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Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study

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ABSTRACT

Objectives: To investigate the prevalence of atrial fibrillation (AF) and cardiovascular risk factors in a general population aged 63-65 years.

Design: Cross-sectional study (based on a prospective age cohort).

Setting: General population in Akershus County, Norway.

Participants: Women and men born in 1950. We included 3706 of 5826 eligible individuals (63.6%); 48.8% were women.

Primary measure: Sex-specific prevalence of known and unknown (screen-detected) AF.

Secondary measures: Risk factors associated with AF and prevalence of cardiovascular risk factors in this age group.

Methods: All participants underwent extensive cardiovascular examinations, including 12-lead ECG. History of AF and other cardiovascular diseases (CVD) were self-reported. Subsequent validation of all reported or detected AF diagnoses was performed.

Results: Mean age was 63.9±0.7 years. Prevalence of ECG-verified AF was 4.5% (women 2.4%, men 6.4%; $p<0.001$), including screen-detected AF in 0.3% (women 0.1%, men 0.6%; $p<0.01$). Hypertension was found in 62.0% (women 57.8%, men 66.0%; $p<0.001$). Overweight or obesity was found in 67.6% (women 59.8%, men 74.9%; $p<0.001$). By multivariate logistic regression, risk factors associated with AF were height (OR 1.67 per 10 cm; 95% CI 1.26-2.22; $p<0.001$), weight (OR 1.15 per 10 kg; 1.01-1.30; p=0.03), hypertension (OR 2.49; 1.61-3.86; $p<0.001$), heart failure (OR 3.51; 1.71-7.24; $p=0.001$), chronic kidney disease (OR 2.56; 1.42-4.60; $p<0.01$) and at least one 1st degree relative with AF (OR 2.32; 1.63-3.31; $p<0.001$), whereas male sex was not significantly associated (OR 1.00; 0.59-1.68; $p=0.99$).

Conclusion: In this cohort from the general population aged 63-65 years, we found a higher prevalence of known AF than previously reported below the age of 65 years. The additional yield of single time point screening for AF was low. Body size and comorbidity may explain most of the sex difference in AF prevalence at this age.

Keywords: Atrial fibrillation, hypertension, obesity, cardiovascular risk, prevalence, screening

Strengths and limitations of this study

- Unselected population-based cohort design inviting all residents in a geographical region born in 1950, with a high participation rate.
- The study was conducted in a completely government-financed healthcare system with equal access for the entire population.
- All reported and detected cases of atrial fibrillation were thoroughly validated.
- The study relied on self-reported cardiovascular disease only, and negative responses to atrial fibrillation were not validated.
- This report is a cross-sectional study of a limited age group, making comparison to other study settings difficult.

BACKGROUND

The prevalence of atrial fibrillation (AF) is on the rise and this arrhythmia is emerging as a major public health problem due to the associated stroke risk and related costs.[1 2] The prevalence in the adult population has been estimated to be 1-2%, but is probably as high as 2-3%, based on recent data.[1] Previous studies in specific age groups have reported a prevalence of AF of 4.2% among subjects 60-69 years of age.[3] The increase in prevalence is most likely due to both aging of the population and improved survival from other types of cardiovascular disease (CVD). Increased awareness and improved detection of subclinical AF may also be contributing factors.

Screening for AF has received increased attention lately. European guidelines recommend opportunistic screening by pulse palpation or electrocardiogram (ECG) in all patients >65 years of age.[4] Despite the emergence of technology for ambulant ECG monitoring, current recommendations are still based on single time point screening by standard ECG, enabling undetected AF to be diagnosed in 1.4% of the population ≥65 years.[5] At this age and above, one or more additional risk factors for stroke, according to the CHA_2DS_2-VASc score, provide a strong indication for anticoagulation.[4] Hence, subjects with hypertension, diabetes or other risk factors for stroke represent a potential target group for screening for AF.[6] Studies have shown that about 50% of incident AF could be attributed to elevated levels of risk factors for AF, of which elevated blood pressure and overweight were the most important contributors.[7] This raises the issue of early detection and subsequent "upstream" treatment of these conditions.

The primary aim of this study was to investigate the sex-specific prevalence of self-reported and ECG-validated AF, including subclinical AF found by screening. We also wanted to identify variables associated with AF diagnosis in this age group and report the prevalence of known cardiovascular risk factors in a contemporary population-based cohort aged 63-65 years.

METHODS

Study population

The Akershus Cardiac Examination (ACE) 1950 Study is a prospective, population-based cohort study of the cerebro- and cardiovascular health among permanent residents in Akershus County, Norway, born in 1950. Design and general methodology have been reported previously.[8] This article is based on cross-sectional data from the baseline examination, performed in the period September 2012 - May 2015.

Study variables

Clinical data included measurements of height, weight, seated blood pressure and 12-lead electrocardiogram (ECG). Body mass index (BMI) was calculated according to the standard formula (kg/m^2), and categorized into overweight (BMI 25.0-29.9 kg/m^2) and obesity (BMI $\geq$30.0 kg/m^2). Body surface area (BSA; m^2) was calculated by the Mosteller formula.[9] A web-based questionnaire for registration of medical history and lifestyle was used. The questionnaire was formulated in the same manner as in previous large Norwegian population studies,[10] and participants were urged to ask study personnel at the baseline visit if they were not able to respond adequately to all questions, to ensure high-quality data collection. Daily use of all types of medication was registered according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Concerning AF, the participants were asked: "Have you ever been diagnosed with atrial fibrillation or atrial flutter?" All self-reported AF was validated according to the following: 1) ECG documentation of AF or atrial flutter according to standard definitions,[4] and if such was not available, 2) a solid description of AF or atrial flutter in the medical record (i.e. DC cardioversion or AF ablation procedure). All ECGs and medical records were evaluated by two physicians, of whom one was a cardiologist. Participants without history of AF, but in whom AF was detected in the study ECG, were classified as previously undiagnosed AF. Participants also reported any familial AF history among 1st degree relatives.

Hypertension was defined as the mean (from the second and third of three readings) systolic blood pressure ≥140 mmHg or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. The diagnoses of heart failure, myocardial infarction and stroke or transient ischemic attack (TIA) were self-reported. Coronary artery disease was defined as self-reported myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting surgery.

Fasting blood samples were analysed on-site and included lipids, blood glucose, HbA1c, and serum creatinine. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR).[11] Chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2.

Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L and/or LDL ≥4.1 mmol/L and/or use of lipid-lowering medication. Diabetes was defined as a self-reported diagnosis or use of hypoglycaemic medication or elevated glucose tests (both HbA1c ≥6.5% and fasting blood glucose ≥7.0 mmol/l).

Higher education was defined as >12 years of formal education, i.e. college/university education at any level. Alcohol consumption, smoking and physical activity was self-reported. Physical activity was classified according to a previously validated model (details provided in Supplementary Table 1).[12]

For individuals with AF, we calculated the CHA_2DS_2-VASc stroke risk score. This was based on the presence or history of heart failure, hypertension, diabetes, stroke/TIA, myocardial infarction, age >65 years and female sex (1 point each).

The data are reported according to the STROBE guidelines.[13] The study complies with the Declaration of Helsinki, and was approved by the Norwegian Regional Ethics Committee (ref. 2011/1475). Written informed consent was obtained from all participants.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD), and Student's t-test was used for between-group analysis. Continuous variables not normally distributed are reported as median with interquartile range (IQR) and analysed with the Mann-Whitney U test. Categorical variables are presented as counts and/or proportions (%) and compared by the χ^2 test or Fisher's exact test as appropriate. Logistic regression analysis was used to assess associations between risk factors and AF. All available known risk factors for AF were selected from univariate analyses based on clinical and statistical significance (*p*-value <0.20). Pearson correlation, as well as multicollinearity statistics, was run between each of the independent variables before inclusion in a multivariate logistic regression model. Secondary analyses replacing height and weight with the more commonly used BMI, as well as BSA, were also performed. P-values are two-sided and considered significant when <0.05. Cases with missing data were omitted from descriptive statistics of that particular variable. Hence, the reported proportions represent the valid proportions. As for the regression analysis, a complete case analysis was performed. Statistics were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York, USA).

RESULTS

General cohort profile

A total of 3706 participants (from 5827 eligible participants; 63.6% participation rate) were enrolled and examined in the ACE 1950 Study. Women and men were evenly represented, with 1807 (48.8%) women and 1899 (51.2%) men (participation rate 63.7% among women, 63.5% among men; p=0.86). Akershus University Hospital enrolled 2473 participants, and Bærum Hospital (Vestre Viken Hospital Trust) 1233 participants, within their respective catchment areas. The majority were of Caucasian ethnicity (3624; 97.8%). All participants were born in 1950, and the mean age at inclusion was 63.9 ±0.7 years. Baseline characteristics are presented in *Table 1.*

Prevalence of known and unknown AF

A flowchart illustrating the validation of AF is shown in *Figure 1*. History of AF was reported by 193 (5.2%) participants. After validation, 153 (4.1%) had a verified AF diagnosis. Hence, the positive predictive value (PPV) of self-reported AF, compared to the direct review of medical records and ECGs, was 79.3%. Previously unknown AF was diagnosed by ECG in 12 (0.3%) participants. The total prevalence of validated AF was 4.5% (n=165; 2.4% among women, 6.4% among men; $p<0.001$), as shown in *Figure 1* and *Table 2*. Nine subjects had a history of atrial flutter (or atrial flutter in study ECG), without any previous diagnosis of AF. These were counted as AF. Permanent AF was identified in 48 cases *(Table 2)*.

Clinical characteristics of AF

Table 3 shows sex-specific characteristics of individuals with AF compared to the rest of the cohort. Both women and men with AF were significantly taller and heavier than those without AF. Other measures of body size, such as waist and hip circumference, and BSA, were also higher among individuals with AF, regardless of sex. Obesity was found in 41.8% of participants with AF vs. 21.7% in unaffected participants ($p<0.001$). Hypertension, heart failure and chronic kidney disease were more prevalent in individuals with AF of both sexes, whereas coronary heart disease was more prevalent only among men with AF. Otherwise there were only minor sex differences. With regard to level of physical activity, there were no significant differences between the groups.

A higher number of both women and men with AF reported a 1st degree relative with known AF, compared to the rest of the cohort (33.9% vs. 19.2%; $p<0.001$; *Table 3)*. Familial AF was more prevalent in women with AF than in men with AF (56.8% vs. 25.6%; $p<0.001$).

Risk factors for AF

Risk factors associated with AF, assessed by logistic regression, are reported in *Table 4*. In univariate analysis, male sex was associated with increased likelihood of having AF. However, in multivariate analysis, sex was not associated with AF, when adjusting for height, weight and other risk factors. Height, weight, hypertension, heart failure, chronic kidney disease, and family history of AF, were all

significantly associated with AF in multivariate analysis. In secondary analyses, height and weight were replaced with BMI or BSA. In these analyses, male sex remained significantly associated with AF, and a strong association to AF was found for both BMI and BSA, while only minor changes were seen for other variables (data not shown).

Stroke risk in AF

The median CHA_2DS_2-VASc stroke risk score among AF subjects was 1 [IQR 1-2] in men and 2 [IQR 2-2] in women *(Supplementary Table 2)*. In total, 83.6% in the AF group fulfilled our criteria for hypertension. As many as 41.1% of individuals with AF had elevated blood pressure (≥140/≥90 mmHg) at the ACE 1950 baseline visit, regardless of ongoing treatment. Details of stroke risk and medication in individuals with AF are presented in *Supplementary Table 2*. Furthermore, characteristics of screen-detected AF (n=12) are shown in *Supplementary Table 3*. These individuals were generally low-risk; the median CHA_2DS_2-VASc score was 1 [total range 0-2]. However, 75.0% were overweight and 66.7% had hypertension.

Cardiovascular risk factors and diseases

In the complete cohort, the prevalence of CVD and cardiovascular risk factors were generally higher in men than in women *(Table 1)*, with the exception that a higher number of women had hypercholesterolemia ($p<0.01$). There were no sex difference in reported daily smoking (15.3% of women vs. 13.7% of men; $p=0.19$). As shown in *Table 1*, the majority of the cohort was overweight or obese. Obesity was found in 22.6% (24.1% of men, 21.1% of women; $p=0.03$). Among all participants without any antihypertensive medication (n=2359), elevated blood pressure (≥140/≥90 mmHg) was found in 40.3% (38.2% of women, 42.6% of men; $p=0.03$). By decreasing the limit to ≥130/≥80 mmHg, 65.5% (59.8% of women, 71.8% of men; $p<0.001$) of untreated subjects had elevated blood pressure.

Missing data

Basic clinical variables, including height, weight and ECG were available from all 3706 participants, whereas blood pressure was missing in only two participants. Data was missing for <1% of all reported variables, including all self-reported CVD, except for physical activity in which 2.3% (n=84) had missing data on at least one of three physical activity questions.

DISCUSSION

Principal findings

The key results of this study were that we identified a high prevalence of verified AF, whereas single time point screening by 12-lead ECG identified only 0.3% new cases in an unselected contemporary population aged 63-65 years. Although a low burden of advanced CVD was reported, we identified a high burden of obesity and hypertension.

Strengths and limitations

Strengths of this study include the unselected population-based design and a relatively high participation rate. Furthermore, the most important data variables were complete. The thorough validation of all self-reported AF cases also strengthens our findings.

Limitations include uncertainty about the accuracy of self-reported CVD. In particular, we believe heart failure and history of stroke have a high degree of uncertainty, whereas diseases such as diabetes and myocardial infarction may be more easily defined and recognised in the population. The diagnosis of hypertension should, ideally, be based on serial or ambulant blood pressure measurements. Hence, the prevalence may be overestimated.

Negative responses to self-reported AF were not validated. However, this may only have led to an underestimation of the prevalence, due to the unknown number of false negative responses. A validation of self-reported AF in the HUNT study questioned the use of self-reported AF, as sensitivity was low and many AF cases were missed.[14] Our study was not designed as a validation study and therefore sensitivity and specificity of self-reported AF could not be estimated. Still, the

PPV of self-reported AF in our study, 79.3%, was much higher than found in the HUNT study (PPV 56%).[14]

By its design, our study depicts a limited age group, making comparison to other studies difficult. Finally, the study was designed as a cardiovascular cohort study with a special focus on AF. Hence, individuals with known AF may have been more motivated to participate than unaffected individuals, which may represent a selection bias.

Prevalence of AF

To the best of our knowledge, no other study based on unselected population data has reported prevalence of AF as high as 4.5% below the age of 65 years. Most comparable studies have reported a prevalence of 3.7-4.2% in the age group 60-69 years.[1 3] A Swedish study found 2.9% in the more comparable age group 60-64 years,[15] while the Rotterdam study reported <2% in this age group.[16] AF prevalence in our study is particularly high for men (6.4%), while a few studies have reported a prevalence >2.4% among women at this age.[3 17 18]

Single time point screening for AF

The true prevalence of AF cannot be found by single time point ECGs, as some cases will be missed due to the paroxysmal nature of the arrhythmia. Still, opportunistic single time point screening is recommended in current guidelines.[4] However, this is based on studies in which single time point screening typically identified 1.0-1.6% unknown AF by methods comparable to our study.[5 19]

The lower yield of screening in our study may partly be explained by the high prevalence of known AF, and the fact that the population under study has a high level of education and live in a setting with good access to health care and primary care in particular. The population examined was just below 65 years. Hence, our findings confirm that yield of screening in this age group is low. While some studies with similar population-based design have found comparable low rates of new AF,[20] others have shown a much higher yield by more extensive methods such as intermittent or continuous ECG registrations.[21 22] The large discrepancies between studies supports the recommendation that future AF screening should be country- and health system-specific.[23]

A recent white paper on AF screening concluded that screen-detected AF found on single time point screening should be considered for stroke prevention in the same manner as clinical AF.[23] More extensive screening methods should be considered in selected groups, particularly in those >65 years and with additional risk factors. Although alternative methods such as dedicated blood pressure devices have shown promising results as a primary step in screening,[24] ECG confirmation is still mandated for the diagnosis of AF.

Risk factors for AF

Apart from age, hypertension has been accepted as the most important risk factor for AF for decades, largely due to its high occurrence in the general population.[25] More recent data have shown, however, that the risk in both sexes may be higher from obesity.[26] Similar trends have been found in the Framingham Heart Study, in which diabetes and increased BMI have been identified as emerging risk factors.[27]

Height has been demonstrated to be a risk factor for AF and other CVD, independent from weight.[28] It has also been shown that use of BMI as a measure of body size leads to loss of predictive information, compared to weight and height separately.[29] For this reason, with the obvious limitations in our cross-sectional design, we assessed height and weight separately along with other known risk factors for AF. Most studies, including ours, have found that age-adjusted prevalence of AF is higher in men than in women.[30] Still, male sex was, in our study, not associated with AF after assessing the impact of height, weight and other risk factors. This may indicate that differences in the distribution of AF risk factors, including body height and weight, may account for most, if not all, of the higher prevalence of AF in men. This is consistent with findings from three large cohorts resulting in the CHARGE-AF risk score for AF prediction, in which height and weight, but not sex, were found to predict AF.[6]

In our study, we found that most AF subjects were defined as hypertensive, nearly half were obese, and only 13% had no known comorbidity. The rising prevalence of obesity during the last decades may have contributed to an increasing AF prevalence.[26] Our findings support this theory; however, we cannot draw any conclusions based on our limited data.

Numerous studies have found a relationship between AF and both sedentary lifestyle and extreme levels of physical activity.[28] In our study, level of physical activity among AF participants did not differ from the rest of the cohort. However, due to the cross-sectional design, our findings may reflect a variety of lifestyle changes after being diagnosed with AF, as specific recommendations for physical activity in AF are scarce.

The heritability of AF is well-established. For many individuals with AF, the arrhythmia is probably a multifactorial and polygenic phenomenon, and a number of genetic variants associated with increased risk have been identified.[31] Some studies have also shown a strong association between self-reported familial AF and AF occurrence, independent of other risk factors, including genetic variants.[32] In line with these studies, we found that AF occurred twice as often in subjects who had at least one 1st degree relative with AF, at any age, compared to those without familial AF.

Risk factors for cardiovascular disease and stroke

Stroke prevention is of utmost importance in AF, and guideline adherence improves outcomes.[33] In this cohort, stroke risk in the AF group was low *(Supplementary table 2)*. Use of anticoagulation was reported only in 47% of individuals with AF. However, many turned 65 years shortly after inclusion and their indication for anticoagulation would then have been strengthened. Within the small group of individuals with screen-detected AF, the stroke risk was even lower.

Despite the established aims of antihypertensive treatment in the western world, hypertension is still a major cardiovascular risk factor along with obesity.[34] The majority of our cohort was treated for hypertension or had elevated blood pressure at the baseline examination. In fact, among all participants without antihypertensive treatment, ~40% were found with elevated blood pressure. By applying new U.S. guidelines for the management of high blood pressure (≥130/≥80 mmHg),[35] as many as ~65% of the untreated population in this cohort would be classified as hypertensive. Regardless of definitions, this suggests that there is still a potential for improved treatment of this important cardiovascular risk factor. Obesity has reached a prevalence of 35% in the U.S.[36] and >20%

in Norway,[37] similar to the findings in our study. Overweight may, in this age group, be seen as "the new normal", as less than 1/3 of the cohort had BMI <25 kg/m^2.

Clinical implications

Increased awareness with regard to detection and treatment of AF is desirable, particularly because of the increased stroke risk. However, it is still unknown whether screening or more active case-finding for AF will be effective in reducing stroke rates. Current guidelines advise health personnel to carry out simple measures such as pulse palpation and 12-lead ECG more frequently at the age of 65 years and above, or even in younger age groups if risk factors for stroke are present.[4] New and portable single-lead ECG devices may make these recommendations easier to implement, as single time point or even repeated measurements can be performed more easily. However, it is still unknown in which groups of the population screening may be justified. The low yield of single time point screening in our study, supports the opinion that screening below the age of 65 years may only be recommended in selected high-risk groups.[23]

The high prevalence of obesity and untreated hypertension found in this cohort is alarming. These conditions can potentially be prevented in primary care and by public health measures. Prevention of AF by early detection and treatment of these conditions may be as important as early detection of AF itself. Furthermore, nearly half of AF individuals in this study were found with elevated blood pressure, regardless of treatment, underlining a potential also for improved treatment within this group.

Conclusion

In conclusion, we found low prevalence of advanced CVD, but a high burden of hypertension and overweight, in this general population cohort aged 63-65 years. The prevalence of ECG-validated AF was 4.5%, including only 0.3% found through single time point ECG screening. The low yield of screening in this age group may partially be explained by the high prevalence of known AF. We also found that body size and comorbidity may explain most, if not all, of the sex difference in AF prevalence at this age.

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Competing interests: First author TB has (outside this work) received honoraria from Boehringer-Ingelheim, Bayer and Pfizer/Bristol-Myers Squibb. TO has (outside this work) received honoraria or research support from Abbott, AstraZeneca, Bayer, Novartis, Roche, Singulex, and Thermo Fisher. HR has (outside this work) received honoraria or research support from Novartis, CardiNor AS and SpinChip Diagnostics. TO and HR are partners in a patent filed by the University of Oslo regarding the use of secretoneurin as a biomarker in patients with cardiovascular disease and patients with critical illness.

Authors' contributions: TB, KS, TO, PS, HR and AT designed the study. TB, MNL, HIH, JB, MOP, ENA, TV, BK and IEC have performed the baseline examinations and the acquisition of data. TB and PS have performed the validation of AF diagnoses, supported by MNL, JB and AT. TB and MNL have performed the statistical analysis. TB has written the manuscript. AT was the principal investigator (PI) and HR was the co-PI of the study. All authors have revised the manuscript for important intellectual content and have read and approved the final manuscript.

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Data sharing statement: The dataset used in this study is not publicly available, as the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information on: www.ace1950.no

Table 1: Baseline characteristics of the ACE 1950 cohort

	Total N = 3706	Men N = 1899	Women N = 1807	*P*
Age	63.9±0.7	63.9±0.7	63.9±0.6	0.34
Caucasian ethnicity	97.8	97.4	98.2	0.08
Higher education	46.4	50.2	42.3	<0.001
BMI	27.2±4.4	27.7±4.0	26.6±4.8	<0.001
Overweight/obesity (BMI ≥25)	67.6	74.9	59.8	<0.001
Systolic blood pressure, mmHg	138±19	139±18	137±20	0.02
Diastolic blood pressure, mmHg	77±10	80±10	74±9	<0.001
Hypertension	62.0	66.0	57.8	<0.001
Myocardial infarction	4.3	7.4	0.9	<0.001
Coronary heart disease	7.1	11.5	2.4	<0.001
Heart failure	1.6	2.3	0.9	0.001
Atrial fibrillation	4.5	6.4	2.4	<0.001
Stroke/TIA	3.8	5.0	2.5	<0.001
Diabetes mellitus	8.6	11.6	5.4	<0.001
Chronic kidney disease	3.9	3.4	4.3	0.16
Hypercholesterolemia	52.6	50.6	54.7	0.01
COPD	7.2	6.9	7.4	0.60
Obstructive sleep apnoea	6.2	9.0	3.2	<0.001
Current daily smoking	14.5	13.7	15.3	0.19
Current or former daily smoking	61.8	62.2	61.5	0.64
Daily moist tobacco (“snus”)	2.2	3.8	0.4	<0.001
Alcohol				
>14 standard drinks/week	2.8	4.3	1.2	<0.001
“Binge drinking”	16.3	25.3	6.9	<0.001
Physical activity level				
Inactive	19.1	22.5	15.4	<0.001
Low	19.7	19.7	19.7	0.98
Medium	40.3	34.7	46.1	<0.001
High	21.0	23.1	18.8	0.001
Medication				
Any cardiovascular medication (ATC C)	46.1	50.0	41.9	<0.001
Diuretics (ATC C03)	3.1	2.9	3.3	0.52
Beta blockers (ATC C07)	13.4	16.7	9.9	<0.001
Calcium channel blockers (ATC C08)	8.1	9.7	6.4	<0.001
Agents acting on the renin-angiotensin	26.9	30.6	23.0	<0.001
Lipid modifying agents (ATC C10)	26.2	29.6	22.5	<0.001

Categorical variables are reported as percentages. Continuous variables are presented as mean ±SD. P-values indicate difference between sexes. Higher education: ≥12 years of formal education. BMI: Body Mass Index (kg/m^2). TIA: Transient ischemic attack. COPD: Chronic Obstructive Pulmonary Disease. "Binge drinking" is defined as heavy episodic drinking (at least 5 standard drinks of alcohol) at least once per month. Details for classification of physical activity level are provided in Supplementary Table 1. Medication: Self-reported cardiovascular medication according to ATC classification.

Table 2: Prevalence of validated atrial fibrillation at 63-65 years

	Total, n (%) (n=3706)	Men, n (%) (n=1899)	Women, n (%) (n=1807)
Total AF	**165 (4.5)**	**121 (6.4)**	**44 (2.4)**
Paroxysmal AF	105 (2.8)	73 (3.9)	32 (1.8)
Persistent/permanent AF	48 (1.3)	37 (2.0)	11 (0.6)
Previously undiagnosed AF	12 (0.3)	11 (0.6)	1 (0.1)

Previously undiagnosed cases were not classified as paroxysmal/persistent as further follow-up was performed in the clinical setting after the baseline visit.

Table 3: Clinical characteristics of study population by AF prevalence and sex

	Men			Women		
	AF (n=121)	**Without AF (n=1778)**	***p***	**AF (n=44)**	**Without AF (n=1763)**	***p***
Height, cm	180.4±6.7	178.8±6.5	<0.01	168.7±7.0	165.3±5.9	<0.001
Weight, kg	94.0±15.7	88.3±13.6	<0.001	79.6±16.5	72.8±13.4	<0.01
BMI	28.9±4.9	27.6±3.9	<0.01	27.9±5.6	26.6±4.7	0.07
Obesity (BMI ≥30)	52 (43.0)	405 (22.8)	<0.001	17 (38.6)	365 (20.7)	<0.01
Waist circumference, cm	103.4±12.9	99.3±11.0	0.001	93.3±12.7	87.7±12.4	<0.01
Hip circumference, cm	104.0±9.6	101.5±6.8	<0.01	105.5±9.6	102.1±9.2	0.01
Waist-to-hip ratio	0.99±0.08	0.97±0.07	0.02	0.88±0.07	0.85±0.08	0.04
Body surface area, m^2	2.16±0.19	2.09±0.18	<0.001	1.92±0.22	1.82±0.18	<0.01
Hypertension	101 (83.5)	1152 (64.8)	<0.001	37 (84.1)	1007 (57.2)	<0.001
Myocardial infarction	18 (14.9)	123 (6.9)	0.001	0 (0)	17 (1.0)	0.51
Coronary heart disease	28 (23.1)	191 (10.7)	<0.001	0 (0)	44 (2.5)	0.29
Heart failure	13 (10.7)	30 (1.7)	<0.001	3 (6.8)	14 (0.8)	<0.001
Stroke/TIA	9 (7.4)	86 (4.8)	0.20	3 (6.8)	42 (2.4)	0.06
Diabetes mellitus	13 (10.7)	207 (11.6)	0.76	4 (9.1)	93 (5.3)	0.27
Chronic kidney disease	11 (9.1)	54 (3.1)	<0.001	5 (11.4)	73 (4.2)	0.02
Obstructive sleep apnoea	15 (12.4)	156 (8.8)	0.18	3 (6.8)	54 (3.1)	0.16
No comorbidity	15 (12.4)	455 (25.6)	0.001	6 (13.6)	594 (33.7)	<0.01
Hospitalization last 12 months	28 (23.1)	201 (11.3)	<0.001	16 (36.4)	204 (11.6)	<0.001
Current daily smoking	10 (8.3)	249 (14.1)	0.08	8 (18.2)	265 (15.2)	0.58
Familial AF	31 (25.6)	272 (15.3)	<0.01	25 (56.8)	408 (23.1)	<0.001
Higher education	61 (50.4)	889 (50.2)	0.97	18 (40.9)	745 (42.3)	0.85
Physical activity level						
Inactive	30 (25.6)	390 (22.3)	0.40	11 (25.6)	259 (15.1)	0.06
Low/medium	55 (47.0)	960 (54.9)	0.10	27 (62.8)	1129 (65.9)	0.67
High	32 (27.4)	399 (22.8)	0.26	5 (11.6)	325 (19.0)	0.22
Heart rate	56±8	61±10	<0.001	59±8	65±10	<0.01
PQ interval	185±29	175±27	<0.01	182±44	165±25	0.04
QRS duration	105±22	98±14	<0.01	90±14	88±10	0.28

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean ±SD. P-values indicate difference between sexes. BMI: Body Mass Index, kg/m^2. TIA: Transient ischemic attack. No comorbidity: Neither hypertension, coronary heart disease, heart failure, stroke, diabetes, chronic kidney disease, obstructive sleep apnoea nor obesity. Familial AF: Self-report of at least one 1^{st} degree relative with known AF. Higher education: ≥12 years of formal education. Heart rate: Beats per minute in 12-lead ECG. PQ interval and QRS duration are reported in milliseconds. For heart rate, PQ-interval and QRS duration; all subjects with AF in study ECG were excluded (n=60).

Table 4: Risk factors associated with atrial fibrillation

	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Male sex	2.73 (1.92 – 3.87)	<0.001	1.00 (0.59 – 1.68)	0.99
Height per 10 cm	**1.90 (1.59 – 2.28)**	**<0.001**	**1.67 (1.26 – 2.22)**	**<0.001**
Weight per 10 kg	**1.42 (1.29 – 1.55)**	**<0.001**	**1.15 (1.01 – 1.30)**	**0.03**
Hypertension	**3.27 (2.15 – 4.97)**	**<0.001**	**2.49 (1.61 – 3.86)**	**<0.001**
Heart failure	**8.53 (4.71 – 15.48)**	**<0.001**	**3.51 (1.71 – 7.24)**	**0.001**
Familial AF	**2.16 (1.55 – 3.02)**	**<0.001**	**2.32 (1.63 – 3.31)**	**<0.001**
Chronic kidney disease	**2.87 (1.66 – 4.95)**	**<0.001**	**2.56 (1.42 – 4.60)**	**<0.01**
Coronary heart disease	2.88 (1.88 – 4.41)	<0.001	1.56 (0.95 – 2.57)	0.08
History of stroke/TIA	2.09 (1.13 – 3.86)	0.02	1.43 (0.74 – 2.78)	0.29
OSA	1.94 (1.17 – 3.23)	0.01	1.11 (0.63 – 1.97)	0.71
Physical activity – inactive	1.61 (1.10 – 2.37)	0.02	1.38 (0.92 – 2.07)	0.12
Physical activity – high	1.30 (0.88 – 1.94)	0.19	1.20 (0.80 – 1.81)	0.38
Diabetes	1.24 (0.74 – 2.08)	0.41	-	-
Daily smoking	0.72 (0.44 – 1.19)	0.20	-	-
High alcohol consumption	0.81 (0.45 – 2.78)	0.81	-	-

Variables with $p<0.20$ in univariate logistic regression analysis are included in the multivariate analysis. Bold font indicates a significant association in multivariate analysis. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. TIA: Transient ischemic attack. Familial AF: Self-report of at least one 1st degree relative with known AF. OSA: Obstructive sleep apnoea. Physical activity (PA) level: Inactive and high level of PA compared to low/medium PA as reference. High alcohol consumption: >14 standard drinks/week (both sexes).

Legend Figure 1: Flow chart of ACE 1950 study population and AF prevalence

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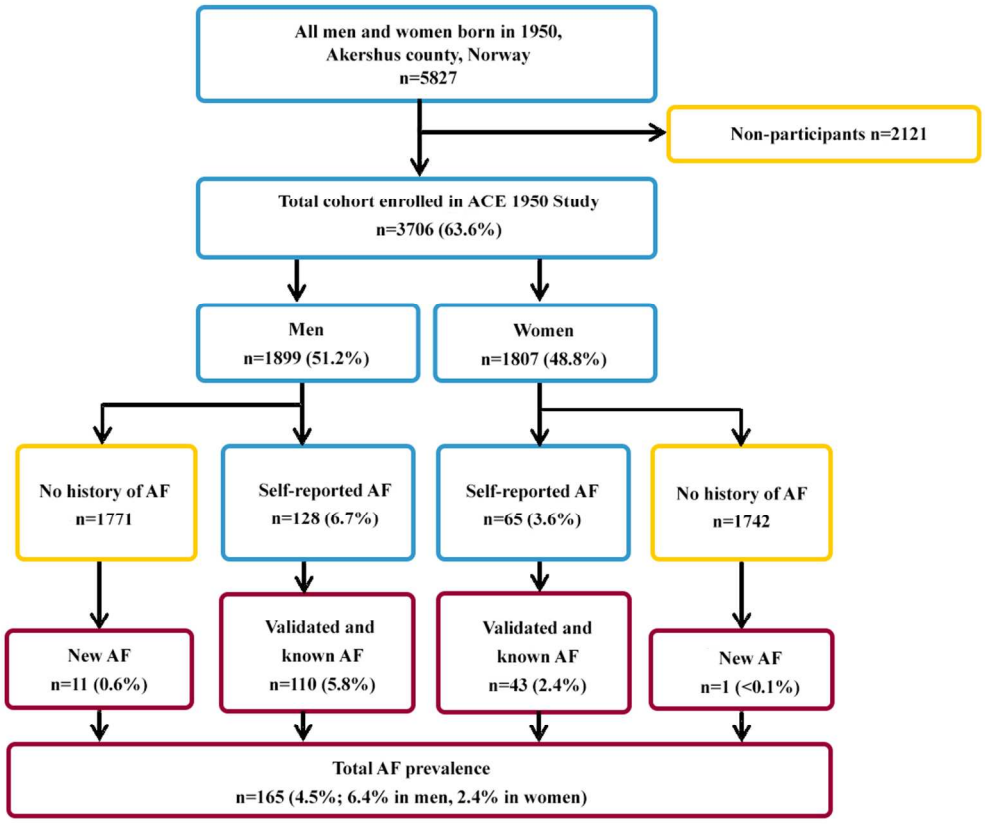

Flow chart of ACE 1950 study population and AF prevalence

297x250mm (96 x 96 DPI)

Supplementary Table 1: Questions used for self-reporting of physical activity and calculation of PAI (Physical Activity Index)

Physical activity[1]
Frequency How frequently do you exercise? Give an average (by exercise we mean, for example, going for walks, skiing, swimming or training/sport). • Never [0] • Less than once a week [0] • Once a week [1] • 2-3 times per week [2.5] • Almost every day [5] **Intensity** If you do such exercise as frequently as once or more times a week: How hard do you push yourself? (Give an average) • I take it easy without breaking into a sweat or losing my breath [1] • I push myself so hard that I lose my breath and break into a sweat [2] • I push myself to near-exhaustion [3] **Duration** How long does each session last? (Give an average) • Less than 15 minutes [0.1] • 16-30 minutes [0.38] • 30 minutes to 1 hour [0.75] • More than 1 hour [1] The response to each question (numbers in clams) was multiplied to calculate a Physical Activity Index (PAI), and this index was used for categorization into four groups: • Inactive [0] • Low PA [0.05-1.50] • Medium PA [1.51-3.75] • High PA [3.76-15.00]

[1] This 3-item self-reported assessment of physical activity and consequent 4-level Physical Activity Index has been validated in the Norwegian HUNT study *(Nord-Trøndelag health study)*, and shown moderate but significant correlation to both measured VO_{2max} and to the *International Physical Activity Questionnaire*.

Reference:

Aspenes ST, Nauman J, Nilsen TI, et al. Physical activity as a long-term predictor of peak oxygen uptake: the HUNT Study. *Med Sci Sports Exerc* 2011;43(9):1675-9.

Supplementary Table 2: Stroke risk and use of medication in individuals with atrial fibrillation

	Total AF (n=165)	Men with AF (n=121)	Women with AF (n=44)	*p*
CHA_2DS_2-VASc score, mean ±SD	1.7 ±1.1	1.4 ±1.0	2.2 ±0.9	<0.001
CHA_2DS_2-VASc score, median [IQR; total range]	2 [1-2; 0-6]	1 [1-2; 0-5]	2 [2-2; 1-6]	<0.001
CHA_2DS_2-VASc ≥2 (men) or ≥3 (women) (%)	52 (31.5)	45 (37.2)	7 (15.9)	<0.01
Elevated blood pressure, (%)	67 (41.1)	46 (38.7)	21 (47.7)	0.30
Anticoagulation, (%)	77 (46.7)	56 (46.3)	21 (47.7)	0.87
Platelet inhibitors, (%)	46 (27.9)	38 (31.4)	8 (18.2)	0.09
Beta-blockers, (%)	97 (58.8)	69 (57.0)	28 (63.6)	0.45
Calcium antagonists, (%)	25 (15.2)	20 (16.5)	5 (11.4)	0.41
Antiarrhythmic drugs, (%)	28 (17.0)	22 (18.2)	6 (13.6)	0.49
Class Ic, (%)	19 (11.5)	14 (11.6)	5 (11.4)	0.97
Class III, (%)	9 (5.5)	8 (6.6)	1 (2.3)	0.45
Digoxin, (%)	4 (2.4%)	3 (2.5)	1 (2.3)	1.00
ACE inhibitors or ATII antagonists, (%)	63 (38.2)	51 (42.1)	12 (27.3)	0.08
Statins, (%)	63 (38.2)	51 (42.1)	12 (27.3)	0.08
Thyroid hormone therapy, (%)	7 (4.2)	1 (0.8)	6 (13.6)	<0.01

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean ±SD. P-values indicate difference between sexes. CHA_2DS_2-VASc score reported both as mean ±SD and median, including range. IQR: Inter-quartile range. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. ACE: Angiotensin converting enzyme. ATII: Angiotensin type 2.

Supplementary Table 3: Stroke risk and comorbidity in screen-detected AF

	New AF at screening (n=12)
Male sex, (%)	11 (91.7)
CHA_2DS_2-VASc score, mean ±SD	1.1 ±0.8
CHA_2DS_2-VASc score, median [total range]	1 [0-2]
CHA_2DS_2-VASc 0, (%)	3 (25.0)
CHA_2DS_2-VASc 1, (%)	5 (41.7)
CHA_2DS_2-VASc 2, (%)	4 (33.3)
Overweight, (%)	9 (75.0)
Hypertension, (%)	8 (66.7)
Elevated blood pressure, (%)	5 (41.7)
Heart failure, (%)	0 (0)
Diabetes, (%)	2 (16.7)
History of stroke, (%)	0 (0)
Myocardial infarction, (%)	1 (8.3)
Chronic kidney disease, (%)	0 (0)
Obstructive sleep apnoea, (%)	1 (8.3)
Daily smoking, (%)	0 (0)

Categorical variables are reported as counts with percentages in parentheses. CHA_2DS_2-VASc score is reported both as mean ±SD and median. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. TIA: Transient ischemic attack.

STROBE Statement—checklist of items that should be included in reports of observational studies

Manuscript: ***Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study***

	Item No	Recommendation	Page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**6-7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**6-7**
Bias	9	Describe any efforts to address potential sources of bias	**-**
Study size	10	Explain how the study size was arrived at	**6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**6-7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**8**
		(*c*) Explain how missing data were addressed	**8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**8-9**
		(b) Give reasons for non-participation at each stage	**-**
		(c) Consider use of a flow diagram	**Fig. 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**8 + Tab. 1**
		(b) Indicate number of participants with missing data for each variable of interest	**11**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**9 + Tab. 2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**9-10 + Tab. 4**
		(*b*) Report category boundaries when continuous variables were categorized	**-**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**-**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**9-10**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**11-12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**12-14**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**15**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**16**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology
Keywords:	Atrial fibrillation, Obesity, Cardiovascular risk, Prevalence, Screening, Cardiac Epidemiology < CARDIOLOGY

Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study

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ABSTRACT

Objectives: To investigate the sex-specific prevalence of atrial fibrillation (AF), including subclinical AF found by screening in a general population aged 63-65 years. The prevalence of cardiovascular risk factors and their association with AF will also be investigated.

Design: Cross-sectional analysis of an observational, prospective, longitudinal, population-based cohort study.

Setting: General population in Akershus county, Norway.

Participants: Women and men born in 1950. We included 3706 of 5827 eligible individuals (63.6%); 48.8% were women.

Methods: All participants underwent extensive cardiovascular examinations, including 12-lead electrocardiogram (ECG). History of AF and other cardiovascular diseases (CVD) were self-reported. Subsequent validation of all reported or detected AF diagnoses was performed.

Results: Mean age was 63.9±0.7 years. Prevalence of ECG-verified AF was 4.5% (women 2.4%, men 6.4%; $p<0.001$), including screen-detected AF in 0.3% (women 0.1%, men 0.6%; $p<0.01$). Hypertension was found in 62.0% (women 57.8%, men 66.0%; $p<0.001$). Overweight or obesity was found in 67.6% (women 59.8%, men 74.9%; $p<0.001$). By multivariate logistic regression, risk factors associated with AF were height (OR 1.67 per 10 cm; 95% CI 1.26-2.22; $p<0.001$), weight (OR 1.15 per 10 kg; 1.01-1.30; p=0.03), hypertension (OR 2.49; 1.61-3.86; $p<0.001$), heart failure (OR 3.51; 1.71-7.24; $p=0.001$), reduced estimated glomerular filtration rate (OR 2.56; 1.42-4.60; $p<0.01$) and at least one 1st degree relative with AF (OR 2.32; 1.63-3.31; $p<0.001$), whereas male sex was not significantly associated (OR 1.00; 0.59-1.68; $p=0.99$).

Conclusion: In this cohort from the general population aged 63-65 years, we found a higher prevalence of known AF than previously reported below the age of 65 years. The additional yield of single time point screening for AF was low. Body size and comorbidity may explain most of the sex difference in AF prevalence at this age.

Keywords: Atrial fibrillation, hypertension, obesity, cardiovascular risk, prevalence, screening

Strengths and limitations of this study

- Unselected population-based cohort design inviting all residents in a geographical region born in 1950.
- The study was conducted in a completely government-financed healthcare system with equal access for the entire population.
- All reported and detected cases of atrial fibrillation were thoroughly validated.
- The study relied on self-reported cardiovascular disease only, and negative responses to atrial fibrillation were not validated.
- This report is a cross-sectional analysis of an age cohort study, making comparison to other study settings difficult.

INTRODUCTION

The prevalence of atrial fibrillation (AF) is on the rise and this arrhythmia is emerging as a major public health problem due to the associated stroke risk and related costs.[1 2] The prevalence in the adult population has been estimated to be 1-2%, but is probably as high as 2-3%, based on recent data.[1] Previous studies in specific age groups have reported a prevalence of AF of 4.2% among subjects 60-69 years of age.[3] The increase in prevalence is most likely due to both aging of the population and improved survival from other types of cardiovascular disease (CVD). Increased awareness and improved detection of subclinical AF may also be contributing factors.

Screening for AF has received increased attention lately. European guidelines recommend opportunistic screening by pulse palpation or electrocardiogram (ECG) in all patients >65 years of age.[4] Despite the emergence of technology for ambulant ECG monitoring, current recommendations are still based on single time point screening by standard ECG, enabling undetected AF to be diagnosed in 1.4% of the population ≥65 years.[5] At this age and above, one or more additional risk factors for stroke, according to the CHA_2DS_2-VASc score, provide a strong indication for anticoagulation.[4] Hence, subjects with hypertension, diabetes or other risk factors for stroke represent a potential target group for screening for AF.[6] Studies have shown that about 50% of incident AF could be attributed to elevated levels of risk factors for AF, of which elevated blood pressure and overweight were the most important contributors.[7] This raises the issue of early detection and subsequent "upstream" treatment of these conditions.

The primary objective of this study was to investigate the sex-specific prevalence of self-reported and ECG-validated AF, including subclinical AF found by screening, in a contemporary population-based cohort aged 63-65 years. Secondary objectives were to investigate the prevalence of cardiovascular risk factors and their association with AF.

METHODS

Study population

The Akershus Cardiac Examination (ACE) 1950 Study is an observational, longitudinal, population-based cohort study of individuals born in 1950. The identity of all permanent residents of Akershus county born in 1950 were retrieved from the Norwegian Population Registry at the start of the study (n=5827). These were invited by letter and subsequent phone calls. Design and general methodology have been reported previously.[8] In this article, we present data from a cross-sectional analysis of the baseline examination, performed in the period September 2012 - May 2015.

Study variables

Clinical data included measurements of height, weight, seated blood pressure and 12-lead electrocardiogram (ECG). Body mass index (BMI) was calculated according to the standard formula (kg/m^2), and categorized into overweight (BMI 25.0-29.9 kg/m^2) and obesity (BMI ≥30.0 kg/m^2). Body surface area (BSA; m^2) was calculated by the Mosteller formula.[9] A web-based questionnaire for registration of medical history and lifestyle was used. The questionnaire was formulated in the same manner as in previous large Norwegian population studies,[10] and participants were urged to ask study personnel at the baseline visit if they were not able to respond adequately to all questions, to ensure high-quality data collection. Daily use of all types of medication was registered according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Concerning AF, the participants were asked: "Have you ever been diagnosed with atrial fibrillation or atrial flutter?" All self-reported AF was validated according to the following: 1) ECG documentation of AF or atrial flutter according to standard definitions,[4] and if such was not available, 2) a solid description of AF or atrial flutter in the medical record (i.e. DC cardioversion or AF ablation procedure). All ECGs and medical records were evaluated by two physicians, of whom one was a cardiologist. Available information in the medical records including ECGs, as well as the study ECG, was used to classify AF as paroxysmal vs. persistent/permanent. Participants without history of AF, but in whom AF was detected in the study ECG, were classified as previously undiagnosed AF.

Participants also reported any familial AF history among 1st degree relatives. For individuals with AF, we calculated the CHA_2DS_2-VASc stroke risk score. This was based on the presence or history of heart failure, hypertension, diabetes, stroke/TIA, myocardial infarction, age >65 years and female sex. Hypertension was defined as the mean (from the second and third of three readings) systolic blood pressure ≥140 mmHg or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. The diagnoses of heart failure, myocardial infarction and stroke or transient ischemic attack (TIA) were self-reported. Coronary artery disease was defined as self-reported myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting surgery.

Fasting blood samples were analysed on-site and included lipids, blood glucose, HbA1c, and serum creatinine. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate estimated glomerular filtration rate (eGFR).[11] Reduced eGFR (eGFR <60 mL/min/1.73 m^2), indicative of chronic kidney disease, was reported and used for the analyses. Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L and/or LDL ≥4.1 mmol/L and/or use of lipid-lowering medication. Diabetes was defined as a self-reported diagnosis or use of hypoglycaemic medication or elevated glucose tests (both HbA1c ≥6.5% and fasting blood glucose ≥7.0 mmol/l).

Higher education was defined as >12 years of formal education, i.e. college/university education at any level. Alcohol consumption, smoking and physical activity was self-reported. Physical activity was classified according to a previously validated model (details provided in Supplementary Table 1).[12]

The data are reported according to the STROBE guidelines.[13] The study complies with the Declaration of Helsinki, and was approved by the Norwegian Regional Ethics Committee (ref. 2011/1475). Written informed consent was obtained from all participants.

Statistical analysis

Continuous variables are reported as mean and standard deviation (SD), and Student's t-test was used for between-group analysis. Continuous variables not normally distributed are reported as median with interquartile range (IQR) and analysed with the Mann-Whitney U test. Categorical variables are presented as counts and/or proportions (%) and compared by the χ^2 test or Fisher's exact test as appropriate. Logistic regression analysis was used to assess associations between risk factors and AF. All available known risk factors for AF were selected from univariate analyses based on clinical and statistical significance (p-value <0.20). Pearson correlation, as well as multicollinearity statistics, was run between each of the independent variables before inclusion in a multivariate logistic regression model. To assess the robustness of the model, we performed a sensitivity analysis in which all candidate variables were put into the same model. Secondary analyses replacing height and weight with the more commonly used BMI, as well as BSA, were also performed. P-values are two-sided and considered significant when <0.05. Cases with missing data were omitted from descriptive statistics of that particular variable. Hence, the reported proportions represent the valid proportions. As for the regression analysis, a complete case analysis was performed. Statistics were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York, USA).

Patient and public involvement

The participants of this study represent a large age cohort from the general population. Although there was no public or participants' involvement in the planning and design of the study, random samples of participants were, during the conduct of the baseline examinations, invited to respond to a questionnaire focusing on how they perceived their participation in the study, and if they had any suggestions to improve the study conduct. Individual study results (blood pressure, cholesterol levels etc.) were sent to all study participants shortly after their study visit, accompanied by individual advice in case any further follow-up was recommended. All scientific study results are continuously communicated to the participants as well as the general population through local media and our own website www.ace1950.no. Newsletters with updated study information have also been sent to all study

participants by mail. A 'participant advisory board' is now currently being formalized, and will be involved in the planning of further follow-up studies of this cohort.

RESULTS

General cohort profile

A total of 3706 participants (from 5827 eligible residents; 63.6% participation rate) were enrolled and examined in the ACE 1950 Study. Women and men were evenly represented, with 1807 (48.8%) women and 1899 (51.2%) men (participation rate 63.7% among women, 63.5% among men; p=0.86). Akershus University Hospital enrolled 2473 participants, and Bærum Hospital (Vestre Viken Hospital Trust) 1233 participants, within their respective catchment areas. The majority were of Caucasian ethnicity (3624; 97.8%). All participants were born in 1950, and the mean age at inclusion was 63.9 ±0.7 years.

Baseline characteristics are presented in *Table 1*. The prevalence of CVD and cardiovascular risk factors were generally higher in men than in women, with the exception that a higher number of women had hypercholesterolemia ($p<0.01$). There were no sex difference in reported daily smoking (15.3% of women vs. 13.7% of men; $p=0.19$). As shown in *Table 1*, the majority of the cohort was overweight or obese. Obesity was found in 22.6% (24.1% of men, 21.1% of women; $p=0.03$).

Prevalence of known and unknown AF

A flowchart illustrating the validation of AF is shown in *Figure 1*. History of AF was reported by 193 (5.2%) participants. After validation, 153 (4.1%) had a verified AF diagnosis. Hence, the positive predictive value (PPV) of self-reported AF, compared to the direct review of medical records and ECGs, was 79.3%. Previously unknown AF was diagnosed by ECG in 12 (0.3%) participants. The total prevalence of validated AF was 4.5% (n=165; 2.4% among women, 6.4% among men; $p<0.001$), as shown in *Figure 1* and *Table 2*. Nine subjects had a history of atrial flutter (or atrial flutter in study ECG), without any previous diagnosis of AF. These were counted as AF. Permanent AF was identified in 48 cases *(Table 2)*.

Clinical characteristics of AF

Table 3 shows sex-specific characteristics of individuals with AF compared to the rest of the cohort. Both women and men with AF were significantly taller and heavier than those without AF. Other measures of body size, such as waist and hip circumference, and BSA, were also higher among individuals with AF, regardless of sex. Obesity was found in 41.8% of participants with AF vs. 21.7% in unaffected participants (p<0.001). Hypertension, heart failure and reduced eGFR were more prevalent in individuals with AF of both sexes, whereas coronary heart disease was more prevalent only among men with AF. Otherwise there were only minor sex differences. With regard to level of physical activity, there were no significant differences between the groups.

A higher number of both women and men with AF reported a 1st degree relative with known AF, compared to the rest of the cohort (33.9% vs. 19.2%; p<0.001; *Table 3)*. Familial AF was more prevalent in women with AF than in men with AF (56.8% vs. 25.6%; p<0.001).

Risk factors for AF

Risk factors associated with AF, assessed by logistic regression, are reported in *Table 4*. In univariate analysis, male sex was associated with increased likelihood of having AF. However, in multivariate analysis, sex was not associated with AF, when adjusting for height, weight and other risk factors. Height, weight, hypertension, heart failure, reduced eGFR, and family history of AF, were all significantly associated with AF in multivariate analysis. A sensitivity analysis, in which all independent variables were included, did not change the results *(Supplementary Table 2)*. In secondary analyses, height and weight were replaced with BMI or BSA. In these analyses, male sex remained significantly associated with AF, and a strong association to AF was found for both BMI and BSA, while only minor changes were seen for other variables (data not shown).

Stroke risk in AF

The median CHA_2DS_2-VASc stroke risk score among AF subjects was 1 [IQR 1-2] in men and 2 [IQR 2-2] in women *(Supplementary Table 3)*. In total, 83.6% in the AF group fulfilled our criteria for hypertension. As many as 41.1% of individuals with AF had elevated blood pressure (≥140/≥90

mmHg) at the ACE 1950 baseline visit, regardless of ongoing treatment. Details of stroke risk and medication in individuals with AF are presented in *Supplementary Table 3*. Furthermore, characteristics of screen-detected AF (n=12) are shown in *Supplementary Table 4*. These individuals were generally low-risk; the median CHA_2DS_2-VASc score was 1 [total range 0-2]. However, 75.0% were overweight and 66.7% had hypertension.

Missing data

Basic clinical variables, including height, weight and ECG were available from all 3706 participants, whereas blood pressure was missing in only two participants. Data was missing for <1% of the participants for all reported variables, including all self-reported CVD, except for physical activity in which 2.3% (n=84) had missing data on at least one of three physical activity questions.

DISCUSSION

Principal findings

The key results of this study were that we identified a high prevalence of verified AF, whereas single time point screening by 12-lead ECG identified only 0.3% new cases in an unselected contemporary population aged 63-65 years. Body size and cardiovascular comorbidity, but not sex, were independently associated with prevalent AF at this age.

Strengths and limitations

Strengths of this study include the unselected population-based design and complete, or nearly complete, data on all participants. For example, 12-lead ECGs were available from all 3706 participants. The thorough validation of all self-reported AF cases also strengthens our findings.

Limitations include uncertainty about the accuracy of self-reported CVD. In particular, we believe heart failure and history of stroke have a high degree of uncertainty, whereas diseases such as diabetes and myocardial infarction may be more easily defined and recognised in the population. The diagnosis of hypertension should, ideally, be based on serial or ambulant blood pressure measurements. Hence, the prevalence may be overestimated.

Negative responses to self-reported AF were not validated. However, this may only have led to an underestimation of the prevalence, due to the unknown number of false negative responses. A validation of self-reported AF in the HUNT study questioned the use of self-reported AF, as sensitivity was low and many AF cases were missed.[14] Our study was not designed as a validation study and therefore sensitivity and specificity of self-reported AF could not be estimated. Still, the PPV of self-reported AF in our study, 79.3%, was much higher than found in the HUNT study (PPV 56%).[14] Furthermore, classification of AF as paroxysmal or persistent/permanent was made based on available ECGs and medical records, and we cannot rule out that some individuals may have been misclassified.

By its design, our study depicts a limited age group, making comparison to other studies difficult. Finally, the study was designed as a cardiovascular cohort study with a special focus on AF. Hence, individuals with known AF may have been more motivated to participate than unaffected individuals, which may represent a selection bias.

Prevalence of AF

To the best of our knowledge, no other study based on unselected population data has reported a prevalence of AF as high as 4.5% below the age of 65 years. Most comparable studies have reported a prevalence of 3.7-4.2% in the age group 60-69 years.[1 3] A Swedish study found 2.9% in the more comparable age group 60-64 years,[15] while the Rotterdam study reported <2% in this age group.[16] AF prevalence in our study is particularly high for men (6.4%), while a few studies have reported a prevalence >2.4% among women at this age.[3 17 18]

Single time point screening for AF

The true prevalence of AF cannot be found by single time point ECGs, as some cases will be missed due to the paroxysmal nature of the arrhythmia. Still, opportunistic single time point screening is recommended in current guidelines.[4] However, this is based on studies in which single time point screening typically identified 1.0-1.6% unknown AF by methods comparable to our study.[5 19]

The lower yield of screening in our study may partly be explained by the high prevalence of known AF, and the fact that the population under study has a high level of education and live in a setting with good access to health care and primary care in particular. The population examined was just below 65 years. Hence, our findings confirm that yield of screening in this age group is low. While some studies with similar population-based design have found comparable low rates of new AF,[20] others have shown a much higher yield by more extensive methods such as intermittent or continuous ECG registrations.[21 22] The large discrepancies between studies supports the recommendation that future AF screening should be country- and health system-specific.[23]

A recent white paper on AF screening concluded that screen-detected AF found on single time point screening should be considered for stroke prevention in the same manner as clinical AF.[23] More extensive screening methods should be considered in selected groups, particularly in those >65 years and with additional risk factors. Although alternative methods such as dedicated blood pressure devices have shown promising results as a primary step in screening,[24] ECG confirmation is still mandated for the diagnosis of AF.

Risk factors for AF

Apart from age, hypertension has been accepted as the most important risk factor for AF for decades, largely due to its high occurrence in the general population.[25] More recent data have shown, however, that the risk in both sexes may be higher from obesity.[26] Similar trends have been found in the Framingham Heart Study, in which diabetes and increased BMI have been identified as emerging risk factors.[27]

Height has been demonstrated to be a risk factor for AF and other CVD, independent from weight.[28] It has also been shown that use of BMI as a measure of body size leads to loss of predictive information, compared to weight and height separately.[29] Most studies, including ours, have found that age-adjusted prevalence of AF is higher in men than in women.[30] Still, male sex was, in our study, not associated with AF after assessing the impact of height, weight and other risk factors. This may indicate that differences in the distribution of AF risk factors, including body height and weight, may

account for most, if not all, of the higher prevalence of AF in men at this age. This is consistent with findings from three large cohorts resulting in the CHARGE-AF risk score for AF prediction, in which height and weight, but not sex, were found to predict AF.[6]

In our study, we found that most AF subjects were defined as hypertensive, nearly half were obese, and only 13% had no known comorbidity. The rising prevalence of obesity during the last decades may have contributed to an increasing AF prevalence.[26] Our findings support this theory; however, we cannot draw any conclusions based on our limited data.

The heritability of AF is well-established. For many individuals with AF, the arrhythmia is probably a multifactorial and polygenic phenomenon, and a number of genetic variants associated with increased risk have been identified.[31] Some studies have also shown a strong association between self-reported familial AF and AF occurrence, independent of other risk factors, including genetic variants.[32] In line with these studies, we found that AF occurred twice as often in subjects who had at least one 1st degree relative with AF, at any age, compared to those without familial AF.

Stroke risk in AF

Stroke prevention is of utmost importance in AF, and guideline adherence improves outcomes.[33] In this cohort, stroke risk in the AF group was low *(Supplementary table 3)*. Use of anticoagulation was reported only in 47% of individuals with AF. However, many turned 65 years shortly after inclusion and their indication for anticoagulation would then have been strengthened. Within the small group of individuals with screen-detected AF, the stroke risk was even lower.

Clinical implications

Increased awareness with regard to detection and treatment of AF is desirable, particularly because of the increased stroke risk. However, it is still unknown whether screening or more active case-finding for AF will be effective in reducing stroke rates. Current guidelines advise health personnel to carry out simple measures such as pulse palpation and 12-lead ECG more frequently at the age of 65 years and above, or even in younger age groups if risk factors for stroke are present.[4] New and portable single-lead ECG devices may make these recommendations easier to implement, as single time point

or even repeated measurements can be performed more easily.[23] However, it is still unknown in which groups of the population screening may be justified. The low yield of single time point screening in our study, supports the opinion that screening below the age of 65 years may only be recommended in selected high-risk groups.

The high prevalence of obesity and untreated hypertension found in this cohort is alarming. These conditions can potentially be prevented in primary care and by public health measures. Prevention of AF by early detection and treatment of these conditions may be as important as early detection of AF itself. Nearly half of AF individuals in this study were found with elevated blood pressure, regardless of treatment, underlining a potential also for improved treatment within this group.

Conclusion

The prevalence of known AF was higher than previously reported below the age of 65 years, and higher in men than in women. Single time point screening for AF revealed a low number of previously unknown AF. Height, weight and comorbidity, but not sex, were independently associated with AF at this age.

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Authors' contributions: TB, KS, TO, PS, HR and AT designed the study. TB, MNL, HIH, JB, MOP, ENA, TV, BK and IEC have performed the baseline examinations and the acquisition of data. TB and PS have performed the validation of AF diagnoses, supported by MNL, JB and AT. TB and MNL have performed the statistical analysis. TB has written the manuscript. AT was the principal investigator (PI) and HR was the co-PI of the study. All authors have revised the manuscript for important intellectual content and have read and approved the final manuscript.

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Data sharing statement: The dataset used in this study is not publicly available, as the Data Protection Authority approval and patient consent do not allow for such publication. However, the study group welcomes initiatives for cooperation, and data access may be granted upon application. More information on: www.ace1950.no

Table 1: Baseline characteristics of the ACE 1950 cohort

	Total N = 3706	Men N = 1899	Women N = 1807	*P*
Age	63.9±0.7	63.9±0.7	63.9±0.6	0.34
Caucasian ethnicity	97.8	97.4	98.2	0.08
Higher education	46.4	50.2	42.3	<0.001
BMI	27.2±4.4	27.7±4.0	26.6±4.8	<0.001
Overweight/obesity (BMI ≥25)	67.6	74.9	59.8	<0.001
Systolic blood pressure, mmHg	138±19	139±18	137±20	0.02
Diastolic blood pressure, mmHg	77±10	80±10	74±9	<0.001
Hypertension	62.0	66.0	57.8	<0.001
Myocardial infarction	4.3	7.4	0.9	<0.001
Coronary heart disease	7.1	11.5	2.4	<0.001
Heart failure	1.6	2.3	0.9	0.001
Atrial fibrillation	4.5	6.4	2.4	<0.001
Stroke/TIA	3.8	5.0	2.5	<0.001
Diabetes mellitus	8.6	11.6	5.4	<0.001
Reduced eGFR	3.9	3.4	4.3	0.16
Hypercholesterolemia	52.6	50.6	54.7	0.01
COPD	7.2	6.9	7.4	0.60
Obstructive sleep apnoea	6.2	9.0	3.2	<0.001
Current daily smoking	14.5	13.7	15.3	0.19
Current or former daily smoking	61.8	62.2	61.5	0.64
Daily moist tobacco (“snus”)	2.2	3.8	0.4	<0.001
Alcohol				
>14 standard drinks/week	2.8	4.3	1.2	<0.001
“Binge drinking”	16.3	25.3	6.9	<0.001
Physical activity level				
Inactive	19.1	22.5	15.4	<0.001
Low	19.7	19.7	19.7	0.98
Medium	40.3	34.7	46.1	<0.001
High	21.0	23.1	18.8	0.001
Medication				
Any cardiovascular medication (ATC C)	46.1	50.0	41.9	<0.001
Diuretics (ATC C03)	3.1	2.9	3.3	0.52
Beta blockers (ATC C07)	13.4	16.7	9.9	<0.001
Calcium channel blockers (ATC C08)	8.1	9.7	6.4	<0.001
Agents acting on the renin-angiotensin	26.9	30.6	23.0	<0.001
Lipid modifying agents (ATC C10)	26.2	29.6	22.5	<0.001

Categorical variables are reported as percentages. Continuous variables are presented as mean ±SD. P-values indicate difference between sexes. Higher education: ≥12 years of formal education. BMI: Body Mass Index (kg/m^2). TIA: Transient ischemic attack. COPD: Chronic Obstructive Pulmonary Disease. "Binge drinking" is defined as heavy episodic drinking (at least 5 standard drinks of alcohol) at least once per month. Details for classification of physical activity level are provided in Supplementary Table 1. Medication: Self-reported cardiovascular medication according to ATC classification.

Table 2: Prevalence of validated atrial fibrillation at 63-65 years

	Total, n (%) (n=3706)	Men, n (%) (n=1899)	Women, n (%) (n=1807)
Total AF	**165 (4.5)**	**121 (6.4)**	**44 (2.4)**
Paroxysmal AF	105 (2.8)	73 (3.9)	32 (1.8)
Persistent/permanent AF	48 (1.3)	37 (2.0)	11 (0.6)
Previously undiagnosed AF	12 (0.3)	11 (0.6)	1 (0.1)

Previously undiagnosed cases were not classified as paroxysmal/persistent as further follow-up was performed in the clinical setting after the baseline visit.

Table 3: Clinical characteristics of study population by AF prevalence and sex

	Men			Women		
	AF (n=121)	**Without AF (n=1778)**	***p***	**AF (n=44)**	**Without AF (n=1763)**	***p***
Height, cm	180.4±6.7	178.8±6.5	<0.01	168.7±7.0	165.3±5.9	<0.001
Weight, kg	94.0±15.7	88.3±13.6	<0.001	79.6±16.5	72.8±13.4	<0.01
BMI	28.9±4.9	27.6±3.9	<0.01	27.9±5.6	26.6±4.7	0.07
Obesity (BMI ≥30)	52 (43.0)	405 (22.8)	<0.001	17 (38.6)	365 (20.7)	<0.01
Waist circumference, cm	103.4±12.9	99.3±11.0	0.001	93.3±12.7	87.7±12.4	<0.01
Hip circumference, cm	104.0±9.6	101.5±6.8	<0.01	105.5±9.6	102.1±9.2	0.01
Waist-to-hip ratio	0.99±0.08	0.97±0.07	0.02	0.88±0.07	0.85±0.08	0.04
Body surface area, m^2	2.16±0.19	2.09±0.18	<0.001	1.92±0.22	1.82±0.18	<0.01
Hypertension	101 (83.5)	1152 (64.8)	<0.001	37 (84.1)	1007 (57.2)	<0.001
Myocardial infarction	18 (14.9)	123 (6.9)	0.001	0 (0)	17 (1.0)	0.51
Coronary heart disease	28 (23.1)	191 (10.7)	<0.001	0 (0)	44 (2.5)	0.29
Heart failure	13 (10.7)	30 (1.7)	<0.001	3 (6.8)	14 (0.8)	<0.001
Stroke/TIA	9 (7.4)	86 (4.8)	0.20	3 (6.8)	42 (2.4)	0.06
Diabetes mellitus	13 (10.7)	207 (11.6)	0.76	4 (9.1)	93 (5.3)	0.27
Reduced eGFR	11 (9.1)	54 (3.1)	<0.001	5 (11.4)	73 (4.2)	0.02
Obstructive sleep apnoea	15 (12.4)	156 (8.8)	0.18	3 (6.8)	54 (3.1)	0.16
No comorbidity	15 (12.4)	455 (25.6)	0.001	6 (13.6)	594 (33.7)	<0.01
Hospitalization last 12 months	28 (23.1)	201 (11.3)	<0.001	16 (36.4)	204 (11.6)	<0.001
Current daily smoking	10 (8.3)	249 (14.1)	0.08	8 (18.2)	265 (15.2)	0.58
Familial AF	31 (25.6)	272 (15.3)	<0.01	25 (56.8)	408 (23.1)	<0.001
Higher education	61 (50.4)	889 (50.2)	0.97	18 (40.9)	745 (42.3)	0.85
Physical activity level						
Inactive	30 (25.6)	390 (22.3)	0.40	11 (25.6)	259 (15.1)	0.06
Low/medium	55 (47.0)	960 (54.9)	0.10	27 (62.8)	1129 (65.9)	0.67
High	32 (27.4)	399 (22.8)	0.26	5 (11.6)	325 (19.0)	0.22
Heart rate	56±8	61±10	<0.001	59±8	65±10	<0.01
PQ interval	185±29	175±27	<0.01	182±44	165±25	0.04
QRS duration	105±22	98±14	<0.01	90±14	88±10	0.28

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean ±SD. P-values indicate difference between AF and non-AF (within each sex). BMI: Body Mass Index, kg/m^2. TIA:

Transient ischemic attack. No comorbidity: Neither hypertension, coronary heart disease, heart failure, stroke, diabetes, reduced eGFR, obstructive sleep apnoea nor obesity. Familial AF: Self-report of at least one 1st degree relative with known AF. Higher education: ≥12 years of formal education. Heart rate: Beats per minute in 12-lead ECG. PQ interval and QRS duration are reported in milliseconds. For heart rate, PQ-interval and QRS duration; all subjects with AF in study ECG were excluded (n=60).

Table 4: Risk factors associated with atrial fibrillation

	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Male sex	2.73 (1.92 – 3.87)	<0.001	1.00 (0.59 – 1.68)	0.99
Height per 10 cm	**1.90 (1.59 – 2.28)**	**<0.001**	**1.67 (1.26 – 2.22)**	**<0.001**
Weight per 10 kg	**1.42 (1.29 – 1.55)**	**<0.001**	**1.15 (1.01 – 1.30)**	**0.03**
Hypertension	**3.27 (2.15 – 4.97)**	**<0.001**	**2.49 (1.61 – 3.86)**	**<0.001**
Heart failure	**8.53 (4.71 – 15.48)**	**<0.001**	**3.51 (1.71 – 7.24)**	**0.001**
Familial AF	**2.16 (1.55 – 3.02)**	**<0.001**	**2.32 (1.63 – 3.31)**	**<0.001**
Reduced eGFR	**2.87 (1.66 – 4.95)**	**<0.001**	**2.56 (1.42 – 4.60)**	**<0.01**
Coronary heart disease	2.88 (1.88 – 4.41)	<0.001	1.56 (0.95 – 2.57)	0.08
History of stroke/TIA	2.09 (1.13 – 3.86)	0.02	1.43 (0.74 – 2.78)	0.29
OSA	1.94 (1.17 – 3.23)	0.01	1.11 (0.63 – 1.97)	0.71
Physical activity (low/normal as ref.)				
Inactive	1.61 (1.10 – 2.37)	0.02	1.38 (0.92 – 2.07)	0.12
High level	1.30 (0.88 – 1.94)	0.19	1.20 (0.80 – 1.81)	0.38
Diabetes	1.24 (0.74 – 2.08)	0.41	-	-
Daily smoking	0.72 (0.44 – 1.19)	0.20	-	-
High alcohol consumption	0.81 (0.45 – 2.78)	0.81	-	-

Variables with $p<0.20$ in univariate logistic regression analysis are included in the multivariate analysis (a complete analysis of all candidate variables are included in Supplementary Table 2). Bold font indicates a significant association in multivariate analysis. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. TIA: Transient ischemic attack. Familial AF: Self-report of at least one 1st degree relative with known AF. OSA: Obstructive sleep apnoea. Physical activity (PA) level: Inactive and high level of PA compared to low/medium PA (combined to one group) as the reference group. High alcohol consumption: >14 standard drinks/week (both sexes).

Legend Figure 1: Flow chart of ACE 1950 study population and AF prevalence

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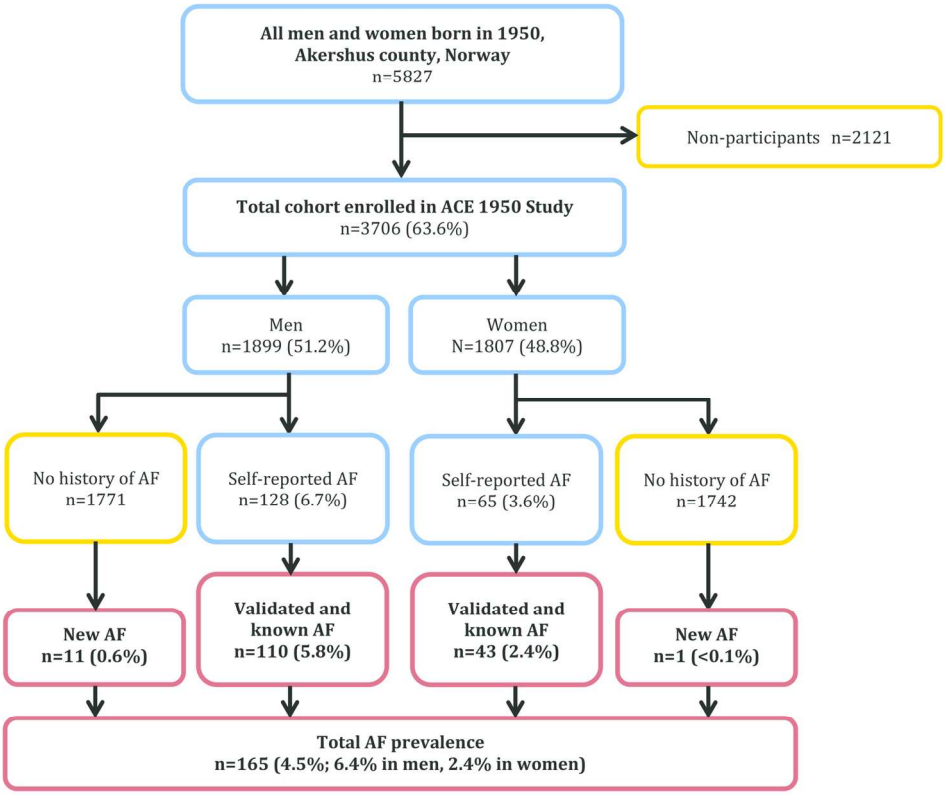

Flow chart of ACE 1950 study population and AF prevalence

146x124mm (300 x 300 DPI)

Supplementary Table 1: Questions used for self-reporting of physical activity and calculation of PAI (Physical Activity Index)

Physical activity[1]

Frequency
How frequently do you exercise? Give an average (by exercise we mean, for example, going for walks, skiing, swimming or training/sport).

- Never [0]
- Less than once a week [0]
- Once a week [1]
- 2-3 times per week [2.5]
- Almost every day [5]

Intensity
If you do such exercise as frequently as once or more times a week: How hard do you push yourself? (Give an average)

- I take it easy without breaking into a sweat or losing my breath [1]
- I push myself so hard that I lose my breath and break into a sweat [2]
- I push myself to near-exhaustion [3]

Duration
How long does each session last? (Give an average)

- Less than 15 minutes [0.1]
- 16-30 minutes [0.38]
- 30 minutes to 1 hour [0.75]
- More than 1 hour [1]

The response to each question (numbers in clams) was multiplied to calculate a Physical Activity Index (PAI), and this index was used for categorization into four groups:

- Inactive [0]
- Low PA [0.05-1.50]
- Medium PA [1.51-3.75]
- High PA [3.76-15.00]

[1] This 3-item self-reported assessment of physical activity and consequent 4-level Physical Activity Index has been validated in the Norwegian HUNT study *(Nord-Trøndelag health study)*, and shown moderate but significant correlation to both measured VO_{2max} and to the *International Physical Activity Questionnaire*.

Reference:

Aspenes ST, Nauman J, Nilsen TI, et al. Physical activity as a long-term predictor of peak oxygen uptake: the HUNT Study. *Med Sci Sports Exerc* 2011;43(9):1675-9.

Supplementary Table 2: Additional sensitivity analysis for risk factors associated with atrial fibrillation

'Original model' as depicted in Table 4 of the manuscript. The 'complete model' is an additional analysis including all candidate variables in the same model.

	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI) 'Original model'	*p*	Multivariate OR (95% CI) 'Complete model'	*p*
Male sex	2.73 (1.92 – 3.87)	<0.001	1.00 (0.59 – 1.68)	0.99	1.03 (0.61 – 1.74)	0.92
Height per 10 cm	**1.90 (1.59 – 2.28)**	**<0.001**	**1.67 (1.26 – 2.22)**	**<0.001**	**1.62 (1.21 – 2.16)**	**0.001**
Weight per 10 kg	**1.42 (1.29 – 1.55)**	**<0.001**	**1.15 (1.01 – 1.30)**	**0.03**	**1.16 (1.02 – 1.32)**	**0.02**
Hypertension	**3.27 (2.15 – 4.97)**	**<0.001**	**2.49 (1.61 – 3.86)**	**<0.001**	**2.47 (1.59 – 3.83)**	**<0.001**
Heart failure	**8.53 (4.71 – 15.48)**	**<0.001**	**3.51 (1.71 – 7.24)**	**0.001**	**3.37 (1.61 – 7.08)**	**0.001**
Familial AF	**2.16 (1.55 – 3.02)**	**<0.001**	**2.32 (1.63 – 3.31)**	**<0.001**	**2.35 (1.64 – 3.35)**	**<0.001**
Reduced eGFR	**2.87 (1.66 – 4.95)**	**<0.001**	**2.56 (1.42 – 4.60)**	**<0.01**	**2.43 (1.33 – 4.43)**	**<0.01**
Coronary heart disease	2.88 (1.88 – 4.41)	<0.001	1.56 (0.95 – 2.57)	0.08	1.60 (0.96 – 2.66)	0.07
History of stroke/TIA	2.09 (1.13 – 3.86)	0.02	1.43 (0.74 – 2.78)	0.29	1.49 (0.77 – 2.90)	0.24
OSA	1.94 (1.17 – 3.23)	0.01	1.11 (0.63 – 1.97)	0.71	1.07 (0.60 – 1.92)	0.82
Physical activity (low/normal as ref.)						
Inactive	1.61 (1.10 – 2.37)	0.02	1.38 (0.92 – 2.07)	0.12	1.39 (0.92 – 2.11)	0.12
High level	1.30 (0.88 – 1.94)	0.19	1.20 (0.80 – 1.81)	0.38	1.20 (0.79 – 1.81)	0.39
Diabetes	1.24 (0.74 – 2.08)	0.41	-	-	0.68 (0.39 – 1.20)	0.19
Daily smoking	0.72 (0.44 – 1.19)	0.20	-	-	0.94 (0.55 – 1.59)	0.81
High alcohol consumption	0.81 (0.45 – 2.78)	0.81	-	-	0.87 (0.34 – 2.24)	0.78

Variables with $p<0.20$ in univariate logistic regression analysis were included in the original multivariate analysis ('original model'). Bold font indicates a significant association in multivariate analysis. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. TIA: Transient ischemic attack. Familial AF: Self-report of at least one 1st degree relative with known AF. OSA: Obstructive sleep apnoea. Physical activity (PA) level: Inactive and high level of PA compared to low/medium PA (combined to one group) as the reference group. High alcohol consumption: >14 standard drinks/week (both sexes).

Supplementary Table 3: Stroke risk and use of medication in individuals with atrial fibrillation

	Total AF (n=165)	Men with AF (n=121)	Women with AF (n=44)	*p*
CHA_2DS_2-VASc score, mean ±SD	1.7 ±1.1	1.4 ±1.0	2.2 ±0.9	<0.001
CHA_2DS_2-VASc score, median [IQR; total range]	2 [1-2; 0-6]	1 [1-2; 0-5]	2 [2-2; 1-6]	<0.001
CHA_2DS_2-VASc ≥2 (men) or ≥3 (women) (%)	52 (31.5)	45 (37.2)	7 (15.9)	<0.01
Elevated blood pressure, (%)	67 (41.1)	46 (38.7)	21 (47.7)	0.30
Anticoagulation, (%)	77 (46.7)	56 (46.3)	21 (47.7)	0.87
Platelet inhibitors, (%)	46 (27.9)	38 (31.4)	8 (18.2)	0.09
Beta-blockers, (%)	97 (58.8)	69 (57.0)	28 (63.6)	0.45
Calcium antagonists, (%)	25 (15.2)	20 (16.5)	5 (11.4)	0.41
Antiarrhythmic drugs, (%)	28 (17.0)	22 (18.2)	6 (13.6)	0.49
Class Ic, (%)	19 (11.5)	14 (11.6)	5 (11.4)	0.97
Class III, (%)	9 (5.5)	8 (6.6)	1 (2.3)	0.45
Digoxin, (%)	4 (2.4%)	3 (2.5)	1 (2.3)	1.00
ACE inhibitors or ATII antagonists, (%)	63 (38.2)	51 (42.1)	12 (27.3)	0.08
Statins, (%)	63 (38.2)	51 (42.1)	12 (27.3)	0.08
Thyroid hormone therapy, (%)	7 (4.2)	1 (0.8)	6 (13.6)	<0.01

Categorical variables are reported as counts with percentages in parentheses. Continuous variables are reported as mean ±SD. P-values indicate difference between sexes. CHA_2DS_2-VASc score reported both as mean ±SD and median, including range. IQR: Inter-quartile range. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. ACE: Angiotensin converting enzyme. ATII: Angiotensin type 2.

Supplementary Table 4: Stroke risk and comorbidity in screen-detected AF

	New AF at screening (n=12)
Male sex, (%)	11 (91.7)
CHA_2DS_2-VASc score, mean ±SD	1.1 ±0.8
CHA_2DS_2-VASc score, median [total range]	1 [0-2]
CHA_2DS_2-VASc 0, (%)	3 (25.0)
CHA_2DS_2-VASc 1, (%)	5 (41.7)
CHA_2DS_2-VASc 2, (%)	4 (33.3)
Overweight, (%)	9 (75.0)
Hypertension, (%)	8 (66.7)
Elevated blood pressure, (%)	5 (41.7)
Heart failure, (%)	0 (0)
Diabetes, (%)	2 (16.7)
History of stroke, (%)	0 (0)
Myocardial infarction, (%)	1 (8.3)
Reduced eGFR, (%)	0 (0)
Obstructive sleep apnoea, (%)	1 (8.3)
Daily smoking, (%)	0 (0)

Categorical variables are reported as counts with percentages in parentheses. CHA_2DS_2-VASc score is reported both as mean ±SD and median. Hypertension: Mean systolic blood pressure ≥140 mmHg, or mean diastolic blood pressure ≥90 mmHg, or current use of any antihypertensive medication. Elevated blood pressure: ≥140 mmHg (systolic) or ≥90 mmHg diastolic regardless of treatment. TIA: Transient ischemic attack.

STROBE Statement—checklist of items that should be included in reports of observational studies

Manuscript: ***Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65-year-old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study***

	Item No	Recommendation	Page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5-6**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5-6**
Bias	9	Describe any efforts to address potential sources of bias	**-**
Study size	10	Explain how the study size was arrived at	**5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**5-6**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**7**
		(*b*) Describe any methods used to examine subgroups and interactions	**7**
		(*c*) Explain how missing data were addressed	**7**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	**7**

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**7**
		(b) Give reasons for non-participation at each stage	**-**
		(c) Consider use of a flow diagram	**Fig. 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**8 + Tab. 1**
		(b) Indicate number of participants with missing data for each variable of interest	**10**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**8-9 + Tab. 1-2**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**8-9 + Tab. 4**
		(*b*) Report category boundaries when continuous variables were categorized	**-**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**-**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**9 + suppl. tab. 2**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**10**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**10-11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11-13**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**13-14**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**15**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.