**Long Term Prognostic Impact of Sex-specific Longitudinal Changes in Blood Pressure.**

**The EPIC-Norfolk Prospective Population Cohort Study**

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**ABSTRACT**

**Aims:** We aimed to determine the sex differences in longitudinal systolic and diastolic blood pressure (SBP and DBP) trajectories in mid-life and delineate the associations between these and mortality (all-cause, cardiovascular, non-cardiovascular) and incident cardiovascular disease (CVD) in old age.

**Methods:** Participants were selected from the European Prospective Investigation into Cancer, Norfolk (EPIC-Norfolk) cohort study. Sex-specific trajectories were determined using group-based trajectory models using three clinic BP measurements acquired between 1993 and 2012 (mean exposure ~12.9 years). Multivariable Cox regressions determined the associations between trajectories and incident outcomes over the follow-up (2012-2018, median follow-up 9.4 years).

**Results:** 2897 men (M) and 3819 women (F) were included. At baseline, women were younger (F-55.5, M-57.1), had a worse cardiometabolic profile and were less likely to receive primary CVD prevention including antihypertensive treatment (F-36.0%, M-42.0%). Over the exposure period, women had lower SBP trajectories while men exhibited more pronounced SBP decreases over this period. Over the follow-up period women had lower mortality (F-11.9%, M-20.5%) and CVD incidence (F-19.8%, M-29.6%). Compared to optimal SBP (≤120 mmHg) and DBP (≤70 mmHg) trajectories, hypertensive trajectories were associated with increased mortality and incident CVD in both men and women during follow-up at univariable level. These associations were nevertheless not maintained upon extensive confounder adjustment including antihypertensive therapies.

**Conclusion:** We report sex disparities in CVD prevention which may relate to worse cardiometabolic profiles and less pronounced longitudinal SBP decreases in women. Effective anti-hypertensive therapy may offset the adverse outcomes associated with prolonged exposure to high blood pressure.

**Keywords:** Blood pressure; longitudinal; trajectory; sex-specific; mortality; cardiovascular disease;

**GRAPHICAL ABSTRACT**

**Graphical Abstract.** Summary of the main study findings.

EPIC – European Prospective Investigation into Cancer; LDL-c – low-density lipoprotein cholesterol; HbA1c – Glycated Haemoglobin; EtOH – alcohol use; BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; CVD – cardiovascular disease

**INTRODUCTION**

While the magnitude of blood pressure (BP) elevation predicts the strength of association between hypertension and adverse outcomes1–3, long-term exposure to elevated BP values is also important. Long-term BP trajectories allow additional factors including antihypertensive treatment and ageing-related changes in arterial stiffness and BP4 to be considered. Group based trajectory modelling (GBTM) is a data-driven approach which allows the derivation of clusters of individuals exhibiting statistically similar longitudinal trajectories of a given parameter, such as blood pressure5. Unlike approaches which define longitudinal trajectories *a priori*, GBTM does not rely on assumptions based on subjective and inflexible *ex ante* assignment rules6. GBTM therefore enables the identification of new and previously unrecognised longitudinal trajectories6. In this data driven approach, the clusters thus identified do not represent distinct fixed entities but rather convenient groupings of individuals following similar trajectories. Individuals are assigned to each trajectory group based on a probability of group membership and therefore the interpretation of such trajectories depends on these considerations5,6.

Hypertensive trajectories are associated with an increased risk of incident stroke7, renal disease8, cardiovascular disease (CVD)9–11 and mortality12–14. Nevertheless, significant sex differences have been demonstrated in BP trajectories15. These may also mediate sex differences in CVD epidemiology, given recent findings of such differences in the relationship between longitudinal BP trajectories and incident atrial fibrillation (AF)11. Nevertheless, no studies have previously evaluated the associations between sex-specific longitudinal BP trajectories and mortality and overall incident CVD. Furthermore, current hypertension guidelines lack sex-specific recommendations1–3.

In this study, we aimed to determine the sex differences in longitudinal SBP and DBP trajectories in mid-life and delineate the associations between these and mortality (all-cause, cardiovascular and non-cardiovascular) and incident CVD in older age using data from the European Prospective Investigation into Cancer - Norfolk Cohort (EPIC-Norfolk).

**METHODS**

**Ethical considerations**

This study was conducted in accordance with the Declaration of Helsinki (1975) and later amendments. Ethical approval was obtained from the Norwich Ethics Committee. All participants gave informed signed consent for the examination of medical records and use of the data.

**Data Source**

Participants were selected from the European Prospective Investigation into Cancer, Norfolk (EPIC-Norfolk) prospective cohort study. Study recruitment methods have been previously described16. Briefly, men and women aged 40-79 (at study baseline) from 35 General Practices in Norfolk, England were invited to participate. Three health checks (HC) occurred between 1993-1998 (study baseline), 1998-2000 and 2004-2012. At each HC, data on age, demographic characteristics, behavioural parameters, systolic and diastolic BP measurements and medication were collected. Self-reported co-morbidities were ascertained during the first and second HCs. A follow-up questionnaire obtained between 2000-2006 ascertained self-reported co-morbidities before the third health check17.

**Inclusion and Exclusion Criteria**

Figure 1 illustrates the participant flowchart. Out of 6769 participants who attended the first three HCs of the EPIC-Norfolk study, 6716 (2897 men and 3819 women) were included in the mortality analyses, after the exclusion of 53 participants with missing data. A total of 690 men and 504 women with prevalent CVD at the third HC (2004-2012) were further excluded from the incident CVD analyses, including 2207 men and 3315 women.

**Definition of Exposure, Confounders and Outcomes**

*Outcomes*

All-cause mortality was ascertained using death certificate data from the Office of National Statistics18. Cardiovascular mortality was ascertained using death certificate data and International Classification of Disease 10 (ICD-10) codes (I10-79) and ICD-9 codes (401-448) obtained through record linkage with the National Health Service (NHS) hospital information system and ENCORE (East Norfolk Commission Record) to allow notification of any hospital admission. Incident cardiovascular disease was defined as the first date of any hospital admission/primary care diagnosis with a diagnosis comprised withing the ICD-10 codes of I11-I79 and ICD-9 codes of 402-448, excluding diagnoses of essential hypertension (ICD-10: I10 and ICD-9: 401). Previously published validation studies of random samples from EPIC-Norfolk assessing the diagnoses of stroke18, heart failure19 have shown that these parameters were ascertained with high accuracy. Furthermore, the United Kingdom National Health Service (NHS) captures almost all incident events and the EPIC-Norfolk study participants were registered with a General Practitioner and assigned an NHS number, allowing extremely robust record linkage. Therefore, the outcomes employed in our study were ascertained with high accuracy. Participants were followed up until the end of March 2018.

*Exposures*

Blood pressure measurements were acquired by a trained nurse after participants had been seated for 3 minutes in a quiet room. Two readings were taken using an aneroid Accutorr Sphygmomanometer (Datascope, UK) using an appropriately sized cuff with the participants’ arm in the horizontal position in line with the mid-sternum20. The mean of the two readings was then recorded.

Longitudinal SBP and DBP trajectories across the first three HCs (mean exposure 12.9 years) were determined separately for men and women using Group-Based Trajectory Models (GBTM) and the *traj* Stata plugin21. Trajectories were modelled using the censored normal distribution. The selection of the GBTM model with an optimal number of quadratic groups was informed by the Bayesian Information Criterion (BIC). The model with the least negative BIC which contained at most 6 distinct groups was chosen, ensuring that no group contained less than 1% of the considered population.

*Confounders*

Potential confounders considered were measured at the third HC (age, sex, ethnicity, body mass index, physical activity levels, low-density lipoprotein cholesterol, smoking status and units of alcohol drunk) or ascertained from a follow-up questionnaire obtained before (2000-2006) the third HC (self-reported cancer, asthma and chronic obstructive pulmonary disease). Covariates were chosen based on clinical judgement and previous literature7,11,12,22–24. The estimated glomerular filtration rate was computed using the creatinine values measured at the third HC using the Modification of Diet in Renal Disease (MDRD) formula25. Co-morbid cardiovascular disease was defined as a self-reported diagnosis of angina, myocardial infarction, cerebrovascular disease or peripheral vascular disease on/before the follow-up questionnaire or incident CVD (ICD-10: I11-I79, ICD-9: 402-448) reported during the exposure period. Co-morbid diabetes mellitus was defined as a self-reported diagnosis of diabetes reported on/before the follow-up questionnaire, glycated haemoglobin levels >6.5% (47.5 mmol/mol) or self-reported anti-diabetic medication at the third HC.

**Statistical analysis**

Data were analysed using Stata 15.1 SE (StataCorp 2017, Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC). A 5% threshold of statistical significance was used (P<0.05).

*Missing Data*

Six variables collected at the third HC contained missing data. Table 1 details the proportion of missing data for these variables. Supplementary Table 1 summarises third HC characteristics stratified by whether data on any of of these variables were missing. 2364 (35.2%) participants had missing data on at least one variable. Those were significantly more likely to be younger and have higher incidence of adverse events (all-cause mortality, cardiovascular mortality and incident CVD). Data missingness was likely dependent only on observed but not unobserved data, and subsequently missing-at-random26. A multiple imputation by chained equation algorithm with 20 iterations was implemented. Variables were imputed using predictive mean matching drawing from five nearest neighbours. Age, sex, ethnicity and third HC data: weight, height, educational level, SBP, DBP, heart rate, pre-existing co-morbidities, medication and two Nelson-Aalen cumulative hazard functions (incident all-cause and cardiovascular mortality) were used as predictors.

*Descriptive Statistics*

Participant characteristics at the third HC were compared between men and women using the χ2 test, student’s t-test or Mann-Whitney U test as appropriate.

*Cox Regression Analyses*

For the mortality analyses, participants were followed-up from the third HC until either death or end of follow-up. Participants in the incident CVD analyses were followed-up from the third HC until either the incidence of a cardiovascular event, death or end of follow-up. Given that for this part of the analysis we determined cause-specific hazard ratios27, death was considered a censoring event. The median follow-up time was calculated separately for men and women using the reverse Kaplan-Meier method.

Sex-specific Cox regression models were computed for all outcomes of interest. A further sensitivity Cox regression analysis was undertaken assessing the relationship between BP trajectories and all-cause mortality only amongst participants without prevalent CVD at the third health check. The satisfaction of the proportional hazards assumption for the exposures was verified using log-negative-log plots. The BP trajectory group containing the lowest measurements was assigned as reference for all analyses. Sequentially adjusted models were constructed: Model A – Univariable; Model B – Multivariable adjustment for age and ethnicity; Model C – Model B + body mass index, physical activity level, smoking and alcohol consumption; Model D – Model C + pre-existing co-morbidities (cardiovascular disease, diabetes mellitus, cancer, asthma, chronic obstructive pulmonary disease) and serum low-density lipoprotein cholesterol; Model E – Model D + antihypertensive treatment.

**RESULTS**

*Descriptive Statistics*

Table 1 summarises the participant sex-specific characteristics at the third HC. 2897 (43.1%) men and 3819 (56.9%) women were included. Compared to men (mean age (standard deviation) = 70.07 (8.25) years), women were younger (68.47 (8.05) years). SBP and DBP measurements were higher amongst men than women. Compared to men, women had lower rates of self-reported co-morbid cardiovascular disease, diabetes mellitus, cancer, asthma and chronic obstructive pulmonary disease on or before the third health check. Women also had lower rates of self-reported therapy with aspirin, lipid-lowering agents, anti-diabetic and anti-hypertensive agents. Over the follow-up period, men had higher rates of incident mortality (all-cause, cardiovascular and non-cardiovascular) as well as incident CVD.

*Longitudinal Blood Pressure Trajectories*

There were 6 distinct SBP trajectories amongst men included in the mortality analyses (Figure 2 and Supplementary Table 2), which were characterised according to the 2018 ESC guidelines1. A total of 14.7% belonged to trajectory 1 (stable optimal SBP), 45.4% to trajectory 2 (stable normal/high normal SBP), 29.9% to trajectory 3 (stable grade 1 hypertension), 2.2% to trajectory 4 (well-controlled grade 1 hypertension), 1.2% to trajectory 5 (grade 1 🡪 grade 2 hypertension) and 6.6% to trajectory 6 (grade 2 🡪 grade 1 hypertension). Amongst women included in the mortality analyses, 5 SBP trajectories were revealed: 23.6% belonged to trajectory 1 (stable optimal SBP), 44.2% to trajectory 2 (rising normal/high normal SBP), 26.8% to trajectory 3 (stable grade 1 hypertension), 3.0% to trajectory 4 (grade 2 🡪 grade 1 hypertension) and 2.4% to trajectory 5 (grade 1 🡪 grade 2 hypertension), respectively.

Amongst men included in the incident CVD analyses, 5 SBP trajectories were revealed (Figure 3 and Supplementary Table 3): 19.4% belonged to trajectory 1 (borderline stable optimal SBP), 50.2% to trajectory 2 (rising normal/high normal SBP), 21.3% to trajectory 3 (rising grade 1 hypertension), 4.1% to trajectory 4 (grade 1 hypertension 🡪 high-normal SBP) and 5.0% to trajectory 5 (grade 2 🡪 grade 1 hypertension). Amongst women included in the incident CVD analyses, there were 5 similar SBP trajectories: 12.6% belonged to trajectory 1 (stable optimal SBP), 37.8% to trajectory 2 (rising normal/high-normal SBP), 37.2% to trajectory 3 (high-normal SBP 🡪 grade 1 hypertension), 2.4% to trajectory 4 (grade 1 🡪 grade 2 hypertension) and 9.9% to trajectory 5 (decreasing grade 1 hypertension) and

All analysed groups revealed 5 distinct DBP trajectories, which were similar in all groups: trajectory 1 (low optimal DBP), trajectory 2 (high optimal DBP), trajectory 3 (normal/high-normal DBP), trajectory 4 (grade 1 hypertension 🡪 normal DBP) and trajectory 5 (stable grade 1/grade 2 hypertension).

*Cox Regression Analyses*

Median follow-up periods (interquartile range) were 9.4 (8.0-10.9) and 9.4 (7.8-11.0) years for men and women, respectively. Univariable analyses (Model A) showed that compared to SBP trajectory 1 participants (stable optimal SBP), the other SBP trajectories were associated with increased risk of incident all-cause, cardiovascular and non-cardiovascular mortality amongst both sexes (Figure 4 and Supplementary Tables 4-6). In men, trajectories 3-6 were associated with 2-fold increases in the risk of all-cause mortality, while trajectories 2-6 were associated with up to 3-fold increases for the same outcome (Figure 4). Nevertheless, these associations with any of the mortality outcomes were not revealed upon confounder adjustment (Models B-E). In men, similar patterns were revealed between DBP trajectories and incident mortality. In univariable analyses (Model A), trajectories 2-4 were associated with 35-50% reductions in the risk of incident all-cause mortality compared to trajectory 1 (low optimal DBP), which were also not revaled upon confounder adjustment (Models B-E). Nevertheless, there were a few significant associations between DBP trajectories and cardiovascular mortality amongst men. Compared to trajectory 1 (low optimal DBP), trajectories 2 (high optimal DBP) and 3 (normal/high-normal DBP) were associated with significantly lower cardiovascular mortality in all models considered (Models A-E).

The sensitivity all-cause mortality analysis considering only participants without prevalent CVD at the third health checked revealed results consistent with the main analyses (Supplementary Table 7).

Amongst men, compared to SBP trajectory 1 (stable optimal SBP), trajectories 2-5 were associated with significant increases between 30% and 3-fold in incident CVD in the univariable model (Model A). The associations between trajectories 2-4 and incident CVD were not revelead after confounder adjustment (Models B-E). Nevertheless, the association between trajectory 5 (grade 2 🡪 grade 1 hypertension) was revealed upon adjustment for age, ethnicity, BMI, physical activity level, smoking and alcohol consumption and pre-existing co-morbidities (Models B-D), but not after further adjustment for antihypertensive treatment (Model E) (Figure 5, Supplementary Table 8). There were no statistically significant relationships between DBP trajectories 2-5 (compared to trajectory 1) and incident CVD amongst men across all models considered.

Amongst women, compared to SBP trajectory 1 (stable optimal SBP), trajectories 3-5 were associated with significant 2- to 3-fold increases in the risk of incident CVD at univariable level (Model A). The associations between trajectories 2-4 and incident CVD were not revealed upon confounder adjustment (Models B-E). Nevertheless, the association between trajectory 5 (decreasing grade 1 hypertension) and incident CVD was revealed upon adjustment for age and ethnicity (Model B), but not after further confounder adjustment (Models C-E). . Compared to DBP trajectory 1 (low optimal DBP), trajectories 2-5 were associated with significant 30% to 2-fold increases in the risk of incident CVD amongst women. The associations between trajectories 2, 3 and 5 and incident CVD were not revealed upon confounder adjustment (Models B-E), while the association between trajectory 4 (grade 1 hypertension 🡪 normal DBP) and inident CVD was revealed upon adjustment for age, ethnicity, BMI, physical activity and smoking, alcohol consumption (Models B-C) but not after further adjustment for pre-existing co-morbidities and antihypertensive treatment (Models D-E).

**DISCUSSION**

In this prospective cohort study with long-term historical BP data spanning ~13 years, we determined the sex differences in longitudinal BP trajectories in mid-life and have delineated their associations with mortality (all-cause, cardiovascular and non-cardiovascular) and incident CVD in later life. We found that women were significantly younger, but demonstrated a worse cardiometabolic profile at baseline with higher baseline LDL-c levels, lower levels of physical activity and higher prevalence of smoking. Women were also less likely to receive primary CVD prevention, antihypertensive and anti-diabetic treatment. They nevertheless tended to have SBP trajectories characterised by lower mean measurements, while men tended to exhibit more pronounced decreases in SBP over the duration of the exposure period. Despite overall lower mortality and incident CVD rates amongst women, the excess risk of these adverse outcomes associated with hypertensive trajectories was higher in women than in men at univariable level. While the univariable associations between longitudinal BP trajectories and mortality were rendered non-significant upon only age and ethnicity adjustment amongst both sexes, the associations between hypertensive BP trajectories and incident mortality amongst men were maintained after comprehensive adjustment for age, ethnicity, lifestyle factors, co-morbidities and baseline LDL-c levels. Further adjustment for anti-hypertensive treatment rendered this association non-significant, suggesting that the long-term adverse effects of hypertension may be offset by appropriate and timely antihypertensive treatment.

Several previous investigations assessed the relationship between long-term BP burden and CVD. A dose-response relationship between cumulative exposure to elevated BP and incident CVD and cardiovascular mortality has been previously reported13,28–31. Furthermore, several investigations have reported that prolonged exposure to elevated BP trajectories is associated with increased atherosclerotic burden22, incident stroke7, heart failure9, AF11, overall CVD9, all-cause mortality24 and cardiovascular mortality12. Recent findings indicate that long-term BP trajectories may differ by sex15. Indeed, sex differences have also been recently reported for incident AF11. Amongst 7670 men and 8376 women from a Norwegian prospective cohort with a mean age at the beginning of the exposure period of ~40 years (mean age of our cohort at the beginning of the exposure period was 56.2 years), stronger associations between elevated/hypertensive BP trajectories and incident AF were documented amongst women than in men11. However, no previous investigations have assessed the relationship between the different phenotypes of longitudinal BP changes and adverse outcomes separately amongst men and women. Our study is the first to report these relationships.

Our results suggest that men exhibit higher SBP trajectories than women, with men in the reference SBP trajectory having a mean SBP of ~120 mmHg throughout the exposure period while women in the reference group ~110 mmHg. Nevertheless, more pronounced SBP decreases were recorded in men. This may be attributed to a tendency of undertreating hypertension in women, illustrated by lower utilisation of antihypertensive agents in women than in men at the end of the exposure period (36% versus 42%, respectively). Our results are largely consistent with previous findings suggesting a larger unused potential for cardiovascular prevention by BP reduction strategies in women than in men32. Furthermore, we also found that compared to low optimal DBP (<70 mmHg), DBP trajectories characterised by high normal values (80-90 mmHg) were associated with lower risk of all-cause and cardiovascular mortality in men, even after full multivariable adjustment. Such associations were nevertheless not revealed in women (who had lower CVD prevalence at baseline) or in participants included in the incident CVD analyses (who were free of prevalent CVD at baseline), suggesting that long-term exposure DBP <70 mmHg may be deleterious in patients with pre-existing CVD, which has been previously reported in larger studies with shorter follow-up33,34.

The overall lack of association between the other BP trajectories and outcomes may be related to the characteristics of the included participant sample: mean body mass index ~26.5-26.9 kg/m2, estimated glomerular filtration rate ~73 mL/min/1.73 m2, glycated haemoglobinlevels ~5.8% (39.9 mmol/mol), LDL cholesterol levels ~ 3.0 mmol/L, ~95% non-smokers. Furthermore, a high proportion of participants were undergoing CVD primary prevention with aspirin, lipid-lowering and antihypertensive agents at the end of the exposure period. The included sample thus comprised of relatively healthy participants undergoing appropriate primary prevention in whom incident CVD would be less likely to result in a fatal event. This may also be explained by survivorship bias, in which the inclusion of a healthier sub-population surviving over a ~13 year-old period spanning the first three health checks of the EPIC-Norfolk study may have led to the underestimation of the mortality and incident CVD risk. Further studies replicating our analytic strategy are therefore warranted to determine the same associations in other cohorts with differing distributions of ethnicity, cardiovascular risk profile and co-morbidities to ensure the external validity of our findings.

Our results may inform primary CVD prevention practice by highlighting the importance of sex differences in the natural course and management of hypertension from mid-life onwards. While women exhibited BP trajectories characterised by initial lower values, men received more aggressive antihypertensive therapy, resulting in more pronounced longitudinal BP decreases. Suboptimal primary CVD prevention amongst women is also reflected in poorer cardiometabolic health at baseline and higher relative risk increases associated with exposure to non-optimal BP values in women at univariable level. These results therefore reflect important between-sex disparities in primary prevention which need to be addressed in order to ensure appropriate and fair provision of care. Therefore, a programme of systematic population screening for hypertension with a special emphasis on early diagnosis in women should be implemented in order to address the sex disparities highlighted by our study. Patient education and regular follow-up are also be warranted to ensure appropriate compliance with antihypertensive therapy. Furthermore, the results of our study in addition to previous literature33,34 highlight that lowering diastolic BP to values <70 mmHg may be deleterious in men as well as patients with pre-existing cardiovascular disease and such stringent BP treatment targets should be avoided.

Our study benefited from several strengths. We used data from EPIC-Norfolk, a large, prospective cohort with robust ascertainment of exposures, confounders and outcomes. Furthermore, EPIC-Norfolk benefits from long-term follow-up, allowing the determination of long-term BP trajectories over 12 years and the adjudication of outcomes over a median follow-up of 9.4 years after the exposure period. We were able to control for wide range of important demographic, lifestyle, social and medical factors. Furthermore, we employed robust statistical methods to adjudicate longitudinal BP trajectory group membership.

Naturally, there were also limitations. We included >99% White Caucasian participants, and thus ethnicity-stratified analyses could not be performed. Further studies are required to determine these associations amongst other ethnicities. BP trajectories were adjudicated based on measurements from three health-checks. Nevertheless, no other BP measurements were acquired and therefore BP variations occurring between these health checks were not considered, introducing potential uncertainty regarding the development of BP trajectories between the health checks. Furthermore, we used self-reported comorbidity, which may lead to inaccuracies. We nevertheless employed a combined definition of the comorbidities considered by also employing medication data, biomarkers measured at the health checks and incident diagnoses reported during the exposure period in order to minimise potential inaccuracies in the ascertainment of self-reported comorbidities. Furthermore, having only included a subgroup of the EPIC-Norfolk prospective study which attended the first three health checks of the study spanning ~13 years, our analyses may be prone to survivorship bias. Nevertheless, this is an inherent limitation of any study analysing longitudinal changes in blood pressure. Despite adjusting for a wide range of participant characteristics at the beginning of the follow-up, data describing the evolution of these co-variates over the follow-up were not available, which did not allow longitudinal co-variate changes to be considered. As an observational study, we were not able to account for residual confounders.

In conclusion, using data from a large-scale prospective cohort study, we determined the sex differences in longitudinal BP trajectories in midlife and delineated the associations between these and mortality and incident CVD in older age. While men exhibited higher BP longitudinal trajectories than women, these were characterised by more pronounced BP decreases throughout the exposure period of the study, which may be attributed to the relative undertreatment of women. This suggests important between-sex disparities in primary CVD prevention. Exposure to hypertensive SBP and DBP trajectories was associated with higher mortality and incident CVD risk amongst both sexes at univariable level. Nevertheless, these associations were not maintained upon extensive confounder adjustment including antihypertensive therapy, suggesting that effective therapy may offset the adverse outcomes associated with prolonged exposure to high blood pressure. Our results also highlight that longitudinal exposure to low DBP values <70 mmHg may be independently associated with higher risk of all-cause and cardiovascular mortality amongst men.

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**CONFLICT OF INTEREST**

There are no conflicts of interest to declare.

**AUTHORS’ CONTRIBUTIONS**

TAP and PKM conceived the study. RNL was responsible for record linkage. NJW and KTK are PIs of EPIC-Norfolk Cohort. TAP performed literature search, data analysis and writing the first draft of the paper. TAP and PKM verified the underlying data. All authors contributed in writing of the paper. PKM is the guarantor.

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**TABLES**

**Table 1**. Third health check characteristics and incident outcomes of included participants from the European Prospective Investigation in Cancer (EPIC)-Norfolk (unless otherwise stated), stratified by sex.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Men** | **Women** | **P value** |
|  | 2897 | 3819 |  |
| Age, mean (SD) |  |  |  |
| 1st Health Check  *(1993-1998)* | 57.13 (8.02) | 55.54 (7.81) | **<0.001** |
| 2nd Health Check  *(1998-2000)* | 60.75 (8.07) | 59.15 (7.87) | **<0.001** |
| 3rd Health Check  *(2004-2012)* | 70.07 (8.25) | 68.47 (8.05) | **<0.001** |
| Ethnicity, N (%) |  |  | 0.359 |
| White | 2883 (99.52) | 3810 (99.764) |  |
| Black | 2 (0.07) | 2 (0.05) |  |
| South Asian | 3 (0.10) | 2 (0.05) |  |
| Other | 9 (0.31) | 5 (0.13) |  |
| Weight (kg), mean (SD) | 81.19 (12.04) | 68.08 (12.44) | **<0.001** |
| Height (cm), mean (SD) | 173.50 (6.58) | 160.54 (6.18) | **<0.001** |
| Body Mass Index (kg/m2),  mean (SD) | 26.95 (3.58) | 26.41 (4.56) | **<0.001** |
| Systolic Blood Pressure  (mmHg), mean (SD) |  |  |  |
| 1st Health Check | 134.70 (16.28) | 129.42 (16.98) | **<0.001** |
| 2nd Health Check | 134.66 (16.57) | 129.66 (17.35) | **<0.001** |
| 3rd Health Check | 136.62 (15.39) | 135.94 (17.15) | 0.096 |
| Diastolic Blood Pressure  (mmHg), mean (SD) |  |  |  |
| 1st Health Check | 83.44 (10.57) | 79.12 (10.38) | **<0.001** |
| 2nd Health Check | 83.35 (10.70) | 78.92 (10.55) | **<0.001** |
| 3rd Health Check | 79.40 (9.59) | 77.16 (8.98) | **<0.001** |
| Estimated Glomerular Filtration Rate\* (mL/min/1.73 m2), mean (SD) | 73.17 (17.40) | 72.44 (20.93) | 0.206 |
| Creatinine (mmol/L), mean (SD) | 93.24 (20.86) | 73.29 (16.56) | **<0.001** |
| *Missing*, N (%) | 872 (30.10) | 1184 (31.00) | 0.427 |
| HbA1c (%), mean (SD) | 5.84 (0.67) | 5.80 (0.56) | **0.010** |
| *Missing*, N (%) | 206 (7.11) | 331 (8.67) | **0.020** |
| LDL cholesterol (mmol/L),  mean (SD) | 2.91 (0.97) | 3.36 (0.97) | **<0.001** |
| *Missing*, N (%) | 217 (7.49) | 335 (8.77) | 0.058 |
| Units of alcohol drunk,  median (IQR) | 6.00 (1.00-12.00) | 2.00 (0.00-6.00) | **<0.001** |
| *Missing*, N (%) | 97 (3.35) | 153 (4.01) | 0.158 |
| Educational Level, N (%) |  |  | **<0.001** |
| None | 635 (21.92) | 1115 (29.20) |  |
| O-level | 279 (9.63) | 522 (13.67) |  |
| A-level | 1384 (47.77) | 1581 (41.40) |  |
| University Degree | 599 (20.68) | 601 (15.734) |  |
| Physical activity level, N (%) |  |  | **<0.001** |
| Inactive | 1086 (37.49) | 1381 (36.16) |  |
| Moderately inactive | 731 (25.23) | 1232 (32.26) |  |
| Moderately active | 519 (17.92) | 644 (16.87) |  |
| Active | 520 (17.95) | 511 (13.38) |  |
| *Missing* | 41 (1.42) | 51 (1.34) |  |
| Smoking status, N(%) |  |  | **0.024** |
| Yes | 90 (3.11) | 159 (4.16) |  |
| No | 2762 (95.34) | 3604 (94.37) |  |
| *Missing* | 45 (1.55) | 56 (1.47) |  |
| **Pre-existing co-morbidities** |  |  |  |
| Cardiovascular disease, N (%) | 881 (30.41) | 817 (21.39) | **<0.001** |
| Diabetes mellitus, N (%) | 315 (10.87) | 265 (6.94) | **<0.001** |
| Cancer, N (%) | 178 (6.14) | 369 (9.66) | **<0.001** |
| Asthma, N (%) | 247 (8.53) | 390 (10.21) | **0.020** |
| Chronic Obstructive Pulmonary Disease, N (%) | 215 (7.42) | 363 (9.51) | **0.003** |
| **Drug Therapy** |  |  |  |
| Aspirin, N (%) | 758 (26.16) | 500 (13.09) | **<0.001** |
| Lipid-lowering agents, N (%) | 814 (28.1) | 730 (19.11) | **<0.001** |
| Non-steroidal anti-inflammatory drugs, N (%) | 908 (31.34) | 794 (20.79) | **<0.001** |
| Anti-diabetic drugs, N (%) | 168 (5.80) | 103 (2.70) | **<0.001** |
| Antihypertensive agents, N (%) | 1218 (42.04) | 1375 (36.00) | **<0.001** |
| ACE Inhibitors, N (%) | 616 (21.26) | 486 (12.73) | **<0.001** |
| Beta-Blockers, N (%) | 433 (14.95) | 415 (10.87) | **<0.001** |
| Loop Diuretics, N (%) | 119 (4.11) | 170 (4.45) | 0.492 |
| Other Diuretics, N (%) | 326 (11.25) | 563 (14.74) | **<0.001** |
| Angiotensin Receptor Blockers, N (%) | 174 (6.01) | 264 (6.91) | 0.136 |
| Calcium Channel Blockers, N (%) | 407 (14.05) | 428 (11.21) | **<0.001** |
| **Incident Outcomes†** | | | |
| Mortality, N (%) |  |  |  |
| All-cause | 595 (20.54) | 453 (11.86) | **<0.001** |
| Cardiovascular | 160 (5.52) | 133 (3.48) | **<0.001** |
| Non-cardiovascular | 435 (15.02) | 320 (8.38) | **<0.001** |
| Incident cardiovascular disease‡, N(%) | 653 (29.59) | 656 (19.79) | **<0.001** |

SD – standard deviation, IQR – interquartile range, HbA1c – Glycated Haemoglobin; LDL – low-density lipoprotein, ACE - Angiotensin-converting enzyme;

\*Estimated Glomerular Filtration Rate was calculated using the *Modification of Diet in Renal Disease* formula25.

**†**Incident outcomes measured during the follow-up period from the third health check (2004-2012) until the end of March 2018, resulting in a median follow-up of 9.44 years.

‡Incident cardiovascular disorders reported only amongst patients without pre-existing cardiovascular disease at the third health check (N = 2207 men; 3315 women).

Statistically significant results (*P* < 0.05) are highlighted in **bold**.

**FIGURES**

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**Figure 1**. Participant Population Flowchart.

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**Figure 2.** Blood pressure trajectories amongst men (n = 2897) and women (n = 3819) participants included in the mortality analyses.

SBP trajectories in men: Trajectory 1 – stable optimal SBP, Trajectory 2 – stable normal/high normal SBP, Trajectory 3 – stable grade 1 hypertension, Trajectory 4 – well-controlled grade 1 hypertension, Trajectory 5 – grade 1 🡪 grade 2 hypertension, Trajectory 6 – grade 2 🡪 grade 1 hypertension.

SBP trajectories in women: Trajectory 1 – stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – stable grade 1 hypertension, Trajectory 4 – grade 2 🡪 grade 1 hypertension, Trajectory 5 – grade 1 🡪 grade 2 hypertension

DBP trajectories: Trajectory 1 - low optimal DBP, Trajectory 2 – high optimal DBP, Trajectory 3 – normal/high-normal DBP, Trajectory 4 – grade 1 hypertension 🡪 normal DBP, Trajectory 5 – stable grade 1/grade 2 hypertension

95% confidence intervals are represented as dashed grey lines.

**Figure 3.** Long-term blood pressure patterns amongst men (n = 2207) and women (n = 3315) participants included in the incident cardiovascular disease analyses.

SBP trajectories in men: Trajectory 1 – borderline stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – rising grade 1 hypertension, Trajectory 4 – grade 1 hypertension 🡪 high-normal SBP, Trajectory 5 – grade 2 🡪 grade 1 hypertension.

SBP trajectories in women: Trajectory 1 – stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – high-normal SBP 🡪 grade 1 hypertension, Trajectory 4 – decreasing grade 1 hypertension, Trajectory 5 – grade 1 🡪 grade 2 hypertension.

DBP trajectories: Trajectory 1 - low optimal DBP, Trajectory 2 – high optimal DBP, Trajectory 3 – normal/high-normal DBP, Trajectory 4 – grade 1 hypertension 🡪 normal DBP, Trajectory 5 – stable grade 1/grade 2 hypertension.

95% confidence intervals are represented as dashed grey lines.

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**Figure 4.** Results of Cox regressions assessing the association between blood pressure phenotypes and all-cause mortality.

Model A – Univariable

Model B – Multivariable adjustment for age and ethnicity

Model C – Model B + body mass index, physical activity level, smoking and alcohol consumption

Model D – Model C + pre-existing co-morbidities (cardiovascular disease, diabetes mellitus, cancer, asthma, chronic obstructive pulmonary disease) and serum low-density lipoprotein cholesterol

Model E – Model D + antihypertensive treatment

SBP trajectories in men: Trajectory 1 – borderline stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – rising grade 1 hypertension, Trajectory 4 – grade 1 hypertension 🡪 high-normal SBP, Trajectory 5 – grade 2 🡪 grade 1 hypertension.

SBP trajectories in women: Trajectory 1 – stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – high-normal SBP 🡪 grade 1 hypertension, Trajectory 4 – decreasing grade 1 hypertension, Trajectory 5 – grade 1 🡪 grade 2 hypertension.

DBP trajectories: Trajectory 1 - low optimal DBP, Trajectory 2 – high optimal DBP, Trajectory 3 – normal/high-normal DBP, Trajectory 4 – grade 1 hypertension 🡪 normal DBP, Trajectory 5 – stable grade 1/grade 2 hypertension.

Median (interquartile range) follow-up was 9.4 (8.0-10.9) years amongst both men and women, respectively.

SBP – systolic blood pressure; DBP – diastolic blood pressure

**Chart

Description automatically generated**

**Figure 5.** Results of Cox regressions assessing the association between blood pressure phenotypes and incident cardiovascular disease amongst participants without prevalent cardiovascular disease at the third health check of the EPIC-Norfolk study.

Model A – Univariable

Model B – Multivariable adjustment for age and ethnicity

Model C – Model B + body mass index, physical activity level, smoking and alcohol consumption

Model D – Model C + pre-existing co-morbidities (cardiovascular disease, diabetes mellitus, cancer, asthma, chronic obstructive pulmonary disease) and serum low-density lipoprotein cholesterol

Model E – Model D + antihypertensive treatment

SBP trajectories in men: Trajectory 1 – borderline stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – rising grade 1 hypertension, Trajectory 4 – grade 1 hypertension 🡪 high-normal SBP, Trajectory 5 – grade 2 🡪 grade 1 hypertension.

SBP trajectories in women: Trajectory 1 – stable optimal SBP, Trajectory 2 – rising normal/high normal SBP, Trajectory 3 – high-normal SBP 🡪 grade 1 hypertension, Trajectory 4 – decreasing grade 1 hypertension, Trajectory 5 – grade 1 🡪 grade 2 hypertension.

DBP trajectories: Trajectory 1 - low optimal DBP, Trajectory 2 – high optimal DBP, Trajectory 3 – normal/high-normal DBP, Trajectory 4 – grade 1 hypertension 🡪 normal DBP, Trajectory 5 – stable grade 1/grade 2 hypertension.

Median (interquartile range) follow-up was 9.4 (8.0-10.9) and 9.4 (7.8-11.0) years amongst men and women, respectively.

SBP – systolic blood pressure; DBP – diastolic blood pressure