Excessive Orthostatic Changes in Blood Pressure are Associated with Incident Heart Failure in Older Men: a prospective analysis from The British Regional Heart Study

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Abstract  
**Aim:** To assess the association between excessive orthostatic changes in blood pressure and risk of incident heart failure in older, community-dwelling men.   
**Methods and Results:** This was a prospective cohort study of 3505 men (mean age 68.5 years; standard deviation 5.5 years) who did not have heart failure, myocardial infarction or stroke at baseline. Excessive orthostatic change in blood pressure was defined continuously and categorically as orthostatic hypotension (sitting-to-standing decrease in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg), orthostatic hypertension (sitting-to-standing increase in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg) and orthostatic normotension (neither orthostatic hypotension, nor orthostatic hypertension). There was a U-shaped association between orthostatic change in blood pressure and risk of incident heart failure. After adjustment for possible confounders, the hazard ratio for incident heart failure was 1.65 (95% CI 1.24–2.18) in men with orthostatic hypotension and 1.20 (95% CI 0.91–1.57) in men with orthostatic hypertension. The individual systolic and diastolic components of these categories were each associated with different risk of heart failure, with the systolic component being more predictive of heart failure than the diastolic component.  
**Conclusion:** Excessive orthostatic changes in blood pressure (increases or decreases) are associated with risk of incident heart failure in older, community-dwelling men, and may be an early sign of cardiovascular dysfunction. Patients with excessive orthostatic blood pressure changes may benefit from cardiovascular disease risk assessment. Further prospective studies in diverse cohorts are needed to confirm our findings.  
  
  
Key Words  
Heart failure; Cardiovascular epidemiology; Orthostatic hypotension; Orthostatic hypertension; Risk factors.

Introduction  
  
Heart failure is a growing, but already major, worldwide public health problem (1). It has a lifetime risk of almost 40% at 90 years of age (2, 3). Major clinical risk factors include age, hypertension, myocardial infarction, valvular heart disease, left ventricular hypertrophy, obesity and diabetes (4). Biochemical risk factors include increased concentrations of circulating inflammatory proteins and markers of cardiac stress and myocardial injury (4). The prognosis of heart failure is poor and comparable to some types of cancer, with 5-year survival rates approximately 57% (5, 6). Identifying novel risk factors may facilitate earlier diagnosis and inform preventative strategies (7).   
  
Observational studies have described an association between exaggerated orthostatic blood pressure changes and incident cardiovascular disease (8-10). Such positional variability in blood pressure may mark a derangement of autonomic nervous system adaptation to postural changes, and these derangements may be related to cardiovascular disease (11). Increases or decreases in blood pressure on standing each increase risk of cerebral infarction (12), lacunar stroke (13) and death due to cerebrovascular disease (14). Exaggerated orthostatic changes in blood pressure are also associated with increased levels of high-sensitivity troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) (15), circulating markers strongly associated with future risk of developing heart failure (16, 17). Indeed, in younger adults, there is a strong association between orthostatic hypotension – a decrease in blood pressure on standing – and risk of incident heart failure (9). However, the predictive role of orthostatic hypotension in older adults – in whom the burden of both orthostatic hypotension and heart failure is greatest (18-20) – is unclear. Furthermore, although orthostatic hypertension – an increase in blood pressure on standing – has been associated with biochemical and clinical predictors of heart failure, including high-sensitivity troponin T (15), NT-proBNP (15) and left ventricular hypertrophy (21), paradoxically, two prospective studies in middle-aged adults have shown increases in blood pressure on standing to be associated with reduced risk of heart failure (10, 15).  
  
The aim of this study was to examine the prospective association between orthostatic blood pressure change and risk of incident heart failure in older, community-dwelling men.

Methods

*Study Population –* The British Regional Heart Study is an on-going prospective cohort study. It initially recruited 7735 men aged 40-59 years between 1978 and 1980 (22). The majority of participants (>99%) were of white European ethnicity. Seated and standing blood pressure measurements were first taken during the 20th year re-examination of the cohort, between 1998 and 2000. The baseline data for the present analysis is from this re-examination, to which all surviving men were invited. During the re-examination, men completed a questionnaire about lifestyle and medical background, underwent physical examination and provided a fasting venous blood sample. 4252 men (77% response rate) of those invited for re-examination attended. Ethical approval was obtained from the National Research Ethics Service Committee London.  
  
*BP measurement* – Blood pressure was measured on the right arm using an automatic Dinamap 1846SX. The bladder centre of the cuff was aligned over the brachial artery. If arm circumference was <32 cm, an adult cuff was used; ≥32 cm and a large adult cuff was used. For sitting measurements, participants were asked to rest their arm on the examination table so that the upper arm was at chest level. During measurements, participants were encouraged to remain silent and keep the arm still. The Dinamap blood pressure monitor overestimated systolic blood pressure by ~8 mmHg compared with the standard mercury sphygmomanometer which was the standard reference instrument for blood pressure measurement at the time (23). 8 mmHg was therefore subtracted from the raw systolic blood pressure readings.   
  
The Dinamap was set to take repeated measurements at one minute intervals. Four consecutive blood pressure measurements – two sitting, followed by two standing – were taken. Participants had not been seated nor supine for a prescribed duration prior to the first measurement. After the second sitting measurement had completed, the participant was asked to stand. The first standing blood pressure measurement was made within one minute of the participant standing. The second standing blood pressure measurement began after one minute, but before two minutes, of standing.   
  
*Definition of orthostatic changes in blood pressure* – Orthostatic changes in blood pressure were categorised into orthostatic hypotension, orthostatic hypertension and orthostatic normotension. “Orthostatic hypotension” was defined by consensus (37) as a decrease in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg that occurred between either the first or second standing blood pressure measurements and the mean of the two sitting blood pressure measurements. If the decrease only affected systolic blood pressure, this was classified as “isolated systolic orthostatic hypotension”. If the drop only affected diastolic blood pressure, this was classified as “isolated diastolic orthostatic hypotension”. If the drop affected both systolic and diastolic blood pressure, this was classified as “combined systolic and diastolic orthostatic hypotension”. There is no consensus definition of orthostatic hypertension, but a recent review (10) has suggested the definition should mirror the thresholds used to define orthostatic hypotension. “Orthostatic hypertension” was therefore defined as an increase in systolic blood pressure ≥20 mmHg and/or diastolic BP ≥10 mmHg that occurred between either the first or second standing blood pressure measurements and the mean of the two sitting blood pressure measurements. Orthostatic hypertension was also sub-divided into “isolated systolic orthostatic hypertension”, “isolated diastolic orthostatic hypertension” and “combined systolic and diastolic orthostatic hypertension”. Men in the “orthostatic normotension” group had neither orthostatic hypotension, nor orthostatic hypertension.  
  
*Follow-up –* Follow-up took place between the 20th year re-screening examination of The British Regional Heart Study (between 1998 and 2000) and June 2016. All-cause mortality and morbidity events were based on data collected during this period. Survival times were censored at date of heart failure, death from any cause or end of the follow-up period, whichever occurred first. Evidence of non-fatal myocardial infarction and heart failure was obtained by ad-hoc reports from general practitioners and supplemented by biennial review of primary care records, which included correspondence from secondary care. Incident heart failure was based on doctor diagnosis and confirmed by a review of available clinical information including symptoms, signs, investigations and response to treatment. The incidence and determinants of heart failure cases identified through this process have been reported previously and are consistent with results from other studies (24, 27). Incident heart failure included incident non-fatal heart failure as well as death from heart failure (ICD 9th revision code 428 or ICD 10th revision I28). Case definitions – based on primary care record reviews – have been reported previously (26). Atrial fibrillation (AF) was defined according to Minnesota codes 8.3.1 and 8.3.3. Hypertension was defined as mean sitting blood pressure ≥140/90 mmHg. Antihypertensive medications were defined as use of any antihypertensive medication as per British National Formulary (version 38) code 3.1. Chronic obstructive pulmonary disease (COPD) was defined as a forced expiratory volume in one second to forced vital capacity ratio of <0.7.  
  
Methods used for data collection, measurement and classification for measures of lipids, lung function, smoking status, physical activity, alcohol intake and social class have been reported previously (22, 24-26). NT-proBNP concentration was determined using the Elecsys 2010 (Roche Diagnostics, Burgess Hill, UK) (27, 28). Troponin T was measured by a high sensitivity method on an e411 (Roche Diagnostics, Burgess Hill, UK) using the manufacturer’s calibrators and quality control material (28). Methods for measurements of other markers of cardio-metabolic risk have been described previously (28-36). Predicted glomerular filtration rate (eGFR) was estimated from serum creatinine with the MDRD formula: eGFR = 186 × (Creatinine / 88.4)− 1.154 × (Age)− 0.203 . A resting 12-lead electrocardiogram (ECG) was recorded.  
  
*Statistical Analysis –* Statistical analyses were conducted in SAS 9.4. F-tests and chi-squared tests were used to examine the association between baseline characteristics and categories of orthostatic change in blood pressure. Continuous variables that were skewed (triglycerides, glucose, CRP, IL-6, NT-proBNP and high-sensitivity troponin T) were log-transformed to approximate normality for parametric tests. Restricted cubic splines were used to visually depict the association between orthostatic changes in blood pressure and risk of incident heart failure. Regression analysis of survival data was based on the Cox proportional hazards model. The multivariate-adjusted hazards ratio compared risk of incident heart failure between men with orthostatic hypotension, orthostatic hypertension and orthostatic normotension (reference group) at baseline. BMI, heart rate, average sitting systolic blood pressure, total cholesterol, IL-6 and NT-proBNP were fitted as continuous variables. Physical activity (inactive or not inactive), smoking status (never smoked, ex-smoker for 0–15 years, ex-smoker for >15 years and current smoker), alcohol consumption (0–15 units per week and >16 units per week), social class (manual or non-manual) and the presence or absence of AF (0/1), diabetes (0/1), chronic kidney disease (CKD) (0/1), COPD (0/1) and anti-hypertensive medication use (0/1) were fitted as categorical variables. We further adjusted for incident myocardial infarction as a time-dependent variable.   
  
Study Population – Of the 4252 men, 4045 had measurements of biochemistry. Men with prevalent heart failure (n=117), MI (n=261), stroke (n=101) and incomplete sitting and standing blood pressure measurements (n=61) were excluded, leaving 3505 participants for the present analysis.  
  
  
  
  
Results  
  
The mean age of the 3505 men was 68.5 years (standard deviation 5.5 years). Over a mean follow-up of 13.3 years, there were 336 cases of incident heart failure. The overall incidence rate was 7.18 cases of heart failure per 1,000 persons per year. At baseline, 20.3% of men had orthostatic hypotension; 23.9% had orthostatic hypertension (Table 1). Compared to those with orthostatic normotension, men with orthostatic hypotension were older, had lower BMI, more likely to be prescribed anti-hypertensive medications, have hypertension, AF, CKD and COPD. Men with orthostatic hypertension were less likely to have hypertension and more likely to have lower BMI. Orthostatic hypotension was associated with a range of circulating cardiovascular risk markers, including HDL, eGFR, IL-6, VWF, NT-proBNP and high-sensitivity troponin T; orthostatic hypertension was not associated with these markers. Specific markers of cardiovascular risk (CRP, IL-6, NT-proBNP and high-sensitivity troponin T) were differentially distributed among the individual systolic and diastolic components of orthostatic hypotension and orthostatic hypertension (Table 2). Current smoking, alcohol consumption, physical inactivity, social class, prevalent diabetes and circulating concentrations of total cholesterol, urate and CRP were not associated with orthostatic hypotension or orthostatic hypertension.   
  
There were 6.1 new cases of heart failure per 1,000 persons per year among those with orthostatic normotension, 7.6 new cases per 1,000 persons per year among those with orthostatic hypertension and 10.0 new cases per 1,000 persons per year among those with orthostatic hypotension. When orthostatic change in blood pressure was assessed continuously, risk of incident heart failure was U-shaped: increases and decreases in orthostatic blood pressure were each associated with increased risk of heart failure, regardless of whether the change was in systolic or diastolic blood pressure, or if it occurred within or after one minute of standing (Figure 1).   
  
When orthostatic change in blood pressure was categorised by threshold changes in blood pressure, compared to men with orthostatic normotension, men with orthostatic hypotension had statistically significantly increased risk of incident heart failure, while men with orthostatic hypertension did not (Table 3). The individual systolic and diastolic components of orthostatic hypotension and orthostatic hypertension were associated with different risk of incident heart failure (Table 4). The age-adjusted hazard ratio for risk of incident heart failure in men with isolated systolic orthostatic hypotension was 1.71 (95% CI 1.28 – 2.30), compared to 1.35 (95% CI 0.78 – 2.34) in men with isolated diastolic orthostatic hypotension and 2.57 (95% CI 1.49 – 4.46) in men with combined systolic and diastolic orthostatic hypotension. It was 1.70 (95% CI 1.08 – 2.68) in men with isolated systolic orthostatic hypertension, compared to 0.96 (95% CI 0.70 – 1.32) in men with isolated diastolic orthostatic hypertension and 1.41 (95% CI 0.83 – 2.40) in men with combined systolic and diastolic orthostatic hypertension (Table 4). When we further adjusted for BMI, resting heart rate, sitting systolic blood pressure, alcohol consumption, smoking status, physical activity, social class, AF, diabetes, CKD, COPD, IL-6, NT-proBNP and incident MI, the associations remained, except in the case of combined systolic and diastolic orthostatic hypotension, which was significantly attenuated and no longer statistically significant (Tables 3 and 4). In the multivariate models, the hazard ratio for incident heart failure was 1.65 (95% CI 1.24 – 2.18) in men with orthostatic hypotension and 1.20 (95% CI 0.91 – 1.57) in men with orthostatic hypertension. It was 1.83 (95% CI 1.34 – 2.51) in men with isolated systolic orthostatic hypotension and 1.88 (95% CI 1.18 – 3.00) in men with isolated systolic orthostatic hypertension. The association was not statistically significant in the case of isolated diastolic orthostatic hypotension nor isolated diastolic orthostatic hypertension (Table 4). The overall pattern remained when we further adjusted for baseline high-sensitivity troponin T (a marker of myocardial injury; data not shown).   
  
Discussion  
  
In this study of older, community-dwelling men who did not have heart failure, myocardial infarction or stroke at baseline, there was a U-shaped relationship between orthostatic change in blood pressure and risk of incident heart failure: risk increased as orthostatic change in blood pressure increased, regardless of whether it was a rise, or fall, in systolic or diastolic blood pressure. Exaggerated falls in blood pressure on standing (orthostatic hypotension) are well-recognised among clinicians, while exaggerated increases in blood pressure on standing (orthostatic hypertension) are under-appreciated. Our study extends the current literature by showing that both conditions, depending on the thresholds used to define them, are associated with increased risk of developing heart failure in older men, and the systolic component of change in orthostatic blood pressure appears more strongly associated with risk than the diastolic component.  
  
Diastolic blood pressure has generally been omitted in definitions of orthostatic hypertension (10). Our findings suggest orthostatic increase in diastolic blood pressure is not benign and, like orthostatic increase in systolic blood pressure, is also associated with increased risk of heart failure. Thresholds to define “orthostatic hypertension” may need to above an increase of ≥10 mmHg diastolic blood pressure, as when this threshold was used to classify men with orthostatic hypertension in the present study, it attenuated the association with risk of heart failure.   
  
*Orthostatic Hypotension and Risk of Heart Failure –* There is a strong association between orthostatic hypotension and risk of heart failure in middle-aged adults (8). Whether this is the case in older adults, in whom heart failure and orthostatic hypotension are each approximately 5 times more prevalent than in middle-aged adults (18-20), is less clear. Among eight prospective studies included in a meta-analysis, four had a mean age >65 years and there was a statistically significant association between orthostatic hypotension and risk of incident heart failure in only one of these (9, 38). In general, follow-up in middle-aged cohorts has been over 10 years, but shorter in older cohorts (9). Differences in follow-up duration may account for the inconsistencies between studies.   
  
Our findings suggest the association between orthostatic hypotension and risk of incident heart failure in older adults is independent of important predictors of heart failure, including IL-6 (a proinflammatory cytokine implicated in the aetiology of heart failure (39)), high-sensitivity troponin T (a marker of myocardial injury) and NT-proBNP (a marker of cardiac stress). Furthermore, our findings show even if the decrease in blood pressure on standing is below clinical thresholds used to define orthostatic hypotension, risk of heart failure is still increased.   
  
*Orthostatic Hypertension and Risk of Heart Failure –* To the best of our knowledge, the present study is the first to prospectively examine the association between orthostatic hypertension and risk of heart failure in older adults. Studies in younger cohorts show an association between clinical and biochemical predictors of heart failure, including left ventricular hypertrophy, high-sensitivity troponin T and NT-proBNP, and orthostatic hypertension (15, 21). However, two prospective studies in middle-aged adults have shown increases in blood pressure on standing to be associated with reduced risk of heart failure (10, 15). The ages at baseline in these cohorts were 54.2 years and 45.6 years, compared to 68.5 years in the present study. If the underlying mechanisms, and affected bodily systems, causing exaggerated orthostatic increases in blood pressure are different in younger and older people, the prognostic role of this clinical sign, with respect to risk of developing heart failure, may be different across age groups.  
  
The mechanisms underlying the association between exaggerated orthostatic changes in blood pressure and increased risk of heart failure are unknown but are likely to be multifactorial. Orthostatic hypotension has been associated with inflammatory mediators (40-42) and left ventricular hypertrophy (43) (both are implicated in the aetiology of heart failure), while orthostatic increases and decreases in blood pressure have each been associated with markers of myocardial injury (high-sensitivity troponin T) and cardiac stress (NT-proBNP) (15); biochemical predictors of risk of developing heart failure. Thus, we speculate that exaggerated orthostatic changes in blood pressure in older adults may be an early sign of cardiovascular dysfunction. Indeed, blood pressure variability in general (not that which is specifically orthostatic) is associated with adverse cardiovascular outcomes, and consistent with the findings in the present analysis, risk is particularly related to variability in systolic blood pressure (44).   
An alternative explanation for the observed association between orthostatic hypotension and risk of heart failure is reverse causality. An early sign of heart failure may be the impairment of quick adaptations of cardiac output in response to baroreceptor signalling of decreased blood pressure in the carotid bulb, due to venous pooling upon standing. In this case, heart failure that is otherwise asymptomatic would manifest as orthostatic hypotension; orthostatic hypotension itself, directly or indirectly, would not be causing heart failure. However, this explanation would not apply to the observed association between orthostatic hypertension and risk of heart failure.   
  
In the present study, men with combined systolic and diastolic orthostatic hypertension had increased risk of heart failure, while those with combined systolic and diastolic orthostatic hypotension did not. This may reflect the limited number of men with combined systolic and diastolic orthostatic hypotension, or it may suggest the different components of orthostatic hypotension and orthostatic hypertension (isolated systolic, isolated diastolic and combined systolic and diastolic orthostatic changes in blood pressure) are driven by different aetiological mechanisms. If this were the case, it may explain the different risk of heart failure associated with the different components of orthostatic blood pressure changes observed in the present study, but further studies are required to support, or refute, this hypothesis.   
  
Strengths of our study include the long duration of follow-up, that we examined an older cohort and adjusted for biochemical risk factors known to increase risk of heart failure, including NT-proBNP. We also examined the individual systolic and diastolic components of orthostatic change in blood pressure; a distinction made infrequently in the past. Limitations of our study include that our sample consisted only of men and that the vast majority (>99%) were of white European ethnicity. Hence, the generalisability of our findings is limited. We did not have measurements of orthostatic change in blood pressure beyond three minutes and would have misclassified men with orthostatic changes in blood pressure that were delayed beyond this point in time.   
  
In conclusion, exaggerated orthostatic changes in blood pressure – be they orthostatic increases or decreases in blood pressure – are associated with increased risk of incident heart failure in older, community-dwelling men. The exaggerated changes may be an early sign of cardiovascular compromise and/or dysfunction. Therefore, older adults in whom exaggerated orthostatic changes in blood pressure are found may benefit from cardiovascular disease risk assessment. Further prospective studies in diverse populations are needed to confirm our finding and clarify how to define orthostatic hypertension, in terms of diagnostic thresholds.  
  
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Conflicts of Interest  
None  
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Figure Legends  
Figure 1: Association of orthostatic change in systolic (panels A and B) and diastolic (panels C and D) blood pressure with risk of incident heart failure.

Appendices  
None

Table 1: Baseline characteristics of the study population stratified by category of orthostatic change in blood pressure. \* = Geometric mean (interquartile range); all other values are the arithmetic mean (standard deviation) or proportions. Orthostatic normotension was the reference group for hypothesis testing.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Orthostatic Hypotension (n=710)** | **Orthostatic normotension (n=1956)** | **Orthostatic hypertension (n=839)** | **p for overall difference** |
|  | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |  |
| Age, years | 69.4 (5.5) | 68.3 (5.4) | 68.3 (5.5) | <.0001 |
| BMI, kg/m2 | 26.5 (3.6) | 27 (3.7) | 26.7 (3.5) | 0.011 |
| Waist Circumference, cm | 96.7 (10.2) | 97.3 (10.3) | 96.1 (10.4) | 0.0177 |
| Sitting systolic BP, mmHg | 161.2 (23.8) | 147.8 (23.1) | 145.8 (23.9) | <.0001 |
| Sitting diastolic BP, mmHg | 89.5 (12) | 85.3 (10.5) | 83 (10.9) | <.0001 |
| Heart rate, beats per minute | 67.4 (14.6) | 65.5 (11.7) | 65.1 (12.7) | 0.0008 |
| Arm circumference, cm | 30 (2.7) | 30.5 (2.8) | 30.3 (2.7) | <.0001 |
| Current smokers (%) | 13.80 | 13.16 | 12.31 | 0.6778 |
| Moderate to heavy alcohol consumption (%) | 19.23 | 20.32 | 19.04 | 0.6769 |
| Inactive (%) | 33.80 | 31.13 | 30.87 | 0.3687 |
| Manual Social Class (%) | 52.12 | 50.15 | 50.78 | 0.6674 |
| Resting tachycardia (HR >90) (%) | 7.06 | 3.39 | 4.05 | 0.0002 |
| **Co-morbid conditions (%)** |  |  |  |  |
| Prevalent AF | 4.38 | 2.56 | 3.46 | 0.0507 |
| Prevalent Diabetes | 5.49 | 5.67 | 5.36 | 0.9433 |
| Prevalent CKD | 16.12 | 12.76 | 13.96 | 0.082 |
| BP medications | 31.48 | 26.76 | 26.58 | 0.0411 |
| Hypertension | 85.92 | 71.83 | 69.73 | <.0001 |
| COPD | 31.12 | 26.24 | 23.71 | 0.0039 |
| **Circulating cardiovascular risk markers** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |  |
| Cholesterol, mmol/L | 6.0 (1.1) | 6.0 (1.1) | 6.0 (1.1) | 0.9602 |
| LDL, mmol/L | 3.9 (1.0) | 3.9 (1.0) | 3.9 (1.0) | 0.8881 |
| HDL, mmol/L | 1.4 (0.4) | 1.3 (0.30) | 1.3 (0.30) | 0.0122 |
| Triglycerides\*, mmol/L | 1.6 (1.1 - 2.2) | 1.6 (1.1 - 2.2) | 1.6 (1.1 - 2.2) | 0.1644 |
| Glucose\*, mmol/L | 5.9 (5.3 - 6.2) | 5.9 (5.2 - 6.1) | 5.8 (5.2 - 6.1) | 0.3465 |
| Phosphate, mmol/L | 1.2 (0.2) | 1.2 (0.2) | 1.2 (0.2) | 0.0026 |
| eGFR, ml/min/1.73m2 | 72.1 (12.7) | 73.3 (12.1) | 72.6 (13.1) | 0.0748 |
| CRP\*, mg/L | 1.8 (0.8 - 3.3) | 1.7 (0.8 - 3.4) | 1.6 (0.7 - 3.3) | 0.2559 |
| IL-6\*, pg/ml | 2.6 (1.6 - 3.9) | 2.4 (1.5 - 3.3) | 2.3 (1.5 - 3.2) | 0.0029 |
| VWF, IU/dl | 145.9 (48.4) | 135.7 (44.3) | 135.7 (44.4) | <.0001 |
| Urate, mmol/L | 0.4 (0.1) | 0.4 (0.1) | 0.4 (0.1) | 0.2474 |
| NT-proBNP\*, pg/ml | 108.9 (50.9 - 212.7) | 83.9 (42.1 - 160.8) | 86.5 (40.9 - 159.2) | <.0001 |
| Troponin T\*, pg/ml | 12.4 (9.2 - 16.1) | 11.4 (8.5 - 15.5) | 11.6 (8.7 - 15.5) | 0.0002 |

Table 2: The age-adjusted mean (standard error) of specific markers of cardiovascular risk and their distribution among the components of orthostatic hypotension (OHypo) and orthostatic hypertension (OHyper). In each case, the mean shown is the geometric mean.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Isolated systolic OHypo (n=450) | Isolated diastolic OHypo (n=155) | Combined systolic and diastolic OHypo (n=105) | Orthostatic Normotension (n=1956) | Isolated systolic OHyper (n=118) | Isolated Diastolic OHyper (n=596) | Combined systolic and diastolic OHyper (n=125) | p for overall difference |
| CRP, mg/L | 1.59 (1.05) | 1.68 (1.09) | 2.33 (1.11) | 1.7 (1.03) | 1.5 (1.11) | 1.56 (1.05) | 1.97 (1.10) | 0.0089 |
| IL-6, pg/ml | 2.41 (1.03) | 2.59 (1.05) | 2.89 (1.07) | 2.38 (1.01) | 2.35 (1.06) | 2.3 (1.03) | 2.3 (1.06) | 0.0302 |
| NT-proBNP, pg/ml | 92.07 (1.05) | 109.22 (1.09) | 143.21 (1.11) | 85.93 (1.02) | 88.84 (1.10) | 87.38 (1.04) | 85.43 (1.10) | <.0001 |
| High-sensitivity troponin T, pg/ml | 11.83 (1.02) | 12.61 (1.04) | 12.38 (1.04) | 11.49 (1.01) | 11.61 (1.04) | 11.82 (1.02) | 11.17 (1.04) | 0.0848 |

Table 3: Hazard ratios (95% confidence intervals) for incident heart failure by category of orthostatic change in blood pressure. Orthostatic normotension refers to the absence of orthostatic hypotension and orthostatic hypertension

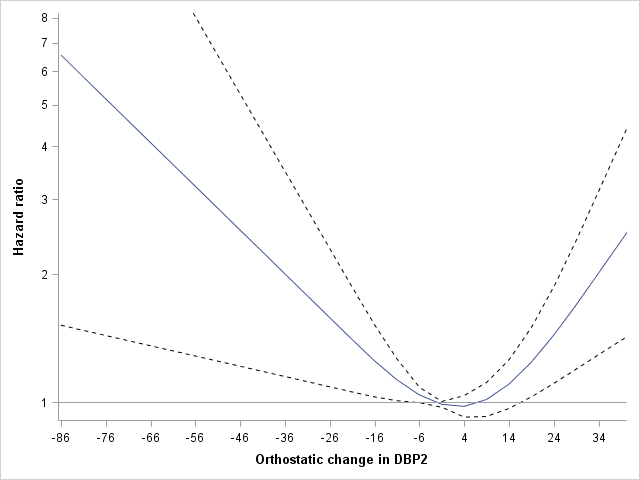
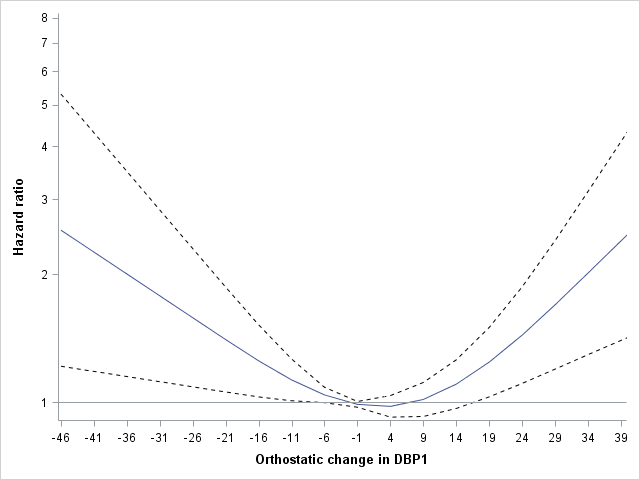
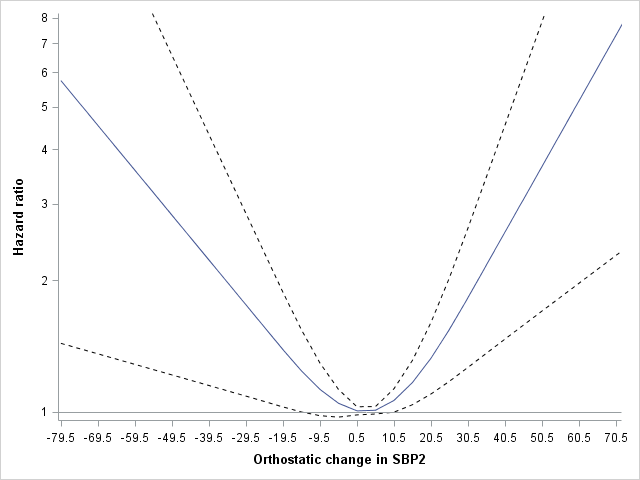
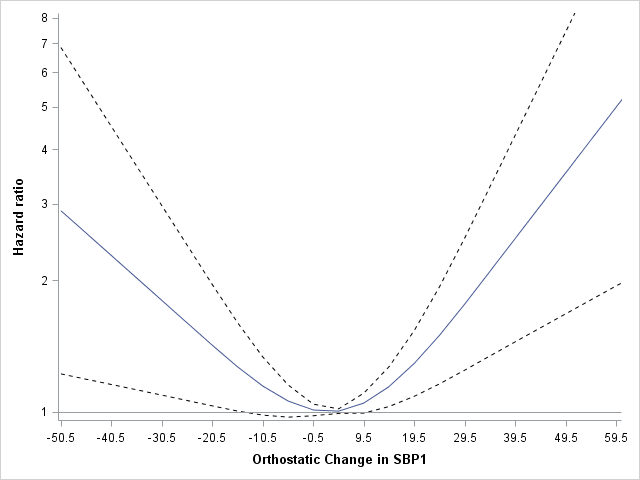
|  |  |  |  |
| --- | --- | --- | --- |
|  | Orthostatic Hypotension | Orthostatic Normotension | Orthostatic Hypertension |
| Number (%) | 710 (20.3) | 1956 (55.8) | 839 (23.9) |
| Incidence (per 1000 person years) | 10.0 | 6.1 | 7.6 |
| Age-adjusted model | 1.73 (1.33 - 2.24) | 1.00 | 1.14 (0.88 - 1.49) |
| Model 1 | 1.68 (1.28 - 1.15) | 1.00 | 1.19 (0.92 - 1.55) |
| Model 2 | 1.62 (1.24 - 2.12) | 1.00 | 1.17 (0.90 - 1.53) |
| Model 3 | 1.56 (1.19 - 2.04) | 1.00 | 1.16 (0.89 - 1.51) |
| Model 4 | 1.62 (1.22 - 2.15) | 1.00 | 1.21 (0.92 - 1.58) |
| Model 4 + Incident MI | 1.65 (1.24 - 2.18) | 1.00 | 1.20 (0.91 - 1.57) |

Model 1: Adjusted for age, BMI, heart rate, average sitting systolic blood pressure, physical activity, smoking status, alcohol consumption, social class, total cholesterol. Model 2: Model 1 plus prevalent AF, diabetes, CKD, COPD and anti-hypertensive medication use. Model 3: Model 2 plus IL-6. Model 4: Model 3 plus NT-proBNP.

Table 4: Hazard ratios (95% confidence intervals) for incident heart failure by the specific systolic and diastolic components of orthostatic hypotension and orthostatic hypertension

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Isolated systolic OHypo | Isolated diastolic OHypo | Combined systolic and diastolic OHypo | Orthostatic Normotension | Isolated systolic OHyper | Isolated Diastolic OHyper | Combined systolic and diastolic OHyper |
| Number (%) | 450 (12.8) | 155 (4.4) | 105 (3.0) | 1956 (55.8) | 118 (3.4) | 596 (17.0) | 125 (3.6) |
| Incidence (per 1000 person years) | 10.6 | 7.2 | 11.9 | 6.1 | 13.0 | 6.2 | 8.7 |
| Age-adjusted model | 1.71 (1.28 - 2.30) | 1.35 (0.78 - 2.34) | 2.57 (1.49 - 4.46) | 1.00 | 1.7 (1.08 - 2.68) | 0.96 (0.7 - 1.32) | 1.41 (0.83 - 2.40) |
| Model 1 | 1.74 (1.28 - 2.35) | 1.27 (0.73 - 2.20) | 2.05 (1.17 - 3.59) | 1.00 | 1.78 (1.12 - 2.82) | 1.00 (0.72 - 1.37) | 1.53 (0.90 - 2.60) |
| Model 2 | 1.70 (1.26 - 2.31) | 1.18 (0.67 - 2.06) | 1.90 (1.08 - 3.33) | 1.00 | 1.79 (1.13 - 2.84) | 0.96 (0.70 - 1.32) | 1.57 (0.92 - 2.68) |
| Model 3 | 1.65 (1.21 - 2.23) | 1.16 (0.66 - 2.03) | 1.73 (0.97 - 3.10) | 1.00 | 1.74 (1.10 - 2.75) | 0.96 (0.70 - 1.31) | 1.55 (0.91 - 2.65) |
| Model 4 | 1.79 (1.31 - 2.45) | 1.46 (0.83 - 2.56) | 1.08 (0.54 - 2.16) | 1.00 | 1.94 (1.22 - 3.08) | 0.96 (0.69 - 1.33) | 1.75 (1.02 - 2.99) |
| Model 4 + Incident MI | 1.83 (1.34 - 2.51) | 1.50 (0.85 - 2.64) | 1.08 (0.54 - 2.16) | 1.00 | 1.88 (1.18 – 3.00) | 0.94 (0.68 - 1.31) | 1.84 (1.08 - 3.16) |

Model 1: Adjusted for age, BMI, heart rate, average sitting systolic blood pressure, physical activity, smoking status, alcohol consumption, social class, total cholesterol. Model 2: Model 1 plus prevalent AF, diabetes, CKD, COPD and anti-hypertensive medication use. Model 3: Model 2 plus IL-6. Model 4: Model 3 plus NT-proBNP. OHypo = orthostatic hypotension; OHyper = orthostatic hypertension.



A

B

C

D

Figure 1: Association of orthostatic change in systolic (panels A and B) and diastolic (panels C and D) blood pressure with risk of incident heart failure

Orthostatic change in blood pressure was modelled as restricted cubic splines with three equally spaced knots. The models adjusted for age, mean sitting systolic blood pressure, BMI, heart rate, social class, physical activity, smoking status, alcohol consumption, total cholesterol, prevalent AF, diabetes, CKD, COPD, anti-hypertensive drug use, circulating IL-6, high-sensitivity troponin T and NT-proBNP. SBP1 refers to change in systolic blood pressure between the first standing and mean sitting blood pressure measurements; SBP2 between the second standing systolic measurement and mean sitting blood pressure measurements; DBP1 refers to change in diastolic blood pressure between the first standing and mean sitting blood pressure measurements; DBP2 between the second standing diastolic measurement and mean sitting blood pressure measurements.