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Long-term blood pressure trajectories and incident atrial fibrillation in women and men: the Tromsø Study

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Aims To explore sex-specific associations between long-term individual blood pressure (BP) patterns and risk of incident atrial fibrillation (AF) in the general population.

Methods and results Blood pressure was measured in 8376 women and 7670 men who attended at least two of the three population-based Tromsø Study surveys conducted in 1986–87, 1994–95, and 2001. Participants were followed for incident AF throughout 2013. Latent mixed modelling was used to identify long-term trajectories of systolic BP and hypertension. Cox regression was used to estimate associations between the identified trajectories and incident AF. Elevated systolic BP throughout the exposure period (1986–2001) independently and differentially increased risk of AF in women and men. In women, having elevated systolic BP trajectories doubled AF risk compared to having persistently low levels, irrespective of whether systolic BP increased, decreased, or was persistently high over time, with hazard ratios of 1.88 (95% confidence interval 1.37–2.58), 2.32 (1.61–3.35), and 1.94 (1.28–2.94), respectively. In men, those with elevated systolic BP that continued to increase over time had a 50% increased AF risk: 1.51 (1.09–2.10). When compared to those persistently normotensive, women developing hypertension during the exposure period, and women and men with hypertension throughout the exposure period had 1.40 (1.06–1.86), 2.75 (1.99–3.80), and 1.36 (1.10–1.68) times increased risk of AF, respectively.

Conclusion Long-term BP and hypertension trajectories were associated with increased incidence of AF in both women and men, but the associations were stronger in women.

Keywords Blood pressure • Hypertension • Atrial fibrillation • Epidemiology • Sex • Trajectories

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting about 9.5 million people in the European Society of Cardiology member countries, and causing a significant impairment in quality of life, increased risk of myocardial infarction, stroke, heart failure, and premature death.[1–3] The prevalence of AF is increasing worldwide and anticipated to grow into an epidemic in the coming decades as the world's population ages.[2,4] Hypertension plays a crucial role in AF development[5–8]

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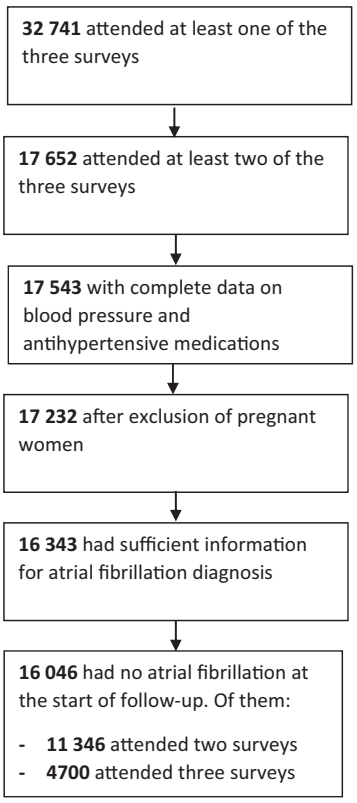

Figure 1 Flowchart of participants. The Tromsø Study 1986–2001.

being the most important population-attributable risk factor responsible for 14% of all AF cases[8]. Hypertension is associated with a 1.8-fold increased risk of incident AF and promotes progression from paroxysmal to permanent AF.[9] However, since hypertension is a modifiable AF risk factor, exploring longitudinal trends in blood pressure (BP) is important. First, long-term patterns of BP may reflect cumulative exposure to increased AF risk and therefore provide additional prognostic information for AF development. Secondly, it can potentially add to the existing knowledge[10,11] on whether decrease in BP over time and hypertension management could reverse the risk of AF development.

The Framingham Heart Study demonstrated that both persistently elevated systolic BP and longer antihypertensive treatment were associated with increased risk of incident AF.[12] However, the associations between BP and AF risk may differ in women and men as there are substantial sex differences in AF epidemiology as well as in incidence and types of hypertension with aging.[13–16] Prevalence of AF is almost twice as high in men as in women,[14] while risk of adverse outcomes after AF onset is higher in women.[13,15] In subjects over 60 years of age, hypertension, in particular isolated systolic hypertension, is more prevalent in women.[16] Furthermore, women with AF are older and have a more favourable risk factor profile including lower body mass index, lower proportion of diabetes, myocardial infarction, and smoking compared to their male counterparts, except for higher BP.[14]

In the present study, we aimed to explore sex-specific long-term individual patterns of systolic BP, diastolic BP, hypertension, and use of antihypertensive medications and their associations with the risk of incident AF using data from the population-based longitudinal Tromsø Study.

Methods

Study design and participants

The Tromsø Study is a large population-based longitudinal cohort study that has been described in detail previously.[17] In short, seven consecutive surveys of the same general design were conducted in the municipality of Tromsø, Northern Norway between 1974 and 2016. Both random samples and total birth cohorts of women and men of a wide age range were invited to participate, and many of the participants attended several surveys. The present study included participants who attended at least two of the Tromsø 3 (1986–87), Tromsø 4 (1994–95), and Tromsø 5 (2001) surveys, had complete data on BP and antihypertensive treatment, were not pregnant at examinations, had sufficient information for AF validation, and were free of AF at the time of study examinations (*Figure 1*). After the last survey attended and until 31st December 2013, 8376 women and 7670 men were followed up for incident AF. The study flow and number of participants attended different surveys is depicted in *Figure 2*.

The Tromsø Study has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments and approved by the Norwegian Data Protection Authority (14/01463-8/CGN) and by the Regional Committee for Medical and Health Research Ethics, (2009/2536/REC North). From the Tromsø 4 survey and onwards, participants provided written informed consent, and living participants from prior surveys were provided the opportunity to withdraw from the study.

Measurement of blood pressure and other cardiovascular risk factors

Information on each participant at each survey was collected by questionnaires, physical examinations, and blood samples, following a standardized protocol. Systolic and diastolic BP, and heart rate were measured using Dinamap Vital Signs Monitor 1846 (Critikon Inc., Tampa, FL, USA) which is a non-invasive, microprocessor-controlled device, and uses the oscillometric method. The proper cuff size was selected based on the circumference of the upper right arm in the individual participant. After 2 min seated rest with the cuff on, three measurements of systolic BP, diastolic BP, and heart rate were recorded with 1-min intervals. The mean of the last two measurements was taken as the clinic BP and used in the analyses. Hypertension was defined as systolic BP $\geq$ 140 mmHg, and/or diastolic BP $\geq$ 90 mmHg, and/or current use of antihypertensive medications.

Information on current use of antihypertensive medications (yes/no), leisure time physical activity level (inactive/low activity/moderate activity/high activity), current smoking (yes/no), current pregnancy (yes/no), coffee consumption (cups per day), and comorbidities (diabetes, angina pectoris, history of myocardial infarction, and history of stroke; yes/no) was obtained from the questionnaires. Weight and height were measured with light clothing on, but without shoes, and were used to calculate body mass index as weight (kg) divided by squared height (m). Non-fasting blood samples were collected for analyses of serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides. Total cholesterol and triglycerides were analysed by enzymatic colorimetric methods with commercially available kits (CHOD-PAP for cholesterol, GPO-PAP for triglycerides; Boehringer-Mannheim). High density lipoprotein-cholesterol was measured after the precipitation of

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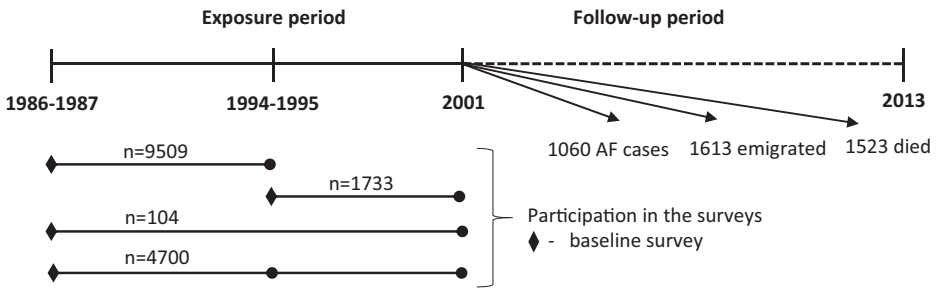

Figure 2 Description of the exposure and the follow-up periods of the study. The Tromsø Study 1986–2013.

lower-density lipoprotein with heparin and manganese chloride. Echocardiography was performed on a subgroup of the participants in the Tromsø 4 and 5 surveys.[18]

Documentation of incident atrial fibrillation

Using the unique Norwegian national 11-digit identification number, all participants were linked to the diagnosis registry at the University Hospital of North Norway which is the only hospital in the area and includes diagnoses from the out- and inpatient clinic, and to the Norwegian Cause of Death Registry.[19] Possible cases of incident AF were identified through a broad search using the International Classification of Diseases, 9th Revision (ICD-9) codes 410–414, 427, 428, 430–438, and 798–799 and the ICD-10 codes I20–I25, I46–I48, I50, I60–I69, R96, R98, and R99. Following a detailed protocol and based on data from hospital and out-of-hospital records, an independent endpoint committee validated all possible events that were identified through the broad search. Atrial fibrillation was considered as confirmed when documented by electrocardiogram. We excluded 899 participants in whom AF was suspected (terms such as arrhythmia, tachycardia, palpitations, atrial flutter, and/or AF were mentioned in their medical records), but no electrocardiographic documentation for AF could be found (*Figure 1*). Transient AF occurring within 28 days after acute myocardial infarction or in relation to cardiac surgery, as well as AF occurring during the last 7 days of life were not classified as AF cases. Participants who died or emigrated from Tromsø during the follow-up period were identified through the National Registry.

Statistical analyses

All statistical analyses were sex-specific and performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Sex-specific means (standard deviations) and numbers (percentages) were calculated to describe baseline characteristics of the study population, measured at the first attended survey, in 1986–87 or 1994–95. Mean values (except for age) and percentages were adjusted for age using linear or logistic regression, respectively. Mean values for left atrial diameter/body surface area (cm/m^2), left ventricular mass/height$^{2.7}$ ($g/m^{2.7}$), left ventricular mass/height$^{1.7}$ ($g/m^{1.7}$), and left ventricular ejection fraction (%), and proportions of left ventricular hypertrophy (left ventricular mass/height$^{2.7}$ > 47 $g/m^{2.7}$ in women and > 50 $g/m^{2.7}$ in men) were adjusted for year of birth using linear mixed models or generalised estimating equations, respectively.[5] Trajectory analysis (SAS Proc Traj) was used to determine clusters of participants who followed similar long-term patterns (trajectories) of systolic BP, diastolic BP, hypertension, and use of antihypertensive medications over the exposure period (from 1986 to 2001). Trajectory analysis, or latent class models analysis, is based on a semiparametric group-based modelling strategy and fits longitudinal data to a number of discrete latent trajectories via maximum likelihood.[20] The number of trajectory groups was limited to five for BP variables, and to three for hypertension and use of antihypertensive medications. We first tested models with different numbers of trajectory groups, and then models with different functional forms of trajectory groups (only intercept, linear term, quadratic term). The Bayesian information criterion was used to assess the model fit.

Cox regression analysis was used to estimate associations between belonging to a certain trajectory group of systolic BP, diastolic BP, hypertension, and use of antihypertensive medications and the risk of incident AF. For each of the participants the follow-up period started at a time of the last attended survey (1994–95 or 2001) and ended the date of first documented AF, the date of censoring due to migration or death, or the end of the follow-up period at 31st December 2013, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the trajectory groups with the most favourable trajectory (having the lowest BP, being free of hypertension, or not using antihypertensive medications throughout the exposure period) used as a reference. Hazard ratios were first adjusted for baseline age alone, and then for baseline age, resting heart rate, total cholesterol, HDL cholesterol, triglycerides, body mass index, leisure time physical activity level, smoking status, and number of the Tromsø Study surveys attended. Sensitivity analysis was conducted with adding to the models other potential confounders/mediating factors for the association between the trajectory groups and AF (coffee consumption, diabetes, angina, history of myocardial infarction, and stroke).

Results

At baseline, systolic BP, diastolic BP, and prevalence of hypertension were higher in men, while the proportion of participants using antihypertensive medications was higher in women (Table 1). Women had lower body mass index, more favourable blood lipid profile, and reported lower physically activity level compared to men. The proportion of smokers did not differ between women and men and exceeded 40%. During a median follow-up of 12.9 years, 441 (5.3%) women and 619 (8.1%) of men developed AF (*Figure 2*).

Five common long-term systolic BP trajectories were identified both in women and men (*Figure 3*, Supplementary material online, *Figure S1*). Based on BP level at the beginning of the exposure period the trajectory groups were numbered from the lowest (Group 1) to the highest (Group 5). In women, mean systolic BP in Group 1 was within the normotensive range throughout the exposure period. Group 2 was normotensive in the beginning, but then mean systolic BP increased and crossed the cut-off value of 140 mmHg by the end of the exposure period. Groups 3, 4, and 5 were hypertensive throughout, though in

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Table 1 Baseline sample characteristics of women and men. The Tromsø Study 1986–95.

Characteristics	Women (n = 8376)	Men (n = 7670)	P-value
Age (years)	40.2 (12.0)	40.7 (13.0)	0.015
Systolic blood pressure (mmHg)	125.6 (18.0)	133.2 (14.5)	<0.001
Diastolic blood pressure (mmHg)	75.4 (10.8)	78.4 (10.8)	<0.001
Resting heart rate (b.p.m.)	77.3 (12.4)	72.2 (12.6)	<0.001
Hypertension[a] (%)	1693 (15.7)	2353 (27.8)	<0.001
Use of antihypertensive medications (%)	310 (1.6)	230 (1.5)	<0.001
Body mass index (kg/m^2)	23.5 (3.7)	24.7 (3.0)	<0.001
Serum total cholesterol (mmol/L)	5.79 (1.33)	5.90 (1.24)	<0.001
Serum HDL cholesterol (mmol/L)	1.64 (0.38)	1.36 (0.34)	<0.001
Serum triglycerides (mmol/L)	1.18 (0.69)	1.63 (1.01)	<0.001
Leisure time physical activity level (%)			
Inactive	1816 (21.8)	1577 (20.6)	0.062
Low activity	5280 (63.2)	3783 (49.4)	<0.001
Moderate activity	1154 (13.5)	1965 (25.4)	<0.001
High activity	104 (1.1)	336 (3.9)	<0.001
Smoking (%)	3613 (43.3)	3347 (43.6)	0.715

Values are mean (standard deviation) or number (%); the means (except age) and percentages are adjusted for age between sexes using linear or logistic regression, respectively. Due to missing observations, numbers (n) for the variables may be marginally less.
b.p.m., beats per minute; HDL, high-density lipoprotein; mmHg, millimetres of mercury; mmol/L, millimoles per litre.
[a]Hypertension was defined as systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, and/or current use of antihypertensive medications.

Group 3 mean systolic BP increased, in Group 4 it decreased, and in Group 5 it remained high throughout the exposure period. In men, Groups 1 and 2 were normotensive throughout the exposure period, although in Group 2 mean systolic BP values were slightly higher. Groups 3, 4, and 5 were hypertensive. In Group 3 mean systolic BP increased slightly, in Group 4 mean systolic BP increased substantially, and in Group 5 mean systolic BP decreased substantially during the exposure period. In both age-adjusted and multivariable-adjusted models, the risk of incident AF was approximately doubled in Groups 3, 4, and 5 in women, and approximately 1.5 times increased in trajectory Groups 3 and 4 in men, as compared to Group 1 (*Table 2*).

Five diastolic BP trajectory groups were identified in women and men (*Figure 4*, Supplementary material online, *Figure S2*). In both women and men, mean diastolic BP in Groups 1 and 2 remained within the normotensive range, and in Group 3 mean diastolic BP was around 90 mmHg throughout the exposure period. Groups 4 and 5 had elevated mean diastolic BP throughout the exposure period, although mean diastolic BP in Group 4 increased and in Group 5 decreased over time. Displaying diastolic BP patterns classified as Groups 3, 4, or 5 in women and classified as Groups 4 or 5 in men progressively increased risk of developing AF when compared to Group 1 in both age- and multivariable-adjusted analyses (*Table 2*).

For presence or absence of hypertension at each of the three surveys, three trajectory groups were identified in both sexes (*Figure 5*): normotensive participants throughout (Group 1), participants who were normotensive at the beginning, but developed hypertension during the exposure period (Group 2), and participants who had hypertension throughout (Group 3). In women, the risk of AF was 1.40 (95% CI 1.06–1.86) and 2.75 (95% CI 1.99–3.80) times increased in Group 2 and Group 3, respectively, compared to Group 1. In men, only being hypertensive throughout the exposure period increased risk of future AF with multivariable-adjusted HR of 1.36, 95% CI 1.10–1.68 (*Table 2*). Three trajectory groups were identified for use of antihypertensive medications at each of the surveys during the exposure period (*Figure 6*). Participants who started to use antihypertensive medications during the exposure period (Group 2) or who used antihypertensive medications throughout (Group 3) had gradually increased risk of developing AF in both women and men (*Table 2*).

Over the exposure period, left atrial diameter, left ventricular mass, and proportion of left ventricular hypertrophy increased gradually from the lowest to the highest systolic BP trajectory group in both sexes (Supplementary material online, *Table S1*). Left ventricular ejection fraction remained stable over time in all systolic BP trajectory groups except Groups 1 and 4 in women where it increased. Proportion of women and men using antihypertensive medications increased during the exposure period in all systolic BP, diastolic BP, and hypertension trajectory groups, except for those without hypertension throughout (Supplementary material online, *Table S2*). In both women and men who reported use of antihypertensive medications, BP was not properly controlled: mean systolic and diastolic BP values in antihypertensive medication trajectory Groups 2 and 3 were often above the cut-off values of 140 mmHg and 90 mmHg, respectively (Supplementary material online, *Table S3*). Interaction terms between sex and the trajectory groups were statistically significant for systolic BP (P < 0.001), hypertension (P < 0.001), and use of antihypertensive medications (P = 0.008), but not for diastolic BP (P = 0.320).

Discussion

Hypertension is an important modifiable risk factor for AF, and both daytime BP load and long-term BP changes have been reported to be associated with AF risk in the general population.[12,21–23] The present findings add to this by demonstrating differential associations between long-term patterns/trajectories of systolic BP, diastolic BP, hypertension, and use of antihypertensive medications and AF risk in

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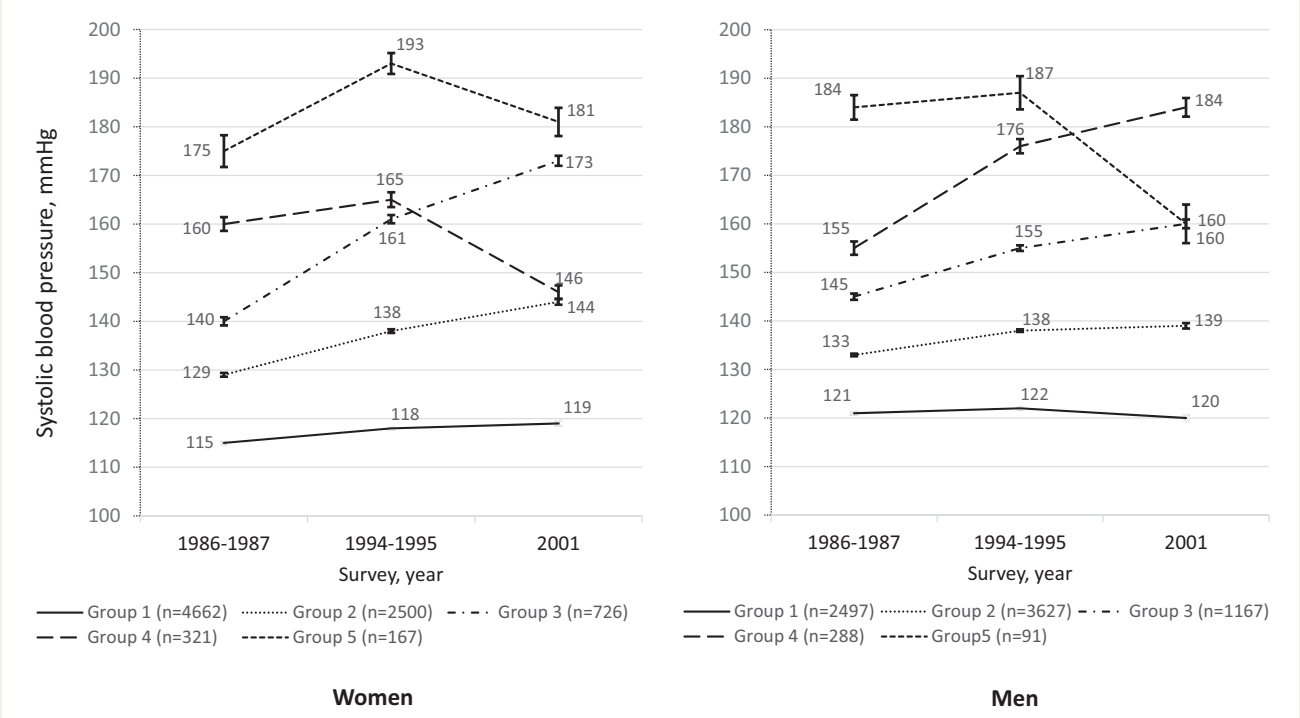

Figure 3 Long-term trajectory groups for systolic blood pressure in women and men. The Tromsø Study 1986–2001. Sex-specific means and 95% confidence intervals of systolic blood pressure (mmHg) presented according the three surveys and the five systolic blood pressure trajectory groups.

women and men. Although both women and men with long-term elevated levels of systolic and diastolic BP had increased risk of future AF development, the associations were stronger in women. Moreover, shorter exposure to hypertension resulted in higher AF risk in women compared to men.

Our findings add new information to the existing knowledge base about risk factors and prevention of AF as they demonstrate that effects of elevated BP levels and hypertension may take years to appear and that analysing long-term exposure to risk factors can improve the prediction of AF compared to single time point measurements. For example, in our study women in the systolic BP trajectory Groups 2 (BP means increased from 129 mmHg to 144 mmHg) and 4 (BP means decreased from 160 mmHg to 146 mmHg) had similar, slightly elevated systolic BP by the end of the exposure period. Therefore, these women would have the same systolic BP if measured only once at the end of the exposure period (144 mmHg in Group 2 and 146 mmHg in Group 4). However, Group 2 was normotensive during most of the exposure period, while Group 4 had substantially elevated systolic BP levels throughout. As demonstrated, these groups were at different risk of incident AF: adjusted HRs were 1.12 (0.84–1.48) for Group 2 and 2.32 (1.61–3.35) for Group 4. In comparison, our study demonstrated that men with substantially elevated systolic BP in whom BP decreased somewhat over the exposure period (Group 5) were not at increased AF risk, probably reflecting the low number of men in this group. The association between hypertension and an increased risk of AF has been demonstrated previously.[6–9] Not only elevated BP but also upper normal BP levels have been shown to increase future risk of AF.[24,25] Moreover, the degree to which BP in hypertensive patients is controlled provides important prognostic information in respect to future AF development.[11,26] However, there is limited evidence on how long-term changes in BP affect AF risk in men and women in the general population. The Malmö Preventive Project cohort demonstrated that annual increase in both systolic and diastolic BP in men adjusted for baseline BP increased the risk of incident AF by 4% per mmHg and 6% per mmHg, respectively.[22] However, BP changes were calculated as differences between two BP measurements separated by an average of 6 years, which does not describe actual individual patterns of BP changes over time.

The Framingham Heart Study explored 16-year trajectories of BP, hypertension, and antihypertensive treatment and their associations with the risk of AF in 4351 participants.[12] The risk of AF was doubled in participants who had initially elevated levels of systolic BP and then either decreased or increased systolic BP. The present analysis adds to this by demonstrating sex-differences in the systolic BP trajectories and the stronger associations with incident AF in women than in men. In contrast to our findings, diastolic BP trajectories in the Framingham Heart Study were not an independent predictor of AF.[12] However, the Framingham Heart Study cohort was older than ours, and the authors mentioned that their findings might be limited given that four of the five diastolic BP trajectory groups had diastolic BP lower than 90 mmHg throughout the trajectory phase. Indeed, our findings for men demonstrate that only participants with elevated diastolic BP at the start or throughout the exposure period had an

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Table 2 Sex-specific hazard ratios (95% confidence intervals) of incident atrial fibrillation by systolic blood pressure, diastolic blood pressure, hypertension, and antihypertensive medications use trajectory groups. The Tromsø Study 1986–2013.

Trajectory groups	Women ($n = 8376$)			Men ($n = 7670$)		
	Cases/Total	HR (95% CI)[e]	HR (95% CI)[f]	Cases/Total	HR (95% CI)[e]	HR (95% CI)[f]
Systolic blood pressure[a]						
1	96/4662	1.00	1.00	132/2497	1.00	1.00
2	139/2500	1.26 (0.96–1.66)	1.12 (0.84–1.48)	236/3627	0.98 (0.79–1.22)	0.93 (0.74–1.15)
3	104/726	2.03 (1.49–2.77)	1.88 (1.37–2.58)	179/1167	1.54 (1.22–1.95)	1.41 (1.11–1.80)
4	60/321	2.76 (1.95–3.92)	2.32 (1.61–3.35)	56/288	1.60 (1.16–2.22)	1.51 (1.09–2.10)
5	42/167	2.21 (1.48–3.31)	1.94 (1.28–2.94)	16/91	1.12 (0.66–1.90)	1.10 (0.64–1.89)
Diastolic blood pressure[b]						
1	53/1970	1.00	1.00	73/1520	1.00	1.00
2	153/4070	1.07 (0.78–1.46)	0.99 (0.72–1.37)	282/4184	0.90 (0.69–1.16)	0.86 (0.66–1.12)
3	157/1871	1.60 (1.17–2.20)	1.50 (1.08–2.08)	191/1605	1.29 (0.98–1.70)	1.20 (0.91–1.60)
4	35/195	2.12 (1.37–3.27)	1.98 (1.27–3.08)	44/231	1.75 (1.20–2.56)	1.69 (1.14–2.51)
5	43/270	2.16 (1.44–3.24)	1.87 (1.21–2.88)	29/130	2.35 (1.52–3.62)	2.14 (1.36–3.36)
Hypertension[c]						
1	98/5240	1.00	1.00	188/3884	1.00	1.00
2	256/2322	1.51 (1.15–1.99)	1.40 (1.06–1.86)	171/1986	1.19 (0.96–1.47)	1.10 (0.89–1.36)
3	87/814	3.18 (2.38–4.25)	2.75 (1.99–3.80)	260/1800	1.46 (1.19–1.80)	1.36 (1.10–1.68)
Antihypertensive medications use[d]						
1	257/7451	1.00	1.00	439/6881	1.00	1.00
2	80/477	1.98 (1.52–2.57)	1.75 (1.34–2.28)	83/348	1.79 (1.41–2.29)	1.62 (1.26–2.07)
3	104/448	2.79 (2.19–3.54)	2.44 (1.89–3.16)	97/441	2.03 (1.62–2.54)	1.83 (1.45–2.30)

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio.
[a]Systolic blood pressure trajectory groups are presented in *Figure 3*.
[b]Diastolic blood pressure trajectory groups are presented in *Figure 4*.
[c]Hypertension trajectory groups are presented in *Figure 5*.
[d]Antihypertensive medications use trajectory groups are presented on *Figure 6*.
[e]HR (95% CI) are adjusted for age at baseline.
[f]HR (95% CI) are adjusted for baseline age, resting heart rate, body mass index, total cholesterol, HDL cholesterol, triglycerides, leisure time physical activity level, smoking, and number of the Tromsø Study surveys attended.

independently increased risk of AF. In women, these associations were stronger, and even women with borderline normal diastolic BP values over time had increased risk of AF, pointing to the importance of uncontrolled BP for heart disease in women. We also found stronger association between hypertension trajectories and risk of AF in women than in men.

The Atherosclerosis Risk in Communities (ARIC) Study was limited to systolic BP and hypertension and demonstrated different long-term patterns of the parameters in men and women combined.[21] Systolic BP trajectories with borderline, high long-term and very high long-term BP values progressively increased risk of AF when compared to the very low stable trajectory.

Previous studies have demonstrated that chronic exposure to high BP levels leads to left ventricular remodelling and impaired ventricular filling, left atrial enlargement, atherosclerosis development and arterial stiffness.[5,9,27–31] Dilatation of the left atria predisposes to AF development, which may be reduced by treatment with angiotensin receptor blocker.[31,32] Structural and functional changes in the heart may therefore mediate the effect of long-term trajectories of BP and hypertension on the risk of AF. It has been also demonstrated that hypertensive women compared to men are more at risk for development of left ventricular hypertrophy and atrial dilatation, both strong AF risk factors, and regression of left ventricular hypertrophy is more difficult to obtain in women despite antihypertensive treatment.[33,34] Moreover, the general lower cardiovascular risk in women was offset in hypertension with left ventricular hypertrophy.[30] It may therefore explain the identified sex differences and stronger associations between BP trajectories and incident AF in women demonstrated by the present results.

Our findings have implications for both clinical practice and public health actions. Compared to single BP measurements, long-term patterns in BP levels assess cumulative exposure and therefore provide more information for AF risk stratification. Moreover, taking into account the cumulative effect of the exposure to elevated BP, early detection and long-term management of hypertension are important to prevent structural changes in the myocardium and thus contribute to the prevention of AF. Although we found progressively increased AF risk in those using antihypertensive medications over a longer period, it could be just an approximation of hypertension status. All participants who reported use of antihypertensive medications were included irrespective of whether treatment was effective or not, and whether BP was controlled or not. Although at all ages, the

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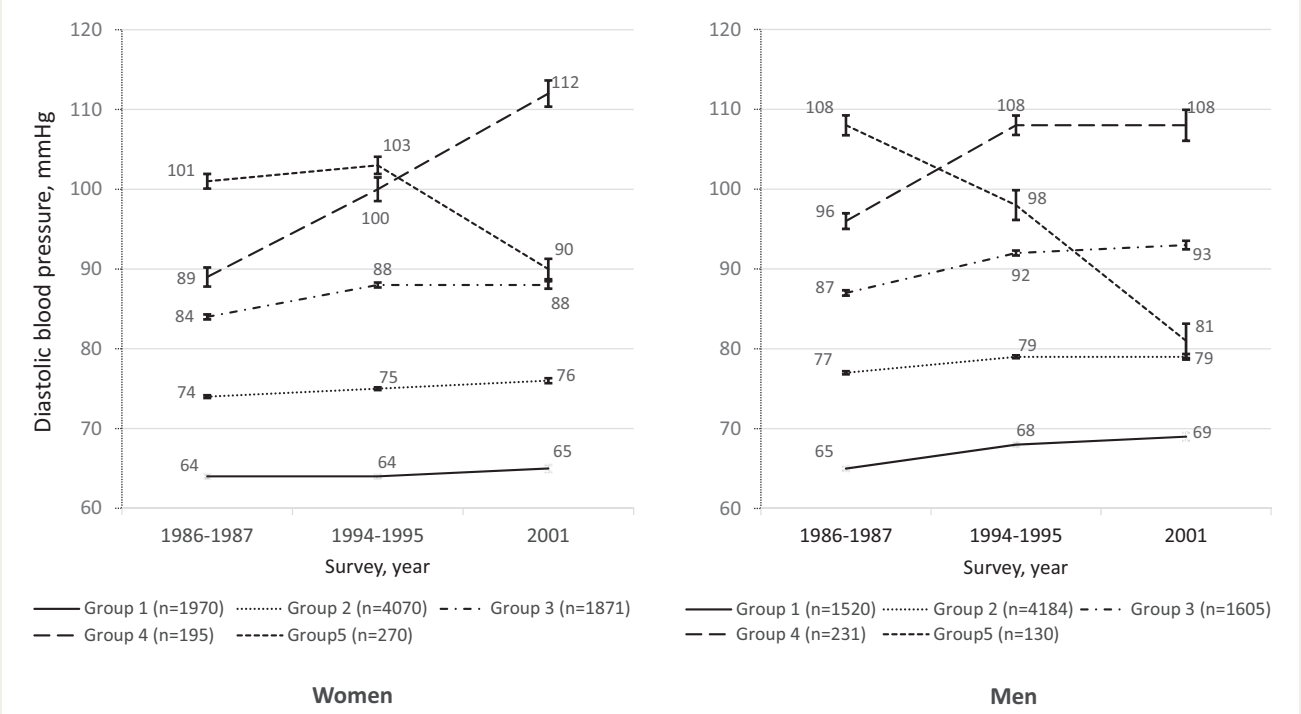

Figure 4 Long-term trajectory groups for diastolic blood pressure in women and men. The Tromsø Study 1986–2001. Sex-specific means and 95% confidence intervals of diastolic blood pressure (mmHg) presented according the three surveys and the five diastolic blood pressure trajectory groups.

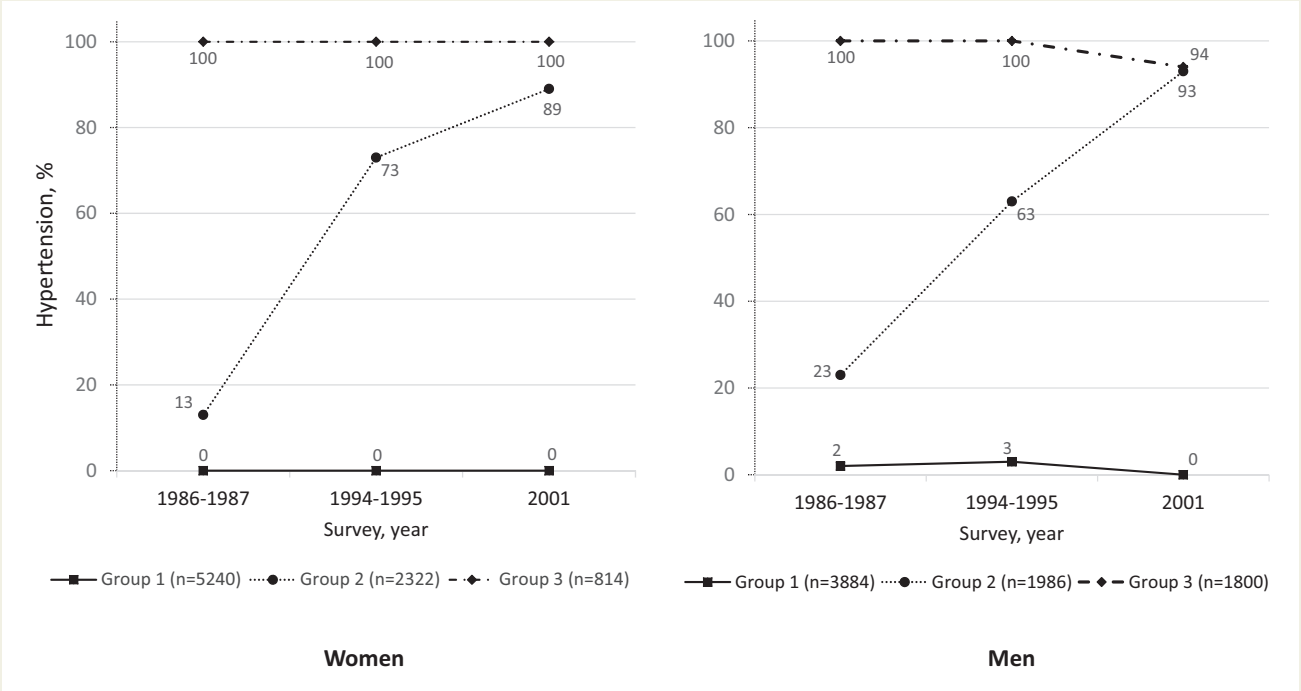

Figure 5 Long-term trajectory groups for hypertension in women and men. The Tromsø Study 1986–2001. Sex-specific proportions of those with hypertension presented according the three surveys and the three hypertension trajectory groups.

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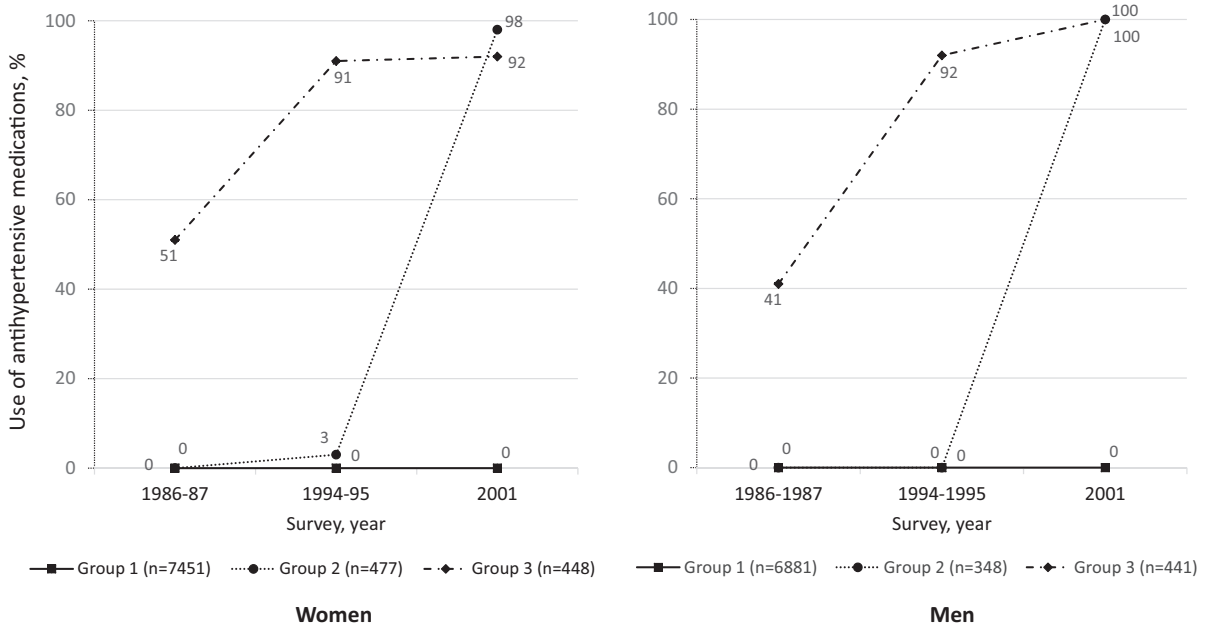

Figure 6 Long-term trajectory groups for use of antihypertensive medications in women and men. The Tromsø Study 1986–2001. Sex-specific proportions of those using antihypertensive medications presented according the three surveys and the three antihypertensive medication trajectory groups.

prevalence and incidence of AF is higher in men than in women,[4] early actions on BP management and control seem to be especially important for women as we found stronger associations between long-term BP trajectories and AF in women than in men.

This large population-based longitudinal study with several observations per subject and a long follow-up provides an unique opportunity to explore associations between long-term individual patterns in BP, hypertension, use of antihypertensive medications, and the risk of incident AF separately in women and men. Blood pressure readings throughout the surveys were obtained with conventional office BP measurement conducted by trained personal using calibrated automated sphygmomanometers and following the same protocol. All AF events were confirmed on electrocardiogram and validated. However, several limitations require comments. First, although conventional office BP measurement has been considered the standard measure of an individual's BP status and the basis for most epidemiological studies, other BP measurement techniques, such as out-of-office BP monitoring, provide readings that are more representative for daily life and enable diagnosis of white-coat and masked hypertension.[5] However, there is no evidence suggesting that using other BP measurement techniques would change profiles/shapes of the BP trajectories. Of note, mean office BP recorded in research settings has been shown to be 10/7 mmHg lower than office BP measured in routine clinical practice.[35] This difference must be considered when it comes to the clinical implications of our findings. Second, over the 16 years of follow-up BP was measured at three time points. Although four or five BP measurements would allow estimating more complex cubic or quadratic trends providing more detailed long-term BP patterns, three time points has been reported to be enough for proper estimation of developmental trajectories.[36] Besides, numerous repeated measurements usually result in greater attrition rates that weaken statistical precision and potentially introduce bias. Third, many of the study participants attended only two of the three surveys limiting the possibility to check whether altering the trajectories would alter outcomes, potentially reducing the robustness of the trajectory analyses, and introducing some between-group bias. However, the associations between trajectory groups and AF risk were adjusted for the number of attended surveys per subject. Fourth, we lacked detailed information on antihypertensive treatment, such as type of drugs or doses. Moreover, information on use of antihypertensive medications as well as on physical activity and smoking was self-reported which might introduce information bias. However, in a cohort study such as ours, this bias would result in non-differential misclassification.

Fifth, sample attrition that is a methodological problem in longitudinal studies might result in a study population that is not entirely representative of the general population. Participants with adverse cardiovascular profile, including hypertension, might have died before the next survey, therefore our study sample may over-represent those who live longer and have healthier cardiovascular profiles. This may lead to underestimation of the associations between BP trajectories and AF risk. Additionally, in spite of thorough ascertainment, adjudication and validation of AF cases it is possible that there were participants with undiagnosed AF. Atrial fibrillation may be silent and/or paroxysmal, and such subjects may fail to get their arrhythmia documented on an electrocardiogram.[37] Moreover, only participants who had contact with the hospital were considered in the AF ascertainment process, and some AF patients might have been taken care of by their general practitioner without hospital contact. The associations were not adjusted for other potential confounders/mediators

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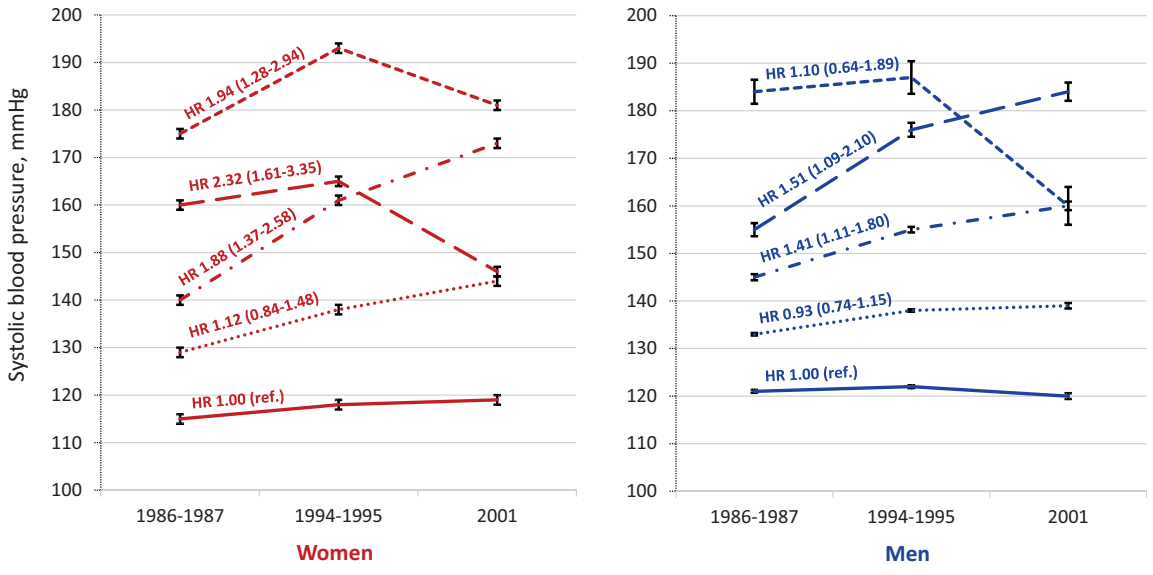

Take home figure Independent associations between long-term systolic blood pressure patterns and risk of atrial fibrillation in women and men. The Tromsø Study 1986–2013. Sex-specific means and 95% confidence intervals of systolic blood pressure (mmHg) presented according to the three surveys and the five systolic blood pressure trajectory groups. Systolic blood pressure trajectory groups were determined using latent class models (SAS Proc Traj). Relative risk of incident atrial fibrillation development during a median follow-up of 12.9 years is presented for each of the trajectory groups using sex-specific multivariable adjusted hazard ratios (HRs) with 95% confidence intervals; group 1 was used as the reference.

such as echocardiographic parameters, markers of inflammation, glucose intolerance, depression, or caffeine intake. Echocardiography was only performed in 15.4% of the participants, and we therefore did not have statistical power to include left atrial diameter and left ventricular hypertrophy in the models. Moreover, recent studies in stroke survivors suggest that left atrial strain may add independent and incremental value to the current risk-prediction models.[38,39] As our study does not include data on precise left atrial volume and strain, it remains to be evaluated to what extent BP trajectories still add information on top of these contemporary techniques for predicting AF. However, in the real world context, most subjects with hypertension are not referred to echocardiography. Thus, the present findings are highly relevant to clinical practice. Finally, caffeine has been shown to elevate BP and independently predict risk of AF.[40] However, additional adjustment for coffee consumption, diabetes, angina pectoris, history of myocardial infarction, and history of stroke in a sensitivity analysis had virtually no effect on the results.

Conclusion

This population-based longitudinal study identified sex-specific long-term individual trajectories of systolic BP, diastolic BP, hypertension, and use of antihypertensive medications. The identified long-term trajectories that reflect cumulative exposure to the risk factors were associated with differential risk of incident AF in women and men (*Take home figure*). The associations were stronger in women where long-term elevated systolic BP, and both elevated and borderline normal diastolic BP were associated with increased AF risk. In men, risk of AF was increased to a smaller extent and only in the elevated BP trajectories. Moreover, shorter exposure to hypertension resulted in increased AF risk in women. Our findings provide additional knowledge for sex-specific AF risk stratification and primary prevention with clinical and public health relevance.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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