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FULL RESEARCH PAPER
Arrhythmias

Hypothetical interventions and risk of atrial fibrillation by sex and education: application of the parametric g-formula in the Tromsø Study

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See the editorial comment for this article 'Habits and heartbeats: learning from historical longitudinal data on primary prevention of atrial fibrillation', by O. Sapir *et al.*, https://doi.org/10.1093/eurjpc/zwad298.

Aims To use the parametric g-formula to estimate the long-term risk of atrial fibrillation (AF) by sex and education under hypothetical interventions on six modifiable risk factors.

Methods and results We estimated the risk reduction under hypothetical risk reduction strategies for smoking, physical activity, alcohol intake, body mass index, systolic, and diastolic blood pressure in 14 923 women and men (baseline mean age 45.8 years in women and 47.8 years in men) from the population-based Tromsø Study with a maximum of 22 years of follow-up (1994–2016). The estimated risk of AF under no intervention was 6.15% in women and 13.0% in men. This cumulative risk was reduced by 41% (95% confidence interval 17%, 61%) in women and 14% (−7%, 30%) in men under joint interventions on all risk factors. The most effective intervention was lowering body mass index to ≤ 25 kg/m^2, leading to a 16% (4%, 25%) lower risk in women and a 14% (6%, 23%) lower risk in men. We found significant sex-differences in the relative risk reduction by sufficient physical activity, leading to a 7% (-4%, 18%) lower risk in women and an 8% (−2%, −13%) increased risk in men. We found no association between the level of education and differences in risk reduction by any of the interventions.

Conclusion The population burden of AF could be reduced by modifying lifestyle risk factors. Namely, these modifications could have prevented 41% of AF cases in women and 14% of AF cases in men in the municipality of Tromsø, Norway during a maximum 22-year follow-up period.

Lay summary The heart normally has a regular rhythm. However, in an increasing number of adults worldwide, the rhythm is irregular, which is known as arrhythmia. Atrial fibrillation, or AF, is the most common type of arrhythmia. We know that the risk of AF may be related to lifestyle. In this project, we investigated how much the risk of AF in the population could have been reduced by improvements in smoking habits, physical activity level, alcohol intake, body mass index (BMI), and blood pressure. We found that the risk could have been reduced by 41% in women and 14% in men if everyone quit smoking, was sufficiently physically active, limited their alcohol intake to two units per week, lowered their BMI to 25 kg/m^2, and lowered their blood pressure to 130/80 mm Hg. Reducing BMI was the most effective intervention to prevent AF.

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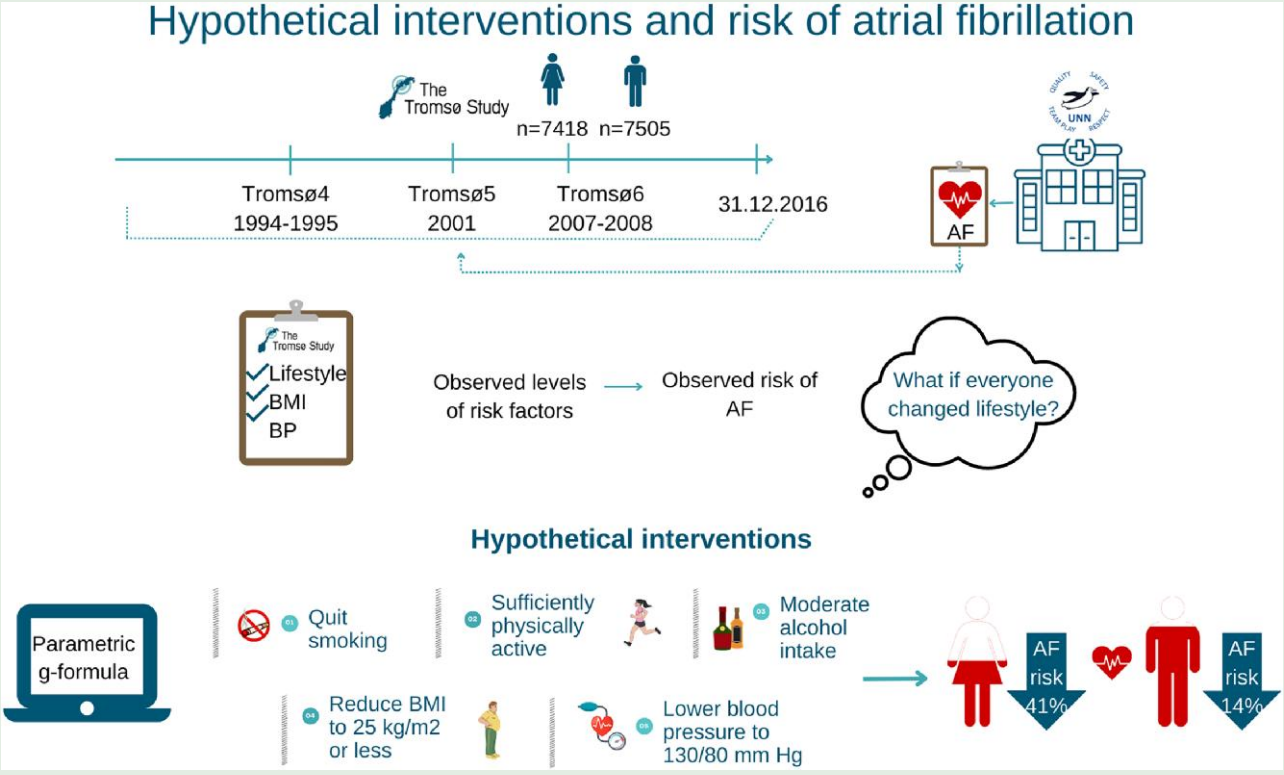
Graphical Abstract

Key finding

- Healthy lifestyle could have prevented 41% of AF cases in women and 14% of AF cases in men.
- We found no difference in the effect of lifestyle changes on AF risk by education level.



Keywords Atrial fibrillation • Sex • Socioeconomic status • Education • Risk reduction behaviour • Primary prevention • Risk factors

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and the cause is often unknown.[1] The risk of AF is associated with unmodifiable risk factors like genetics, sex, age, and ethnicity, and modifiable risk factors like hypertension, obesity, diabetes mellitus, obstructive sleep apnoea, physical activity, smoking, and alcohol consumption.[1,2] Blood pressure (BP) is among the strongest modifiable risk factors in women, while body mass index (BMI) is in men.[3] AF increases the risk of ischaemic stroke, myocardial infarction, heart failure, and premature death.[2] Worldwide prevalence in adults is estimated to be between 2% and 4%, and a 2.3-fold rise is expected.[4] Additionally, the prevalence of modifiable risk factors such as hypertension, obesity, diabetes, and physical inactivity is increasing, and AF imposes a significant burden on both the patient and the health care system.[5] Thus, preventing AF is a significant public health challenge.

Modification of lifestyle risk factors to prevent AF is now highlighted as a potential fourth pillar in AF management together with anticoagulation, rate control, and rhythm control.[4] Additionally, individual changes in modifiable risk factors like systolic and diastolic BP (SBP and DBP) and BMI affect the incidence rate of AF and are important targets for primary prevention.[3,6] Therefore, a risk modification strategy is crucial to reduce morbidity, years of life lost, and the medical costs attributable to AF. However, the literature has several gaps and specific AF primary prevention strategies including modification of lifestyle risk factors are few.[2,4,7,8]

The current knowledge on modifiable risk factors and AF is mostly based on observational studies.[2] A few randomized controlled trials have examined the effects of interventions on lifestyle and AF risk or AF symptoms, showing inconclusive results.[9–12] However, no study has yet examined the effect of joint lifestyle interventions for primary prevention of AF. For this objective, randomized controlled trials are the gold standard, but they are often time consuming not feasible, unaffordable, or unethical. Therefore, the emulation of a target trial by using Robins' parametric g-formula is an alternative method to assess the impact of interventions on the risk of incident AF.[13] To our knowledge, only one previous study has applied the parametric g-formula to estimate the effect of interventions on AF risk, but that study focused only on BMI.[6]

Persons with low socioeconomic status (SES) have poorer cardiovascular health.[14] The current literature on AF and SES is, however, inconclusive. A review from 2018 found no association between SES and incident AF,[15] but more recent studies have found socioeconomic disadvantages across the life course and low family income to be associated with increased AF risk.[16,17]

We aimed to estimate the effect of various hypothetical interventions using the parametric g-formula on lifestyle and metabolic risk

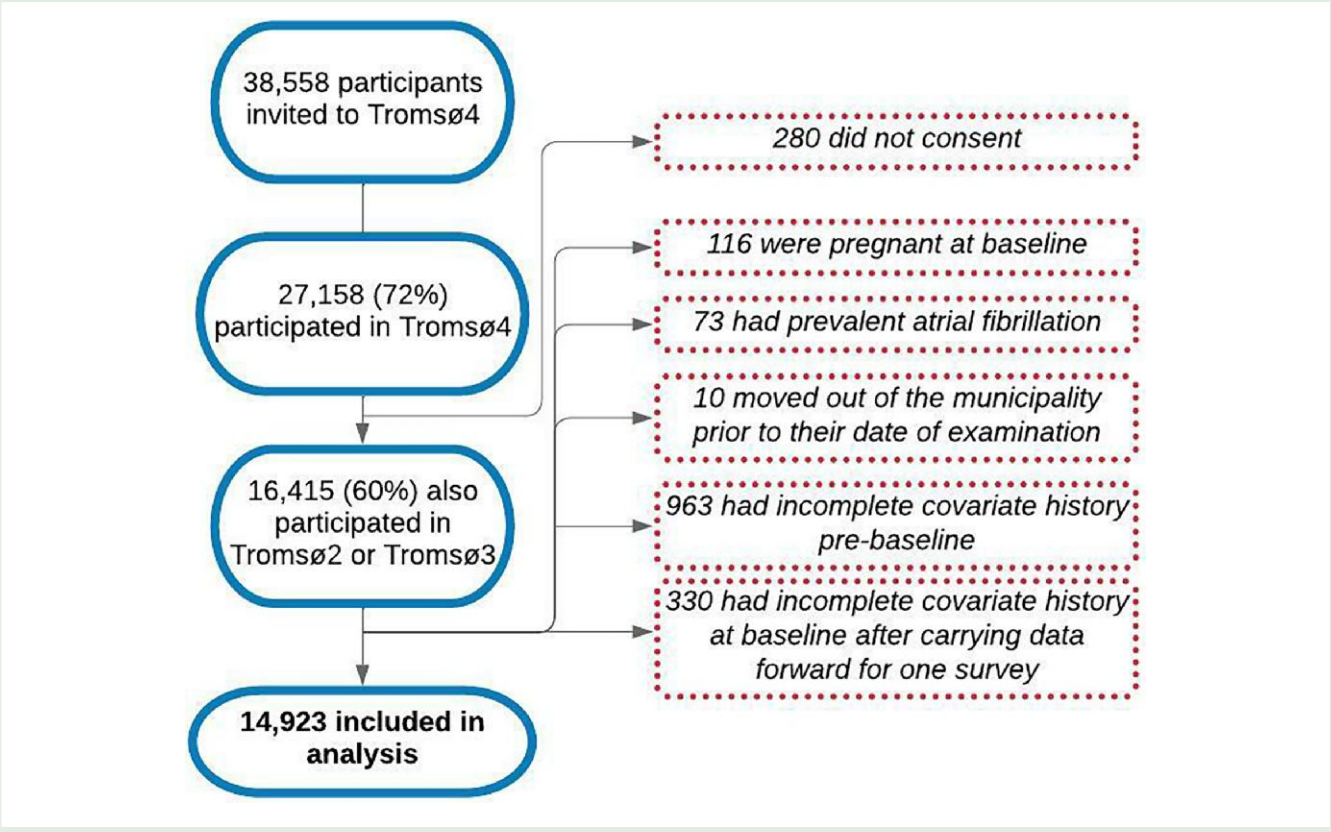


Figure 1 Flowchart of participants, the Tromsø Study 1994–2008.

factors on the risk of incident AF and to investigate if the effect varied with sex and SES using data from the population based on the longitudinal Tromsø Study.

Materials and methods

Study population

Tromsø is the largest municipality in Northern Norway with 78 000 residents.[18] Around 90% of the residents live in urban areas, and 85% were born in Norway.[18] The Tromsø Study is a prospective, population-based cohort study conducted in the municipality of Tromsø, Norway. It consists of seven completed surveys, Tromsø1-7, conducted between 1974 and 2016.[19] Tromsø4 (1994–1995) was used as baseline in this study, and all participants were followed up with for incident AF both prospectively and retrospectively. All residents of Tromsø aged ≥ 25 years were invited to Tromsø4, with 72% participation ($n = 27\,158$). Of these, $n = 26\,878$ gave written informed consent. Because we needed at least one pre-baseline measurement in order to adjust for pre-baseline covariates, only $n = 16\,415$ Tromsø4 participants that also participated in Tromsø2 (1979–1980, $n = 16\,621$) or Tromsø3 (1986–1987, $n = 21\,862$) were eligible for this study. Of these, $n = 9661$ also attended Tromsø5 (2001, $n = 8130$) and/or Tromsø6 (2007–2008, $n = 12\,984$), where random samples or selected birth cohort were invited. Among those eligible for our study, 91% of those invited to Tromsø5, and 82% of those invited to Tromsø6, participated in Tromsø 5 and Tromsø 6, respectively. Participants were excluded from the analyses if they were pregnant at baseline ($n = 116$), had prevalent AF ($n = 73$), had moved out of the municipality before their date of examination ($n = 10$), had incomplete covariate history pre-baseline ($n = 963$) or at baseline after carrying data forward for one survey ($n = 330$). Women who were pregnant at Tromsø2 or Tromsø3 had their covariates set to missing for that time point. In total, $n = 14\,923$ women and men were included (*Figure 1*).

Measurements

Data collection in the Tromsø Study included questionnaires, physical examinations, and blood sampling. The different surveys used standardized protocols and similar methods that are described elsewhere.[19] In brief, information on education, smoking, physical activity during leisure time, alcohol consumption, diabetes, history of heart attack or stroke, marital status, physical activity at work, and pregnancy was collected from questionnaires. Detailed information measuring smoking and harmonization of education, physical activity during leisure time, and alcohol consumption across the different surveys is given in the *Supplementary material online*. Height, weight, and BP were measured, and non-fasting blood samples were collected by trained personnel at the physical examination (*Supplementary material online*). Emigration and death were identified through the Population Register of Norway.

Identification and validation of incident AF

Incident cases of AF were identified by linkage to the diagnosis registry at the University Hospital of North Norway and the Norwegian Cause of Death Registry using the unique Norwegian national 11-digit identification number. Both in- and out-patient clinical diagnoses are included in the registry. Potential incident cases of AF were detected for validation by manual and/or digital searches for the International Classification of Diseases, 9th Revision

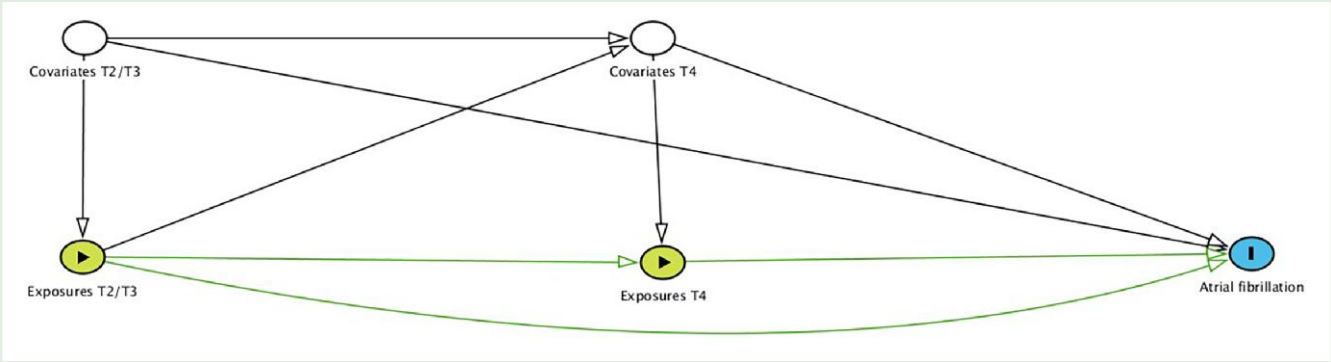


Figure 2 Directed acyclic graph of the causal structure between time-varying exposures, time-varying covariates, and the risk of atrial fibrillation.

(ICD-9) codes 410–414, 427, 428, 430–438, and 798–799, and ICD-10 codes 120–125, 146–148, 150, 160–169, R96, R98, and R99.[20] Additionally, for participants with cerebrovascular or cardiovascular events but without an arrhythmia diagnosis, medical hospital records were searched for notes on AF.[21] An independent endpoint committee confirmed and validated all AF events documented on an electrocardiogram following a strict protocol.[21] Participants with suspected AF but without documentation on an electrocardiogram ($n = 105$), those having AF after the end of follow-up period ($n = 65$), and those having AF after moving out of the municipality ($n = 24$) were considered AF-free in the analyses. One participant had a date of AF after a date of death. The date of AF was in this case changed to match the date of death.

Follow-up and missingness

Each participant was followed up with from the date of participation in Tromsø4 until the date of first documented AF, emigration, death, or end of follow-up period (31 December 2016), whichever came first. The maximum follow-up period was 22 years. AF risk factors were updated for participants of Tromsø5 or Tromsø6 that were still in the follow-up period. The last observation was carried forward from the previous survey if a covariate was missing for one of the time points. Thus, in accordance with exclusion criteria, all participants had complete covariate history pre-baseline (e.g. Tromsø2 and/or 3) and baseline (e.g. Tromsø4). Participants were censored on 31 December 2008 after carrying data over from Tromsø4 to Tromsø5 if a covariate was missing for both Tromsø5 and Tromsø6.

Risk reduction strategies

We conducted hypothetical interventions on six modifiable risk factors, chosen based on reviews and clinical guidelines.[2,4] In our model, we made all participants hypothetically (i) quit smoking, (ii) become sufficiently physically active (i.e. perform at least 180 min per week of moderate physical activity or 90 min per week of vigorous physical activity), (iii) drink alcohol moderately (>one $\leq$ two units per week), (iv) lower their BMI to 25 kg/m^2, (v) lower their SBP to 130 mm Hg, and (iv) lower their DBP to 80 mm Hg. These interventions were performed at each time point, both individually and as combinations of interventions 5 + 6, 1–4, and all joint interventions 1–6.

Statistical methods

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and stratified by sex, due to known sex-differences in AF epidemiology.[3,4,20,22–27] Survey-specific descriptive characteristics of the study sample were estimated by means (standard deviations) and proportions (numbers).

We used the parametric g-formula to estimate the long-term risk of AF under no intervention and under the selected interventions described above. The parametric g-formula is a generalization of standardization for time-varying exposures, and AF risk is estimated by a weighted sum of overall risk factor histories of the probability of AF conditional on its risk factors.[28] The parametric g-formula also correctly adjusts for time-varying confounders, which is a methodological challenge where standard regression models fail. For example, to assess the effect of interventions on BMI on AF risk, physical activity is a time-varying confounder because it affects the risk of AF, and changes in physical activity may lead to changes in future BMI. Additionally, physical activity level is affected by past BMI. The most common adjustment method is to add both BMI and physical activity as time-varying covariates in a regression model. This allows us to estimate the effect of present BMI on AF risk, but not the total effect of past and present or future BMI (and hence the effect of change in BMI). This total effect can be biased because adjusting for present physical activity is equal to conditioning on a collider (between past physical activity and past BMI), and this may introduce selection bias.[13,29] Robins' parametric g-formula can overcome this bias. The parametric g-formula has previously been used to estimate the effect of hypothetical interventions on, among others, the risk of myocardial infarction,[30,31] ischaemic stroke,[32,33] and diabetes.[34]

In short, the estimation process is as follows. First, for each time-period from the baseline to the end of the follow-up period, use linear and logistic regression to model each risk factor, risk of non-AF death, and risk of AF as a function of prior risk factor history. Second, simulate a cohort under the selected interventions in five steps: (i) use the observed values of covariates at baseline; (ii) predict values of covariates at the next time point using the coefficients from the regression models; (iii) 'intervene' by setting the values of the covariates to the intervention-values; (iv) predict the probability of AF and non-AF death using these new values; (iv) repeat steps (ii) through (iv) for each time period and estimate the population risk as the average of the subject-specific risks. The 95% confidence limits were defined as the 2.5% and 97.5%iles using non-parametric bootstrapping with 1000 samples.

Time-fixed variables included in the model as potential confounders were baseline (e.g. Tromsø4 covariates) sex, age, education, marital status, physical activity at work, history of myocardial infarction and stroke, and pre-baseline (e.g. Tromsø2 and Tromsø3 covariates) smoking status, physical activity during leisure time, alcohol consumption, BMI, SBP, DBP, and total cholesterol level. The number of cigarettes per day, physical activity during leisure time, alcohol consumption, BMI, diabetes mellitus, SBP, DBP, total cholesterol, and HDL cholesterol were modelled as time-varying covariates in the listed

order. In *Figure 2*, we present a directed acyclic graph (DAG) of the causal structure between time-varying exposures, time-varying covariates, and the risk of AF. In Supplementary material online, *Figure S2*, we present a DAG of the assumed causal relationship between variable measurements at each visit and AF. Both DAGs are made using DAGitty.[35] We present population risk ratios and risk differences by comparing the estimated long-term risk of AF under each intervention with the risk under no intervention (the natural course), in addition to the average and cumulative percent intervened. The validity of our models was examined by comparing the observed risk of AF and death, and the observed means of the time-varying confounders, with those predicted by the models.

We investigated if the effect of the interventions varied by education level by performing a sub-group analysis on those with university/college education (≥4 years and <4 years) vs. lower levels (high school 10–12 years and/or primary school 7–10 years). Effect modification was also assessed by sub-groups of sex. The SAS macro and its documentation are available online (https://causalab.sph.harvard.edu/software/).

Results

Baseline characteristics

We included 14 923 women and men aged 28–82 years (*Table 1*). For women, mean age at baseline was 46 years, 26% had college or university-level education, 40% were daily smokers, 49% were sufficiently physically active, 63% had an alcohol intake of at least one unit per week, mean (standard deviation) BMI was 24.7 (4.0) kg/m^2, and SBP was 129 (18.6) mmHg. For men, the mean age at baseline was 48 years, 29% had college or university-level education, 37% were daily smokers, 55% were sufficiently physically active, 78% had an alcohol Intake of at least one unit per week, mean BMI was 25.8 (3.3) kg/m^2, and SBP was 137 (16.8) mmHg. In women and men, respectively, there were 420 and 932 incident cases of AF and 588 and 1130 deaths during a maximum 22-year follow-up period. The incidence rate of AF was 2.92 per 1000 person-years in women and 6.87 per 1000 person-years in men.

Simulated and observed risk of AF

The simulated and observed long-term risk of AF was 6.15% and 7.04% in women, and 13.0% and 14.6% in men (*Table 2*). For the time-varying covariates, the simulated and observed values had small mean differences, indicating that the model under the null was satisfactory (see Supplementary material online, *Figure S1*).

Effect of single interventions

Of the interventions, only the reduction of BMI was statistically significant, associated with a 16% reduced risk in women [95% confidence interval (CI) 4%, 25%], and a 14% reduced risk in men (95% CI 6%, 23%) (*Table 2*). Although not significant, all other single interventions were associated with a reduced risk of AF in women. In men, weaker intervention effects were observed, and interventions to become sufficiently physically active were significantly associated with an 8% increased risk.

Effect of joint interventions

The joint intervention on smoking, physical activity, alcohol, and BMI was significantly associated with a reduced risk of 35% in women (95% CI 9%, 54%). The joint intervention on all covariates (smoking, physical activity, alcohol, BMI, SBP, and DBP) was associated with a significantly reduced risk of 41% in women (95% CI 17%, 61%). In men, the joint interventions were protective but not significant. The average percent intervened on was 87% in women and 94% in men for the joint intervention on all covariates.

Sub-group analysis by sex and education level

In sub-group analyses of women and men, the relative and absolute effect of being sufficiently physically active was significantly different between women and men [There was a 7% reduced risk (95% CI −4%, 18%) in women vs. an 8% increased risk (95% CI −2%, −13%) in men, and a risk difference of −0.43 (−1.10, 0.25) in women and of 1.01 (0.23, 1.78) in men] (*Table 2*). We observed a borderline significant sex difference for the joint intervention on all covariates, $P = 0.06$. In sub-groups analyses of education at university/college level compared to high school and/or primary school, no significant differences in the relative or absolute effect of any interventions were found (*Table 3*).

Discussion

We found that risk reduction strategies including quitting smoking, sufficient physical activity, moderate alcohol intake, BMI reduction, and lowering BP could have prevented 41% of incident AF in women and 14% in men. We found notable sex differences in the relative risk reductions by joint interventions and in the relative and absolute risk reduction by sufficient physical activity. We found no significant differences in the absolute or relative effect of any interventions between the educational level sub-groups.

In our study, lowering BMI was the only intervention that was significantly associated with reduced risk of AF in both women and men. In men, we found a slightly increased risk of AF by the intervention of physical activity. Some studies have demonstrated a high prevalence of AF in male endurance athletes, and studies investigating wider ranges of physical activity levels and risk of AF have found results varying from decreased risk to a U-shaped relationship, but increased risk has also been demonstrated.[36] The Tromsø Study has previously shown a J-shaped association between physical activity and AF with an increased risk of AF in the highest physical activity levels, especially among men.[36] This may explain parts of the finding in our study of an increased risk of AF by the intervention in physical activity in men. This may also be a part of the explanation for the difference in the effect of the joint interventions between women and men (41% vs. 14% reduced risk) because the effect of the intervention on physical activity may outweigh the beneficial effect of reducing BMI in men, but not in women. Our study found small effects of each single intervention (3–15% change in risk). However, the effect of the joint interventions was greater overall (41% reduced risk in women and 14% reduced risk in men). This may imply multiplicative effects where several small changes have large benefits regarding the risk of AF, especially in women.

If existing literature demonstrated a clear social gradient in AF risk, one could also expect to find a social gradient in the effect of lifestyle interventions on AF risk. However, existing literature on these risks is inconclusive. A systematic review from 2018 that includes 12 studies found no association between education and the risk of AF.[15] A Danish study from 2020 that includes almost 2.5 million individuals found that a higher level of education was associated with a lower risk of AF in young individuals, but this association decreased with age and was almost absent for the oldest age groups.[37] We did not find any significant differences in the absolute or relative effect of the joint interventions in the different levels of education. To our knowledge, no other studies have investigated the effect of interventions on modifiable risk factors on AF risk in levels of SES or investigated if the effect of modifiable risk factors on AF risk differs between levels of SES.

Table 1 Descriptive characteristics by sex and survey[a]

	Women			Men		
	Tromsø4 1994–95	Tromsø5 2001	Tromsø6 2007–08	Tromsø4 1994–95	Tromsø5 2001	Tromsø6 2007–08
n	7418	2633	3888	7505	2381	3671
Age, years	45.8 (9.3)	52.7 (9.2)	60.8 (9.3)	47.8 (10.6)	54.3 (10.3)	61.7 (10.0)
Education						
≤10 years of schooling	37.0 (2744)	37.2 (2549)	38.6 (1493)	32.4 (2434)	32.0 (2151)	32.0 (1153)
High school diploma	37.3 (2764)	37.5 (2574)	36.3 (1405)	38.3 (2878)	38.6 (2595)	38.6 (1392)
College or university <4 years	13.2 (981)	13.1 (897)	12.5 (483)	16.4 (1233)	16.8 (1128)	17.4 (628)
College or university ≥ 4 years	12.5 (929)	12.3 (841)	12.6 (486)	12.8 (960)	12.6 (843)	11.9 (430)
Daily smoking, %						
Non-smoker	59.9 (4444)	61.8 (4241)	78.7 (3045)	62.6 (4696)	64.6 (4340)	81.3 (2929)
1–4 cigarettes/day	3.0 (224)	2.8 (195)	1.4 (55)	1.8 (137)	1.9 (126)	0.9 (34)
5–14 cigarettes/day	27.3 (2023)	26.4 (1812)	14.9 (575)	18.4 (1380)	17.9 (1203)	11.4 (410)
15–24 cigarettes/day	9.0 (668)	8.2 (566)	4.6 (178)	14.5 (1087)	13.5 (905)	5.9 (211)
≥25 cigarettes/day	0.8 (59)	0.7 (47)	0.4 (14)	2.7 (205)	2.1 (143)	0.5 (19)
Leisure time physical activity[b], %						
Inactive	7.0 (517)	6.0 (412)	4.3 (166)	7.4 (557)	6.3 (425)	6.1 (221)
Insufficiently active	43.7 (3239)	42.2 (2897)	50.6 (1957)	37.6 (2823)	37.2 (2496)	52.8 (1902)
Sufficiently active	49.4 (3662)	51.8 (3552)	45.1 (1744)	55.0 (4125)	56.5 (3796)	41.1 (1480)
Alcohol consumption, %						
0 units per week	37.2 (2758)	34.1 (2343)	16.2 (626)	22.0 (1652)	19.8 (1333)	9.1 (329)
>0 ≤ 1 unit per week	23.0 (1703)	23.2 (1590)	29.0 (1120)	15.4 (1159)	15.1 (1015)	23.0 (828)
>1 ≤ 2 units per week	16.9 (1253)	17.4 (1191)	24.4 (942)	15.7 (1179)	16.0 (1073)	19.8 (714)
>2 ≤ 3 units per week	9.3 (691)	10.0 (688)	8.4 (326)	12.8 (958)	13.2 (889)	15.5 (557)
>3 ≤ 4 units per week	5.3 (390)	5.7 (393)	13.2 (510)	9.2 (689)	9.1 (611)	15.4 (556)
>4 units per week	8.4 (623)	9.6 (656)	8.9 (343)	24.9 (1868)	26.7 (1796)	17.2 (619)
Body mass index, kg/m^2	24.7 (4.0)	25.2 (4.3)	26.7 (4.6)	25.8 (3.3)	26.0 (3.4)	27.2 (3.6)
Systolic blood pressure, mm Hg	129 (18.6)	130 (19.2)	137 (24.1)	137 (16.8)	137 (17.0)	141 (20.7)
Total serum cholesterol, mmol/L	6.0 (1.3)	6.0 (1.2)	5.9 (1.1)	6.2 (1.2)	6.0 (1.2)	5.6 (1.1)
Serum high-density lipoprotein cholesterol, mmol/L	1.7 (0.4)	1.6 (0.4)	1.7 (0.4)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)
Diabetes, %	0.9 (64)	1.4 (95)	4.8 (184)	1.6 (117)	1.9 (125)	5.5 (198)
Heart attack at baseline, %	0.5 (38)			3.7 (275)		
Stroke at baseline, %	0.6 (45)			1.2 (92)		
Marital status						
Single	17.4 (1293)	17.3 (1184)	13.9 (536)	22.1 (1656)	22.3 (1499)	18.0 (648)
Married/registered partnership	64.6 (4789)	65.3 (4480)	68.7 (2655)	65.6 (4925)	66.1 (4443)	71.0 (2558)
Widow/widower	4.0 (298)	3.9 (266)	4.5 (174)	1.4 (103)	1.2 (81)	1.2 (45)
Divorced	11.8 (872)	11.5 (790)	11.2 (433)	9.1 (680)	8.6 (579)	8.2 (295)
Separated	2.2 (166)	2.1 (141)	1.8 (69)	1.9 (141)	1.7 (115)	1.6 (57)
Physical activity at work						
Mostly sedentary	40.4 (2996)	40.3 (2768)	40.3 (1559)	46.4 (3479)	46.0 (3091)	46.8 (1688)
A lot of walking	36.2 (2683)	36.3 (2489)	36.3 (1404)	24.1 (1811)	24.4 (1640)	25.1 (905)
A lot of walking and lifting	21.6 (1601)	21.5 (1474)	21.1 (815)	18.8 (1413)	19.1 (1282)	17.9 (645)
Heavy manual labour	1.9 (138)	1.9 (130)	2.3 (89)	10.7 (802)	10.5 (704)	10.1 (365)

The Tromsø Study 1994–2008.
[a]Numbers are given as percent (number) or as mean (standard deviation).
[b]Inactive = no minutes of light or hard physical activity per week. Sufficiently active ≥180 min per week moderate physical activity or ≥90 min: insufficiently active = all other levels.

To our knowledge, only one previous study has investigated the effect of interventions on incident AF risk using the parametric g-formula.[6] Conner et al. only considered BMI as an intervention variable and found a 30% (95% CI 2%, 50%) risk reduction in women and an 18% (95% CI −1%, 34%) risk reduction in men for BMI 18.5–29.9 kg/m^2 compared to BMI 30–41 kg/m^2.[6] This is in line with our main finding of BMI as the only single intervention of statistical significance in both women and men. However, because results from the parametric

Table 2 Risk of atrial fibrillation under hypothetical interventions by sex[a]

No.	Intervention	22-year risk of AF, % (95% CI)	Population risk ratio (95% CI)	Population risk difference[b] (95% CI)	Cumulative percent intervened on[c]	Average per cent intervened on[d]
	Women ($n = 7418$)					
0	Natural course	6.15 (5.47, 6.78)	1	0	0	0
1	All become non-smokers	5.88 (5.02, 6.68)	0.96 (0.88, 1.04)	−0.26 (−0.71, 0.21)	41	15
2	Physical activity > 180 min low/moderate intensity or >90 min hard int	5.73 (4.89, 6.66)	0.93 (0.82, 1.04)**	−0.43 (−1.10, 0.25)**	62	27
3	Alcohol intake >1 ≤ 2 units per week	5.33 (3.97, 6.68)	0.87 (0.66, 1.08)	−0.82 (−2.05, 0.50)	90	47
4	BMI ≤ 25 kg/m^2	5.19 (4.35, 6.03)	0.84 (0.75, 0.96)	−0.96 (−1.53, −0.23)	60	40
5	SBP ≤ 130 mm Hg	5.74 (4.63, 6.75)	0.93 (0.79, 1.08)	−0.41 (−1.28, 0.47)	67	43
6	DBP ≤ 80 mmHg	6.02 (5.23, 6.78)	0.98 (0.90, 1.05)	−0.13 (−0.61, 0.31)	53	29
7	Interventions 5–6	5.55 (4.67, 6.41)	0.90 (0.79, 1.02)	−0.60 (−1.31, 0.11)	77	54
8	Interventions 1–4	4.02 (2.79, 5.50)	0.65 (0.46, 0.91)*	−2.13 (−3.40, −0.53)	99	73
9	Interventions 1–6	3.61 (2.37, 5.04)	0.59 (0.39, 0.83)*	−2.54 (−3.74, −1.07)	100	87
	Men ($n = 7505$)					
0	Natural course	13.0 (12.1, 14.0)	1	0	0	0
1	All become non-smokers	13.4 (12.3, 14.7)	1.03 (0.99, 1.08)	0.38 (−0.15, 1.02)	40	14
2	Physical activity > 180 min low/moderate intensity or >90 min hard int	14.0 (12.6, 15.4)	1.08 (1.02, 1.13)**	1.01 (0.23, 1.78)**	58	24
3	Alcohol intake >1 ≤ 2 units per week	12.2 (10.3, 14.2)	0.94 (0.81, 1.09)	−0.82 (−2.49, 1.15)	92	49
4	BMI ≤ 25 kg/m^2	11.1 (9.79, 12.6)	0.86 (0.77, 0.94)	−1.89 (−2.95, −0.80)	74	53
5	SBP ≤ 130 mm Hg	12.1 (10.6, 13.5)	0.93 (0.84, 1.01)	−0.97 (−2.07, 0.18)	84	56
6	DBP ≤ 80 mmHg	13.6 (12.4, 15.1)	1.05 (0.99, 1.12)	0.61 (−0.18, 1.56)	72	43
7	Interventions 5–6	12.7 (11.4, 14.0)	0.97 (0.89, 1.05)*	−0.35 (−1.38, 0.63)	91	70
8	Interventions 1–4	11.5 (9.35, 14.1)	0.89 (0.73, 1.08)*	−1.50 (−3.53, 1.00)	99	80
9	Interventions 1–6[9]	11.3 (8.91, 14.1)	0.86 (0.70, 1.07)*	−1.77 (−3.99, 0.93)	100	94

The Tromsø Study 1994–2008.
AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Estimated using the parametric g-formula with fixed covariates: age, sex, education, former smoking, marital status, work time physical activity and history of myocardial infarction and/or stroke; and time-varying covariates smoking, physical activity, alcohol use, BMI, systolic and diastolic blood pressure, total cholesterol and diabetes mellitus.
[b]Observed risk 7.04% in women and 14.59% in men.
[c]The percentage of the population intervened in at least one of the periods.
[d]Average percent of the population intervened in a given period.
*Test for equality between men and women, $0.05 < P < 0.10$.
**Test for equality between men and women, $P < 0.05$.

g-formula are strongly dependent on baseline exposure values, the absolute and relative risk reductions are not always comparable across studies. In this case, baseline BMI was higher in the study from Conner *et al.* than in our study. Additionally, the target BMIs for interventions were different.

Few other studies have reported the effects of prospective risk factor reduction on AF primary prevention.[2] The Tromsø Study has recently demonstrated that individual changes in SBP and DBP in women and in BMI in men had the largest contribution among the studied risk factors on changes in AF incidence.[3] Reviews have summarized some of the existing, mostly observational, evidence on lifestyle and risk factor modification for reduction of AF incidence.[1,2,38] The reviewed studies have, however, used more conventional methods that require additional assumptions and can, therefore, not be directly compared with our estimates.

This study has several strengths. First, the Tromsø Study is a large, population-based cohort with high participation proportions, and includes participants from both urban and rural areas. The study sample is similar to the general Norwegian adult population regarding age and sex, but physical activity level and educational level are slightly higher than in the general population.[39] Consequently, a limitation of this study may be an overrepresentation of physically active persons and persons with higher education. Second, AF incidence is ascertained with high sensitivity, and events from both in- and out-patient clinics are included from the only hospital in the area. However, up to 40% of AF patients are asymptomatic, and some symptomatic cases are treated in primary health care only and never referred to the hospital. Therefore, a likely limitation is that the incidence is underestimated because not all AF patients seek the hospital.[3] Third, we adjusted for time-varying confounders affected by prior exposures and simulated long-term joint interventions on modifiable risk factors using the parametric g-formula. Time-varying confounding is a methodological challenge where many conventional methods fail.[29] Methods that use stratification, regression,

Table 3 Risk of atrial fibrillation under hypothetical interventions by education at baseline[a]

No.	Intervention	Population risk ratio (95% CI)		Population risk difference[b]	
		Education at university/college level	High school and/or primary school	Education at university/college level	High school and/or primary school
0	Natural course	Ref. (8.94% risk)	Ref. (9.74%)	Ref. (8.94% risk)	Ref. (9.74%)
1	All become non-smokers	1.02 (0.95, 1.07)	1.02 (0.97, 1.07)	0.17 (−0.47, 0.61)	0.15 (−0.34, 0.67)
2	Physical activity > 180 min low/moderate intensity or >90 min hard int	1.03 (0.92, 1.11)	1.04 (0.98, 1.11)	0.31 (−0.70, 1.01)	0.42 (−0.20, 1.07)
3	Alcohol intake >1 ≤ 2 units per week	0.85 (0.66, 1.07)	0.93 (0.81, 1.06)	−1.38 (−3.18, 0.64)	−0.66 (−1.91, 0.62)
4	BMI ≤ 25 kg/m^2	0.91 (0.76, 1.05)	0.85 (0.78, 0.93)	−0.83 (−2.14, 0.40)	−1.47 (−2.19, −0.73)
5	SBP ≤ 130 mm Hg	0.85 (0.70, 0.98)	0.97 (0.87, 1.05)	−1.35 (−2.75, −0.22)	−0.33 (−1.26, 0.48)
6	DBP ≤ 80 mmHg	1.10 (1.01, 1.20)	1.01 (0.95, 1.07)	0.87 (0.08, 1.84)	0.06 (−0.49, 0.65)
7	Interventions 5–6	0.94 (0.80, 1.06)	0.97 (0.89, 1.04)	−0.50 (−1.82, 0.52)	−0.30 (−1.08, 0.34)
8	Interventions 1–4	0.78 (0.55, 1.06)	0.84 (0.69, 1.01)	−1.93 (−4.06, 0.57)	−1.55 (−3.07, 0.07)
9	Interventions 1–6	0.72 (0.48, 1.02)	0.82 (0.65, 0.98)	−2.54 (−4.81, 0.14)	−1.79 (−3.44, −0.20)

The Tromsø Study 1994–2008.
BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Estimated using the parametric g-formula with fixed covariates: age, sex, education, former smoking, marital status, work time physical activity and history of myocardial infarction and/or stroke; and time-varying covariates smoking, physical activity, alcohol use, BMI, systolic and diastolic blood pressure, total cholesterol and diabetes mellitus. Test for equality between sub-groups of education at university/college level (≥4 years and <4 years) and high school (10–12 years) and/or primary school (7–10 years), found no significant differences (all $P > 0.05$).
[b]Observed risk 10.25% for participants with education at university/college level and 11.09% for participants with high school and/or primary school.

or matching to adjust for time-varying covariates will fail to estimate the joint effect of a time-varying covariate on an outcome because these methods for adjustment introduce selection bias.[29] Thus, by eliminating time-varying confounding they introduce a new bias. The parametric g-formula overcomes this bias and provides unbiased and properly adjusted effects of time-varying covariates affected by prior exposures.[29]

Our results are only valid under the general assumptions for cohort studies of no model misspecification, no unmeasured or residual confounding, and no measurement error. Our results support the absence of model misspecification under the null, as the observed and estimated risks under no intervention were rather similar (6.1% and 7.0% in women, and 13.0% and 14.6% in men). The estimated effects are increasingly model dependent when the average percent intervened on approaches 100% and, consequently, more prone to misspecification. This is a potential limitation of our study. Another potential limitation is that unmeasured confounding is plausibly present, as we adjusted for several confounders but did not include data on other potential confounders, for example, diet. Similarly, some measurement error is expected, especially when using self-reported variables on lifestyles like physical activity, smoking, and alcohol consumption. Physical activity and alcohol consumption had to be harmonized from different questionnaires across the included surveys, and, thus, are especially prone to information bias. Further, the parametric g-formula has a set of specific assumptions: counterfactual consistency, sequential exchangeability, and positivity, which are described in detail elsewhere.[29] Consistency implies that interventions should be well defined and that the counterfactual outcome under each intervention should be the same as the observed outcome under the same level of risk factor.[29,32] As Vangen-Lønne et al. pointed out in a similar project on interventions for stroke incidence, the consistency assumption may hold for lifestyle and behavioural risk factors such as smoking and alcohol use but is less likely to hold for metabolic risk factors such as BMI and BP.[32] Consequently, the estimated effects should be interpreted as the effect of a combination of changes or interventions that led to a reduction in BMI or BP observed in the study population during the follow-up period.[32] The sequential exchangeability assumption implies no uncontrolled confounding and no selection bias. The positivity assumption implies that there should be exposed and unexposed individuals within all confounder and prior exposure levels, i.e. that all observed treatment levels should be observed within all confounders. The parametric g-formula is also subject to the g-null paradox; the paradox that some model misspecification is guaranteed in some settings (e.g. when the null hypothesis is true) and as such the null hypothesis may be falsely rejected.[29] We attempted to avoid this paradox by keeping our model flexible and only considering interventions for which we in advance believed to have an effect. Another potential limitation is that 41% of our total cohort only attended the baseline and pre-baseline visits. However, we have no reason to suspect a systematic difference between those who were invited to later surveys and those who were not. Those who were invited to later surveys were on average older but were otherwise considered to be randomly sampled.

Conclusion

We found that the population burden of AF could be reduced by modifying lifestyle risk factors with hypothetical interventions in line with clinical guidelines. Two out of five incident cases of AF in women and almost one out of six cases in men that occurred during a maximum 22-year follow-up period in the Tromsø Study population could have been prevented by six hypothetical scenarios of intervention on lifestyle risk factors. The lowering of BMI was the most effective hypothetical intervention in both women and men. The effect of joint intervention did not differ significantly between those with college/university level education compared to those with high school and/or primary school studies, either on a relative scale or on an absolute scale.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

All authors contributed to conceptualization, methodology, interpretation of data, and writing (review and editing) in this study. L.N. and T.W. did the formal analysis. M.L.L. contributed to the data collection. E.S., M.L.L., and T.W. contributed to supervision. L.N. did the visualization of data and results and the writing of the original draft.

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Data availability

The data underlying this article were provided by the Tromsø Study by permission. Data from the Tromsø Study are available upon reasonable request and application. More information can be found at http://www.tromsoundersøkelsen.no.

Previous presentations: These results have been orally presented at two epidemiology conferences: the NordicEPI conference in Reykjavik, Iceland, 18 August 2022, and at the Norwegian Epidemiological Association conference in Tromsø, Norway, 27 October 2022.

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