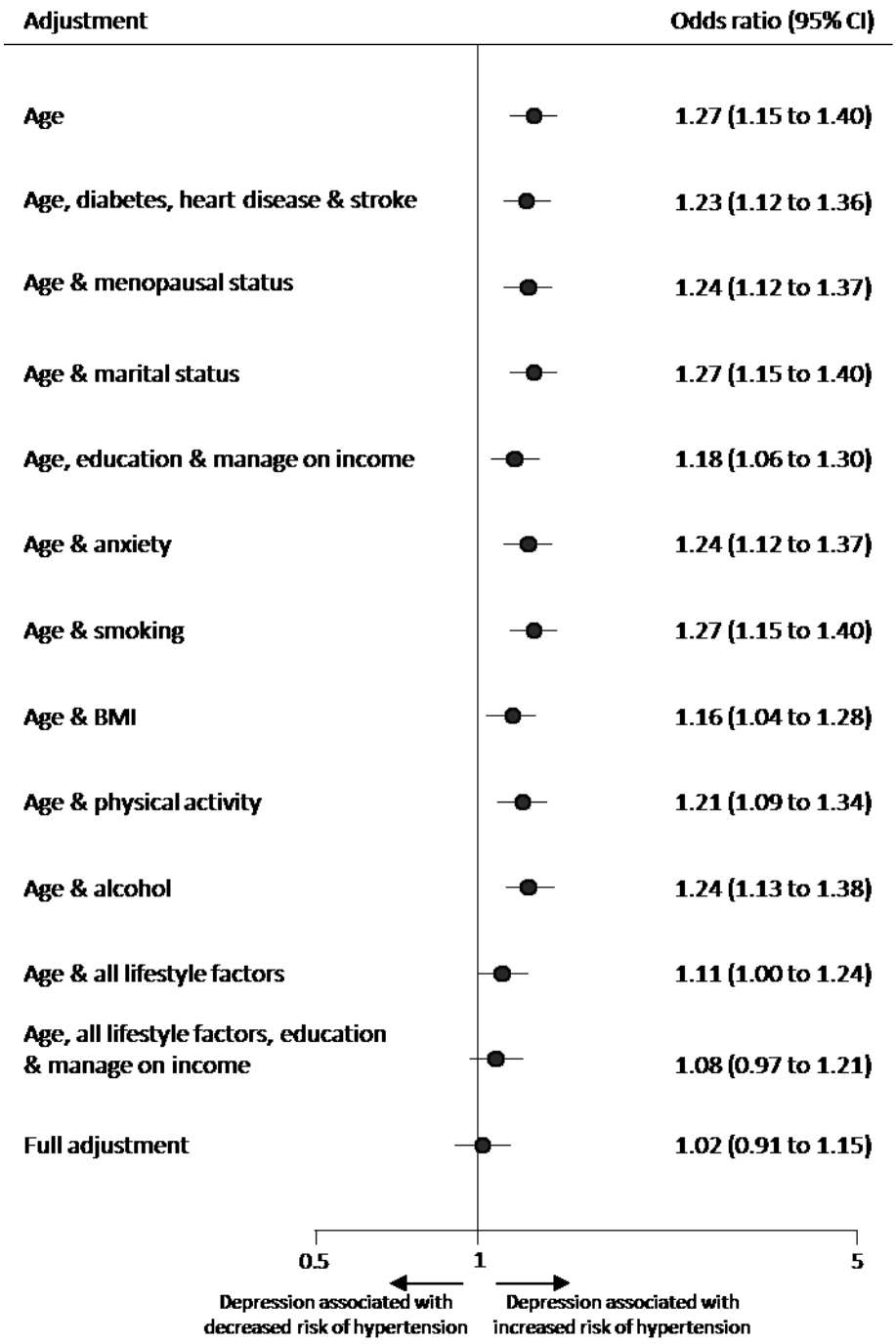
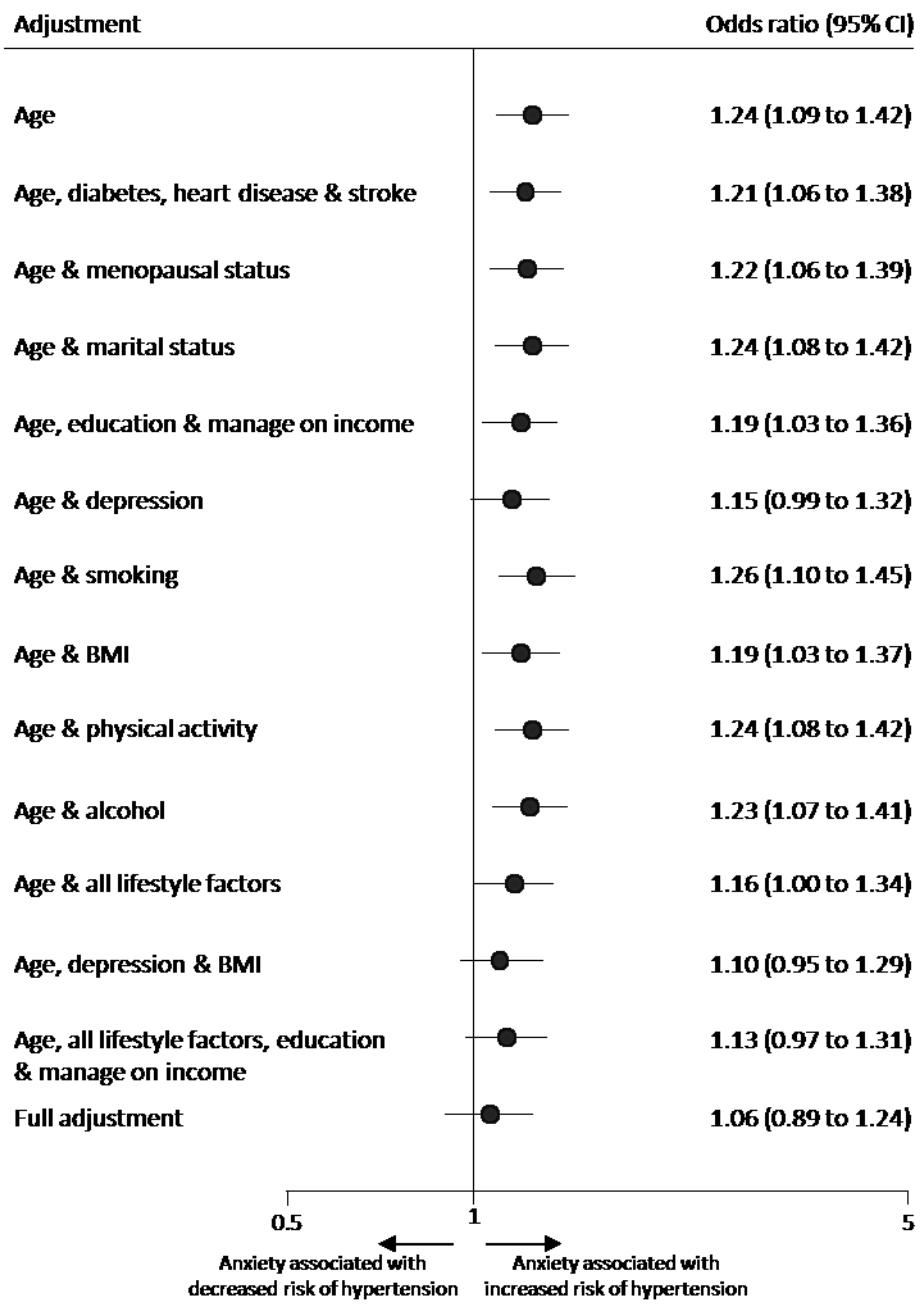

Adjustment
Odds ratio (95% CI)
Age
1.27 (1.15 to 1.40)
Age, diabetes, heart disease & stroke
1.23 (1.12 to 1.36)
Age & menopausal status
1.24 (1.12 to 1.37)
Age & marital status
1.27 (1.15 to 1.40)
Age, education & manage on income
1.18 (1.06 to 1.30)
Age & anxiety
1.24 (1.12 to 1.37)
Age & smoking
1.27 (1.15 to 1.40)
Age & BMI
1.16 (1.04 to 1.28)
Age & physical activity
1.21 (1.09 to 1.34)
Age & alcohol
1.24 (1.13 to 1.38)
Age & all lifestyle factors
1.11 (1.00 to 1.24)
Age, all lifestyle factors, education & manage on income
1.08 (0.97 to 1.21)
Full adjustment
1.02 (0.91 to 1.15)
0.5
1
5
Depression associated with decreased risk of hypertension
Depression associated with increased risk of hypertension

Figure 3


Adjustment
Odds ratio (95% CI)
Age
1.24 (1.09 to 1.42)
Age, diabetes, heart disease & stroke
1.21 (1.06 to 1.38)
Age & menopausal status
1.22 (1.06 to 1.39)
Age & marital status
1.24 (1.08 to 1.42)
Age, education & manage on income
1.19 (1.03 to 1.36)
Age & depression
1.15 (0.99 to 1.32)
Age & smoking
1.26 (1.10 to 1.45)
Age & BMI
1.19 (1.03 to 1.37)
Age & physical activity
1.24 (1.08 to 1.42)
Age & alcohol
1.23 (1.07 to 1.41)
Age & all lifestyle factors
1.16 (1.00 to 1.34)
Age, depression & BMI
1.10 (0.95 to 1.29)
Age, all lifestyle factors, education & manage on income
1.13 (0.97 to 1.31)
Full adjustment
1.06 (0.89 to 1.24)
0.5
1
5
Anxiety associated with decreased risk of hypertension
Anxiety associated with increased risk of hypertension

Supplementary Table 1 Baseline characteristics of participants without hypertension at survey 2, according to depression and anxiety status at survey 2

Characteristic	Depression* N = 1864 n (%)	No Depression N = 6761 n (%)	P-value†	Anxiety* (N = 1111) n (%)	No anxiety (N = 8015) n (%)	P-value†
Age (years; mean ± SD)	49.4 (± 1.47)	49.5 (± 1.44)	0.02	49.5 (± 1.47)	49.5 (± 1.44)	0.67
Area of residence						
Urban	712 (36.1)	2426 (36.1)		450 (38.7)	2998 (36.6)	
Rural	1042 (56.1)	3904 (58.2)	0.19	655 (56.3)	4707 (57.5)	0.25
Remote	105 (5.7)	384 (5.7)		59 (5.1)	488 (6.0)	
Marital status						
Married/de facto	1401 (76.0)	5759 (85.6)		883 (76.4)	6906 (84.2)	
Separated/divorced/widowed	373 (20.2)	762 (11.3)	<0.001	235 (20.3)	1027 (12.5)	<0.001
Single	70 (3.8)	211 (3.1)		38 (3.3)	265 (3.2)	
Smoking						
Never	954 (51.7)	3884 (57.7)		535 (50.1)	4512 (57.1)	
Ex-smoker	447 (24.2)	1833 (27.2)	<0.001	295 (27.7)	2083 (26.4)	<0.001
Current	443 (24.0)	1011 (15.0)		237 (22.2)	1302 (16.5)	
Alcohol intake						
Low risk	921 (50.2)	3801 (56.5)		552 (52.1)	4341 (55.0)	
Non /rarely	807 (44.0)	2581 (38.4)	<0.001	442 (41.7)	3142 (39.8)	0.13
Risky/ high risk	108 (5.9)	345 (5.1)		66 (6.2)	411 (5.2)	
BMI (kg/m^2)						
Normal (18.5-24.9)	800 (46.3)	3353 (52.7)		521 (51.9)	3794 (51.0)	
Underweight (<18.5)	47 (2.7)	89 (1.4)	<0.001	33 (3.3)	108 (1.5)	<0.001
Overweight (25.0-29.9)	536 (31.0)	1971 (31.0)		300 (29.9)	2322 (31.2)	
Obese (≥30)	345 (20.0)	956 (15.0)		149 (14.9)	1221 (16.4)	
BMI (kg/m2; mean ± SD)	26.1 (± 5.3)	25.6 (± 4.7)	<0.001	25.5 (± 4.9)	25.7 (± 4.8)	0.14
Physical activity						
High	427 (24.0)	2077 (31.6)		286 (27.5)	2326 (30.3)	
Moderate	344 (19.3)	1556 (23.7)	<0.001	243 (23.4)	1726 (22.5)	0.35
Low	562 (31.6)	1955 (29.8)		321 (30.9)	2322 (30.2)	
Nil/ Sedentary	447 (25.1)	969 (14.9)		189 (18.2)	1278 (17.0)	
Education level						
High	508 (27.5)	2274 (33.9)		341 (29.4)	2639 (32.3)	
Medium	935 (50.5)	3497 (52.1)	<0.001	574 (49.5)	4248 (51.9)	<0.001
Low	407 (22.0)	945 (14.1)		245 (21.1)	1291 (15.8)	
Ability to manage on income						
Easy/not too bad	780 (42.2)	4162 (62.2)		493 (46.2)	4627 (58.9)	
Difficult some of the time	592 (32.1)	1817 (27.2)	<0.001	332 (31.1)	2213 (28.2)	<0.001
Difficult/Impossible	475 (25.7)	712 (10.6)		242 (22.7)	1018 (13.0)	
Type I or Type II Diabetes Mellitus						
No	1823 (97.8)	6675 (98.7)	0.01	1147 (98.3)	8123 (98.5)	0.50
Yes	41 (2.2)	86 (1.3)		20 (1.7)	120 (1.5)	
History of heart disease						
No	1820 (97.6)	6683 (98.9)	<0.001	1138 (97.5)	8129 (98.6)	<0.01
Yes	44 (2.4)	78 (1.2)		29 (2.5)	114 (1.4)	
History of stroke						
No	1844 (98.9)	6739 (99.7)	<0.001	1154 (98.9)	8204 (99.5)	<0.01
Yes	20 (1.1)	22 (0.3)		13 (1.1)	39 (0.5)	
History of anxiety						
No	1365 (73.2)	6246 (92.4)	<0.001	-	-	-

Yes	499 (26.8)	515 (7.6)		-	-	
History of depression						
No	-	-	-	443 (42.1)	6418 (80.8)	<0.001
Yes	-	-		622 (57.9)	1522 (19.2)	
Menopausal status						
Premenopausal	325 (17.5)	1752 (26.0)	<0.001	213 (18.3)	2029 (24.7)	<0.001
Surgical menopause	609 (32.9)	1523 (22.6)		384 (33.0)	1976 (24.1)	
HRT use	262 (14.1)	713 (10.6)		173 (14.9)	854 (10.4)	
OCP use	49 (2.6)	316 (4.7)		29 (2.5)	340 (4.2)	
Peri-menopausal	427 (23.0)	1682 (25.0)		271 (23.3)	2035 (24.8)	
Post-menopausal	181 (9.8)	749 (11.1)		94 (8.1)	968 (11.5)	

*Numbers with and without each of depression and anxiety are based on women with data on these exposures at S2. Women in whom this information was missing at S2 but present in at least one subsequent survey were however included in the analyses. The denominators for depression and anxiety therefore do not equal the total number of women in included in the generalised estimating equation statistical models.
BMI = body mass index; HRT = hormone replacement therapy; OCP = oral contraceptive use
†p-values of the chi-square test for categorical variables and t-test for continuous variables, comparing each of depression versus no depression and anxiety versus no anxiety

Supplementary Table 2 Odds ratios for the association between depression (defined as CESD-10 score ≥10 or use of medication for depression/antidepressant use) and hypertension incidence (N = 9024)

Adjustment	Odds ratio (95% CI)	p-value
Adjusted for age only	1.30 (1.19 to 1.43)	<0.001
Adjusted for age & anxiety	1.27 (1.16 to 1.40)	<0.001
Adjusted for age & diabetes, heart disease & stroke	1.27 (1.16 to 1.39)	<0.001
Adjusted for age & menopausal status	1.27 (1.16 to 1.39)	<0.001
Adjusted for age, education and manage on income	1.22 (1.11 to 1.34)	<0.001
Adjusted for marital status	1.31 (1.19 to 1.43)	<0.001
Adjusted for age & all lifestyle factors	1.14 (1.03 to 1.26)	<0.01
Adjusted for age and smoking	1.30 (1.19 to 1.43)	<0.001
Adjusted for age and BMI	1.18 (1.08 to 1.30)	<0.001
Adjusted for age and physical activity	1.21 (1.09 to 1.34)	<0.001
Adjusted for age and alcohol status	1.28 (1.17 to 1.40)	<0.001
Adjusted for age, education, manage on income and all lifestyle factors	1.11 (1.01 to 1.23)	0.04
Adjusted for all factors	1.07 (0.96 to 1.19)	0.25

Supplementary Table 3 Odds ratios for the association between depression (defined as CESD-10 score ≥10, used of medication for depression/anti-depressant use, or doctor-diagnosed depression) and hypertension incidence (N =9151)

Adjustment	Odds ratio (95% CI)	p-value
Adjusted for age only	1.27 (1.16 to 1.38)	<0.001
Adjusted for age & anxiety	1.25 (1.14 to 1.37)	<0.001
Adjusted for age & diabetes, heart disease & stroke	1.24 (1.13 to 1.35)	<0.001
Adjusted for age & menopausal status	1.23 (1.13 to 1.34)	<0.001
Adjusted for age, education and manage on income	1.19 (1.09 to 1.30)	<0.001

Adjusted for marital status	1.27 (1.16 to 1.38)	<0.001
Adjusted for age & all lifestyle factors	1.12 (1.02 to 1.23)	0.01
Adjusted for age and smoking	1.26 (1.16 to 1.38)	<0.001
Adjusted for age and BMI	1.16 (1.06 to 1.27)	<0.01
Adjusted for age and physical activity	1.18 (1.07 to 1.30)	<0.01
Adjusted for age and alcohol status	1.21 (1.11 to 1.33)	<0.001
Adjusted for age, education, manage on income and all lifestyle factors	1.09 (0.99 to 1.21)	0.07
Adjusted for all factors	1.06 (0.95 to 1.18)	0.29

Supplementary Table 4 Odds ratios for the association between depression (defined as CESD-10 score ≥10) and hypertension, after excluding women reporting any anti-depressant medication use (N = 7304)

Adjustment	Odds ratio (95% CI)	p-value
Adjusted for age only	1.23 (1.08 to 1.39)	<0.01
Adjusted for age & anxiety	1.22 (1.07 to 1.39)	<0.01
Adjusted for age & diabetes, heart disease & stroke	1.21 (1.06 to 1.37)	<0.01
Adjusted for age & menopausal status	1.21 (1.07 to 1.38)	<0.01
Adjusted for age, education and manage on income	1.16 (1.02 to 1.31)	0.03
Adjusted for marital status	1.23 (1.09 to 1.40)	<0.01
Adjusted for age & all lifestyle factors	1.11 (0.97 to 1.28)	0.12
Adjusted for age and smoking	1.23 (1.09 to 1.40)	<0.01
Adjusted for age and BMI	1.14 (1.00 to 1.30)	0.05
Adjusted for age and physical activity	1.18 (1.03 to 1.34)	0.01
Adjusted for age and alcohol status	1.21 (1.06 to 1.37)	<0.01
Adjusted for age, education, manage on income and all lifestyle factors	1.09 (0.95 to 1.26)	0.22
Adjusted for all factors	1.07 (0.93 to 1.24)	0.33