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CARDIOVASCULAR DISEASE

A cohort study examination of established and emerging risk factors for atrial fibrillation: the Busselton Health Study

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Abstract Atrial fibrillation (AF) is the most common chronic arrhythmia in adults and its prevalence is increasing. Due to its serious cardiovascular complications there is a strong need to understand predisposing risk factors to develop effective prevention strategies. There are a few established risk factors but a number of further risk factors have been suggested including obesity, metabolic syndrome, sleep-disordered breathing, and inflammation. The aim of this study was to investigate established and emerging risk factors for AF in a cohort study of 4,267 adults in Busselton, Western Australia, without a history of AF at baseline in 1994/95 who were followed for 15 years for incident AF events. Baseline measurement included questionnaire, clinical assessment and blood sample. A total of 343 (8 %) experienced AF during follow-up. Cox regression analysis confirmed advancing age, male sex, taller height, being on hypertension treatment and higher body mass index (BMI) as the major common risk factors (all $p < 0.001$). However, further modelling showed the effect of being on hypertension treatment may be stronger in women ($p = 0.001$) and the effect of BMI stronger in men ($p = 0.004$). After adjustment for these factors, no other factors were strongly related ($p < 0.001$) although short PR interval, history of valvular heart disease, stroke, chronic obstructive pulmonary disease, lung function and adiponectin level were marginally related ($p < 0.05$). This cohort study of predictors for incident AF has confirmed the major established risk factors. However, recently suggested potential novel risk factors for AF (inflammation, sleep-disordered breathing, glucose/metabolic disorders) were not confirmed in this study.

Keywords Atrial fibrillation · Cohort study · Busselton Health Study · Risk factor · Cox regression

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Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by chaotic atrial activation leading to loss of atrial mechanical function and an irregular ventricular response. AF is the most common chronic arrhythmia in adults afflicting about 1–2 % of the general population, increasing to about 10 % of persons by 80 years of age [1, 2]. AF can lead to serious complications, including a fivefold increased risk of stroke, threefold increased risk of heart failure, and up to twofold increased risk of death compared to the general population [1–5]. AF is an escalating problem with the number of affected persons in the USA projected to more than double over the next four decades due to an aging population and longer survival with cardiovascular disease [6, 7]. The potential for a similar rise in the burden of AF in other countries underscores the need to develop effective

prevention strategies for AF [8]. To achieve this we first need to understand the contemporary predisposing risk factors for AF.

Apart from advancing age and male gender, established risk factors for AF are cardiac conditions such as heart failure, valvular disease, and myocardial infarction, and cardiovascular risk factors such as hypertension and diabetes [1, 9, 10]. However, other factors potentially playing a role in the genesis of AF have gained attention, including obesity, metabolic syndrome, obstructive sleep apnoea, and inflammation [11–14]. The 'epidemic' of AF has occurred concurrently with obesity. Although earlier studies were discordant [9, 10], more recent population-based studies have indicated a 3–8 % higher incidence of AF with each unit increase in body mass index (BMI) independent of lipid levels, hypertension and diabetes [12, 13]. Obesity is also strongly associated with the metabolic syndrome, a pre-diabetic condition, in addition to an inflammatory state, and both conditions have recently been shown to carry an excess risk of AF [15, 16]. Three risk algorithms for incident AF have been published and all include age, hypertension treatment, systolic blood pressure (BP), and heart failure, two include BMI or weight, two include height, two include diabetes, and each includes particular coronary conditions or measures such as coronary heart disease, PR interval, cardiac murmur, and left ventricular hypertrophy [17–19].

The objective of this study was to investigate established and emerging risk factors for AF in a well characterised Australian cohort [20]. In particular, to establish if obesity, metabolic syndrome, sleep-disordered breathing, and inflammation are independent risk factors for incident AF.

Methods

Study design and participants

This is a prospective community-based cohort study. Invitations to participate were sent to adults listed on earlier Electoral Registers (registration to vote is compulsory in Australia) for the Busselton district and people were asked to complete a questionnaire and present at the survey centre 1994/95 for a range of tests and blood collection. The Busselton community is almost entirely of white Caucasian background. A total of 4,843 participated in the survey (response rate 57 %), after restricting to age 25–84 this became 4,465, after excluding 84 prevalent AF cases identified from a 15-year history of hospital admissions (see below) and from electrocardiogram (ECG) evidence (Minnesota code 8.3) at the survey, this became 4,381, and a further 114 were omitted due to missing body size and other data, leaving 4,267 for analyses. All participants gave informed consent and the 1994/95 survey was approved by the Human Research Ethics Committee of The University of Western Australia.

Measurements and follow-up

The conduct and measurements of the 1994/95 Busselton health survey have been described previously [20]. Survey participants were asked to complete a comprehensive health and lifestyle questionnaire and to undergo various measurements and tests including BP, anthropometry, 12-lead electrocardiogram (ECG; Minnesota coded, available for random three-quarters), spirometry, and fasting blood samples were collected. Sleep disordered breathing was based on the Lavie questionnaire [21] items relating to habitual snoring and the question "Do you fall asleep during the day, particularly if you are not busy?". The physical activity measure was whether or not the participant reported doing any vigorous exercise in a usual week. Blood measures available for this analysis include serum total and HDL cholesterol, triglycerides, plasma glucose and insulin, creatinine, C-reactive protein (CRP), and adiponectin. The ECG-derived history variables were: left ventricular hypertrophy (LVH) (Minnesota codes 3.1, 3.3), left bundle branch block-(LBBB) (7.1), Long PR interval (6.3), and Short PR interval (6.5). As only three participants had multiple ECG abnormalities a combined ECG variable was created with categories LVH, LBBB, long PR interval, short PR interval, None of above and Unknown (ECGs were not available for a random 25 % of participants) where the one participant with both LVH and Long PR interval was included in the LVH category and the two participants with both LBBB and Long PR interval were included in the LBBB category. The MDRD formula for glomerular filtration rate was used as a measure of renal function [22]. The metabolic syndrome score was defined as the number of the five risk components (hypertension, hyperglycemia, hypertriglyceridemia, high density lipoprotein (HDL) cholesterol, waist circumference) meeting the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) 2005 criteria [23]. Insulin resistance was assessed by the homeostasis model assessment (HOMA) score calculated as insulin (uU/mL) × glucose (mmol/L)/22.5 [24].

The Human Research Ethics Committee of the Department of Health of Western Australia gave permission to access the hospital admission and death records from 1980 to 2010 for participants. History of various cardiac and other conditions at baseline were defined as having any hospital admission with a primary or secondary discharge diagnosis for that condition during the 15 years before the survey. The history variables based on hospital admissions were heart failure (ICD9 428), valvular heart disease (ICD9

394–397, 996.02, 996.71, V42.2, V43.3), myocardial infarction or coronary revascularisation (ICD9 410, 412 and procedure codes 5–363 and 5–361 in ICD9 and 36.01, 36.02, 36.05, 36.06, 36.07 and 36.1 in ICD9-CM), stroke, trans ischaemic attack (TIA) or systemic embolism (ICD9 431, 432, 433.x1, 434.x1, 435, 436 and 437.7), peripheral arterial disease (ICD9 440-448), chronic renal disease (ICD9 585, 586), chronic obstructive pulmonary disease (COPD) (ICD9 490–496). History of hypertension treatment was based on self-reported taking of anti-hypertensive medications at the survey or a history of hospital admissions (ICD9 401–405). Diabetes was based on self-reported doctor–diagnosed diabetes or on diabetes treatment (tablets/insulin) at the survey or a history of hospital admissions (ICD9 250).

Incident AF events during the 15-year follow-up period to the end of 2010 were defined as a hospital admission with a primary or other diagnosis of atrial fibrillation/flutter (ICD9-CM 427.31, 427.32, 427.3; ICD10 I48) and no mention of prosthetic heart valve (ICD9-CM 996.02, 996.71, V42.2, V43.3, 35.2; ICD10 T82, Z95, blocks 623, 628, 634, 637) or coronary artery bypass graft procedure (ICD9-CM 36.1; ICD10 blocks 672–679).

Statistical analysis

Variables with skewed distributions were log transformed for use in regression models and descriptive results for these variables are presented in both untransformed and transformed scales. Cox regression models for time from 1994/95 survey to first AF event were used to obtain various adjusted hazard ratios of incident AF (and their 95 % confidence intervals) for a range of established and potential new risk factors. Interactions of risk factors with sex and age were tested. Results from Cox regression models are presented either as estimated coefficients (with standard error and p value) or as estimated hazard ratios (with 95 % confidence interval and p value). The improvement in the prediction performance of models from adding additional risk factors was assessed using the area under the curve (also called C-statistic) [25] and the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) measures [26].

Results

Table 1 shows the (baseline) characteristics of the cohort of 4,267 participants aged 25–84 years who had no history of AF at baseline. The anthropometric, lifestyle, health history and risk factor levels are typical of Australian population cohorts at that time. ECG abnormalities were rare with LVH, LBBB, Long PR interval and Short PR interval being present in about 1 % of the cohort. Similarly, history of heart failure, valvular heart disease, stroke/TIA, peripheral arterial diseases, and chronic renal disease were present in 1 % or less of the cohort. However, around 3 % had a history of MI, 3 % had a history of COPD, 6 % had diabetes, 3 % were taking lipid medications, and around 20 % had a history of hypertension. A total of 16 % met the NCEP ATP III metabolic syndrome criterion of 3 + disordered components.

A total of 343 (8.0 %) experienced an AF event during follow-up and this was slightly higher in men (8.8 %) than women (7.4 %). Cox regression analysis confirmed the higher risk in men and showed an increasing risk with age but with a stronger age trend in women (sex × age interaction p value 0.0065). Given the basic constitutional nature of height and that height was strongly related ($p = 0.0001$) to risk of AF after adjustment for age and sex terms, all remaining potential risk factors were assessed after adjustment for age, sex and height. Table 2 (Model 1) shows the fitted model involving age, sex and height. The estimated coefficients in this model translate to the risk of AF increasing by a factor of 3.25 (95 % CI 2.81–3.77) for each additional 10 years of age in women and by a factor of 2.49 (95 % CI 2.18–2.85) for each additional 10 years of age in men. As a consequence, although the relative risk in men vs women is 2.66 at 25 years of age this gap decreases with age and the risks for men and women are similar for people aged over 60 years. The risk of AF increases by 35 % (adjusted hazard ratio 1.35; 95 % CI 1.16–1.57) for each additional 9 cms (one SD) of height.

Table 3 (left side) shows the estimated hazard ratio for each potential risk factor after adjustment for age, sex and height. Hypertension treatment ($p < 0.0001$) and BMI ($p < 0.0001$) were the strongest risk factors with waist circumference, history of heart failure, history of valvular disease, history of stroke, COPD, fasting insulin and HOMA, metabolic syndrome, and FEV1 % (protective) also moderately or strongly related ($p < 0.01$) to risk of AF. Further modelling indicates the effect of hypertension treatment may be greater in women (hypertension × sex interaction $p = 0.0014$) and the effect of BMI may be greater in men (BMI × sex interaction $p = 0.0035$). Table 2 (Model 2) shows the fitted model involving age, sex, height, history of hypertension treatment and BMI. This model shows that, after adjusting for age, sex and height, hypertension treatment increases the risk of AF by a factor of 2.14 (95 % CI 1.56–2.94) in women and by a factor of 0.98 (95 % CI 0.69–1.40) in men, and that a gain of 4.2 (one SD) in BMI increases risk of AF by 16 % (adjusted hazard ratio 1.16; 95 % CI 1.02–1.32) in women and by 64 % (adjusted hazard ratio 1.64; 95 % CI 1.35–1.99) in men.

Table 1 Characteristics of AF-free Busselton 1994/95 survey cohort at baseline (n = 4,267)

Characteristic	Men (n = 1,861)	Women (n = 2,406)	All (n = 4,267)
Age mean (SD) (years)	52 (15)	52 (16)	52 (15)
24–35	15 %	15 %	15 %
35–44	23 %	26 %	25 %
45–54	20 %	18 %	19 %
55–64	18 %	16 %	17 %
65–74	17 %	17 %	17 %
75–84	8 %	8 %	8 %
Height mean (SD) (cm)	176 (7)	162 (6)	168 (9)
Body mass index mean (SD) (kg/m^2)	27 (3)	26 (5)	26 (4)
Waist circumference mean (SD) (cm)	94 (10)	81 (12)	87 (13)
Waist-hip-ratio mean (SD)	0.94 (0.06)	0.79 (0.06)	0.86 (0.09)
ECG combined variable			
LVH	0.9 %	0.8 %	0.8 %
LBBB	0.3 %	0.7 %	0.6 %
Long PR interval	1.6 %	0.9 %	1.2 %
Short PR interval	0.1 %	0.4 %	0.3 %
None of above	70.0 %	71.3 %	70.8 %
Unknown[a]	27.1 %	25.9 %	26.4 %
Diabetes	6.6 %	5.7 %	6.0 %
Hypertension treatment	17.2 %	20.4 %	19.0 %
History heart failure	0.8 %	0.6 %	0.7 %
History valvular heart disease	0.5 %	0.2 %	0.3 %
History MI or coronary revascularisation	4.3 %	1.1 %	2.5 %
History stroke or TIA	1.5 %	0.5 %	0.9 %
History peripheral arterial disease	1.4 %	0.7 %	1.0 %
History COPD	3.1 %	3.8 %	3.5 %
History chronic renal disease	0.1 %	0.1 %	0.1 %
Smoking			
Never	40.8 %	60.1 %	51.7 %
Former	43.3 %	29.0 %	35.2 %
Current	15.9 %	10.9 %	13.1 %
Alcohol			
Never or former	10.4 %	19.3 %	15.4 %
Light (<140 gms/week)	48.3 %	67.1 %	58.9 %
Moderate (140+ gms/week)	36.8 %	7.4 %	20.2 %
Unknown	4.6 %	6.1 %	5.4 %
Exercise—some vigorous exercise each week	56.6 %	40.6 %	47.6 %
Sleep disordered breathing			
No	64.5 %	86.2 %	76.8 %
Habitual snorer only	28.2 %	11.8 %	18.9 %
Habitual snorer and often fall asleep daytime	7.3 %	2.0 %	4.3 %
Systolic BP mean (SD) (mmHg)	127 (16)	122 (19)	124 (18)
Diastolic BP mean (SD) (mmHg)	78 (10)	73 (10)	75 (10)
Systolic BP—Diastolic BP mean (SD)	50 (13)	49 (15)	49 (14)
Fasting glucose mean (SD) (mmol/L)	5.1 (1.4)	4.9 (1.3)	5.0 (1.3)
Log fasting glucose mean (SD)	1.61 (0.18)	1.57 (0.17)	1.59 (0.18)
Fasting insulin mean (SD) (uU/ml)	7.7 (8.3)	7.2 (7.4)	7.4 (7.8)
Log fasting insulin mean (SD)	1.83 (0.60)	1.78 (0.58)	1.80 (0.59)

Table 1 continued

Characteristic	Men (n = 1,861)	Women (n = 2,406)	All (n = 4,267)
HOMA index mean (SD)	1.9 (4.8)	1.7 (2.5)	1.8 (3.7)
Log HOMA index mean (SD)	0.34 (0.69)	0.24 (0.66)	0.28 (0.67)
Cholesterol mean (SD) (mmol/L)	5.6 (1.0)	5.7 (1.1)	5.6 (1.1)
LDL cholesterol mean (SD) (mmol/L)	3.7 (0.9)	3.6 (1.0)	3.6 (1.0)
HDL cholesterol mean (SD) (mmol/L)	1.2 (0.3)	1.5 (0.4)	1.4 (0.4)
Triglycerides mean (SD) (mmol/L)	1.5 (1.1)	1.2 (0.7)	1.3 (0.9)
Log triglycerides mean (SD)	0.22 (0.56)	0.03 (0.52)	0.11 (0.55)
Lipid medications (yes)	3.0 %	2.5 %	2.7 %
Metabolic syndrome score			
0	31.8 %	39.3 %	36.0 %
1	32.1 %	28.8 %	30.2 %
2	17.8 %	17.2 %	17.5 %
3+	18.3 %	14.8 %	16.3 %
CRP mean (SD) (mg/L)	2.8 (6.9)	3.3 (5.3)	3.0 (6.1)
Log CRP mean (SD)	0.3 (1.2)	0.5 (1.2)	0.4 (1.2)
MDRD eGFR mean (SD) (mL/min/1.73 m^2)	72 (13)	68 (13)	70 (13)
Adiponectin mean (SD) (mg/L)	7.7 (5.2)	13.2 (7.9)	10.8 (7.4)
Log adiponectin mean (SD)	1.8 (0.6)	2.4 (0.6)	2.2 (0.7)
FEV1 %Pred mean (SD)	96 (18)	97 (16)	97 (17)

AF atrial fibrillation, *LVH* left ventricular hypertrophy, *LBBB* left bundle branch block, *ECG* electrocardiogram, *MI* myocardial infarction, *TIA* trans ischaemic attack, *COPD* chronic obstructive pulmonary disease, *BP* blood pressure, *HOMA* homeostasis model assessment, *CRP* C-reactive protein, *FEV1 %Pred* forced expiratory volume 1 s–% predicted

[a] ECG not available for (random) one-quarter

Table 2 Fitted Cox regression models for incident AF

Model term	Model 1 Sex, age and height		Model 2 Sex, age, height, hypertension treatment, and BMI	
	Coefficient (SE)	*p* value	Coefficient (SE)	*p* value
Sex = male	1.6442 (0.6845)	0.0163	−1.0168 (1.0974)	0.3542
Age (years)	0.1179 (0.0075)	<0.0001	0.1099 (0.0081)	<0.0001
Age (years) and Sex = male	−0.02670 (0.00980)	0.0065	−0.01656 (0.01057)	0.1173
Height (cm)	0.03319 (0.00867)	0.0001	0.03747 (0.00870)	<0.0001
Hypertension treatment			0.7609 (0.1615)	<0.0001
Hypertension treatment and sex = male			−0.7775 (0.2431)	0.0014
BMI (kg/m^2)			0.03588 (0.01573)	0.0226
BMI (kg/m^2) and sex = male			0.08196 (0.02809)	0.0035

SE standard error, *BMI* body mass index

Table 3 (right side) shows the estimated hazard ratio (and *p* value) for each remaining potential risk factor after adjustment for age, sex, height, hypertension treatment and BMI. No further risk factors were strongly related ($p < 0.001$) to risk of AF, although several remain moderately or weakly associated including short PR interval (HR = 6.21; $p = 0.011$), history of valvular heart disease (HR = 2.44, $p = 0.034$), stroke/TIA (HR = 2.02, $p = 0.019$), COPD (HR = 1.73, $p = 0.012$), adiponection ($p = 0.007$), and FEV1 %Pred ($p = 0.003$). Note that the metabolic syndrome score adds no further risk assessment value after hypertension treatment and BMI have been considered.

The C-statistics for model prediction performance were 0.845 for the model with just age and sex, this increased marginally to 0.848 when height was added, then further to 0.856 when hypertension treatment was added, and then further increased to 0.861 when BMI was added. The NRI measure of improved risk classification was significantly improved when height was added ($p = 0.008$) and when hypertension treatment was added ($p = 0.002$) but not when BMI was added ($p = 0.129$) whereas the IDI measure improved significantly when hypertension treatment ($p = 0.002$) and BMI were added ($p = 0.001$) and not when height was added ($p = 0.087$).

Table 3 Hazard ratios for potential risk factors for incident AF after adjustment for sex, age and height and after further adjustment for hypertension treatment and BMI

Risk factor	Adjusted for sex, age and height terms		Adjusted for sex, age, height, hypertension treatment and BMI terms	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Body mass index (SD 4.2 kg/m^2)	1.34 (1.21, 1.49)	<0.0001	–	–
Waist circumference (SD 12.7 cm)	1.37 (1.21, 1.55)	<0.0001	0.97 (0.72, 1.31)	0.866
Waist-hip-ratio (SD 0.09)	1.21 (1.02, 1.43)	0.029	0.98 (0.81, 1.18)	0.814
ECG combined variable				
LVH	0.50 (0.12, 2.00)	0.325	0.33 (0.08, 1.33)	0.119
LBBB	2.10 (1.03, 4.28)	0.040	1.84 (0.90, 3.74)	0.092
Long PR interval	1.57 (0.83, 2.96)	0.165	1.29 (0.68, 2.44)	0.434
Short PR interval	5.09 (1.26, 20.59)	0.022	6.21 (1.52, 25.31)	0.011
None of above	1	–	1	–
Unknown	0.76 (0.57, 1.01)	0.056	0.80 (0.60, 1.06)	0.117
Diabetes	1.13 (0.78, 1.63)	0.527	0.98 (0.67, 1.42)	0.904
Hypertension treatment	1.70 (1.35, 2.13)	<0.0001	–	–
History heart failure	2.47 (1.27, 4.83)	0.008	1.82 (0.93, 3.59)	0.082
History valvular heart disease	3.17 (1.40, 7.15)	0.005	2.44 (1.07, 5.55)	0.034
History MI or coronary revascularisation	0.75 (0.43, 1.31)	0.306	0.61 (0.35, 1.08)	0.092
History stroke or TIA	2.13 (1.23, 3.69)	0.007	2.02 (1.17, 3.50)	0.019
History peripheral arterial disease	1.86 (0.99, 3.51)	0.053	1.86 (0.98, 3.51)	0.056
History COPD	1.77 (1.16, 2.72)	0.008	1.73 (1.13, 2.66)	0.012
Smoking				
Never	1	–	1	–
Former	1.16 (0.92, 1.47)	0.21	1.12 (0.88, 1.42)	0.354
Current	0.99 (0.64, 1.53)	0.963	1.01 (0.65, 1.57)	0.969
Alcohol				
Never or former	1	–	1	–
Light (<140 gms/week)	0.81 (0.62, 1.05)	0.108	0.79 (0.61, 1.03)	0.084
Moderate (140+ gms/week)	0.65 (0.45, 0.94)	0.021	0.65 (0.45, 0.94)	0.022
Unknown	0.90 (0.60, 1.36)	0.627	0.90 (0.60, 1.37)	0.631
Exercise—some vigorous exercise each week	0.73 (0.57, 0.93)	0.012	0.80 (0.62, 1.03)	0.085
Sleep disordered breathing				
No	1	–	1	–
Habitual snorer	1.21 (0.92, 1.58)	0.175	1.04 (0.79, 1.37)	0.782
Habitual snorer and often fall asleep daytime	1.17 (0.77, 1.78)	0.468	1.02 (0.67, 1.56)	0.923
Systolic BP (SD 17.8 mmHg)	1.10 (0.99, 1.23)	0.075	1.02 (0.91, 1.14)	0.784
Diastolic BP (SD 10 mmHg)	1.04 (0.93, 1.15)	0.489	0.96 (0.87, 1.07)	0.446
Systolic BP–Diastolic BP (SD 14.5)	1.09 (0.98, 1.22)	0.099	1.05 (0.94, 1.17)	0.376
Log fasting glucose (mmol/L) (SD 0.18)	1.06 (0.97, 1.17)	0.207	0.99 (0.89, 1.10)	0.817
Log fasting insulin (uU/mL) (SD 0.59)	1.19 (1.07, 1.31)	0.001	1.02 (0.90, 1.15)	0.792
Log HOMA index (SD 0.67)	1.17 (1.06, 1.29)	0.001	1.01 (0.90, 1.14)	0.867
Cholesterol (SD 1.08 mmol/L)	0.94 (0.84, 1.06)	0.338	0.93 (0.83, 1.05)	0.251
LDL cholesterol (SD 0.97 mmol/L)	0.96 (0.85, 1.07)	0.446	0.94 (0.84, 1.06)	0.302
HDL cholesterol (SD 0.39 mmol/L)	0.90 (0.81, 1.01)	0.081	1.01 (0.90, 1.14)	0.84
Log triglycerides (mmol/L) (SD 0.55)	1.08 (0.96, 1.22)	0.175	0.96 (0.85, 1.08)	0.498
Lipid medications (yes vs no)	0.88 (0.52, 1.48)	0.634	0.73 (0.43, 1.23)	0.24
Metabolic syndrome score				
0	1	–	1	–
1	1.21 (0.85, 1.73)	0.294	0.95 (0.65, 1.37)	0.778

Table 3 continued

Risk factor	Adjusted for sex, age and height terms		Adjusted for sex, age, height, hypertension treatment and BMI terms	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
2	1.29 (0.89, 1.88)	0.184	0.82 (0.55, 1.24)	0.357
3+	1.75 (1.22, 2.50)	0.002	0.92 (0.60, 1.41)	0.712
Log CRP (mg/L) (SD 1.22)	1.13 (1.01, 1.27)	0.040	1.01 (0.89, 1.15)	0.864
MDRD eGFR (SD 13.1 mL/min/1.73 m^2)	1.00 (0.88, 1.13)	0.965	1.08 (0.95, 1.22)	0.23
Log adiponectin (mg/L) (SD 0.69)	1.08 (0.96, 1.22)	0.178	1.18 (1.05, 1.34)	0.007
FEV1 %Pred (SD 16.6)	0.83 (0.76, 0.91)	<0.0001	0.86 (0.78, 0.95)	0.003

Table shows hazard ratio relative to reference level for categorical variables and per one SD change for continuous variables

SD standard deviation, *BMI* body mass index, *AF* atrial fibrillation. *LVH* left ventricular hypertrophy, *LBBB* left bundle branch block, *ECG* electrocardiogram, *MI* myocardial infarction, *TIA* trans ischaemic attack, *COPD* chronic obstructive pulmonary disease, *BP* blood pressure, *HOMA* homeostasis model assessment, *CRP* C-reactive protein, *FEV1 %Pred* forced expiratory volume 1 s— % predicted

Discussion

This prospective community cohort analysis of 4,267 people without a history of AF and with 343 incident AF occurrences over a 15-year follow-up period has confirmed a number of established risk factors for AF. Age is a major risk factor, albeit slightly stronger in women, and our results of a more than doubling of risk with every additional decade is consistent with previous studies [10, 27]. Whilst we found that men have higher risk than women overall as in most previous studies we also found that the higher relative risk for men decreased with age and older (>60 years) men and women had similar risk. This finding is at odds with the observed increased risk of AF in men in the Cardiovascular Health Study of older people [27], but an age × sex interaction was also found in the Framingham Study [17]. Curiously, gender was not included as a risk factor in the AF clinical risk score developed from the ARIC Study or from three combined cohorts [18, 19].

Height is another immutable risk factor and in our study each additional 9 cms of height was associated with a 35 % higher AF risk. A case–control study of middle-aged individuals found height to be strongly related to lone AF and this was independent of atrial size which is positively correlated with height [28]. Height was also found to be an independent predictor of incident AF in the ARIC Study [18] and a study of middle-aged Swedish men [29]. Further, a large study of women found that the association between birth weight and AF was substantially attenuated after adjustment for height [30]. Whether birth weight or adult height is the true determinant will be difficult to resolve.

A recent meta-analysis involving 5 population-based cohort studies conclusively demonstrated the increased risk of AF in obese individuals and risk increased with increasing BMI [31]. Our findings corroborate BMI is an important risk factor but our finding of a stronger association with BMI in men has not been previously reported. The afore-mentioned meta-analysis reported sex-specific results but, opposite to our finding, showed larger relative risks in women for overweight and obese groups in comparison to the normal weight group. We found a significant protective effect of physical activity (doing some vigorous exercise each week) but this attenuated and was not significant after adjustment for BMI. The same was observed in a more detailed study of physical activity in relation to AF in women [32].

Our finding of a greater risk of AF in people on treatment for hypertension is not surprising as this is well established and published AF risk scores all include anti-hypertensive treatment [17–19]. However, our finding of a stronger effect of hypertension treatment on AF risk in women has not previously been reported and appears to be at odds with the Framingham Study that also investigated the sex × hypertension interaction [17]. Further, in contrast to previous studies, we did not find high BP to be a significant additional risk factor after adjustment for being on anti-hypertensive treatment [2, 17–19, 33].

After accounting for age, sex, height, history of hypertension and BMI we found no further risk factors to be strongly related ($p < 0.001$) to AF risk but did find some to remain moderately or weakly associated ($p < 0.05$). Some of these additional risk factors have already been established in other studies. Cardiac conditions have been shown to be associated with increased risk of AF [10]. The Framingham AF risk score includes PR interval, significant cardiac murmur and history of heart failure [17] whereas the ARIC AF risk score includes precordial murmur, left atrial enlargement and LVH [18]. In our Busselton Study we found short PR interval, history of valvular heart disease and history of stroke all had relative risk estimates exceeding 2 and with marginal statistical significance

($0.01 < p < 0.05$). This is likely to be due to lack of statistical power due to the low prevalence of these conditions in this cohort.

Other risk factors associated ($p < 0.05$) with AF in our Busselton Study include history of COPD, FEV1 %Pred and serum adiponectin. Whilst there are reports of an association between COPD/FEV1 and AF from both cross-sectional [34] and prospective studies [35], the evidence is limited. Few prospective studies have investigated adiponection in relation to AF and none found it to be an independent risk factor [36].

A number of other metabolic and inflammatory related factors, none of which were significant in our Busselton Study, have been suggested as potential new risk factors for AF. Diabetes but not fasting glucose or circulating insulin levels has been shown to be associated with AF [37, 38]. C-Reactive protein, a measure of inflammation, has been associated with AF in a number of studies and despite our negative results the evidence base is accumulating [2, 39–41]. Despite the report of Gami et al. [42] and the conclusion in a recent review that obstructive sleep apnoea (OSA) is established as a risk factor for AF [43], our Busselton finding for sleep disordered breathing was not significant, perhaps due to the limitations of self-report measures or that only those with OSA and not those with only sleep disordered breathing are at increased risk.

Strengths of this study are that it was community-based, included a wide variety of established and potential new risk factors, and with 343 incident AF cases, had over 80 % power to detect hazard ratios of 1.2 or more for a one SD change in a quantitative risk factor and hazard ratios of 1.5 or more for a binary risk factor with 10 % or higher prevalence. Limitations include the low prevalence of some cardiac conditions partly due to a potential healthy response bias arising from recruiting participants from the Electoral Register and for some conditions partly due to use of hospital admissions history only to identify conditions. Some of these low prevalence conditions therefore could not be conclusively confirmed as risk factors. As baseline ECG data were (randomly) missing for about one quarter of the cohort (n = 1,127) we only had their 15-year hospital admissions history to identify prevalent AF. We estimated that an additional 8 prevalent AF cases were therefore missed and hence not excluded from the cohort. As a sensitivity check we re-fitted all models using only the cohort with baseline ECG data (n = 3,140) and found the estimates to be essentially the same albeit with slightly wider confidence intervals due to smaller sample size. Finally, the use of linked hospital admission data to detect incident AF cases means we may have over-estimated the true time to AF onset for the identified incident AF cases and were not able to detect new cases of AF that were diagnosed in primary practice and over the 15 year follow-up period did not have any hospital admission where AF was recognised. Any bias from this is likely to be towards the null hypothesis and thus our hazard ratios may be conservative [44].

This prospective community cohort study of predictors for incident AF has confirmed age, sex, height, hypertension and BMI as the major common risk factors but also suggests the effects of age and hypertension may be stronger in women and the effect of BMI stronger in men. Although not statistically confirmed in this Busselton Study, the less common risk factor of having a cardiac condition remains important. Furthermore, recently suggested potential novel risk factors for AF (inflammation, sleep-disordered breathing, obstructive lung disease, glucose/metabolic disorders) were not confirmed in this study. Thus prevention efforts should continue to focus on BP and weight reduction.

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Conflict of interest The authors declare they have no conflict of interest.

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