openheart

Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium

Bente Morseth ,[1] Bastiaan Geelhoed,[2] Allan Linneberg,[3,4] Lars Johansson,[5] Kari Kuulasmaa ,[6] Veikko Salomaa ,[6] Licia Iacoviello ,[7,8] Simona Costanzo ,[8] Stefan Söderberg ,[5] Teemu J Niiranen,[6,9] Julie K K Vishram-Nielsen,[3,10] Inger Njølstad,[11] Tom Wilsgaard,[11] Ellisiv B Mathiesen,[12,13] Maja-Lisa Løchen ,[11] Tanja Zeller,[2,14] Stefan Blankenberg,[2,14] Francisco M Ojeda,[2] Renate B Schnabel ,[2,14] On behalf of the MORGAM consortium

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2021-001624).

To cite: Morseth B, Geelhoed B, Linneberg A, *et al*. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart* 2021;**8**:e001624. doi:10.1136/openhrt-2021-001624

Received 13 February 2021
Accepted 13 July 2021

For numbered affiliations see end of article.

Correspondence to
Dr Bente Morseth; bente.morseth@uit.no

ABSTRACT

Background The main aim was to examine age-specific risk factor associations with incident atrial fibrillation (AF) and their attributable fraction in a large European cohort. Additionally, we aimed to examine risk of stroke and mortality in relation to new-onset AF across age.

Methods We used individual-level data (n=66 951, 49.1% men, age range 40–98 years at baseline) from five European cohorts of the MOnica Risk, Genetics, Archiving and Monograph Consortium. The participants were followed for incident AF for up to 10 years and the association with modifiable risk factors from the baseline examinations (body mass index (BMI), hypertension, diabetes, daily smoking, alcohol consumption and history of stroke and myocardial infarction (MI)) was examined. Additionally, the participants were followed up for incident stroke and all-cause mortality after new-onset AF.

Results AF incidence increased from 0.9 per 1000 person-years at baseline age 40–49 years, to 17.7 at baseline age ≥70 years. Multivariable-adjusted Cox models showed that higher BMI, hypertension, high alcohol consumption and a history of stroke or MI were associated with increased risk of AF across age groups ($p<0.05$). Between 30% and 40% of the AF risk could be attributed to BMI, hypertension and a history of stroke or MI. New-onset AF was associated with a twofold increase in risk of stroke and death at ages≥70 years ($p\leq0.001$).

Conclusion In this large European cohort aged 40 years and above, risk of AF was largely attributed to BMI, high alcohol consumption and a history MI or stroke from middle age. Thus, preventive measures for AF should target risk factors such as obesity and hypertension from early age and continue throughout life.

Key questions

What is already known about this subject?

► Modifiable risk factors for atrial fibrillation (AF), such as obesity, hypertension, diabetes, smoking and previous cardiovascular disease, may together account for more than 50% of the AF burden. However, although risk factors for AF have been extensively examined, limited attention has been devoted to their attributable fraction in relation to age.

What does this study add?

► In this large cohort of adult and elderly European men and women, risk of AF was primarily attributed to body mass index, hypertension and previous stroke or myocardial infarction, together explaining 30%–40% of the AF risk. Population attributable risk varied with age, with a substantial AF burden attributed to body mass index at ages 40–69 years, whereas population attributable risk for hypertension was highest and significant only at ages ≥60 years. The AF risk attributed to previous myocardial infarction or stroke increased slightly with age.

How might this impact on clinical practice?

► Increased understanding of the relative contribution of modifiable risk factors to the development of AF, as well as complications of AF across age groups, would help target prevention and allocate healthcare resources specific to age group needs.

INTRODUCTION

Atrial fibrillation (AF) has become a disease with significant public health impact, estimated to affect 20 million men and 12 million women worldwide.[1] Major complications of AF include stroke,[2] hospitalisations[3] and mortality.[4] Several predictors for AF have been described, including modifiable risk factors such as obesity, hypertension, diabetes, smoking and previous cardiovascular disease,[5–7] which may together account for more than 50% of the AF burden.[8]

AF incidence increases with age[9–11] and is commonly related to the presence of cardiovascular risk factors or disease in older individuals.[12] On the other hand, transition to unhealthy metabolic risk factor constellations occurs earlier in life,[13] and a recent study suggests that even in early-onset AF, 90% of individuals had metabolic risk factors and comorbidities.[14] Although several large cohort studies have addressed the role of lifestyle risk factor for AF[15 16] and potential sex differences,[17] there is a lack of research on the impact of the risk factors in relation to age at AF onset.

Increased understanding of the contribution of modifiable risk factors in relation to age at AF onset, as well as complications of AF across age groups, would help target prevention and allocate healthcare resources specific to age group needs. The MOnica Risk, Genetics, Archiving and Monograph (MORGAM) consortium provides a unique opportunity to expand the understanding of AF risk factors and complications from middle aged to older individuals. The main aim of this study was to examine age-specific risk factor associations with incident AF and their attributable fraction in European adults and elderly. Furthermore, we aimed to examine the risk of stroke and all-cause mortality after new-onset AF at different ages.

METHODS

Study population

This study is based on the MORGAM consortium, which is a multinational collaborative initiative addressing cardiovascular biomarkers, risk factors and endpoints using pooled and harmonised data from European community-based cohorts.[18] In this study, individual-level data from five cohort studies in the MORGAM consortium[18]; DANMONICA (Denmark),[19] FINRISK (Finland)[20] Moli-sani (Italy),[21] Northern Sweden MONICA,[22] and the Tromsø Study (Norway)[23] were included. Cohort-specific procedures for enrolment and follow-up are provided in the online supplemental D1. In brief, all included cohort studies are population-based with repeated surveys. The studies included in MORGAM are population-based studies covering a specific region in several European countries, recruiting from birth cohorts or random sampling from a national or local population register. Most studies do not specify exclusion criteria.

In total, 66 951 individuals from the five MORGAM cohort studies were included in our analyses, after exclusion due to left censoring (n=448), prevalent AF at baseline (n=879) and/or missing baseline AF information (n=6757). Only individuals aged ≥40 years at baseline were included in order to harmonise the age range.

Risk factors and biomarkers

Data on risk factors were available from the baseline examinations, which were conducted between 1982 and 2010. Systolic blood pressure (SBP), total cholesterol, weight and height were measured by standardised methods and body mass index (BMI) (kg/m^2) was calculated. Information on daily smoking, average alcohol consumption, diabetes, antihypertensive medication, history of stroke and myocardial infarction (MI) was self-reported. Harmonised data from the various studies were transferred to the MORGAM Data Centre in Helsinki.[24]

Biomarkers were available for 39%–49% of the participants (available in FINRISK, Moli-sani, Northern Sweden, and Dan-MONICA) (online supplemental tables S1–S5). Measurements from stored blood samples include C reactive protein (CRP) (n=32 893), which was determined by latex immunoassay CRP16 (Abbott, Architect c8000), and N-terminal-pro B-type natriuretic peptide (Nt-pro-BNP) (n=26 048, measured on the ELECSYS 2010 platform using an electrochemiluminescence immunoassay (Roche Diagnostics). Analyses of estimated glomerular filtration rate (eGFR), CRP, and Nt-proBNP are described in detail elsewhere.[25]

Follow-up for AF, stroke and mortality

Incident AF, non-fatal and fatal stroke events, and death during follow-up were identified by linkage to regional or national hospital discharge registries, diagnosis registries, and causes of death registries, which were also screened for incident AF as a comorbidity of individuals who died of other causes. Follow-up lasted from the date of the baseline examinations to the end of 2010 (DANMONICA, Tromsø and FINRISK) or 2011 (Moli-sani and Northern Sweden), truncated at 10 years for the data analysis (median (IQR): 10.0 (4.8–10.0) years).

Statistical analyses

For each age group (40–49, 50–59, 60–69 and ≥70 years at baseline), AF incidence rates were calculated as the number of AF cases per 1000 person-years within the 10-year follow-up period. The association between risk factors and incident AF within each age stratum was estimated as HR with 95% CI using Cox regression. The goodness-of-fit of all Cox models was checked with respect to the proportional hazard (PH) assumption. In order to assure that the PH assumption was valid during the Cox regressions, interactions with time were adjusted for when needed. The PH assumptions were tested using the Schoenfeld residuals. Prevalent AF cases were excluded from the analysis. Multivariable-adjusted models include adjustment for age, sex, BMI, hypertension (SBP ≥140 mm Hg and/or taking antihypertensive drugs), total serum cholesterol, smoking, history of diabetes, alcohol consumption and study site. We set the follow-up duration to a fixed maximum value (10 years) to avoid large differences in follow-up. Missing data were handled by using available cases.

Population attributable fraction (PAF) was calculated for each categorical risk factor. In each age group, the PAF for a risk factor was estimated using the fully adjusted estimated HRs and the following equation[26]:

$$PAF_i = pd_i * (HR_i - 1)/HR_i$$

where PAF_i is the PAF of the i-th category, HR_i is the fully adjusted HR for the i-th category, pd_i is the proportion of those in the i-th category among the cases during the first 5 years of the follow-up. The total PAF of a risk factor was calculated as the sum of all PAF_i over i=1 to n, where n is the number of categories of the risk factor in question. For each PAF_i and PAF, a 95% CI was calculated using bootstrapping. Bootstrapping was also used to estimate the p values for the differences between PAFs of different age groups for the same risk factor. To decide whether a difference was significant, a (Bonferroni-corrected) alpha level of 0.05/N was used, where N is the number of comparisons per risk factor category level (there are four age groups, so N is (4×4–4)/2=6, so alpha=0.05/6=0.008).

In online supplemental table S6, second-order interactions between covariates were included if they reached significance (taking into account multiple testing). Interactions with time since baseline (included in the analysis as a time-varying covariate) were included when needed to avoid violations of the PH assumption. The PAF analyses used fully adjusted HRs.

In order to estimate the HRs of new-onset AF for stroke and mortality by age-decades, time-dependent multiple adjusted Cox regressions were performed in each age stratum where incident AF was used to predict time to event (where event is (1) stroke and (2) mortality). For the stroke analysis, cases with previous stroke history were excluded.

Analyses were performed in R V.3.5.3, in which Cox regressions were performed using the survival package. We assumed a two-tailed p<0.05 as statistically significant.

Table 1 Baseline characteristics of the pooled MORGAM cohort (n=66 951)

Characteristics	Median (IQR) or n (%)	Missing values
Age (years)	53.5 (46.4–61.2)	0 (0.0%)
Sex (n (%) men)	32 855 (49.1)	0 (0.0%)
BMI (kg/m^2)	26.4 (23.9 to 29.5)	480 (0.7%)
Systolic blood pressure (mm Hg)*	137 (124 to 152)	459 (0.7%)
Total serum cholesterol (mmol/L)	5.9 (5.2 to 6.8)	669 (1.0%)
Daily smoker	17 305 (26.0)	370 (0.6%)
History of diabetes	3526 (5.3)	83 (0.1%)
Taking antihypertensive drugs	11 977 (19.2)	4576 (6.8%)
Hypertension†	33 470 (52.2)	2781 (4.2%)
Average daily alcohol consumption (g)	3.0 (0.0 to 12.0)	11 777 (17.6%)
History of MI or stroke	3625 (5.4)	62 (0.1%)
C reactive protein (mg/L)	1.4 (0.7 to 2.9)	34 058 (50.9%)‡
Nt-proBNP (pg/mL)	52 (27 to 96)	40 903 (61.1%)§
log10 (Nt-proBNP (pg/mL))	1.7 (1.4 to 2.0)	40 903 (61.1%)§
Creatinine (mg/dL)	0.8 (0.7 to 0.9)	34 065 (50.9%)¶
eGFR¶	94.8 (84.0 to 103.5)	34 065 (50.9%)‡

*Mean of two measurements.
†Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
‡Missing by design in the Tromsø Study and partly in other studies than the 1997 cohort of FINRISK (online supplemental tables S2 and S4).
§Missing by design in DAN-MONICA and the Tromsø Study, and partly in other studies except the 1997 cohort of FINRISK (online supplemental tables S1, S2 and S4).
¶Using the Chronic Kidney Disease Epidemiology Collaboration formula with creatinine.
BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MORGAM, MOnica Risk, Genetics, Archiving and Monograph; Nt-proBN, N-terminal-pro B-type natriuretic peptide.

RESULTS

The median age at baseline was 53.5 years (IQR 46.4–61.2), ranging from 40 to 98 years, and 49.1% of the 66 951 participants were men (table 1). The prevalence of previous disease (diabetes and history of MI or stroke) was low (<6%), although more than half of the participants (52.2%) had an SBP ≥140 mm Hg or were taking antihypertensive drugs. About one-fourth (26.0%) of the participants smoked daily. Study characteristics by cohort are shown in online supplemental tables S1–S5. Risk factor distributions at baseline were in general more favourable at younger age (table 2). Prevalence of hypertension, overweight, diabetes and previous MI or stroke increased with age, whereas smoking decreased gradually by age, and daily consumption of alcohol showed a stable pattern across all age groups.

Over a follow-up time of up to 10.0 years, 2021 (3.0%) cases of AF were detected. AF incidence rate increased gradually from 0.9 per 1000 person-years at age 40–49 years to 17.7 at the age of ≥70 years. Adjusted HR for AF increased exponentially with age and was 13.5 times higher (HR 13.53, 95% CI 10.98 to 16.68) at ages ≥70 compared with 40–49 years (figure 1).

Age-stratified unadjusted risk of AF for each risk factor is shown in online supplemental table S7. Age-stratified multivariable-adjusted Cox regression models showed that BMI and a history of MI or stroke were consistently associated with increased risk of AF in all age groups (p<0.001) (table 3), whereas high alcohol consumption, total serum cholesterol, and hypertension increased the risk of AF only at certain ages. For each 5 kg/m^2 increase in BMI, risk of AF increased significantly with 37%–41% (p≤0.001) at ages 40–69 years. At the age of ≥70 years, AF risk was still positively associated with BMI (HR 1.17, 95% CI 1.06 to 1.29), but the risk was lower than at younger ages (difference from ages 40-69: p≤0.033). A history of MI or stroke significantly increased the risk of AF (p≤0.001 at all ages), with highest HRs at age 40–49 years (HR 4.60, 95% CI 2.56 to 8.27; p≥0.011 compared with other age groups). High alcohol consumption significantly increased the risk of AF by 13%–18% at ages up to 70 years (p<0.05), but not in participants ≥70 years. Total serum cholesterol decreased the risk of AF by 4%–11%, but significantly only at ages 50–69 years (p<0.05), whereas hypertension increased the risk of AF by 19%–40%, although significantly only at older ages (≥60 years) (p<0.05). Smoking, CRP and eGFR were not significantly associated with AF, whereas participants with Nt-pro-BNP levels ≥900 pg/mL showed higher AF risk at all ages (p≤0.001).

Table 2 Risk factor distribution by age groups at baseline

	Risk factor distribution (n=66 951)			
	40–49 years (n=24 914)	50–59 years (n=21 824)	60–69 years (n=13 441)	≥70 years (n=6772)
BMI (kg/m^2)	25.5 (23.1 to 28.4)	26.8 (24.2 to 29.8)	27.5 (24.8 to 30.7)	27.0 (24.3 to 30.1)
<30	20 806 (84.0)	16 418 (75.8)	9414 (70.6)	4949 (73.8)
≥30	3951 (16.0)	5250 (24.2)	3926 (29.4)	1757 (26.2)
Systolic blood pressure (mm Hg)*	129 (119 to 141)	138 (125 to 152)	145 (132 to 160)	154 (140 to 170)
<140	18 097 (73.1)	11 658 (53.8)	5277 (39.6)	1667 (24.8)
≥140	6656 (26.9)	10 023 (46.2)	8058 (60.4)	5056 (75.2)
Diabetes	539 (2.2)	1115 (5.1)	1196 (8.9)	676 (10.0)
Daily smoker	7802 (31.4)	5871 (27.0)	2628 (19.7)	1004 (15.0)
Taking antihypertensive drugs	1608 (7.0)	3958 (19.6)	3989 (31.3)	2422 (36.9)
Hypertension†	7389 (31.6)	11 423 (54.7)	9150 (69.5)	5508 (82.2)
Total serum cholesterol (mmol/L)	5.7 (5.0 to 6.5)	6.1 (5.3 to 6.9)	6.1 (5.3 to 6.9)	6.1 (5.3 to 7.1)
≤6.5	18 830 (76.3)	14 074 (65.1)	8556 (64.4)	4162 (62.3)
>6.5	5859 (23.7)	7558 (34.9)	4721 (35.6)	2522 (37.7)
Average daily alcohol consumption (g)	3.0 (0.0 to 12.0)	3.0 (0.0 to 12.0)	2.0 (0.0 to 11.0)	2.0 (0.0 to 12.0)
History of MI or stroke	285 (1.1)	1024 (4.7)	1255 (9.3)	1061 (15.7)
eGFR‡	104.7 (93.9 to 109.3)	96.9 (85.5 to 101.9)	89.8 (78.2 to 95.0)	81.9 (69.9 to 87.9)
C reactive protein (mg/L)	1.0 (0.5 to 2.2)	1.4 (0.7 to 3.0)	1.7 (0.9 to 3.6)	1.9 (1.0 to 3.9)
Nt-proBNP (pg/mL)	35.9 (19.8 to 62.3)	44.9 (25.1 to 78.9)	70.8 (40.2 to 125.5)	126.6 (70.8 to 228.4)
log10 (Nt -proBNP (pg/mL))	1.6 (1.3 to 1.8)	1.7 (1.4 to 1.9)	1.9 (1.6 to 2.1)	2.1 (1.8 to 2.4)

Continuous variables are presented as median and IQR (25th and 75th percentile), binary variables as absolute and relative frequencies.
*Mean of two measurements.
†Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
‡Using the Chronic Kidney Disease Epidemiology Collaboration formula with creatinine.
BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; Nt-pro-BN, N-terminal-pro B-type natriuretic peptide.

Table 4 shows risk of AF attributed to each modifiable risk factor in age strata (ie, PAF for 5-year incident AF). Among lifestyle risk factors, BMI contributed to 8%–18% of the AF risk at ages <70, but at older ages, the relative attribution to BMI was low and non-significant (4.0%, 95% CI −1.31 to 9.20). Hypertension showed significant PAFs of 20% only at ages≥60 years, whereas diabetes showed a significant PAF only at ages≥70 years (6.0%, 95% CI 2.21 to 9.68). A history of stroke or MI contributed significantly to AF risk in all age groups with PAFs increasing gradually from 5% to 10%. Smoking and alcohol intake showed modest and non-significant PAFs. In general, 30%–40% of the AF risk could be attributed to BMI, hypertension and a history of stroke or MI.

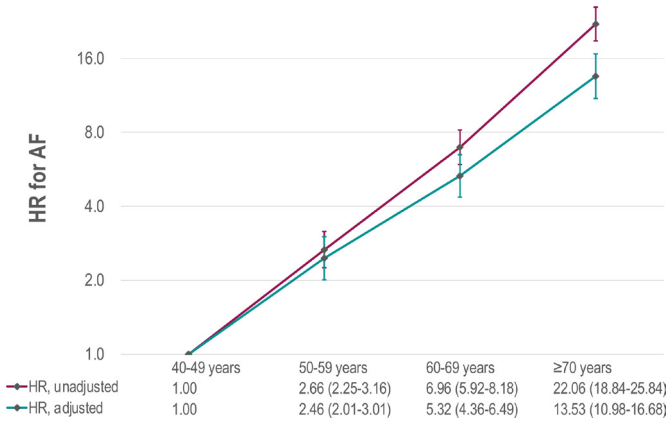

Figure 1 Risk of AF by age groups, presented as HR with 95% CI. HRs were presented on a log scale with base 2, adjusted for sex, BMI, SBP, total serum cholesterol, daily smoking, history of diabetes, antihypertensive drugs, daily alcohol consumption, and study site. AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure.

During the follow-up, 8.4% (n=5622) participants died, whereas 3.1% (n=2055) were diagnosed with stroke. New-onset AF was associated with a 1.8-fold to 2.6-fold increase in risk of death at ages ≥60 years (multivariable-adjusted p≤0.001, figure 2) and with a twofold risk of stroke at ages ≥70 years (HR 2.02, 95% CI 1.46 to 2.79, figure 2).

DISCUSSION

In this large, community-based cohort, risk of new-onset AF was associated with several lifestyle-related risk factors such as overweight, hypertension, high alcohol consumption and a history of MI or stroke. In all age groups, AF burden was largely attributable to BMI, hypertension, and previous stroke or MI, together explaining 30%–40% of the AF risk. However, their PAF varied with age, as we found a substantial AF burden attributed to BMI at ages 40–69 years, but low PAF for BMI among the oldest. PAF for hypertension was highest and significant only at ages ≥60 years, whereas PAF for previous MI or stroke showed

Table 3 Multivariable-adjusted HR for AF by age groups

	Multivariable-adjusted HR for AF			
	40–49 years (n=24 914)	50–59 years (n=21 824)	60–69 years (n=13 441)	≥70 years (n=6772)
BMI (per 5 kg/m^2 increase)	1.41 (1.18 to 1.68,<0.001)	1.37 (1.23 to 1.53,<0.001)	1.37 (1.25 to 1.50,<0.001)	1.17 (1.06 to 1.29, 0.001)*
Diabetes	0.57 (0.18 to 1.80, 0.337)	1.48 (1.04 to 2.09, 0.029)	1.27 (0.96 to 1.66, 0.090)	1.59 (1.23 to 2.06,<0.001)
Daily smoker	1.13 (0.79 to 1.63, 0.501)	1.14 (0.89 to 1.45, 0.305)	1.16 (0.92 to 1.46, 0.220)	1.00 (0.78 to 1.27, 0.988)
Hypertension†	1.40 (0.98 to 2.00, 0.068)	1.19 (0.94 to 1.51, 0.138)	1.32 (1.07 to 1.64, 0.011)	1.29 (1.02 to 1.63, 0.035)
Total serum cholesterol (per mmol/L increase)	0.91 (0.78 to 1.06, 0.242)	0.91 (0.83 to 0.99, 0.039)	0.89 (0.83 to 0.97, 0.004)	0.96 (0.89 to 1.03, 0.283)
Average daily alcohol consumption (per 20 g increase)	1.18 (1.02 to 1.36, 0.025)	1.17 (1.05 to 1.30, 0.005)	1.13 (1.00 to 1.28, 0.049)	0.92 (0.79 to 1.08, 0.327)‡
History of MI or stroke	4.60 (2.56 to 8.27,<0.001)§	1.93 (1.40 to 2.67,<0.001)	1.68 (1.32 to 2.13,<0.001)	1.57 (1.27 to 1.94,<0.001)
eGFR¶	1.07 (0.90 to 1.26, 0.430)	0.93 (0.84 to 1.03, 0.193)	1.00 (0.92 to 1.09, 0.984)	0.88 (0.81 to 0.96, 0.005)
C reactive protein (mg/L)	0.94 (0.83 to 1.06, 0.295)	1.00 (0.97 to 1.03, 0.960)	1.01 (0.99 to 1.02, 0.245)	1.01 (0.99 to 1.02, 0.348)
Nt-pro-BNP (per 10-fold increase)	5.51 (2.70 to 11.24,<0.001)	4.80 (3.29 to 6.98,<0.001)	5.46 (4.08 to 7.31,<0.001)	7.58 (5.62–10.24,<0.001)

Values are HR (95% CI, p value).
Adjusted for age, sex, BMI, total serum cholesterol, daily smoking, diabetes, hypertension, daily alcohol consumption and study site.
*P≤0.033 for difference between ages ≥70, and 50–59 and 60–69, respectively.
†Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
‡p≤0.047 for difference between ages ≥70 and the other age groups.
§P≤0.011 for difference between ages 40–49 and the other age groups.
¶Using the Chronic Kidney Disease Epidemiology Collaboration formula with creatinine.
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; Nt-proBN, N-terminal-pro B-type natriuretic peptide.

a slight increase with age. Finally, we found that newly diagnosed AF was associated with a twofold increase in risk of death and stroke but only at older ages.

AF incidence, risk factors and attributable risks

We observed a substantial increase in AF incidence with age that is comparable to age-specific incidence rates in the Rotterdam Study[11] and the Reykjavik study[9] but somewhat lower than the Framingham Study incidence rates.[10] The increasing incidence of AF[9–11] highlights the importance of modifiable risk factors,[27 28] which can be targeted and may contribute to prevention or deferral of AF onset.

In the present study, several modifiable risk factors such as BMI, previous MI or stroke, hypertension and alcohol consumption were associated with increased risk of AF, the first two consistently in all age groups. These observations are largely in agreement with a study of 10 million individuals in a national Korean health insurance database,[29] which showed that modifiable risk factors such as BMI, high alcohol intake, and hypertension increased the risk of AF in all age groups.

Our study extends previous research by addressing the proportion of incident AF that could be attributed to a

Table 4 Multivariable-adjusted population attributable fraction for AF by age groups

	Population attributable fraction (95% CI)			
	40–49 years (n=24 914)	50–59 years (n=21 824)	60–69 years (n=13 441)	≥70 years (n=6772)
BMI*	8.00 (0.43 to 15.56)	15.32 (7.74 to 22.90)	18.55 (12.18 to 24.92)†	3.95 (–1.31 to 9.20)
Diabetes	–2.19 (–7.39 to 3.01)	3.39 (–0.12 to 6.91)	2.88 (–0.67 to 6.42)	5.95 (2.21 to 9.68)
Daily smoker	2.32 (–5.64 to 10.28)	2.95 (–2.60 to 8.50)	2.57 (–1.35 to 6.48)	0.08 (–2.49 to 2.66)
Hypertension‡	15.03 (–1.74 to 31.79)	10.33 (–2.86 to 23.51)	19.83 (6.97 to 32.70)	20.03 (3.82 to 36.25)
Total serum cholesterol§	–5.54 (–12.25 to 1.17)	–8.94 (–15.63 to –2.25)	–4.93 (–11.04 to 1.17)	–2.98 (–8.97 to 3.00)
Average daily alcohol consumption¶	6.75 (–0.89 to 14.39)	1.84 (–3.33 to 7.00)	3.41 (0.12 to 6.70)	–2.39 (–5.41 to 0.63)
History of MI or stroke	4.49 (0.28 to 8.69)	6.54 (1.62 to 11.46)	7.34 (3.63 to 11.04)	9.88 (5.89 to 13.87)

Adjusted for age, sex, BMI, total serum cholesterol, daily smoking, diabetes, hypertension, daily alcohol consumption and study site.
*Reference category ≤30 kg/m^2.
†Significantly different from age ≥70, p=0.002; all other between-group p>0.008.
‡Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
§Reference category ≤6.5 mmol/L.
¶Reference category <20 g for women,<40 g for men.
AF, atrial fibrillation; BMI, body mass index; MI, myocardial infarction.

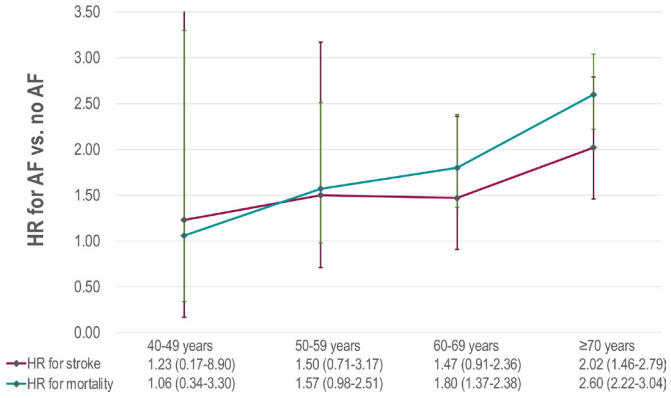

Figure 2 Risk of stroke and mortality according to new-onset AF versus no AF, presented as HR with 95% CI. HRs were adjusted for age, sex, BMI, SBP, total serum cholesterol, daily smoking, history of diabetes, antihypertensive drugs, daily alcohol consumption, and study site. AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure.

risk factor at different ages. The proportion of AF risk attributed to BMI increased with age up to 70 years, with PAFs of 15%–18% which is comparable to the Atherosclerosis Risk in Communities Study.[8] At ages ≥70 years, PAF for BMI was low and not statistically significant, suggesting that at older ages new-onset AF is primarily attributed to factors other than BMI. The risk of AF attributed to hypertension was high at all ages with the highest attributable fractions in participants ≥60 years, accounting for 20% of incident AF, which is similar to results reported from other studies.[8 30] As expected at population level, the risk of AF attributed to previous MI or stroke increased with age, possibly due to the observed age-related increase in prevalence of MI and stroke. Our findings underline the need to prevent and monitor cardiovascular risk factors and disease onset at an early age in order to prevent or postpone AF and its sequelae.

Stroke and mortality after AF onset

Increased risks of stroke and mortality are well-known complications of AF.[17] However, age-specific complications of AF are scarcely examined in large cohorts, although clinically, older age is a strong predictor of stroke in AF patients,[31] manifested through integration in stroke prediction scores such as the ABC and CHA_2DS_2-VASc scores. In the present study, AF significantly predicted stroke only at ages ≥70 years, with a twofold increase in stroke risk. This is in contrast to a large Danish study, showing increased stroke risks due to AF of 1.6–2.0 as early as the age of 50 years.[32] Wolf *et al*[2] found no differences in stroke risk due to AF with advancing age in the Framingham Study, although the proportion of strokes attributed to AF increased from 1.5% at ages 50–59 years to 23% at ages 80–89.[2] Oral anticoagulation or alternative ways of stroke risk reduction need to be addressed thoroughly in all age groups, but with an emphasis in older patients.

We found that AF significantly increased the risk of death at ages ≥60 years, with a 1.8-fold to 2.6-fold increase in mortality in AF patients. A large cohort study of Japanese men and women showed similar mortality rates in relation to AF in the age range 40–69 years.[33] However, AF itself accounts for a comparatively small fraction of deaths worldwide,[1] since the mortality risk in AF patients is attributed to other causes such as heart failure and stroke.[34]

Limitations and strengths

The included cohorts originate from population-based studies to which entire birth cohorts or random samples were invited; however, we cannot rule out selection bias due to selective participation. Previous studies indicate that non-participants may have lower socioeconomic status and higher prevalences of non-communicable diseases.[35] Participation among the oldest old was lower, which prompted us to merge data on participants >70 years, limiting knowledge among this specific group. We did not stratify by sex, as sex differences in AF risk factors were addressed previously in a similar cohort.[17]

Furthermore, misclassification and lack of valid data on potential residual confounders such as physical activity may lead to biased estimates. Combining data from heterogeneous cohorts may introduce misclassification, although we attempted to improve the goodness-of-fit of the Cox models by adjusting for study cohort. Data on risk factors were available only at baseline, and procedures and thresholds may have changed during follow-up. Information on AF is derived from hospital discharge records and individuals with paroxysmal AF and silent AF are probably underrepresented, which may weaken the associations, although validation studies show high positive and negative predictive values for AF diagnoses from diagnosis registers.[36 37]

Strengths of this study include the prospective design with long-term follow-up, rigorously harmonised risk factors and endpoints and a large sample size, representing Europe from North to South.

CONCLUSIONS

In this cohort of adult and elderly European men and women, incidence of AF increased significantly with age. High BMI, hypertension, high alcohol consumption and previous stroke or MI predicted risk of AF across age groups. In particular, the PAF of BMI was substantial at ages 40–69 years, and a large proportion of the AF risk was attributed to hypertension, with an age-related increase. Therefore, preventive measures should target risk factors rigorously from middle-aged to older individuals. Newly diagnosed AF was associated with a high risk of stroke and mortality in risk factor adjusted analyses, in particular at older age. Our study, thus, emphasises the potential role of risk factor control for prevention and adequate patient management after AF diagnosis in the older age groups, including the oldest old.

Author affiliations
[1]School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway
[2]Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany
[3]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg University Hospital, Copenhagen, Denmark
[4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[5]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[6]Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland
[7]Research Center in Epidemiology and Preventive Medicine (EPIMED), University of Insubria, Varese, Italy
[8]Department of Epidemiology and Prevention, IRCCS NEUROMED, Pozzilli (IS), Italy
[9]Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland
[10]Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[11]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[12]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[13]Department of Neurology, University Hospital of North Norway, Tromsø, Norway
[14]German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Hamburg, Germany

Twitter Bente Morseth @MorsethBente

Contributors RBS, BM, BG and M-LL contributed to the conception and the design of the work. M-LL, BG, BM, RBS, KK, VS, TJN, LI, SC, JKKV, IN, EBM, AL, TW, SS and LJ contributed to the acquisition, analysis or interpretation of data for the work. BM, RBS, BG and M-LL drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Funding The MORGAM Project has received funding from EU projects MORGAM (Biomed, BMH4-CT98-3183), GenomEUtwin (FP5, QLG2-CT-2002-01254), ENGAGE (FP7, HEALTH-F4-2007-201413), CHANCES (FP7, HEALTH-F3-2010-242244), BiomarCaRE (FP7, HEALTH-F2-2011-278913), euCanSHare (Horizon 2020, No. 825903) and AFFECT-EU (Horizon 2020, No. 847770); and Medical Research Council, London (G0601463, No. 80983: Biomarkers in the MORGAM Populations). This has supported central coordination, workshops and part of the activities of the MORGAM Data Centre, the MORGAM Laboratories and the MORGAM Participating Centres. TJN was supported by the Emil Aaltonen Foundation, Paavo Nurmi Foundation, Finnish Medical Foundation, and Academy of Finland (grant number 321351). RBS has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under the grant agreement No 648131, from the European Union's Horizon 2020 research and innovation programme under the grant agreement No 847770 (AFFECT-EU) and German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103); German Ministry of Research and Education (BMBF 01ZX1408A) and ERACoSysMed3 (031L0239).

Competing interests RBS has received lecture fees and advisory board fees from BMS/Pfizer outside this work.

Patient consent for publication Not required.

Ethics approval Each participating study was approved by the local ethics committee and/or institutional review board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written or verbal informed consent was obtained from all individual participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each MORGAM study. Approval by the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data.

ORCID iDs
Bente Morseth http://orcid.org/0000-0002-7973-0342
Kari Kuulasmaa http://orcid.org/0000-0003-2165-1411
Veikko Salomaa http://orcid.org/0000-0001-7563-5324
Licia Iacoviello http://orcid.org/0000-0003-0514-5885
Simona Costanzo http://orcid.org/0000-0003-4569-1186
Stefan Söderberg http://orcid.org/0000-0001-9225-1306
Maja-Lisa Løchen http://orcid.org/0000-0002-8532-6573
Renate B Schnabel http://orcid.org/0000-0001-7170-9509

REFERENCES

1 Chugh SS, Havmoeller R, Narayanan K, *et al*. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014;129:837–47.
2 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983–8.
3 Kim MH, Johnston SS, Chu B-C, *et al*. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011;4:313–20.
4 Benjamin EJ, Wolf PA, D'Agostino RB, *et al*. Impact of atrial fibrillation on the risk of death: the Framingham heart study. *Circulation* 1998;98:946–52.
5 Alonso A, Krijthe BP, Aspelund T, *et al*. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102.
6 Everett BM, Cook NR, Conen D, *et al*. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J* 2013;34:2243–51.
7 Wingerter R, Steiger N, Burrows A, *et al*. Impact of lifestyle modification on atrial fibrillation. *Am J Cardiol* 2020;125:289–97.
8 Huxley RR, Lopez FL, Folsom AR, *et al*. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;123:1501–8.
9 Stefansdottir H, Aspelund T, Gudnason V, *et al*. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace* 2011;13:1110–7.
10 Psaty BM, Manolio TA, Kuller LH, *et al*. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96:2455–61.
11 Heeringa J, van der Kuip DAM, Hofman A, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53.
12 Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–962.
13 Murthy VL, Abbasi SA, Siddique J, *et al*. Transitions in metabolic risk and long-term cardiovascular health: coronary artery risk development in young adults (CARDIA) study. *J Am Heart Assoc* 2016;5. doi:10.1161/JAHA.116.003934. [Epub ahead of print: 13 10 2016].
14 De With RR, Marcos EG, Van Gelder IC, *et al*. Atrial fibrillation progression and outcome in patients with young-onset atrial fibrillation. *Europace* 2018;20:1750–7.
15 Schnabel RB, Yin X, Gona P, *et al*. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham heart study: a cohort study. *Lancet* 2015;386:154–62.
16 Magnussen C, Ojeda FM, Wild PS, *et al*. Atrial fibrillation manifestations risk factors and sex differences in a population-based cohort (from the Gutenberg health study). *Am J Cardiol* 2018;122:76–82.
17 Magnussen C, Niiranen TJ, Ojeda FM, *et al*. 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;136:1588–97.
18 Zeller T, Hughes M, Tuovinen T, *et al*. BiomarCaRE: rationale and design of the European BiomarCaRE project including 300,000

participants from 13 European countries. *Eur J Epidemiol* 2014;29:777–90.
19 Gerdes LU, Brønnum-Hansen H, Madsen M, *et al*. Trends in selected biological risk factors for cardiovascular diseases in the Danish MONICA population, 1982-1992. *J Clin Epidemiol* 2000;53:427–34.
20 Borodulin K, Tolonen H, Jousilahti P, *et al*. Cohort profile: the National FINRISK study. *Int J Epidemiol* 2018;47:696–696i.
21 Iacoviello L, Rago L, Costanzo S, *et al*. The Moli-sani project: computerized ECG database in a population-based cohort study. *J Electrocardiol* 2012;45:684–9.
22 Lindroth M, Lundqvist R, Lilja M, *et al*. Cardiovascular risk factors differ between rural and urban Sweden: the 2009 northern Sweden MONICA cohort. *BMC Public Health* 2014;14:825.
23 Jacobsen BK, Eggen AE, Mathiesen EB, *et al*. Cohort profile: the Tromso study. *Int J Epidemiol* 2012;41:961–7.
24 Evans A, Salomaa V, Kulathinal S, *et al*. MORGAM (an international pooling of cardiovascular cohorts). *Int J Epidemiol* 2005;34:21–7.
25 Magnussen C, Niiranen TJ, Ojeda FM, *et al*. Sex-Specific Epidemiology of Heart Failure Risk and Mortality in Europe: Results From the BiomarCaRE Consortium. *JACC Heart Fail* 2019;7:204–13.
26 Benichou J. A review of adjusted estimators of attributable risk. *Stat Methods Med Res* 2001;10:195–216.
27 Kavousi M. Differences in epidemiology and risk factors for atrial fibrillation between women and men. *Front Cardiovasc Med* 2020;7:3.
28 Lau DH, Nattel S, Kalman JM, *et al*. Modifiable risk factors and atrial fibrillation. *Circulation* 2017;136:583–96.
29 Kim YG, Han KD, Choi JI. Non-genetic risk factors for atrial fibrillation are equally important in both young and old age: a nationwide population-based study. *Eur J Prev Cardiol* 2020;2047487320915664.
30 Bose A, O'Neal WT, Wu C, *et al*. Sex Differences in Risk Factors for Incident Atrial Fibrillation (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2019;123:1453–7.
31 Berg DD, Ruff CT, Jarolim P, *et al*. Performance of the ABC scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in engage AF-TIMI 48. *Circulation* 2019;139:760–71.
32 Frost L, Vukelic Andersen L, Godtfredsen J, *et al*. Age and risk of stroke in atrial fibrillation: evidence for guidelines? *Neuroepidemiology* 2007;28:109–15.
33 Sairenchi T, Yamagishi K, Iso H, *et al*. Age-Specific Impact of Atrial Fibrillation on Cardiovascular Mortality Among Japanese Men and Women (The Ibaraki Prefectural Health Study [IPHS]). *Am J Cardiol* 2019;124:1413–9.
34 Healey JS, Oldgren J, Ezekowitz M, *et al*. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016;388:1161–9.
35 Langhammer A, Krokstad S, Romundstad P, *et al*. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. *BMC Med Res Methodol* 2012;12:143.
36 Norberg J, Bäckström S, Jansson J-H, *et al*. Estimating the prevalence of atrial fibrillation in a general population using validated electronic health data. *Clin Epidemiol* 2013;5:475–81.
37 Malmo V, Langhammer A, Bønaa KH, *et al*. Validation of self-reported and hospital-diagnosed atrial fibrillation: the HUNT study. *Clin Epidemiol* 2016;8:185–93.

Supplemental Material

Article title: Age-specific atrial fibrillation incidence, attributable risk factors, and risk of stroke and mortality. Results from the MORGAM Consortium

Supplementary Methods: Description of the included MORGAM cohorts (D1)

DAN-MONICA

The DAN-MONICA study from the Research Center for Prevention and Health includes 11 municipalities from the western part of the suburbs of Copenhagen, Denmark. Random sampling was based on the national population register, stratified by sex and year of birth. The first survey of data collection was carried out in 1982-1984, the second in 1986-1987 and the third in 1991-1992. Surveys 1 and 3 consist of men and women aged 30-70 years and survey 2 consists of men and women aged 30-60 years.

Follow-up was achieved through linkage to the National Cause of Death Register and National Hospital Discharge Register, with endpoint diagnosis based on MORGAM criteria. Follow-up for the cohorts 1, 2, and 3 lasted until 31.12.2010.

Information on prevalent atrial fibrillation (if recorded before the examination date) and incident atrial fibrillation (if recorded during the follow-up period) was obtained from the National Hospital Discharge Register using the Danish modification of ICD: ICD-8 codes 427.93 or 427.94 or the ICD-10 code I48.

Information on incident stroke was obtained from the National Hospital Discharge Register or the Causes of Death Register (either the immediate cause of death, the two intermediate causes, or the underlying cause of death) using the ICD-codes 430-434, 436 (ICD-8) or I60, I61, I63, I64, I69 (ICD-10). Stroke events occurring within 28 days were considered as one event. For stroke events found both in the Hospital Discharge register and the Register of Causes of Death, a stroke diagnosis was given if it was found in either of them.

FINRISK

The FINRISK study is a series of population-based cardiovascular risk factor surveys carried out every five years in five districts of Finland, including North Karelia (in 1982-2002), Northern Savo (former Kuopio, in 1982-2002), Southwestern Finland (in 1982-2002), Oulu Province (in 1997-2002) and the region of Helsinki and Vantaa (in 1992-2002). A stratified random sample was drawn from the national population register; the age-range was 25-74 years. All individuals enrolled in the study received a physical examination, a self-administered questionnaire, and a blood sample was drawn. The cohort is divided in the eastern and the south-western FINRISK cohort.

During follow-up, the National Hospital Discharge Register, the National Causes of Death Register and the National Drug Reimbursement Register were used to identify endpoints. The follow-up extends until December 31st, 2010.

Information on prevalent atrial fibrillation (if recorded before the examination date) and incident atrial fibrillation (if recorded during the follow-up period) was obtained using the the Finnish modification of ICD: ICD-8 code 427.92, the ICD-9 code 427.3 or the ICD-10 code I48.

In cohorts 01, 02, 03 (since 1998), 24 and 34: For stroke events found in the FINMONICA or FINSTROKE registers, the MONICA diagnostic category was used. For events found in the Hospital Discharge Register or the Register of Causes of Death but not in the FINMONICA or FINSTROKE register, the diagnostic classification was done using hospital discharge code or official underlying, antecedent or direct cause of death ICD codes: ICD-8 codes include 430, 431 (excluding codes 431.01, 431.91 of the Finnish adaptation of ICD-8), 432, 433, 434, 436. ICD-9 codes include 430, 431, 433, 434, 436, but excluding codes 4330X, 4331X, 4339X, 4349X of the Finnish adaptation of ICD-9. ICD-10 codes include I60, I61, I63, I64, I69. Stroke events occurring within 28 days were considered as one event. For stroke events found both in the Hospital Discharge register and the Register of Causes of Death, a stroke diagnosis was given if it was found in either of them. Cohorts 03 (up to 1998): The hospital records were reviewed, and the MONICA diagnostic classification was done for all events which had ICD-8 or ICD-9 code 430-438 or ICD-10 code I60-I69 in the Hospital Discharge Register or the Register of Causes of Death.

The Moli-sani Study

The cohort of the Moli-sani study was recruited in the Molise region from city hall registries using multistage sampling. First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged 35 years or over were selected by simple random sampling. Exclusion criteria were pregnancy at the time of recruitment, lack of understanding (e.g. language difficulties), current multiple trauma or coma, or refusal to sign the informed consent. A total of 24325 men (47%) and women (53%) over the age of 35 years were examined at baseline from 2005 to 2010. Participation rate was 70%.

The cohort was followed-up for a median of 4.2 years (maximum 6.5 years) at December 2011. Follow-up is achieved through record linkage to national mortality registries and hospital discharge registers, validation of stroke events was achieved through hospital record linkage and doctors' medical records using updated MORGAM criteria.

Information on prevalent atrial fibrillation was obtained via medical reports at the baseline visit or an affirmative answer to the question "Have you ever been diagnosed with atrial fibrillation?". The question was not asked during the first year of recruitment of participants to the cohort. Information on incident atrial fibrillation was obtained via hospital discharge records with the ICD-9 code 427.3. Death certificates were derived from the Death Registry of the National Health Service, which provides the underlying cause of death in ICD-9, rarely in ICD-10.

Stroke events were selected for further validation if death certificates presented cerebrovascular disease (ICD-9 codes 430-438) as the underlying, antecedent, or direct cause of death; or hospital discharge records revealed a hospitalization with ICD-9 code 430-432, 434, 436 or ICD-9-CM code 38.12. For all cases selected for further validation, the clinical records were searched and 1) If clinical documentation was found, the event was validated using the MONICA procedure. However, if during the validation of a stroke event, CT or MRI revealed a cerebral infarction or haemorrhage, the stroke event was confirmed even if the MONICA criteria were not fulfilled. 2) If clinical documentation was

not found, the event validation was based on the death certificate, the hospital discharge form, or a questionnaire to the general practitioner. If these indicated a stroke, the diagnosis was coded as "unclassifiable" and the source of diagnosis as "clinical or death certificate diagnosis", otherwise as "no stroke".

The Northern Sweden MONICA Study

The Northern Sweden MONICA study covered the two northernmost counties of Sweden, i.e. Norrbotten and Västerbotten with altogether 510 000 inhabitants. Population surveys were conducted in 1986, 1990, 1994, 1999, 2004 and 2009, with altogether 10,517 unique participants. On the first two occasions, 2000 persons aged 25 to 64 years were randomly selected per survey, and in the last three surveys, the upper age limit was extended to 74 years and 2500 individuals were invited per survey. A stratified randomized selection procedure by age and sex (250 persons in each sex/10-year age stratum) has been used. The participation rate was 69-81%. In 1999, all people invited to any of the three previous population surveys were re-invited for repeated measurements to be collected.

Follow-up is available for all cohorts until December 2011, using data from the National Swedish cause of death and in-patient care registers. Deaths were collected from the national death register, maintained at the Central Bureau of Statistics, covering all people who were resident in Sweden (citizens and non-citizens) at the time of death. Residents who die abroad or outside the study area are also included. Incident stroke events occurring in the region between 1985 and 2010 and below the age of 75 were collected and validated according to MONICA criteria by two event registers whose accuracy and validity have been tested against national registers.

Information on prevalent atrial fibrillation (if recorded before the examination date) and incident atrial fibrillation (if recorded during the follow-up period) was obtained using the following ICD codes: ICD-8-SV 42792, ICD-9-SV 427D, ICD-10-SE I489 plus the Swedish modification A to F as fifth position differentiating between flutter and fibrillation, and paroxysmal or chronic flutter/fibrillation.

Linkage to the stroke event register was done to recognize non-fatal or fatal stroke events with any diagnostic category. For events found in the Stroke Event Register, the MONICA diagnostic category was used. The diagnosis of fatal and non-fatal events outside the age limits (above 75) and/or outside the region, was obtained from the national diagnosis register. These diagnoses were not validated. For events which were found in the National Registers but not in the Stroke Event Register, the MORGAM diagnostic category was derived from the non-validated ICD-codes as follows: ICD-8-SV: 43090, 43100, 43399, 43499. ICD-9-SV: 430X, 431, 434, 436X. ICD-10-SE: I60, I61, I63, I64.9. Stroke events occurring within 28 days of each other were considered as one event.

The Tromsø Study

The Tromsø Study is a population-based study in the municipality of Tromsø in northern Norway, with seven surveys conducted every 6-8 years between 1974 and 2016. For the present analyses, data from the third (1986-87) and fourth (1994-95) surveys was used (n=13 878), and the national population registry was used to define the study population. All men born 1925 to 1966 and all women born 1930 to 1966 living in Tromsø were invited to participate in the third survey of the Tromsø Study. The fourth survey was conducted in 1994-95 and is the largest survey so far, inviting all inhabitants in the municipality aged ≥25 years.

Follow-up is available until December 2010 through linkage to the National Cause of Death Registry and the discharge diagnosis registry at the University Hospital of North Norway. Deaths were collected from the Causes of Death Registry maintained at Statistics Norway, covering subjects registered as living in Norway at the time of their death, without regard to whether the death took place in Norway or abroad. Data on mortality, causes of death, including first-ever fatal cardiovascular events, are identified through linkage to the Registry.

Information on prevalent atrial fibrillation (if recorded before the examination date) and incident atrial fibrillation (if recorded during the follow-up period) was obtained from the hospital medical records, recorded on an electrocardiogram and validated by a physician, with the following exclusions: 1) Episode(s) of atrial fibrillation occurring only within the 28 day-period after an acute myocardial infarction; 2) Episode(s) of atrial fibrillation occurring only within the 28 day-period after other acute cardiac events (e.g. heart failure, pulmonary oedema); 3) Episode(s) of atrial fibrillation occurring only within the 28 day-period after surgery; and 4) Episode(s) of atrial fibrillation occurring the terminal last 7 days before death.

Incident stroke was defined as a focal or global neurological impairment of sudden onset and lasting more than 24 h (or leading to death) and of presumed vascular aetiology. Information on imaging (CT, MRI, angiography) and/or spinal tap was used to classify stroke events as either cerebral infarction, intracerebral haemorrhage, subarachnoidal haemorrhage or unclassifiable stroke. Strokes were classified as ischemic only when imaging had ruled out haemorrhagic stroke. Stroke events occurring within 28 days of each other were considered as one event.

The registration of fatal recurrent stroke events is based on diagnoses from the national Causes of Death Registry. These were classified as cause of death code ICD-8: 430-434, 436; ICD-9: 430, 431, 433,434, 436, and ICD-10: I60, I61, I63, I64, I69.

Supplementary Tables: Tables S1-S7

Table S1. Sample characteristics at baseline and during follow-up for the DAN-MONICA cohort (n = 5611)

Characteristics	Median (IQR) or n (%)	Missing values (%)
Age at the date of baseline examination (years)	50.8 (41.4 - 60.7)	0.0
Men	2855 (50.9%)	0.0
BMI (kg/m^2)	24.9 (22.6 - 27.7)	0.1
Systolic blood pressure (mm Hg)[a]	125.0 (114.0 - 139.0)	0.0
Total serum cholesterol (mmol/l)	6.0 (5.3 - 6.8)	0.3
Daily smoker	2404 (42.8%)	0.0
History of diabetes	166 (3.0%)	0.0
Taking antihypertensive drugs	497 (9.2%)	3.4
Hypertension[b]	1542 (28.1%)	2.3
Average daily consumption of alcohol (g)	9.0 (3.0 - 19.0)	0.5
C-reactive protein (mg/L)	1.4 (0.6 - 3.1)	6.2
N-terminal-pro B-type natriuretic peptide (pg/mL)	(-)	100.0
log10(N-terminal-pro B-type natriuretic peptide (pg/mL))	(-)	100.0
Creatinine (mg/dL)	0.8 (0.7 - 0.9)	6.0
Estimated glomerular filtration rate[c]	94.1 (82.3 - 103.3)	6.0
Documented or self-reported history of MI or stroke	232 (4.1%)	0.1
AF during follow-up	142 (2.5%)	0.0
Stroke during follow-up	216 (3.8%)	0.0
Death during follow-up	691 (12.3%)	0.0
Follow-up time (years)	10.0 (10.0 - 10.0)	0.0
Time-to AF among those with AF during follow-up (years)	6.7 (3.7 - 8.3)	
Time-to death among those who died during follow-up (years)	5.9 (3.3 - 8.1)	
Time-to stroke among those with stroke during follow-up (years)	5.7 (3.1 - 7.7)	

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; IQR; interquartile range.
[a]Mean of two measurements.
[b]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[c]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

Table S2. Sample characteristics at baseline and during follow-up for the FINRISK cohort (n=24490)

Characteristics	Median (IQR) or n (%)	Missing values (%)
Age at the date of baseline examination (years)	53.6 (46.7 - 59.9)	0.0
Men	11990 (49.0%)	0.0
BMI (kg/m^2)	26.9 (24.3 - 29.9)	1.7
Systolic blood pressure (mm Hg)[a]	140.0 (127.0 - 155.0)	1.8
Total serum cholesterol (mmol/l)	5.9 (5.2 - 6.7)	2.0
Daily smoker	5206 (21.5%)	1.3
History of diabetes	1581 (6.5%)	0.0
Taking antihypertensive drugs	4284 (19.1%)	8.4
Hypertension[b]	13700 (58.4%)	4.2
Average daily consumption of alcohol (g)	2.0 (0.0 - 9.0)	3.1
C-reactive protein (mg/L)	1.3 (0.7 - 2.8)	78.5
N-terminal-pro B-type natriuretic peptide (pg/mL)	55.8 (28.7 - 102.2)	79.8
log10(N-terminal-pro B-type natriuretic peptide (pg/mL))	1.7 (1.5 - 2.0)	79.8
Creatinine (mg/dL)	0.9 (0.8 - 1.0)	78.8
Estimated glomerular filtration rate[c]	85.0 (73.7 - 94.6)	78.8
Documented or self-reported history of MI or stroke	1575 (6.4%)	0.0
Reporting Unit Aggregate		0.0
FIN-EAS	15522 (63.4%)	
FIN-WES	8968 (36.6%)	
AF during follow-up	716 (2.9%)	0.0
Stroke during follow-up	900 (3.7%)	0.0
Death during follow-up	2143 (8.8%)	0.0
Follow-up time (years)	10.0 (8.9 - 10.0)	0.0
Time-to AF among those with AF during follow-up (years)	6.0 (3.6 - 8.0)	
Time-to death among those who died during follow-up (years)	5.9 (3.3 - 7.8)	
Time-to stroke among those with stroke during follow-up (years)	5.1 (2.7 - 7.6)	

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; IQR; interquartile range.
[a]Mean of two measurements.
[b]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[c]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

Table S3. Sample characteristics at baseline and during follow-up for the Moli-sani Study cohort (n=15549)

Characteristics	Median (IQR) or n (%)	Missing values (%)
Age at the date of baseline examination (years)	55.3 (47.4 - 64.3)	0.0
Men	7456 (48.0%)	0.0
BMI (kg/m^2)	27.7 (24.9 - 30.9)	0.0
Systolic blood pressure (mm Hg)[a]	138.0 (126.0 - 153.0)	0.0
Total serum cholesterol (mmol/l)	5.5 (4.8 - 6.3)	0.7
Daily smoker	3112 (20.0%)	0.1
History of diabetes	1034 (6.7%)	0.5
Taking antihypertensive drugs	4678 (30.2%)	0.5
Hypertension[b]	8752 (56.4%)	0.2
Average daily consumption of alcohol (g)	7.0 (0.0 - 27.0)	5.9
C-reactive protein (mg/L)	1.6 (0.8 - 3.2)	2.1
N-terminal-pro B-type natriuretic peptide (pg/mL)	51.5 (27.4 - 93.6)	7.0
log10(N-terminal-pro B-type natriuretic peptide (pg/mL))	1.7 (1.4 - 2.0)	7.0
Creatinine (mg/dL)	0.8 (0.7 - 0.8)	1.9
Estimated glomerular filtration rate[c]	95.9 (86.8 - 103.5)	1.9
Documented or self-reported history of MI or stroke	432 (2.8%)	0.4
AF during follow-up	213 (1.4%)	0.0
Stroke during follow-up	56 (0.4%)	0.0
Death during follow-up	278 (1.8%)	0.0
Follow-up time (years)	3.8 (3.1 - 4.5)	0.0
Time-to AF among those with AF during follow-up (years)	2.0 (1.1 - 3.0)	
Time-to death among those who died during follow-up (years)	2.3 (1.3 - 3.3)	
Time-to stroke among those with stroke during follow-up (years)	2.2 (0.9 - 3.2)	

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; IQR; interquartile range.
[a]Mean of two measurements.
[b]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[c]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

Table S4. Sample characteristics at baseline and during follow-up for the Tromsø Study cohort (n=13878)

Characteristics	Median (IQR) or n (%)	Missing values (%)
Age at the date of baseline examination (years)	51.1 (44.5 - 65.4)	0.0
Men	6863 (49.5%)	0.0
BMI (kg/m^2)	24.9 (22.8 - 27.4)	0.3
Systolic blood pressure (mm Hg)[a]	136.5 (124.5 - 152.0)	0.0
Total serum cholesterol (mmol/l)	6.4 (5.6 - 7.3)	0.2
Daily smoker	5212 (37.6%)	0.1
History of diabetes	364 (2.6%)	0.1
Taking antihypertensive drugs	1208 (10.3%)	15.3
Hypertension[b]	6275 (50.8%)	10.9
Average daily consumption of alcohol (g)	2.0 (0.0 - 5.0)	71.3
C-reactive protein (mg/L)	(-)	100.0
N-terminal-pro B-type natriuretic peptide (pg/mL)	(-)	100.0
log10(N-terminal-pro B-type natriuretic peptide (pg/mL))	(-)	100.0
Creatinine (mg/dL)	(-)	100.0
Estimated glomerular filtration rate[c]	(-)	100.0
Documented or self-reported history of MI or stroke	878 (6.3%)	0.0
AF during follow-up	672 (4.8%)	0.0
Stroke during follow-up	625 (4.5%)	0.0
Death during follow-up	1995 (14.4%)	0.0
Follow-up time (years)	10.0 (10.0 - 10.0)	0.0
Time-to AF among those with AF during follow-up (years)	6.1 (3.6 - 8.1)	
Time-to death among those who died during follow-up (years)	5.5 (2.9 - 7.8)	
Time-to stroke among those with stroke during follow-up (years)	5.7 (2.7 - 7.9)	

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; IQR; interquartile range.
[a]Mean of two measurements.
[b]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[c]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

Table S5. Sample characteristics at baseline and during follow-up the Northern Sweden MONICA Study cohort (n=7423)

Characteristics	Median (IQR) or n (%)	Missing values (%)
Age at the date of baseline examination (years)	55.4 (47.8 - 63.1)	0.0
Men	3691 (49.7%)	0.0
BMI (kg/m^2)	27.0 (24.2 - 30.3)	0.3
Systolic blood pressure (mm Hg)[a]	132.0 (120.0 - 147.0)	0.1
Total serum cholesterol (mmol/l)	6.1 (5.4 - 7.0)	0.3
Daily smoker	1371 (18.6%)	0.5
History of diabetes	381 (5.1%)	0.0
Taking antihypertensive drugs	1310 (17.9%)	1.6
Hypertension[b]	3201 (43.6%)	1.0
Average daily consumption of alcohol (g)	2.0 (0.0 - 5.0)	2.3
C-reactive protein (mg/L)	1.1 (0.5 - 2.3)	3.7
N-terminal-pro B-type natriuretic peptide (pg/mL)	50.8 (26.3 - 96.4)	10.5
log10(N-terminal-pro B-type natriuretic peptide (pg/mL))	1.7 (1.4 - 2.0)	10.5
Creatinine (mg/dL)	0.7 (0.6 - 0.8)	3.4
Estimated glomerular filtration rate[c]	98.9 (89.1 - 107.0)	3.4
Documented or self-reported history of MI or stroke	508 (6.8%)	0.0
AF during follow-up	278 (3.7%)	0.0
Stroke during follow-up	258 (3.5%)	0.0
Death during follow-up	515 (6.9%)	0.0
Follow-up time (years)	10.0 (7.8 - 10.0)	0.0
Time-to AF among those with AF during follow-up (years)	5.5 (3.1 - 7.6)	
Time-to death among those who died during follow-up (years)	6.0 (3.8 - 8.0)	
Time-to stroke among those with stroke during follow-up (years)	5.3 (2.6 - 7.4)	

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; IQR; interquartile range.
[a]Mean of two measurements.
[b]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[c]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

Table S6. Multivariable-adjusted HR for AF by age groups, additionally adjusted for interactions

	Age at study entry (years)			
	40-49 (n=24914)	50-59 (n=21824)	60-69 (n=13441)	≥70 (n=6772)
BMI (per 5 kg/m^2 increase)	1.40 (1.17 - 1.68, <0.001)	1.37 (1.23 - 1.52, <0.001)	1.37 (1.25 - 1.50, <0.001)	1.17 (1.06 - 1.29, 0.001)
History of diabetes	0.57 (0.18 - 1.80, 0.339)	1.42 (1.00 - 2.01, 0.052)	1.26 (0.96 - 1.65, 0.101)	1.59 (1.23 - 2.07, <0.001)
Daily smoker	1.13 (0.79 - 1.63, 0.501)	1.14 (0.89 - 1.45, 0.306)	1.15 (0.92 - 1.45, 0.224)	1.00 (0.78 - 1.27, 0.992)
Hypertension[a]	1.40 (0.98 - 2.00, 0.068)	1.20 (0.95 - 1.52, 0.129)	1.32 (1.07 - 1.64, 0.011)	1.29 (1.02 - 1.63, 0.034)
Total serum cholesterol (per mmol/l increase)	0.92 (0.78 - 1.08, 0.293)	0.86 (0.79 - 0.94, 0.001)	0.88 (0.82 - 0.96, 0.003)	0.96 (0.89 - 1.05, 0.373)
Average daily alcohol consumption (per 20g increase)	1.18 (1.02 - 1.36, 0.024)	1.17 (1.05 - 1.30, 0.005)	1.13 (1.00 - 1.28, 0.046)	0.92 (0.79 - 1.08, 0.325)
History of MI or stroke	4.63 (2.57 - 8.34, <0.001)	1.90 (1.37 - 2.62, <0.001)	1.67 (1.32 - 2.12, <0.001)[c]	1.58 (1.28 - 1.95, <0.001)[c]
eGFR[b] (per 10 units increase)	1.07 (0.91 - 1.27, 0.420)	0.93 (0.84 - 1.03, 0.194)	1.00 (0.92 - 1.09, 0.980)	0.88 (0.81 - 0.96, 0.004)
C-reactive protein (per mg/L increase)	0.94 (0.83 - 1.06, 0.313)	1.00 (0.97 - 1.03, 0.981)	1.01 (0.99 - 1.02, 0.242)	1.01 (0.99 - 1.02, 0.330)
Nt-proBN (pg/mL) (per 10-fold increase)	5.56 (2.71 - 11.39, <0.001)	4.77 (3.27 - 6.97, <0.001)	5.49 (4.10 - 7.34, <0.001)	7.56 (5.60 - 10.20, <0.001)

Adjusted for age, sex, BMI, total serum cholesterol, daily cigarette smoking, history of diabetes, hypertension, daily consumption of alcohol, study site, cholesterol*cholesterol interaction, FINRISK East*time interaction.

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; HR: hazard ratio; eGFR: estimated glomerular filtration rate; Nt-proBN: N-terminal-pro B-type natriuretic peptide.

p values in parentheses apply to HRs for each unit increase in risk factor within each age group, whereas [c] denotes significant HR differences between age groups.

[a]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.

[b]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.

[c]Significantly different from age 40-49 years, $p<0.008$; all other between-groups differences $p>0.008$.

Table S7. Unadjusted HR for AF by age groups

	Age at study entry (years)			
	40-49 (n=24914)	50-59 (n=21824)	60-69 (n=13441)	≥70 (n=6772)
BMI (per 5 kg/m^2 increase)	1.65 (1.46 - 1.87, <0.001)	1.46 (1.34 - 1.60, <0.001)	1.39 (1.29 - 1.50, <0.001)	1.11 (1.03 - 1.19, 0.008)
History of diabetes	1.24 (0.51 - 3.01, 0.638)	1.97 (1.41 - 2.75, <0.001)	1.61 (1.26 - 2.06, <0.001)	1.46 (1.17 - 1.82, <0.001)
Daily smoker	1.10 (0.82 - 1.48, 0.523)	1.05 (0.85 - 1.30, 0.623)	0.95 (0.78 - 1.17, 0.637)	0.87 (0.72 - 1.07, 0.187)
Hypertension[a]	2.16 (1.62 - 2.88, <0.001)	1.71 (1.40 - 2.10, <0.001)	1.65 (1.36 - 1.99, <0.001)	1.52 (1.24 - 1.86, <0.001)
Total serum cholesterol (per mmol/l increase)	1.12 (1.00 - 1.26, 0.058)	0.93 (0.85 - 1.00, 0.066)	0.88 (0.83 - 0.94, <0.001)	0.94 (0.89 - 0.99, 0.021)
Average daily alcohol consumption (per 20g increase)	1.26 (1.12 - 1.42, <0.001)	1.20 (1.10 - 1.32, <0.001)	1.11 (1.00 - 1.24, 0.055)	0.95 (0.83 - 1.09, 0.466)
History of MI or stroke	6.72 (3.90 - 11.58, <0.001)	2.93 (2.20 - 3.90, <0.001)	2.15 (1.75 - 2.64, <0.001)	1.78 (1.51 - 2.10, <0.001)
eGFR[b] (per 10 units increase)	1.01 (0.86 - 1.19, 0.895)	0.91 (0.83 - 1.00, 0.041)	0.99 (0.92 - 1.07, 0.866)	0.87 (0.80 - 0.94, <0.001)
C-reactive protein (per mg/L increase)	0.97 (0.88 - 1.06, 0.473)	1.01 (0.99 - 1.04, 0.189)	1.01 (1.00 - 1.02, 0.094)	1.01 (1.00 - 1.02, 0.017)
Nt-proBN (pg/mL) (per 10-fold increase)	3.01 (1.40 - 6.44, 0.005)	4.92 (3.38 - 7.16, <0.001)	5.30 (4.07 - 6.92, <0.001)	7.17 (5.53 - 9.31, <0.001)

BMI: body mass index; MI: myocardial infarction; AF: atrial fibrillation; HR: hazard ratio; eGFR: estimated glomerular filtration rate; Nt-proBN: N-terminal-pro B-type natriuretic peptide.
[a]Systolic blood pressure ≥140 mm Hg and/or taking antihypertensive drugs.
[b]Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with creatinine.