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FULL RESEARCH PAPER
Arrhythmias

Sex-specific time trends in incident atrial fibrillation and the contribution of risk factors: the Tromsø Study 1994–2016

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Aims To explore sex-specific time trends in atrial fibrillation (AF) incidence and to estimate the impact of changes in risk factor levels using individual participant-level data from the population-based Tromsø Study 1994–2016.

Methods and results A total of 14 818 women and 13 225 men aged 25 years or older without AF were enrolled in the Tromsø Study between 1994 and 2008 and followed up for incident AF throughout 2016. Poisson regression was used for statistical analyses. During follow-up, age-adjusted AF incidence rates in women decreased from 1.19 to 0.71 per 1000 person-years. In men, AF incidence increased from 1.18 to 2.82 per 1000 person-years in 2004, and then declined to 1.94 per 1000 person-years in 2016. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), physical activity, smoking and alcohol consumption together accounted for 10.9% [95% confidence interval (CI): −2.4 to 28.6] of the AF incidence decline in women and for 44.7% (95% CI: 19.2; 100.0) of the AF incidence increase in men. Reduction in SBP and DBP had the largest contribution to the decrease in AF incidence in women. Increase in BMI had the largest contribution to the increase in AF incidence in men.

Conclusion In the population-based Tromsø Study 1994–2016, AF incidence decreased in women and increased following a reverse U-shape in men. Individual changes in SBP and DBP in women and individual changes in BMI in men were the most important risk factors contributing to the AF incidence trends.

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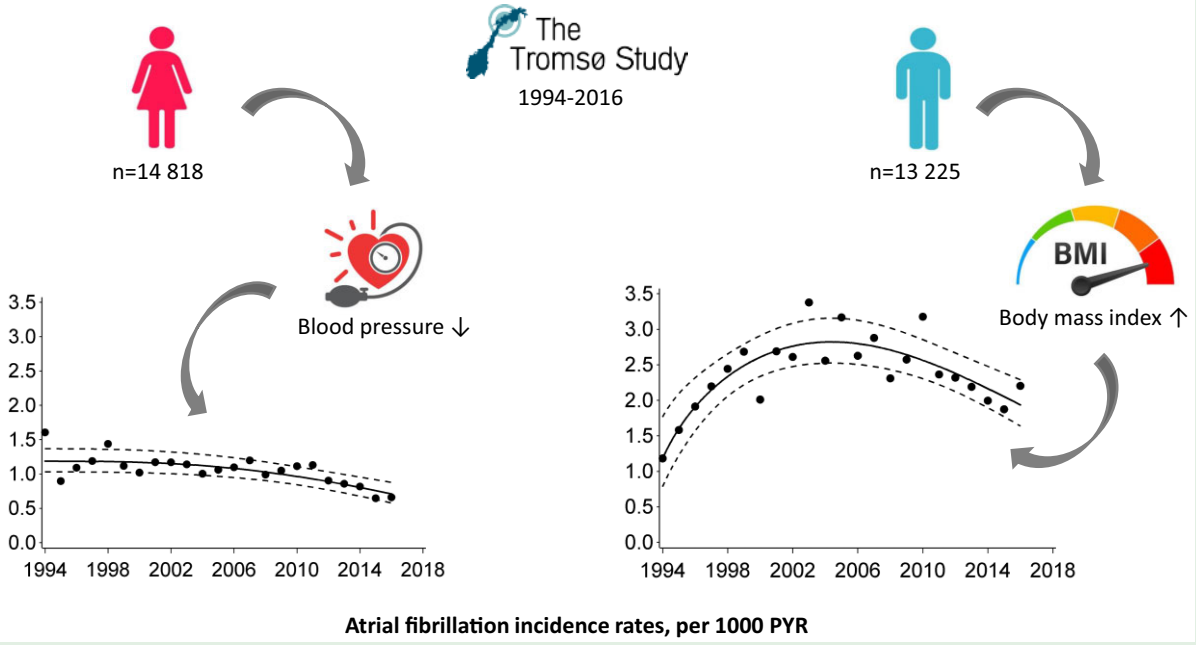
Graphical Abstract



From 1994 to 2016 atrial fibrillation incidence rates decreased in women and increased following a reverse U-shape in men. Reduction in systolic and diastolic blood pressure in women and increase in body mass index in men had the largest contribution to the trends. These findings provide further knowledge in the field of sex-specific risk stratification and personalised prevention of atrial fibrillation in clinical practice.

Keywords Atrial fibrillation • Blood pressure • Body mass index • Incidence • Epidemiology • Sex

Introduction

Atrial fibrillation (AF) is an abnormal heart rhythm that is associated with a significant impairment in quality of life and may lead to thrombosis and increased risk of stroke, myocardial infarction, heart failure, and premature death.[1] AF is the most common arrhythmia seen in clinical practice. Around one in three Europeans is expected to develop AF during their lifetime.[2] Risk of AF increases with age, and men have higher incidence than women.[3,4] However, in general, due to longevity more women than men live with AF. Between 1994 and 2014, 55 440 women and 81 388 men in Norway were diagnosed with AF.[3] In 2014, the cumulative prevalence of AF in Norwegian adults was 3.4% (2.8% in women and 4.0% in men), which is among the highest reported worldwide.[3,5–7]

The prevalence of AF is increasing due to population aging, increasing prevalence of hypertension, obesity and diabetes, improved survival with the conditions predisposing AF such as coronary heart disease and heart failure, and improved survival of AF patients.[5,8] Exploring time trends in the incidence of AF and understanding the contribution of risk factors to the time trends is important to curtail the AF epidemic. Previous studies exploring long-term trends in incidence of AF are scarce and results are inconsistent. Most studies from Western countries have reported an increase in AF incidence beginning at different time periods and starting as early as the 1950 s.[8–10] Following an increase, AF incidence rates stabilised at a higher level in some studies[3,9–11] while in others they decreased to a different extent.[12] While some studies reported similar AF incidence trends in women and men,[12] others demonstrated sex differences.[13,14] None of the studies quantified the contribution of risk factors to AF incidence trends using individual participant-level data. The present study aimed to explore sex-specific time trends in the incidence of AF from 1994 to 2016 in Norway and to estimate the impact of changes in modifiable risk factor levels using individual participant-level data from the population-based Tromsø Study.

Methods

Settings, study design, and participants

The municipality of Tromsø is the largest in Northern Norway with both urban (80%) and rural living areas.[15] Compared with the Norwegian average, the Tromsø population is slightly younger and has higher education but is similar regarding employment rates and income.[16] The main employment sector is tertiary industry: trade, health service, education, public administration; a lesser proportion is employed in secondary and primary industry.[15]

The Tromsø Study is a population-based longitudinal cohort study with seven consecutive surveys conducted in the municipality of Tromsø between 1974 and 2016.[17,18] Both total birth cohorts and random samples of women and men were invited to participate, and many attended several surveys. In the present study, we used data from participants who attended at least one of the surveys conducted in 1994–1995 (Tromsø4), in 2001 (Tromsø5), and in 2007–2008 (Tromsø6). All participants were followed up for incident AF until 31 December 2016. Participation of those invited was 72% in Tromsø4, 79% in Tromsø5, and 66% in Tromsø6. A total of 14 818 women and 13 225 men aged 25 years or older and without a prevalent history of AF attended at least one of the three surveys and their data were used to explore AF incidence trends (*Figure 1*). To estimate survey specific levels of risk factors and comorbidities, we excluded participants with missing information on blood pressure (BP), antihypertensive treatment and/or body mass index (BMI). To estimate the contribution of risk factors to the time trends in AF incidence, we additionally excluded those who did not attend the baseline Tromsø4 survey, leaving a cohort of 13 004 women and 11 557 men.

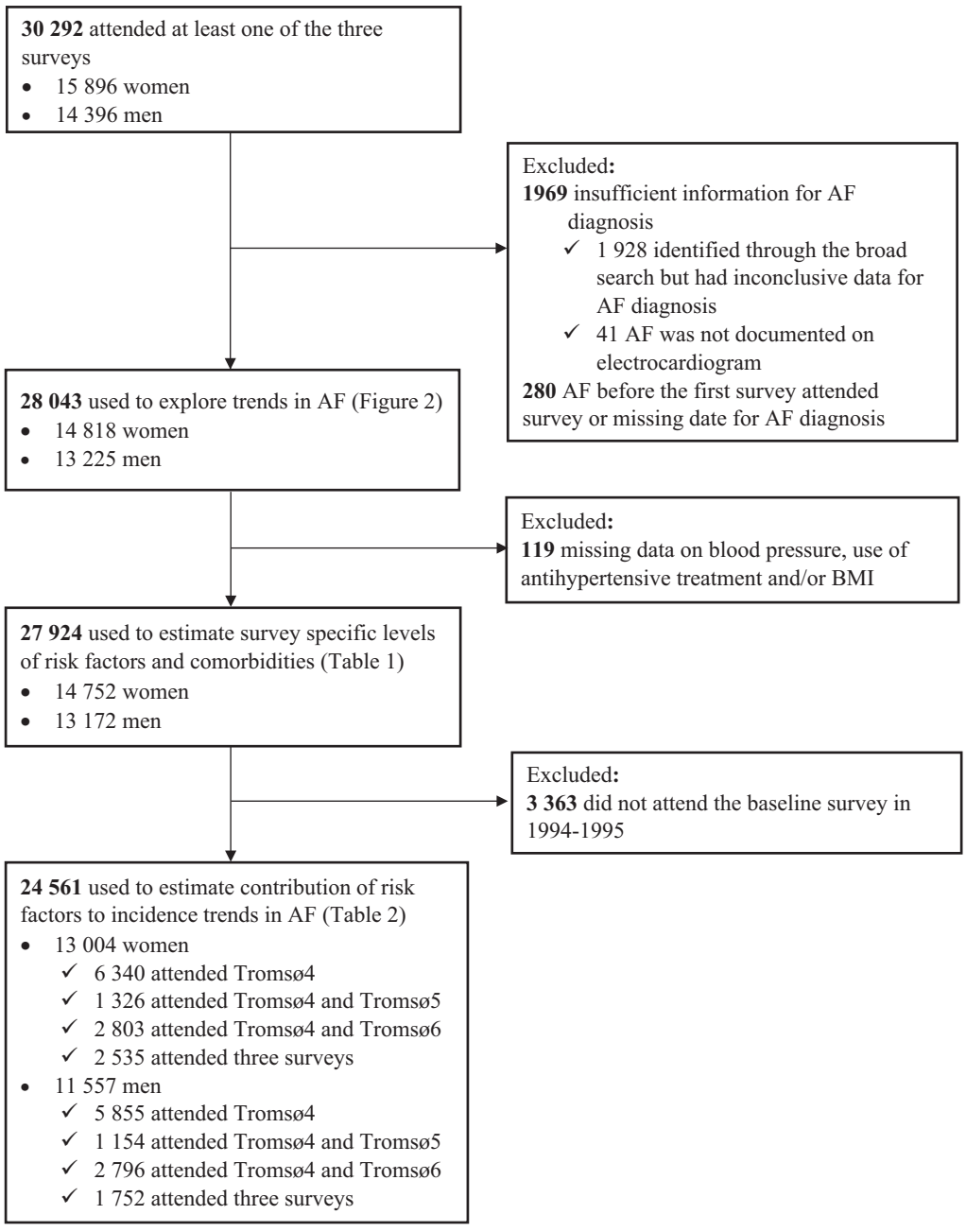


Figure 1 Flowchart of the participants, the Tromsø study 1994–2016.

All participants included in the present study provided written informed consent to participate. The Tromsø Study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. It has been approved by the Regional Committee for Medical and Health Research Ethics, North Norway, and by the Data Inspectorate.

Study procedures and assessment of risk factors and comorbidities

The Tromsø Study surveys have been conducted following the same general design and have been described in detail previously.[17] Information on current smoking (yes/no), leisure time physical activity (sedentary, moderate/active, or highly active), alcohol drinking pattern (never, monthly or less frequently, 2–4 times a month, 2–3 times a week, 4 or more times a week), antihypertensive treatment (yes/no), history of diabetes (yes/no), angina (yes/no), myocardial infarction (yes/no), and stroke (yes/no) was taken from the questionnaire. Questions on physical activity were different in Tromsø4 and for subjects 70 years of age or older in Tromsø5. We recoded answers to these questions to correspond to the three categories used in the other surveys and participant age groups using the following strategy. Those who reported 3 or more hours of hard physical activity (sweating/out of breath) in leisure time weekly during the last year were considered highly active. Those who did not report any hard physical activity and had up to 2 hours of light activity (not sweating or out of breath) in leisure time weekly during the last year were considered as sedentary. The remaining participants were considered having moderate/active level of leisure time physical activity.

Heart rate, systolic BP (SBP) and diastolic BP (DBP) were measured with the Dinamap Vital Signs Monitor 1846 (Critikon Inc., Tampa, FL, USA) in Tromsø4 and Tromsø5 and with the Dinamap ProCare 300 (GE Medical Systems Information Technologies, Tampa, FL, USA) in Tromsø6.[19] The proper cuff size was selected and mounted about 2 cm above the right elbow. After two minutes' rest, three measurements were taken with one-minute intervals. The mean of the last two heart rate (beats per minute, bpm) and BP (mmHg) measurements were used in the current analyses. Hypertension (yes/no) was defined as having SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or using antihypertensive medications. According to hypertension control, all participants were categorized into four groups: no hypertension (SBP < 140 mmHg and DBP < 90 mmHg and not using antihypertensive medications), controlled hypertension (SBP < 140 mmHg and DBP < 90 mmHg and using antihypertensive medications), uncontrolled hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and using antihypertensive medications), and untreated hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and not using antihypertensive medications).

Weight and height were measured with light clothing and no shoes. BMI (kg/m^2) was calculated as weight (kg) divided by the square of height (m). Obesity was defined as having BMI ≥ 30 kg/m^2. Non-fasting serum levels of total cholesterol (mmoL/L), high density high-density lipoprotein (HDL) cholesterol (mmoL/L), and triglycerides (mmoL/L) were measured at the Department of Clinical Chemistry, the University Hospital of North Norway.

Identification of incident atrial fibrillation and follow-up

To identify incident cases of AF, all participants of Tromsø4, Tromsø5, and Tromsø6 were linked to the diagnosis registry at the University Hospital of North Norway and to the Norwegian Cause of Death Registry. The University Hospital of North Norway is the only hospital in the area, and the diagnosis registry includes diagnoses from the out- and inpatient clinic. Potential cases of AF were selected for validation through a broad search using the International Classification of Diseases, 9th Revision codes 410–414, 427, 428, 430–438, and 798–799, the International Classification of Diseases, 10th Revision codes I20–I25, I46–I48, I50, I60–I69, R96, R98, and R99.[19] In addition, we manually searched medical hospital records for notes on AF for participants with cerebrovascular or cardiovascular events.[4] Using medical hospital records and following a detailed protocol, an independent endpoint committee validated all the identified events. AF was considered confirmed when documented by an electrocardiogram. Participants in whom AF was suspected, but where no electrocardiographic documentation for AF could be found, were excluded from the analyses (*Figure 1*). Transient AF 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, was not classified as AF cases. To identify those who died or emigrated from the municipality of Tromsø, all participants were linked to the National Population Register.

Statistical analyses

All statistical analyses were sex-specific and conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Survey-specific means (standard deviations) and numbers (proportions) were estimated to describe the study sample. Means (except age means) and percentages were adjusted for age using linear mixed models or generalized estimating equations, respectively, and estimated for the age of 54 years. In incidence analyses, the data file was structured in long format with one record for each follow-up year for each person, and age was updated every year that the participants were under follow-up. Individual follow-up was calculated as the time (years) between study entry and the date of incident AF, date of emigration, death, or end of follow-up, whichever came first. Annual incidence rates were estimated for the overall mean age in the subsample (54 years) as the number of AF events per 1000 person-years using Poisson regression with fractional polynomials of the follow-up period as the main predictor and age as a covariate. We chose the best-fitting fractional polynomials out of a maximum of two terms using the Akaike information criterion.

The proportion of change in AF incidence rates from 1994 to 2016 attributed to the individual change in risk factors was estimated for each risk factor and for all risk factors together in those who attended the baseline Tromsø4 survey. For this purpose, we have used time dependent models and have censored those who did not attend the follow-up examinations. We first estimated AF incidence rates in 1994 and 2016 using the same Poisson regression model adjusted for age, and then with additional adjustment for the individual risk factors. End of follow-up was defined 2001 for those who did not attend the 2001 survey and as 2007 for those who did not attend the 2007–2008 survey. Change in AF incidence was calculated using the following equation:

$$ID = IR_{2016} - IR_{1994}$$

where ID is incidence difference and IR is incidence rate per 1000 person-years. Explained change due to the change in individual risk factors was estimated using the following equation:

$$\frac{ID_{\text{age-adjusted}} - ID_{\text{age- and risk factor-adjusted}}}{ID_{\text{age-adjusted}}}$$

where ID is incidence difference. Bootstrapped samples with replacement ($n = 1000$) were drawn to estimate 95% confidence intervals (CIs) for the explained change. In a sensitivity analysis, the proportion of change in AF incidence rates from 1994 to 2016 attributed to the change in individual risk factors was additionally estimated in women and men without a history of myocardial infarction.

Results

Time trends in atrial fibrillation risk factors

In both women and men, age-adjusted means of SBP and DBP decreased over the study period, and most of the decline occurred between 1994–1995 and 2001. The proportion of hypertension decreased from 1994–1995 to 2001 and then increased in 2007–2008. The proportion of women and men with controlled and uncontrolled hypertension increased, and proportion of women and men with untreated hypertension decreased during the study period. The proportion of men with uncontrolled and, more notably, untreated hypertension across the surveys was substantially higher than the corresponding proportions in women. In both sexes, controlled DBP was more common than controlled SBP. BMI increased over the study period, particularly in men.

The proportion of smokers decreased from 1994–1995 to 2007–2008 in both women and men, but in men it decreased to a greater extent than in women (*Table 1*). The level of physical activity increased from sedentary to moderate/active and highly active in women, but in men the shift in proportions was predominantly from sedentary to highly active. Alcohol drinking pattern in the cohort shifted over the study period towards drinking more often, particularly in women. The prevalence of diabetes increased from 1.5% in 1994–1995 to 3.1% in women and to 3.7% in men in 2007–2008. The proportions of men with a history of myocardial infarction or stroke at the end of the study period were higher than the corresponding proportions in women: 3.6 vs. 1% and 1.9 vs. 1.2%, respectively. Serum total cholesterol levels declined markedly from Tromsø4 to Tromsø6 in both women and men.

Atrial fibrillation incidence and relation to risk factors

From 1994 to 2016, 969 women developed AF over 249 662 person-years, while the corresponding number of AF cases in men was 1164 over 217 084 person-years. Over the study period, age-adjusted AF incidence rates in women decreased gradually from 1.19 per 1000 person-years in 1994 to 0.71 per 1000 person-years in 2016 (*Figure 2*). In men, AF incidence rates increased from 1.18 per 1000

Table 1 Sex specific age-adjusted levels of risk factors in 1994–1995, 2001 and 2007–2008: the Tromsø study

	Women ($n = 14\,752$)			Men ($n = 13\,172$)		
Tromsø Study surveys[a]	**1994–1995 ($n = 13\,004$)**	**2001 ($n = 4230$)**	**2007–2008 ($n = 6565$)**	**1994–1995 ($n = 11\,557$)**	**2001 ($n = 3219$)**	**2007–2008 ($n = 5706$)**
Age, mean (SD), years	45.8 (14.7)	58.8 (14.2)	57.1 (12.8)	45.2 (13.6)	59.4 (14.2)	57.1 (12.2)
Blood pressure, mean (SD), mmHg						
Systolic	138.4 (21.4)	132.4 (23.4)	131.1 (24.8)	141.0 (16.6)	136.9 (20.1)	136.6 (20.3)
Diastolic	78.4 (12.3)	77.1 (12.7)	73.8 (10.1)	81.9 (11.5)	80.0 (11.9)	80.0 (10.2)
Hypertension, *n* (%)	3669 (39.4)	2071 (33.1)	2974 (35.9)	4527 (50.8)	1735 (45.2)	2669 (48.2)
Hypertension control, *n* (%)						
Controlled hypertension	137 (1.2)	212 (3.8)	486 (6.1)	138 (1.5)	191 (4.0)	445 (6.1)
Controlled systolic blood pressure	142 (1.3)	230 (4.1)	501 (6.3)	149 (1.6)	202 (4.4)	469 (6.5)
Controlled diastolic blood pressure	361 (2.8)	542 (6.6)	1273 (12.7)	288 (2.9)	434 (7.1)	922 (10.8)
Uncontrolled hypertension	547 (3.7)	584 (5.5)	954 (7.4)	448 (4.4)	450 (6.7)	791 (8.5)
Uncontrolled systolic blood pressure	542 (3.6)	566 (5.3)	939 (7.2)	437 (4.3)	439 (6.4)	767 (8.1)
Uncontrolled diastolic blood pressure	323 (2.4)	254 (2.7)	167 (1.3)	298 (3.1)	207 (3.6)	314 (3.7)
Untreated hypertension	2985 (29.0)	1275 (20.2)	1534 (16.7)	3941 (39.9)	1094 (29.4)	1733 (27.6)
Untreated elevated systolic blood pressure	2823 (27.3)	1221 (18.6)	1501 (15.8)	3672 (37.5)	1027 (27.2)	1633 (25.9)
Untreated elevated diastolic blood pressure	1334 (12.1)	502 (8.3)	353 (4.0)	1756 (18.2)	507 (12.8)	783 (11.9)
Resting heart rate, mean (SD), bpm	75.1 (11.8)	72.7 (12.1)	66.5 (10.2)	71.1 (12.0)	69.1 (12.5)	64.6 (10.9)
BMI, mean (SD), kg/m^2	25.3 (4.2)	26.1 (4.6)	26.1 (4.7)	25.8 (3.3)	26.6 (3.6)	27.0 (3.8)
Obesity, *n* (%)	1403 (12.5)	809 (17.0)	1306 (18.0)	1062 (9.5)	549 (16.7)	1164 (19.6)
Smoking, *n* (%)	4806 (33.2)	1185 (30.6)	1390 (23.4)	4351 (35.8)	916 (31.1)	1091 (21.4)
Physical activity, *n* (%)[b]						
Sedentary	4952 (43.9)	900 (23.2)	1186 (18.9)	3276 (31.3)	711 (23.8)	1118 (20.7)
Moderate/active	7092 (51.2)	2392 (66.1)	3975 (66.9)	6429 (56.7)	1683 (56.4)	2789 (51.5)
Highly active	839 (4.7)	350 (10.0)	815 (13.8)	1771 (12.1)	531 (19.3)	1455 (27.7)
Alcohol drinking pattern, *n* (%)						
Never	1978 (18.6)	617 (11.5)	905 (10.5)	939 (9.9)	264 (7.0)	419 (6.9)
Monthly or less frequently	4825 (37.7)	1085 (30.3)	1998 (30.8)	2799 (26.7)	615 (19.8)	1456 (25.3)
2–4 times a month	4681 (29.2)	1167 (35.0)	2281 (36.5)	5065 (38.5)	1027 (40.2)	2381 (43.1)
2–3 times a week	1329 (9.1)	574 (16.9)	993 (15.1)	2349 (19.2)	668 (25.0)	1074 (18.8)
4 or more times a week	145 (1.2)	111 (2.9)	289 (4.0)	374 (3.8)	192 (6.3)	327 (5.2)
Diabetes, *n* (%)	172 (1.5)	139 (2.1)	271 (3.1)	146 (1.5)	115 (2.2)	285 (3.7)
Angina, *n* (%)	351 (1.9)	236 (1.6)	231 (1.2)	429 (3.8)	305 (3.2)	321 (2.7)
Myocardial infarction, *n* (%)	133 (0.7)	131 (0.8)	169 (1.0)	354 (3.2)	292 (3.5)	401 (3.6)
Stroke, *n* (%)	122 (0.9)	114 (1.4)	131 (1.2)	140 (1.3)	126 (1.7)	183 (1.9)
Blood lipids, mean (SD), mmoL/L						
Total cholesterol	6.35 (1.37)	6.02 (1.23)	5.54 (1.11)	6.18 (1.21)	5.89 (1.11)	5.42 (1.06)
HDL cholesterol	1.66 (0.40)	1.54 (0.39)	1.63 (0.43)	1.38 (0.35)	1.31 (0.36)	1.33 (0.38)
Triglycerides	1.42 (0.84)	1.38 (0.79)	1.36 (0.91)	1.73 (1.18)	1.70 (1.06)	1.70 (1.02)

Means (except age means) and percentages are age-adjusted (using linear mixed models or generalized estimating equations, respectively) and estimated for the age of 54 years. Due to this reason percentages do not add up to 100%. Due to missing, the number of observations may be marginally different for each variable (within 1.0%).
BMI, body mass index; b.p.m., beats per minute; SD standard deviation.
[a]All differences between the surveys were significant ($P < 0.05$) except for myocardial infarction in men.
[b]Physical activity values in 1994–1995 and among those 70 years or older in 2001 were asked about differently but as far as possible converted into groups similar to the other surveys.

person-years to 2.82 per 1000 person-years in 2004, and then declined to 1.94 per 1000 person-years in 2016.

While some AF risk factors such as SBP, DBP, smoking, and physical inactivity decreased over the study period, others, such as alcohol consumption, BMI, and obesity increased especially in men (*Table 1*). *Table 2* shows the proportion of change in AF incidence rates over the study period attributable to changes in individual risk factors in women and men. Favourable changes in SBP and DBP had the largest contribution to the decrease in AF incidence rates over the study period in women, explaining 8.2% (95% CI: 3.2–19.1) and 19.3% (95% CI: 8.3–38.7) of the decline, respectively. Individual changes in BMI also contributed to the decline in AF incidence in women, but to a smaller extent, whereas changes in smoking, physical activity and alcohol drinking pattern had no impact. Changes in SBP, DBP, BMI, smoking, physical activity, and alcohol drinking pattern together accounted for 10.9% (95% CI: −2.4 to 28.6) of the decline in AF incidence in women.

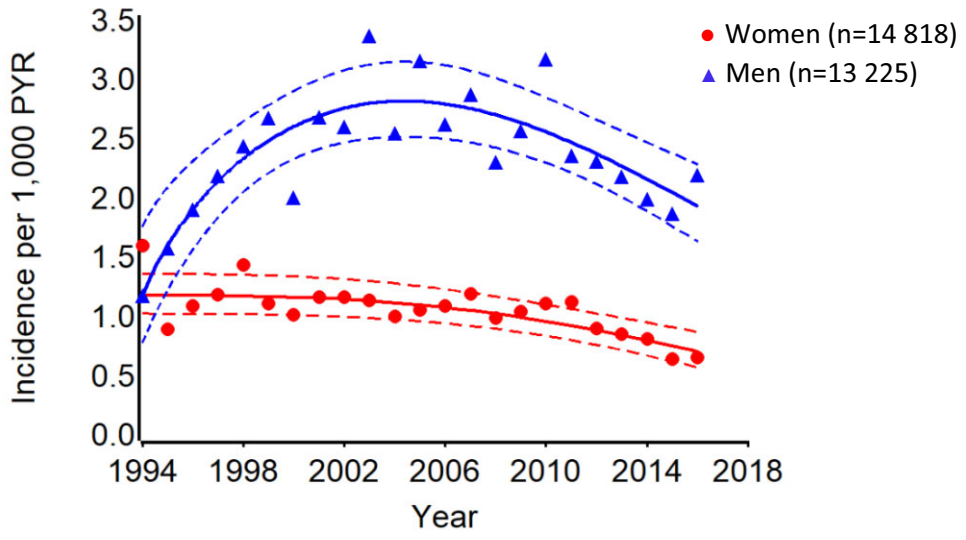


Figure 2 Sex specific age-adjusted incidence trends in atrial fibrillation, the Tromsø study 1994–2016. Incidence rates are estimated for the overall mean age of the sample (54 years). PYR, person-years.

Excluding women with a history of myocardial infarction, the estimated decrease in AF incidence was like that estimated for all women in the study (*Table 2*). However, the contribution of risk factors to the decrease in AF incidence rates became more pronounced when women with a prior history of myocardial infarction were excluded: changes in all the risk factors together accounted for 13.5% (95% CI: −0.5 to 33.7) of the decline.

In contrast to women, AF incidence rates in men increased over the study period, and the increase in BMI had the single largest contribution, accounting for 42.9% (95% CI: 24.7–100.0) of the increase. A decline in DBP had a favourable, but minor effect on AF incidence trends in men. Individual changes in smoking and alcohol drinking pattern contributed to the AF incidence trends in men explaining 10.5% (95% CI: 0.7–37.0) and 8.8% (95% CI: 3.7–62.5) of the increase, respectively. The combination of changes in SBP, DBP, BMI, smoking, physical activity, and alcohol drinking pattern together accounted for 44.7% (95% CI: 19.2–100.0) of the increase in AF incidence in men.

The estimated increase in AF incidence rates in men without a history of myocardial infarction was less pronounced compared to the incidence increase estimated for all men in the study: 0.66 (57.5%) vs. 0.73 (64.4%) per 1000 person-years, respectively. The contribution of BMI and alcohol drinking pattern to the increase in AF incidence became more pronounced within the cohort without a prior history of myocardial infarction compared to the overall cohort of men. Changes in all the risk factors together accounted for 53.7% (95% CI: 19.3–100.0) of the increase (*Table 2*).

Discussion

This study reports sex-specific time trends in AF incidence rates between 1994 and 2016. Our study is the first to report sex-specific impact of individual risk factors on the time trends in AF incidence. In women, AF incidence decreased gradually during follow-up, while AF incidence rates in men increased following a reversed U-shape over the same period. We found substantial sex differences in the impact of individual risk factors on the AF incidence trends. Changes in modifiable cardiovascular risk factors like BP, BMI, smoking, physical activity, and alcohol drinking pattern accounted for 11% of the incidence trend in women and 45% in men. Favourable changes in SBP and DBP had the largest contribution to the decrease in AF incidence rates seen in women, while unfavourable change in BMI was the most important contributor to the increase in AF incidence seen in men.

Time trends in atrial fibrillation

The Global Burden of Disease Study has reported a 22.3% (95% uncertainty interval 8.6–40.3) increase in age-standardized AF incidence rates in Norway from 1990 to 2017 whereas the rates in most of Western European countries and globally decreased.[20] Another study based on Global Burden of Disease data from 1990–2017 has demonstrated heterogenous time trends in age-standardized AF incidence rates for 20 countries across Europe.[12] Austria, Denmark, and Sweden have all reported peaks in incidence in the middle of the study period, which is in line with our findings in men. A recent registry study based on the entire Norwegian population from 2004 to 2014 demonstrated more stable time trends in AF incidence, especially in women.[3] However, analysis of AF incidence was limited to in-patient admissions only, and definition of AF cases was not verified by electrocardiogram or additional medical records. Our study expands the current knowledge from Global Burden of Disease studies[12,20] and adds to a previous Norwegian registry study.[3]

Contribution of blood pressure to the atrial fibrillation time trends

Sex differences in the association between BP and the risk of AF incidence have been demonstrated previously. We recently reported that long-term elevated SBP was associated with a two-fold increased risk of incident AF in women compared to normotensive women in the Tromsø Study. The risk of incident AF in men with an elevated SBP was less pronounced, a 10–50% higher risk compared with normotensive men.[19] Furthermore, elevated SBP was associated with an increased risk for both paroxysmal and permanent AF in women but only with risk for

Table 2 Change in incidence of atrial fibrillation from 1994 to 2016 accounted for by risk factors in women and men: the Tromsø study

Models	Women		Men	
	Estimated change in AF incidence from 1994 to 2016, per 1000 PYR (%)[a]	Explained change by risk factors, % (95% CI)[b]	Estimated change in AF incidence from 1994 to 2016, per 1000 PYR (%)[a]	Explained change by risk factors, % (95% CI)[b]
General population	*n* = 13 004		*n* = 11 557	
Model 1, age adjusted	−0.49 (50.4)	Ref.	0.73 (64.4)	Ref.
Model 1 + SBP	−0.45 (46.4)	8.2 (3.2; 19.1)	0.76 (69.3)	−5.2 (−26.0; 2.5)
Model 1 + DBP	−0.39 (43.0)	19.3 (8.3; 38.7)	0.77 (74.5)	−6.2 (−37.6; −0.2)
Model 1 + smoking	−0.50 (51.7)	−3.1 (−9.4; 1.8)	0.65 (55.4)	10.5 (0.7; 37.0)
Model 1 + physical activity	−0.48 (49.3)	1.4 (−4.1; 10.3)	0.80 (71.2)	−9.7 (−39.0; 8.3)
Model 1 + alcohol drinking pattern	−0.49 (50.5)	−0.6 (−6.8; 6.9)	0.66 (59.2)	8.8 (3.7; 62.5)
Model 1 + BMI	−0.47 (50.7)	3.1 (0.1; 7.2)	0.41 (36.9)	42.9 (24.7; 100.0)
Model 1 + SBP, DBP, smoking, physical activity, alcohol drinking pattern, BMI	−0.43 (47.5)	10.9 (−2.4; 28.6)	0.40 (37.1)	44.7 (19.2; 100.0)
Population without history of myocardial infarction	*n* = 12 871		*n* = 11 203	
Model 1, age adjusted	−0.47 (49.7)	Ref.	0.66 (57.5)	Ref.
Model 1 + SBP	−0.42 (44.9)	10.3 (4.0; 24.1)	0.70 (63.2)	−7.2 (−45.6; 4.1)
Model 1 + DBP	−0.35 (40.2)	24.6 (11.7; 49.0)	0.71 (58.4)	−8.2 (−72.2; 0.3)
Model 1 + smoking	−0.49 (51.2)	−3.8 (−11.3; 1.3)	0.57 (48.0)	13.1 (−0.4; 84.1)
Model 1 + physical activity	−0.47 (49.1)	0.4 (−5.6; 9.5)	0.72 (63.4)	−9.3 (−55.6; 14.8)
Model 1 + alcohol drinking pattern	−0.47 (50.0)	1.1 (−8.2; 6.4)	0.61 (53.0)	7.3 (0.2; 100.0)
Model 1 + BMI	−0.45 (49.9)	3.6 (0.4; 8.2)	0.32 (27.5)	51.8 (25.3; 100.0)
Model 1 + SBP, DBP, smoking, physical activity, alcohol drinking pattern, BMI	−0.40 (46.1)	13.5 (−0.5; 33.7)	0.30 (27.5)	53.7 (19.3; 100.0)

AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; PYR, person-years; SBP, systolic blood pressure.
[a]ID = IR_{2016}-IR_{1994}; (IR_{2016}-IR_{1994})/IR_{1994}; IR = incidence rate per 1000 PYR.
[b](ID_0–ID_1)/ID_0 × 100%; ID = incidence difference.

paroxysmal AF in men.[21] Thus, it could be expected that reduction in BP would have a particularly favourable impact on AF incidence in women, as demonstrated in the present study. In the Women's Health Study, SBP was a better predictor of AF than DBP,[22] while the present analysis found reduction in DBP to have the largest contribution to the decline in AF incidence in women. Our findings may reflect that BP control was achieved to a higher degree for DBP than SBP. However, it should be noted that BP was self-reported in the Women's Health Study compared to the standardised measurements performed in the Tromsø Study. Although participants in the Women's Health Study were health professionals, we cannot exclude that these methodological differences may have influenced the diverse findings.

In the Global Burden of Disease Study 1990–2017, elevated SBP was found to be the leading risk factor for age-standardized AF mortality rates, and in line with our findings, the percentage contribution was higher in women than in men.[20] In the Framingham Heart Study cohort, hypertension predicted AF comparably in both sexes.[23,24] Of note, hypertension was defined as SBP ≥ 160 mmHg or DBP ≥ 95 mmHg or use of antihypertensive medication in the Framingham Heart Study, reflecting older definitions of hypertension. The higher cut-off values as well as including antihypertensive medication as a part of the composite variable may potentially explain the lack of sex differences. Odds ratios in the Framingham Heart Study were also adjusted for intermediate factors such as electrocardiographic left ventricular hypertrophy and valvular heart disease that could have attenuated the association between hypertension and AF risk. Moreover, age of the Framingham Heart Study cohort was restricted to subjects 55–94 years.

Contribution of body mass index to the atrial fibrillation time trends

BMI increase in women had almost no effect on the AF incidence trend, potentially reflecting that BMI did not increase as much in women as in men in the present study. Increase in BMI and obesity in men was more pronounced between 1994–1995 and 2001 than between 2001 and 2007–2008, coinciding with the doubled AF incidence rate during this period in men. Additionally, it has previously been shown that higher BMI potentially has a greater influence on AF development in men than in women.[25–27] When using normal weight as a reference, both overweight and obesity had larger adjusted hazard ratios for AF in men than in women in a Danish study.[28] Also, a European study showed sex differences in the association of BMI with incident AF.[2] Enlarged left atrial size is more likely in obese individuals,[25] and larger left atrial diameter was strongly associated with AF onset in the subset of participants in the Tromsø Study who underwent echocardiography.[29]

Contribution of alcohol consumption to the atrial fibrillation time trends

In a recent European community-based pooled cohort ($n = 107\,845$) alcohol consumption was associated with incident AF: drinking 3–5 days a week increased the risk of AF compared with never drinkers with HR = 1.25.[30] Sex-specific results were not presented. Our study adds to previous publications by demonstrating that an unfavourable change in alcohol drinking pattern over time had no effect on the time trend in AF incidence rates in women whereas in men it accounted for 9% of the AF incidence increase. These results are in line with the Global Burden of Disease Study 1990–2017, where the percentage contribution of alcohol use to the AF mortality was higher in men than in women.[20] In contrast, alcohol consumption was not associated with AF risk in the Framingham Heart Study in either sex.[23,24] However, it was measured in ounces of ethanol a week and included into the models as a continuous variable that could have attenuated the association between alcohol consumption and AF risk as it has been shown to be nonlinear.[30]

Contribution of coronary heart disease to the atrial fibrillation time trends

Coronary heart disease is an important predisposing condition for developing AF, especially in men.[23] Excluding men with myocardial infarction from the analyses resulted in a higher proportion of the increase in AF incidence explained by the risk factors. This demonstrates the significant contribution of myocardial infarction as a risk factor for the increasing AF incidence rates in men. Moreover, AF incidence rates in men started to decline after 2004, and the decline was steeper compared to that in women. This could also be explained by a higher prevalence of clinical and subclinical coronary heart disease in men. The incidence of clinical coronary heart disease events is declining in both women and in men, but because coronary heart disease is more prevalent in men, the decline in AF incidence may have started later in men. These findings are in line with the Framingham Heart Study where myocardial infarction was associated with the development of AF in men but not in women.[23,24]

Implications

Our findings demonstrate that personalized medical care might be affected by sex-specific nuances. Even though both women and men share the same AF risk factors, the impact of prioritizing specific targets for intervention will potentially result in better outcomes. Recent publications have reported that controlled hypertension was less prevalent in women than in men.[31,32] Our findings regarding the BP contribution to AF incidence trends imply that improved control of DBP and especially SBP in clinical practice would contribute to decreased AF risk, particularly in women. The adverse contribution of BMI to the change in AF incidence in men and to a lesser extent in women, underscores the need for public-health initiatives promoting a healthy weight as well as continuous clinical follow-up in primary health care. Given our results on an adverse effect of alcohol drinking pattern on AF incidence trends, strategies on reduction of alcohol consumption may potentially prevent a substantial number of AF cases in men. As both hypertension, obesity and alcohol consumption represent unhealthy lifestyle in countries with high socio-demographic index,[20] targeted preventive strategies must be taken into consideration, particularly in these countries.

Strengths and limitations

Strengths of this study are the population-based design, the large sample of repeated individual data, standardized diagnostic criteria and survey methods, rigorous validation of cases, and high attendance. Verification of cardiovascular outcomes through expert review of medical records is considered the gold standard of data collection.[33,34] However, in the present study case identification was retrospective based on existing medical records, which is a limitation. We have not identified AF cases who were treated in primary health care only and never referred to the hospital either for inpatient treatment or in the outpatient setting. In Sweden, 22% of patients with AF were seen only in primary care practices.[7] Unfortunately, we do not have corresponding information on AF patients in Norway. It is therefore likely that we missed some participants with AF, including patients with silent AF and/or paroxysmal AF that failed to be detected on an electrocardiogram. Furthermore, patients with transient AF as well as patients with AF documented only in the terminal phase of life were not classified as having AF in this study. This might result in underestimation of risk factors contribution to the AF incidence trends. Although the evidence in clinical use of classifying AF by underlying drivers is lacking,[35] risk factors for these patients may differ from the general population.

The associations between time trends in AF incidence and risk factors were based on participants with updated risk factors, which could have introduced response and/or survival bias. Diabetes, angina, myocardial infarction, stroke, smoking, physical activity, and alcohol drinking pattern were self-reported which could also have led to over- or underestimation of the prevalence of risk factors. Data on some of the potential AF risk factors and predisposing conditions such as obstructive sleep apnoea, heart failure or valvular disease were not available for the Tromsø Study surveys used in this analysis. CIs for the explained change by risk factors in men were wide, which is due to limited power. Although participation rates were relatively high, non-attendees could differ from those who attended the study, affecting external validity. Non-attendees have been shown to be slightly younger, more likely to be men and/or single compared to attendees.[17] To increase the participation rate, subjects under the age of 25 years were not invited to the Tromsø4 survey. Finally, sex-specific time trends in AF incidence rates described in this study cannot be extrapolated to other cohorts. However, the novel findings on sex differences in the impact of individual changes in risk factors levels on AF are of major importance, and probably also valid for other populations.

Conclusion

In this rigorous population-based longitudinal study, AF incidence rates decreased from 1994 to 2016 in women and increased following a reversed U-shape in men. Changes in risk factors associated with a change in AF incidence differed between women and men. The demonstrated decline in BP was the single largest contributing factor responsible for the decline in AF incidence in women, whereas a substantial increase in BMI was the largest factor contributing to the increase in incident AF in men. By addressing sex-specific differences in the contribution of modifiable risk factors to change in AF incidence, we provide further knowledge in the field of sex-specific risk stratification and personalised prevention of AF in clinical practice. Our results also demonstrate that there is a large proportion of change in AF incidence that is not explained by changes in established modifiable risk factors. This suggests that further research on less traditional risk factors is required.

Author contributions

All authors contributed to the conception and/or design of the work. M.L.L., E.B.M., and I.N. contributed to the acquisition of data for the work. E.S. ran the analysis for the work. All authors contributed to the interpretation of data for the work. E.S. drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article were provided by the Tromsø Study by permission. The data are available upon reasonable request and application for data access to the Tromsø Study. More information may be found on http://www.tromsoundersokelsen.no.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
2. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njølstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the biomarCaRE consortium (biomarker for cardiovascular risk assessment in Europe). *Circulation* 2017;**136**:1588–1597.
3. Kjerpeseth LJ, Igland J, Selmer R, Ellekjaer H, Tveit A, Berge T, Kalsto SM, Christophersen IE, Myrstad M, Skovlund E, Egeland GM, Tell GS, Ariansen I. Prevalence and incidence rates of atrial fibrillation in Norway 2004–2014. *Heart* 2020;**107**:201–207.
4. Nyrnes A, Mathiesen EB, Njølstad I, Wilsgaard T, Løchen ML. Palpitations are predictive of future atrial fibrillation. An 11-year follow-up of 22,815 men and women: the Tromsø study. *Eur J Prev Cardiol* 2013;**20**:729–736.
5. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;**167**:1807–1824.
6. Norberg J, Bäckström S, Jansson JH, Johansson L. Estimating the prevalence of atrial fibrillation in a general population using validated electronic health data. *Clin Epidemiol* 2013;**5**:475–481.
7. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. *J Intern Med* 2013;**274**:461–468.
8. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the framingham heart study: a cohort study. *Lancet* 2015;**386**:154–162.
9. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;**114**:119–125.
10. Chamberlain AM, Gersh BJ, Alonso A, Chen LY, Berardi C, Manemann SM, Killian JM, Weston SA, Roger VL. Decade-long trends in atrial fibrillation incidence and survival: a community study. *Am J Med* 2015;**128**:260–267.e261.
11. Vasan RS, Zuo Y, Kalesan B. Divergent temporal trends in morbidity and mortality related to heart failure and atrial fibrillation: age, sex, race, and geographic differences in the United States, 1991–2015. *J Am Heart Assoc* 2019;**8**:e010756.
12. Al-Khayatt BM, Salciccioli JD, Marshall DC, Krahn AD, Shalhoub J, Sikkel MB. Paradoxical impact of socioeconomic factors on outcome of atrial fibrillation in Europe: trends in incidence and mortality from atrial fibrillation. *Eur Heart J* 2021;**42**:847–857.
13. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace* 2011;**13**:1110–1117.
14. Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Nielsen JC, Sørensen HT. 30-year Nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *Int J Cardiol* 2016;**225**:30–36.
15. Hopstock LA, Grimsgaard S, Johansen H, Kanstad K, Wilsgaard T, Eggen AE. The seventh survey of the Tromsø study (Tromsø7) 2015–2016: study design, data collection, attendance, and prevalence of risk factors and disease in a multipurpose population-based health survey. *Scand J Public Health* 2022;**50**:919–929.
16. Kristoffersen AE, Broderstad AR, Musial F, Stub T. Prevalence, and health- and socio-demographic associations for visits to traditional and complementary medical providers in the seventh survey of the Tromsø study. *BMC Complement Altern Med* 2019;**19**:305.
17. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the tromso study. *Int J Epidemiol* 2012;**41**:961–967.
18. Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njølstad I. The sixth survey of the Tromso study (Tromso 6) in 2007–08: collaborative research in the interface between clinical medicine and epidemiology: study objectives, design, data collection procedures, and attendance in a multipurpose population-based health survey. *Scand J Public Health* 2013;**41**:65–80.
19. Sharashova E, Wilsgaard T, Ball J, Morseth B, Gerdts E, Hopstock LA, Mathiesen EB, Schirmer H, Løchen ML. Long-term blood pressure trajectories and incident atrial fibrillation in women and men: the Tromsø study. *Eur Heart J* 2020;**41**:1554–1562.
20. Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, Adawi S, Lu Y, Bragazzi NL, Wu J. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990–2017: results from the global burden of disease study 2017. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:574–582.
21. Espnes H, Ball J, Løchen ML, Wilsgaard T, Njølstad I, Mathiesen EB, Gerdts E, Sharashova E. Sex-specific associations between blood pressure and risk of atrial fibrillation subtypes in the Tromsø study. *J Clin Med* 2021;**10**:1514.
22. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;**119**:2146–2152.
23. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. *JAMA* 1994;**271**:840–844.
24. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N–9N.
25. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471–2477.
26. Ball J, Løchen ML, Wilsgaard T, Schirmer H, Hopstock LA, Morseth B, Mathiesen EB, Njølstad I, Tiwari S, Sharashova E. Sex differences in the impact of body mass index on the risk of future atrial fibrillation: insights from the longitudinal population-based Tromsø study. *J Am Heart Assoc* 2018;**7**:e008414.

27. Poorthuis MHF, Sherliker P, de Borst GJ, Carter JL, Lam KBH, Jones NR, Halliday A, Lewington S, Bulbulia R. Joint associations between body mass index and waist circumference with atrial fibrillation in men and women. *J Am Heart Assoc* 2021;**10**:e019025.
28. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the danish diet, cancer, and health study. *Am J Med* 2005;**118**: 489–495.
29. Tiwari S, Schirmer H, Jacobsen BK, Hopstock LA, Nyrnes A, Heggelund G, Njølstad I, Mathiesen EB, Løchen ML. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø study from 1994 to 2010. *Heart* 2015;**101**:1302–1308.
30. Csengeri D, Sprünker NA, Di Castelnuovo A, Niiranen T, Vishram-Nielsen JK, Costanzo S, Söderberg S, Jensen SM, Vartiainen E, Donati MB, Magnussen C, Camen S, Gianfagna F, Løchen ML, Kee F, Kontto J, Mathiesen EB, Koenig W, Stefan B, de Gaetano G, Jørgensen T, Kuulasmaa K, Zeller T, Salomaa V, Iacoviello L, Schnabel RB. Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. *Eur Heart J* 2021;**42**:1170–1177.
31. Osude N, Durazo-Arvizu R, Markossian T, Liu K, Michos ED, Rakotz M, Wozniak G, Egan B, Kramer H. Age and sex disparities in hypertension control: the multi-ethnic study of atherosclerosis (MESA). *Am J Prev Cardiol* 2021;**8**:100230.
32. Leung AA, Williams JVA, McAlister FA, Campbell NRC, Padwal RS. Worsening hypertension awareness, treatment, and control rates in Canadian women between 2007 and 2017. *Can J Cardiol* 2020;**36**:732–739.
33. Varmdal T, Løchen ML, Wilsgaard T, Njølstad I, Nyrnes A, Grimsgaard S, Mathiesen EB. Data from national health registers as endpoints for the Tromsø study: correctness and completeness of stroke diagnoses. *Scand J Public Health* 2021:14034948211021191.
34. Davidson J, Banerjee A, Muzambi R, Smeeth L, Warren-Gash C. Validity of acute cardiovascular outcome diagnoses recorded in European electronic health records: a systematic review. *Clin Epidemiol* 2020;**12**:1095–1111.
35. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2020;**42**:373–498.