Title

Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population based cohorts of 20 million participants

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Summary

Established primary prevention strategies of cardiovascular diseases are based on understanding of risk factors, but whether the same risk factors are associated with atrial fibrillation (AF) remains unclear.

We conducted a systematic review and field synopsis of the associations of 23 cardiovascular risk factors and incident AF, which included 84 reports based on 28 consented and 4 electronic health record cohorts of 20,420,175 participants and 576,602 AF events. We identified 3 to 19 reports per risk factor and heterogeneity in AF definition, quality of reporting, and adjustment. We extracted relative risks (RR) and 95% confidence intervals [CI] and visualised the number of reports with inverse (RR [CI]<1.00), or direct (RR [CI]>1.00) associations. For hypertension (13/17 reports) and obesity (19/19 reports), there were direct associations with incident AF, as there are for coronary heart disease (CHD). There were inverse associations for non-White ethnicity (5/5 reports, with RR from 0.35 to 0.84 [0.82-0.85]), total cholesterol (4/13 reports from 0.76 [0.59-0.98] to 0.94 [0.90-0.97]; 8/13 reports with non-significant inverse associations), and diastolic blood pressure (2/11 reports from 0.87 [0.78-0.96] to 0.92 [0.85-0.99]; 5/11 reports with non-significant inverse associations), and direct associations for taller height (7/10 reports from 1.03 [1.02-1.05] to 1.92 [1.38-2.67]), which are in the opposite direction of known associations with CHD.

A systematic evaluation of the available evidence suggests similarities as well as important differences in the risk factors for incidence of AF as compared with other cardiovascular diseases, which has implications for the primary prevention strategies for atrial fibrillation.

Key words

atrial fibrillation, risk factors, primary prevention, clinical guidelines, cardiovascular disease.

What is known on this topic:

- Atrial fibrillation is the world's most common heart rhythm disorder, and leading cause of fatal and disabling strokes, yet current clinical practice guidelines offer no recommendations for primary prevention in individuals without pre-existing cardiovascular disease.

- Established primary prevention strategies of other cardiovascular diseases (e.g. coronary heart disease and stroke), are based on understanding of risk factors, but whether the same risk factors are associated with incident atrial fibrillation remains unclear.

- There is a lack of systematic reviews and field synopses of risk factors for atrial fibrillation among general populations and populations initially free from diagnosed CVD.

What this paper adds:

- A systematic evaluation of evidence from 28 consented and 4 electronic health record cohorts confirms the importance of hypertension and obesity, but suggests important differences in the risk factors for incident atrial fibrillation as compared with other cardiovascular diseases.

- Non-white ethnicity, shorter height, higher cholesterol and higher diastolic blood pressure all showed some evidence of being associated with lower risk of incident AF. This contrasts with the known associations of these risk factors in the opposite direction with coronary heart disease.

- The evidence for the widely held clinical opinion that alcohol use is associated with incident AF in the primary preventative setting was modest.

- These findings provide a systematic basis on which to direct research into the primary prevention of AF.

Introduction

Atrial fibrillation (AF) is the world's most common heart rhythm disorder, affecting 33.5 million people globally in 2010.(1) AF accounts for 1 in 4 ischaemic strokes,(2) doubles the risk of death,(3) places an economic burden on healthcare systems,(4) and is projected to affect twice as many people by 2050.(5, 6) Yet to date, there have been no clinical trials of healthy participants without cardiovascular disease (CVD), and with AF as the primary outcome.(7) The focus of trials has instead been on prevention of stroke and thromboembolism after diagnosis of AF. Community screening programmes for detection of AF,(8) are also designed to identify patients at high risk of stroke and thromboembolism, and do not identify those who are at an initially high risk of later developing AF. Thus, current clinical guidelines make no recommendations for the primary prevention of AF itself, among people without CVDs.(9-11)

Established primary prevention strategies of other CVDs, such as coronary heart disease (CHD),(12) and stroke,(13) are based on understanding of risk factors, but the extent to which the same risk factors are associated with the incidence of AF is not fully understood. Ultimately, it is not known whether existing CVD prevention strategies can also work in preventing AF, or whether there may be important clinical differences. In synthesising available evidence the conventional (near universal) approach is to examine risk factors one at a time. Single risk factor systematic reviews and meta-analyses have been carried out for alcohol,(14-16) C–reactive protein,(17) diabetes mellitus,(18) obesity,(19) physical activity,(20, 21) and renal function(22) in relation to AF risk. Each of these reviews uses non-identical methods, for example varying in the extent to which incident AF is analysed among people free from pre-existing CVD. While there is an important ongoing role for the vertical approach of a single risk factor meta-analysis (particularly if methods can be aligned), there is also a complementary role for a horizontal 'field synopsis' approach across multiple potential risk factors. The term field synopsis is defined as a systematic evaluation of evidence in which the (i) overall amount, (ii) extent of replication, and (iii) protection from bias is considered across the whole field.(23, 24) One advantage of a field synopsis in multifactorial diseases is to

provide an unbiased empirical basis for prioritising further research into risk factors with preventive potential.

We therefore conducted a systematic review and field synopsis of the associations of a wide range of demographic, behavioural, and biological CVD risk factors and incidence of AF in general populations and populations initially free from diagnosed CVD. Field synopses' of cumulative evidence,(23, 24) are common in genetics but have seldom been applied in the context of preventive medicine. Our objectives were (i) to determine the amount of evidence for each risk factor, (ii) to evaluate the extent to which each risk factor shows concordant or discordant associations with AF incidence across independent study populations, and (iii) to systematically appraise the quality of the observational evidence across the field of AF prevention research.

Methods

Our approach to the search, selection, data collection and analysis of reports was systematic, and guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist.(25)

Search strategy

We queried the PubMed database using the search terms listed in appendix p 3, for original research reports that were published in English up to 1 October 2015; involving prospective, population based cohorts that were either initially free from diagnosed CVD at baseline or were general population cohorts in which the proportion of people with diagnosed CVD at baseline was low reflecting prevalence in the general population. Cohorts were of any age, and without prior AF; and investigated the association between "risk factors" and incident AF, over any follow–up period, and using Cox proportional hazards or Poisson regression models adjusted or stratified for age and sex as a minimum. We shortlisted 23 cardiovascular risk factors (listed in **table 1**) for review, based on clinical relevance as an established predictor or treatment target in the prevention of CVD,(12) or on clinical opinion of an association with AF,(9) and on expert consensus between authors. Reference lists of identified reports, existing reviews and meta–analyses (which were not restricted to prospective population based cohorts: alcohol,(14-16) C–reactive protein,(17) diabetes mellitus,(18) obesity,(19) physical activity,(20, 21) and renal function(22)), were hand–searched for additional reports. Two out of three authors (JW, SH, VA) reviewed the inclusion of each report based on title, then abstract, then full–text. Disagreements were resolved by joint full–text review with a third independent reviewer (RH).

Data extraction

From each report the following information was extracted: design of cohort (consented participant cohort with research measures at baseline and follow up, or electronic health record (EHR) cohort in which anonymised data collected as part of usual clinical care was used for baseline and follow–up measures), country, sample size (number of participants at baseline) and

number of AF events over follow–up (based on the highest figure reported), age range, proportion of female participants, mean or median follow–up, methods of AF ascertainment, risk factor definition, statistical model, and risk factors used in adjustment. We extracted data on whether cardiovascular events, prevalent at baseline and incident during follow–up and preceding AF were accounted for. For each risk factor, we extracted adjusted relative risks (RR), and 95% confidence intervals [95% CI]. Where there were multiple RR reported within a publication, or across multiple publications from the same cohort, we selected the most adjusted estimate, modelled with the highest number of AF cases.

Summary and visualisation of risk factor associations

We summarised the overall results of the field of cohort epidemiology of AF by plotting the number of reports with inverse (RR<1.00), null or mixed (RR=1.00 or shows opposite associations among subpopulations), or direct relationship (RR>1.00) with AF incidence. We regarded the association as significant if the 95% CI did not cross unity. Unless stated, RR are given as originally reported. For each factor, we then plotted the RR and 95% CI using R–3.2.0 (CALIBERdatamanage package, available at: caliberresearch.org).

Summary and visualisation of quality of reporting and analysis

We summarised the quality of reporting by completeness of the items listed in the above data extraction section (items not reported (NR) are clearly indicated in tables and figures). We summarised the quality of analysis by assessment of the number (%) of adjustment made for the 23 risk factors, and whether adjustment was made for 6 standard CVD risk factors (age, sex, smoking, blood pressure, lipids and diabetes mellitus), and for prevalent and incident CVD events. We visualised these as “Swiss cheese” plots.(26)

Results

Characteristics of included reports

73 out of 2777 publications were included (figure S1: appendix p 4) with 84 reports on 32 cohorts from 10 countries and 20,420,175 participants.(16, 27-98) As **table 2** shows, 28 (87.5%) cohorts involved consented participants with 39,900 (6.9%) events, and 4 cohorts (12.5%) were EHR–based with 536,702 (93.1%) events. AF events were ascertained from a research electrocardiogram (40 reports (47.6%)), diagnosis codes from medical records (60 reports (71.4%)), or using a combination of both methods (24 reports (28.6%)). As table S1 (appendix pp 5–7) shows, 17 reports (20.2%) described using two out of four types of medical records (i.e. general practitioner, hospital care, prescriptions, or mortality records), but no report used three or all four types combined.

Quality of reporting

Age range was not reported in 30 reports (35.7%), mean or median follow–up in 18 reports (21.4%), and risk factor definition was not reported in 9 reports (10.7%). Information was consistently reported on country, sample size, female participants, and AF events.

Quality of analysis

Overall, 63 reports (75.0%) lacked adjustment for all six standard CVD risk factors (table S2: appendix pp 8–9). Age was adjusted for in 84 reports (100.0%), sex in 80 reports (95.2%), smoking in 49 reports (58.3%), blood pressure in 63 reports (75.0%), lipids in 32 reports (38.1%), and diabetes mellitus in 59 reports (70.2%). The total number of adjustment factors ranged from 2–14 factors, with a median of 8 factors. There was lack of adjustment for prevalent CVD in 30 reports (35.7%), and for incident CVD in 69 reports (82.1%).

Associations of 23 risk factors and incidence of AF

A summary of the heterogeneity of associations of 23 risk factors and incidence of AF are visualised in **figure 1**, and for each factor separately in figures 2–6 and S2–S19 (appendix pp 12–29). There was no evidence of small study bias.

Demographic factors

For age, all 15 reports showed significant direct associations, but these were heterogeneous. RR [95%CI] ranged from 1.02 [1.01–1.03] to 1.14 [1.10–1.18] for every 1–year, from 1.43 [1.29–1.59] to 1.65 [1.57–1.74] for every 5–year, from 1.09 [1.09–1.09] to 2.35 [2.03–2.72] for every 10–year, and from 1.36 [1.27–1.45] to 4.34 [3.72–5.07] for every standard deviation (NR) year increase in age (figure S2).(28, 32, 35, 37, 43, 47, 50, 55, 67, 70, 88, 90, 94, 98) For men (compared to women), 1 report showed a significant inverse association (0.70 [0.50–0.90]),(79) 2 reports were inverse but non-significant (from 0.95 to 0.96),(88, 98) and 8 reports showed significant direct associations (from 1.45 [1.29–1.63] to 1.90 [1.58–2.29]) (figure S3).(37, 43, 47, 50, 55, 70, 94) For African American, Asian, Chinese, Hispanic and Non-Hispanic Black (compared to White) ethnicities, all 5 reports showed significant inverse associations (from 0.35 [NR–NR] to 0.84 [0.82–0.85]).(28, 44, 85, 92) Only 1 country reported estimates for the association of ethnicity and incidence of AF (**figure 2**). For socio–economic status, 2 reports showed significant inverse associations, 3 reports were inverse but non-significant, and 1 report showed a mixed association (see appendix p 10 and figure S4 for further details).

Health behaviours

For current smoking, 1 report was inverse but non-significant (0.78),(35) 1 report showed a mixed association,(47) 5 reports were direct but non-significant (from 1.01 to 1.20),(54, 56, 70, 83, 88) and 6 reports showed significant direct associations (from 1.32 [1.19–1.46] to 2.00 [1.40–2.80]) (figure S5).(28, 37, 40, 47, 78, 79) For physical activity, 3 reports showed significant inverse associations, 4 reports were inverse but non-significant, 2 reports showed null or mixed associations, and 2 reports showed significant direct associations (see appendix p 10 and figure

S6). For alcohol intake in drinks per day or week, in grams per day or week, or for current alcohol drinkers, 2 reports showed significant inverse associations (from 0.65 [0.45–0.94] to 0.96 [0.93–0.99]),(53, 83) 1 report was inverse but non-significant (0.97),(46) 1 report showed a null association,(28) 3 reports were direct but non-significant (from 1.04 to 1.20),(35, 70, 79) and 3 reports showed significant direct associations (from 1.39 [1.22–1.58] to 2.90 [1.61–5.23]).(16, 64, 88) All 10 alcohol reports defined alcohol intake differently, and as shown for the 3 direct alcohol associations, the increased risk of developing AF was only among the highest alcohol intake categories (**figure 3**).

Blood pressure

For every 10–22mmHg increase in systolic blood pressure, or systolic blood pressure ≥160mmHg, 1 report showed a null association,(79) 5 reports were direct but non-significant (from 1.01 to 1.24),(35, 47, 55, 83, 84) and 8 reports showed significant direct associations (from 1.14 [1.05–1.25] to 2.63 [1.83–3.78])(figure S7).(46, 47, 50, 56, 65, 69, 90, 91) For every 10–11mmHg increase in diastolic blood pressure, or diastolic blood pressure ≥95–100mmHg, 2 reports showed significant inverse associations (from 0.87 [0.78–0.96] to 0.92 [0.85–0.99]),(35, 50, 69) 5 reports were inverse but non-significant (from 0.82 to 0.99),(36, 47, 55, 83, 84, 91) 2 reports were direct but non-significant (from 1.02 to 1.23),(40, 47, 65) and 2 reports showed significant direct associations (from 1.24 [1.10–1.40] to 2.02 [1.20–3.41]).(44, 46, 90) No EHR cohorts reported estimates for the association of diastolic blood pressure and incidence of AF (**figure 4**). For hypertension, 1 report was inverse but non-significant (0.93),(88) 3 reports were direct but non-significant (from 1.21 to 1.37),(35, 55, 79) and 13 reports showed significant direct associations (from 1.28 [1.08–1.51] to 2.60 [1.60–4.40]) (figure S8).(28, 31, 37, 40, 47, 50, 56, 67, 70, 87, 91, 98)

Lipid profile

For every 10–50mg/dl increase in total cholesterol, or total cholesterol ≥220–280mg/dl, 4 reports showed significant inverse associations (from 0.76 [0.59–0.98] to 0.94 [0.90–0.97]),(32, 47, 53, 61) 8 reports were inverse but non-significant (from 0.57 to 0.99),(35, 41, 47, 56, 67, 71, 83, 88)

and 1 report was direct but non-significant (1.13).(71) Both inverse and direct associations were shown in the 3 total cholesterol reports that adjusted for prevalent and incident CVD events (**figure 5**). For every 10–40mg/dl increase in low–density lipoprotein cholesterol, or low–density lipoprotein cholesterol ≥150mg/dl, 2 reports showed significant inverse associations (from 0.72 [0.56–0.92] to 0.92 [0.88–0.96]),(32, 61) 4 reports were inverse but non-significant (from 0.85 to 0.95),(41, 55, 71, 83) and 1 report was direct but non-significant (1.15) (figure S9).(71) For every 15mg/dl increase in high–density lipoprotein cholesterol, or high–density lipoprotein cholesterol ≥60mg/dl, 5 reports were inverse but non-significant (from 0.85 to 0.98),(32, 47, 71) 2 reports showed null or mixed associations,(41, 47) and 3 reports were direct but non-significant (from 1.01 to 1.16) (figure S10).(61, 67, 83) For triglycerides, 3 reports were inverse but non-significant, 1 report showed a mixed association, 2 reports were direct but non-significant, and 3 reports showed significant direct associations (see appendix p 10 and figure S11).

Diabetes mellitus, renal function

For diabetes mellitus (type unspecified), 2 reports were inverse but non-significant (from 0.86 to 0.98),(83, 98) 8 reports were direct but non-significant (from 1.02 to 1.49),(37, 47, 54, 56, 58, 67, 70) and 6 reports showed significant direct associations (from 1.17 [1.16–1.19] to 1.80 [1.30–2.60]) (figure S12).(28, 40, 50, 79, 88, 95) For renal function, 3 reports were inverse but non-significant, 5 reports were direct but non-significant, and 3 reports showed significant direct associations (see appendix p 11 and figure S13).

Anthropometric factors

For every 1–10cm increase in height, or height ≥173cm, 3 reports were direct but non-significant (from 1.14 to 1.17),(47, 67, 70) and 7 reports showed significant direct associations (from 1.03 [1.02–1.05] to 1.92 [1.38–2.67]),(34, 46, 47, 53, 56, 79, 89) (**figure 6**). For weight, all 8 reports showed significant direct associations (see appendix p 11 and figure S14). For every 1–10kg/m^2 increase in body mass index, or body mass index ≥25–30kg/m^2, all 19 reports showed significant

direct associations (from 1.04 [1.02–1.05] to 2.24 [1.41–3.58]) (figure S15).(28, 31, 34, 37, 39, 48, 55, 56, 60, 67, 70, 76, 79, 81, 83, 88-91)

Inflammatory biomarkers

For C–reactive protein, 4 reports were direct but non-significant, and 4 reports showed significant direct associations (see appendix p 11 and figure S16). For fibrinogen, 2 reports were inverse but non-significant, 1 report was direct but non-significant, and 3 reports showed significant direct associations (see appendix p 11 and figure S17).

Thyroid function, autoimmune disease

For every 1.0mU/L decrease in thyroid stimulating hormone, or thyroid stimulating hormone <0.10–0.45mU/L, 1 report was inverse but non-significant (0.34),(82) 5 reports were direct but non-significant (from 1.06 to 2.85),(51, 77, 82) and 2 reports showed significant direct associations (from 1.41 [1.25–1.59] to 3.10 [1.70–5.50]) (figure S18).(72, 96) For autoimmune diseases, all 3 reports showed significant direct associations (see appendix p 11 and figure S19).

Discussion

To our knowledge this is the first example of a field synopsis evaluating associations across multiple risk factors and disease incidence. We systematically evaluated 84 reports from 32 independent cohorts for the impact of 23 cardiovascular risk factors on incidence of AF. Unlike previous overviews of AF risk factors,(10, 99) we focussed exclusively on primary prevention among populations initially free from diagnosed CVD or general populations in which baseline levels of CVD reflected prevalence in the general population. We found some evidence that ethnicity, height, diastolic blood pressure and serum cholesterol, are associated with AF incidence in opposite directions to their known associations with CHD and stroke. Furthermore we found only modest evidence for the widely held clinical opinion that excess alcohol is associated with risk of AF. Taken together our findings suggest that primary prevention strategies for AF may require some different elements from the current approaches used for other CVDs.

Concordant associations

For some risk factors – hypertension, and higher body mass index – there were consistent, direct associations with incident AF, as there are for CHD. This could reflect a causal link with AF, or that the risk factor causes CHD, which in turn causes AF. Surprisingly, we found that only 3 (out of 14) reports investigating the association between systolic blood pressure and incident AF accounted for both prevalent and intercurrent incident cardiovascular events, and only 1 of which reported a significant direct association. Several post hoc analyses of trials have suggested a possible benefit of ACE/ARB–inhibitors,(100) and other blood–pressure lowering medications,(101) for prevention of AF. However, we demonstrate that across all 23 risk factors, the available observational evidence does not fully consider a mechanism or confounding of reported associations by intercurrent CHD.

Current clinical guidelines include alcohol in a list of potentially “reversible” causes of AF, but acknowledge that there is no evidence to suggest addressing any of these is effective in preventing AF.(9) We found a small number of reports (3 out of 10) suggesting a direct association between

alcohol intake and AF incidence. This is in contrast to three existing alcohol reviews (Samokhvalov, *et al.* (2010) to April 2009,(14) Kodama, *et al.* (2011) to January 2009,(15) and Larsson, *et al.* (2014) to January 2014(16)), which have reported dose–response relationships. There are several possible explanations as to why our findings differ. Unlike the previous alcohol reviews, ours considers (i) only prospective studies (Samokhvalov, *et al.* and Kodama, *et al.* included retrospective studies; similarly Larsson *et al.* focused on prospective studies), (ii) only general population cohorts (Larsson, *et al.* included one cohort with pre-existing CVD), (iii) only incident AF events (Kodama, *et al.* included studies on AF recurrence), (iv) only estimates from Cox or Poisson regression (Samokhvalov, *et al.,* Kodama, *et al.*, and Larsson, *et al.* all included estimates from logistic regression), (v) only the most adjusted alcohol estimate per cohort (Samokhvalov, *et al.* included the study with the most comprehensive alcohol data, while Larsson, *et al.* did not report an approach to selecting from multiple estimates per cohort), and lastly (vi) our more recent review and more inclusive field synopsis method includes 8 reports that have not been included in the previous reviews.(28, 35, 46, 53, 70, 79, 83, 88) Based on the 3 direct alcohol associations we identified, the increased risk of developing AF was confined to the highest alcohol intake levels, as opposed to there being a J–shaped or dose–response relationship. Overall, our findings indicate that at present, there is limited consistent evidence on which recommended alcohol intake levels for primary prevention of AF could be based.

Discordant associations

We found some evidence that white ethnicity, taller height, lower total cholesterol and lower diastolic blood pressure might confer a higher risk of incident AF, which is in the opposite direction to their known associations with incident CHD.(12) Our findings regarding cholesterol suggest that reducing cholesterol may not be relevant for the primary prevention of AF, and are in line with an existing meta–analysis of trial evidence, which did not support the role of statins for prevention of AF in participants with underlying CVD.(102) Previously, it been demonstrated that blood pressure has markedly different associations with the incidence of twelve individual cardiovascular diseases (not including AF).(103) We now provide some, albeit mixed, evidence that this may also be the

case for AF. The direct and inverse associations shown for systolic and diastolic blood pressure respectively, may indicate high pulse pressure, which is a marker of arterial stiffness and is more prevalent in older populations.(104) Two earlier studies found an association between pulse pressure and incidence of AF,(69, 84) however pulse pressure was not considered in this review as its clinical utility is not well defined.(105)

Clinical implications

The observational evidence summarised here suggests that programmes for AF primary prevention may need to differ slightly from those which have guided clinicians and public health practitioners in the primary prevention of other CVDs. Existing management strategies to tackle obesity, smoking, alcohol and hypertension may have a role but the current evidence is insufficient to design AF specific interventions. The risk factors included in available prediction tools for 5 or 10 year risk of incident AF are supported by our systematic review, and these tools should be used more frequently in clinical practice.(47, 70) Such risk prediction tools could identify high–risk individuals for inclusion in primary prevention trials in AF, where there is the largest knowledge gap.

Overall characteristics of the field

Overall, we found a relatively "young" field, which has been rapidly expanding over the last five years (see figure S20: appendix p 30). Although we included 32 cohorts of 20 million participants and 600,000 AF events, we found a limited number of reports (between 3 and 19) per risk factor. Although we identified some efforts at pooling studies (e.g. the CHARGE–AF consortium of 5 cohorts, 3 countries, and 1771 AF events(47)), the amount of evidence available is markedly smaller than the scale of cohort evidence available on risk factors for CHD or stroke incidence (e.g. the emerging risk factor collaboration consists of over 100 cohorts(106)). Next, we found that the AF field is beginning to span both consented population and electronic health record studies, with all 7 EHR reports published in 2011–2015. In the era of "big data" research, EHRs offer the potential for studying associations at much larger scale, at population–level, in comparison with other risk factors, and across a wide range of diseases.(107) None of the EHR cohorts analysed continuous

measures of blood pressure, lipids, body mass index, or renal function. Linking data from consented population and EHR sources therefore represents an important research opportunity to investigate risk factors for AF at depth and at scale. Finally, we found considerable heterogeneity in study design and reporting, and a lack of consistent approach to adjustment for other risk factors (visualised as a “Swiss cheese”). Field synopses allow for differences in study designs, however in order to further inform primary preventive programmes and estimate the precision effect of each risk factor in meta-analyses; there is a need for large–scale strategic co–ordination of the field of AF prevention research.

Strengths and Limitations

The principle strength of our study – evaluation across a comprehensive range of risk factors – is also the principle weakness. In order to evaluate the breadth of the field there is a necessary restriction in the depth of analysis of any one risk factor, or relations between them. As we only searched the PubMed database, it is possible that we may have missed relevant studies. We conducted a sensitivity analysis for the year 2013, and found no further eligible studies in EMBASE, which is consistent with other reports showing limited additional value of searching biomedical databases beyond PubMed.(108, 109) There are of course other publications in support of searching multiple databases to identify further studies.(110, 111) However, as we did not perform meta-analysis, we have not introduced any computational bias in to the present work and therefore consider our results and conclusions unlikely to change. Field synopses provide a systematic foundation, unbiased by a particular interest in one or more risk factors,(112) for hypothesis generation and further research. One example of this would be to evaluate the extent to which the findings in relation to ethnicity, height and lipids(113) might be inter–related.

Conclusions

A systematic evaluation of the available evidence suggests similarities as well as important differences in the risk factors for AF as compared with other cardiovascular diseases. This has implications for the primary prevention of atrial fibrillation.

Contributions

VA analysed, interpreted and visualised the data, and drafted the report. HH conceived the original research idea, and led the project as principal investigator. JW, RH, SH, VA conducted the literature search and selection of reports. JPC, PP, KIM contributed to the study methodology. AB contributed to the writing of the report. AB, RH, RS, SH contributed to the clinical interpretation the data. AB, HH, JPC, JW, KIM, PP, RH, RS, SH, VA critically appraised and commented on interim drafts of the report, and approved the final version.

Conflicts of interest

All authors declare no conflicts of interest for the submitted work.

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Table and figures legends

Table 1. 23 cardiovascular risk factors investigated for their associations with incident atrial fibrillation in populations based cohorts

Table 2. Characteristics of included reports, sorted by cohort and number of atrial fibrillation events

Figure 1. Associations of 23 risk factors for incidence of atrial fibrillation according to number of reports, number of events, and direction of association

Figure 1 legend: AF – atrial fibrillation, EHR – electronic health record, [ ] – referent category, sig. – significant.

Risk factor and reference group definitions are detailed in individual risk factors plots (figures 2–6 and S2–S19).

Each dot represents one report, colour–coded to indicate the direction of association, and in order of most extreme inverse to most extreme direct point estimate. Dots are scaled by the number of AF events (<100, 100–<1000, 1000–<10000, 10000–<100000, or ≥100000). References correspond to each dot from left to right sequence. Associations are classified as inverse (relative risk (RR) <1.00), null or mixed (RR=1.00 or show opposite associations among subpopulations), or direct (RR>1.00). Association were regarded as significant if the 95% CI did not cross unity.

Figure 2. Association of ethnicity and incidence of atrial fibrillation: 5 reports from 1 country with 386 115 events

Figure 2 legend: EHR – electronic health record, age range in years, follow–up in years (mean, median, or maximum), AF – atrial fibrillation, CI – confidence interval, N/23 – number (of factors) out of 23, CVD – cardiovascular disease, SD – standard deviation, NR – not reported, USA – United States of America, ● – yes, ○ – no, -- – not applicable.

Risk factor adjustment refers to whether adjustment was made for the 23 risk factors under review, 6 CVD risk factors, and prevalent and incident CVD events. Example: ARIC adjusted for 5/23 risk factors, age, sex, blood pressure (i.e. any of systolic blood pressure, diastolic blood pressure, hypertension, or blood pressure lowering medication), and diabetes mellitus, but not smoking or lipids (i.e. any of total cholesterol, low–density lipoprotein cholesterol, high–density lipoprotein cholesterol, triglycerides, hyperlipidaemia, or lipid lowering medication), and prevalent, but not incident CVD events.

For cohort abbreviations see table 2.

Figure 3. Association of alcohol intake and incidence of atrial fibrillation: 10 reports from 5 countries with 18 997 events

Figure 3 legend: see figure 2 abbreviations, and g – grams, (w) – women, (m) – men.

Figure 4. Association of diastolic blood pressure and incidence of atrial fibrillation: 11 reports from 7 countries with 4796 events

Figure 4 legend: see figure 2 abbreviations, and mmHg – millimetres of mercury.
Risk factor adjustment for BP in this instance refers to whether systolic blood pressure, hypertension, or blood pressure lowering medication were adjusted for.

Figure 5. Association of total cholesterol and incidence of atrial fibrillation: 13 reports from 8 countries with 7129 events

Figure 5 legend: see figure 2 abbreviations, and mg/dl – milligrams per decilitre, mmol/l – millimoles per litre.
Risk factor adjustment for lipids in this instance refers to whether low–density lipoprotein cholesterol, high–density lipoprotein cholesterol, triglycerides, hyperlipidaemia, or lipid lowering medication were adjusted for. Total cholesterol reported as mmol/l for CHS, GPPS, TS and BHS was converted to mg/dl using the conversion 1mmol/l = 38·66976 mg/dl.

Figure 6. Association of height and incidence of atrial fibrillation: 10 reports from 6 countries with 7181 events

Figure 6 legend: see figure 2 abbreviations, and cm – centimetres, (m) – men, (w) – women.

Table 1.

Demographic factors	Age
	Sex
	Ethnicity
	Socio–economic status
Health behaviors	Smoking
	Physical activity
	Alcohol intake
Blood pressure	Systolic blood pressure
	Diastolic blood pressure
	Hypertension
Cholesterol	Total cholesterol
	Low–density lipoprotein cholesterol
	High–density lipoprotein cholesterol
	Triglycerides
Metabolic	Diabetes mellitus
	Renal function
Anthropometry	Height
	Weight
	Body Mass Index
Inflammation	C–reactive protein
	Fibrinogen
	Thyroid function
	Autoimmune diseases

Table 2.

						AF ascertainment:				Factors included in review:																							
Cohort	Country	Age range	Sample size	Women (%)	Mean / median follow–up	Electrocardiogram	Medical records	Self–report	AF events	Age	Sex	Ethnicity	Socio–economic status	Current smoking	Alcohol intake	Physical activity	Systolic blood pressure	Diastolic blood pressure	Hypertension	Total cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides	Diabetes mellitus	Kidney disease	Weight	Height	Body mass index	Fibrinogen	C–reactive protein	Thyroid disease	Autoimmune disease	Reference
consented observational / health screening cohorts																																	
WHI–OS	United States	50–79	81317	100	11.5	○	●	○	9792	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(27)
		50–79	81892	100	9.8	○	●	○	8252	●	○	●	●	●	●	○	○	○	●	○	○	○	○	●	○	○	○	●	○	○	○	○	(28)
COSM	Sweden	45–79	44410	0	12.0	○	●	○	4568	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(29)
		45–83	43841	0	10.9	○	●	○	4488	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(16)
NPMS	Japan	20–NR	223877	68	5.9	●	○	○	2974	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	(30)
		20–NR	28449	66	4.5	●	○	○	265	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	●	○	○	○	○	(31)
		20–NR	28449	66	4.5	●	○	○	265	●	○	○	○	○	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	○	(32)
SMC	Sweden	49–83	36513	100	12.0	○	●	○	2915	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(33)
		45–83	35178	100	10.9	○	●	○	2757	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(16)
DCHS	Denmark	50–64	55273	52	13.5	○	●	○	2581	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	●	○	○	○	○	(34)
		50–64	47589	53	5.7	○	●	○	553	●	○	○	●	●	●	○	●	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○	(35)
		50–64	38400	49	5.7	○	●	○	418	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(36)
MPP	Sweden	26–61	30865	32	23.3	○	●	○	2312	●	●	○	○	●	○	○	○	○	●	○	○	○	○	●	○	○	○	●	○	○	○	○	(37)
ARIC	United States	45–64	14352	55	20.6	●	●	○	1794	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(38)
		45–64	14219	55	18.2	●	●	○	1775	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(39)
		45–64	14598	55	17.1	●	●	○	1520	○	○	○	○	●	○	○	○	○	●	○	○	○	○	●	○	○	○	○	○	○	○	○	(40)
		45–64	13969	55	18.7	●	●	○	1433	○	○	○	○	○	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	○	(41)
		45–64	14858	55	16.8	●	●	○	1209	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	(42)
		45–65	15407	55	14.8	●	●	○	1085	●	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(43)
		45–64	14419	55	16.0	●	●	○	1068	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(44)
		45–64	10328	57	10.1	○	●	○	788	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	(45)
		45–64	14546	55	NR	●	●	○	515	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	●	○	○	○	○	○	(46)
		46–94	10675	57	NR	●	●	○	419	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	(47)
CHS	United States	65–89	5685	58	11.2	●	●	○	1585	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(48)
		65–NR	5365	57	10.0	●	●	○	1172	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(44)
		65–NR	5446	58	8.7	●	●	○	1061	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(49)
		65–NR	5491	45	6.9	●	●	●	897	●	●	○	○	○	○	○	●	●	●	○	○	○	○	●	○	○	○	○	○	●	○	○	(50)
		65–NR	2673	56	NR	●	●	○	812	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(51)
		65–NR	5043	60	NR	●	●	○	624	○	○	○	○	●	○	○	○	○	○	○	●	○	●	○	○	●	○	○	○	○	○	○	(47)
		65–NR	4321	59	7.4	●	●	●	579	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	●	○	○	○	○	○	○	○	(52)
		65–NR	4844	58	3.3	●	●	●	304	○	○	○	○	○	●	○	○	○	○	●	○	○	○	○	○	○	●	○	○	○	○	○	(53)
MDCS	Sweden	44–73	30441	60	11.2	○	●	○	1430	○	○	○	○	●	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	(54)
		41–71	5135	59	14.0	○	●	○	284	●	●	○	○	○	○	○	●	●	●	○	○	●	○	○	○	○	○	●	○	●	○	○	(55)
GPPS	Sweden	47–56	6903	0	NR	○	●	○	1253	○	○	○	●	●	○	●	●	○	●	●	○	○	○	●	○	○	●	●	○	○	○	○	(56)
IPHS	Japan	40–79	132250	69	13.8	●	○	○	1232	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	(57)
WHS	United States	45–NR	33372	100	16.4	●	●	○	1027	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	(58)
		45–NR	34759	100	14.4	●	●	○	968	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(59)
		NR–NR	34309	100	12.9	●	●	○	834	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(60)
		45–NR	23738	100	16.4	●	●	○	795	○	○	○	○	○	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	○	(61)
		45–NR	24746	100	15.4	●	●	○	786	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	(62)
		45–NR	24734	100	14.4	●	●	○	747	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	○	○	(63)
		45–NR	34715	100	12.4	●	●	○	653	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(64)
		45–NR	34221	100	12.4	●	●	○	644	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(65)
NorPD	Norway	40–45	309540	52	NR	○	●	○	863	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(66)
TS	Norway	25–NR	22815	52	11.1	○	●	○	822	●	○	○	○	○	○	○	○	○	●	●	●	○	○	●	○	○	●	●	○	○	○	○	(67)
		25–84	6315	51	10.9	○	●	○	566	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	○	○	(68)
FHS	United States	35–91	5331	55	16.0	●	○	○	698	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(69)
		45–95	4764	55	NR	●	○	○	457	●	●	○	○	●	●	○	○	○	●	○	○	○	○	●	○	○	●	●	○	○	○	○	(70)
		30–87	2608	56	11.9	●	○	○	259	○	○	○	○	○	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	○	(71)
		60–NR	2007	59	NR	●	○	○	192	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(72)
		NR–NR	2863	55	6.2	●	●	○	148	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	○	○	(73)
		46–94	2838	55	NR	●	○	○	143	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	(47)
MCS	Sweden	26–61	6031	0	25.0	○	●	○	667	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	(74)
AGES	Iceland	46–94	4469	60	NR	●	●	○	408	●	●	○	○	●	○	○	●	●	●	●	●	○	●	●	●	●	●	○	○	○	○	○	(47)
		45–95	4467	60	NR	●	●	○	408	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	(75)
		45–95	4238	63	4.2	○	●	○	226	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(76)

						AF ascertainment:				Factors included in review:																								
Cohort	Country	Age range	Sample size	Women (%)	Mean / median follow–up	Electrocardiogram	Medical records	Self–report	AF events	Age	Sex	Ethnicity	Socio–economic status	Current smoking	Alcohol intake	Physical activity	Systolic blood pressure	Diastolic blood pressure	Hypertension	Total cholesterol	HDL cholesterol	LDL cholesterol	Triglycerides	Diabetes mellitus	Kidney disease	Weight	Height	Body mass index	Fibrinogen	C–reactive protein	Thyroid disease	Autoimmune disease	Reference
RS	Netherlands	45–NR	9166	57	6.8	●	●	○	402	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(77)
		55–NR	5668	65	7.2	●	●	○	371	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(78)
		55–NR	3203	59	NR	●	●	○	177	●	●	○	○	○	○	○	●	●	●	●	●	○	●	●	●	●	●	○	○	○	○	○	(47)
		45–95	3203	59	NR	●	●	○	177	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	(75)
CCHS	Denmark	40–79	18167	56	NR	○	●	○	379	○	●	○	○	●	●	○	●	○	●	○	○	○	○	●	○	●	●	●	○	○	○	○	(79)
		20–NR	8410	58	7.5	○	●	○	268	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	(80)
HABC	United States	70–79	2717	52	NR	○	●	○	371	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(81)
		70–79	1850	52	8.1	●	○	○	17	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(82)
BHS	Australia	25–84	4267	56	NR	○	●	○	343	○	○	○	○	●	●	○	●	●	○	●	●	●	●	●	●	○	○	●	○	●	○	○	(83)
		18–90	1048	48	20.0	○	●	○	14	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(82)
MESA	United States	45–84	6630	53	7.8	○	●	○	307	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(84)
		45–84	6721	53	7.0	○	●	○	305	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(85)
		45–84	4534	52	8.2	○	●	○	221	○	○	○	○	○	○	○	○	○	○	●	●	●	●	○	○	○	○	○	○	○	○	○	(71)
		45–84	5793	53	7.7	○	●	○	199	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(86)
		45–84	5311	53	5.3	○	●	○	182	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	(87)
CIRCS	Japan	30–80	7206	63	6.4	●	●	●	296	●	●	○	○	●	●	○	○	○	●	●	○	○	○	●	○	○	○	●	○	○	○	○	(88)
S–HS	Sweden	60–60	4021	52	13.6	○	●	○	285	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	●	●	○	○	○	○	(89)
OCS	Norway	40–59	1997	0	30.0	●	●	○	270	●	○	○	○	○	○	●	●	●	○	○	○	○	○	○	○	○	○	●	○	○	○	○	(90)
TSS	Japan	30–84	8360	53	12.8	●	●	●	253	○	○	○	○	○	○	○	●	●	●	○	○	○	○	○	○	○	○	●	○	○	○	○	(91)
L85PS	Netherlands	85–85	420	64	5.2	●	○	○	39	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(82)
SHIP	Germany	20–81	2891	47	10.1	●	○	○	34	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(82)
		Participants:	1112394						AF events:	39900																							
administrative / electronic health records cohorts																																	
HCUP	United States	18–NR	13967949	57	3.2	○	●	○	375318	○	○	●	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	(92)
D–EHR	Denmark	16–NR	4182335	51	4.8	○	●	○	156484	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	(93)
		10–NR	4518484	49	9.2	○	●	○	126217	●	●	○	●	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	●	(94)
		18–100	5081087	45	NR	○	●	○	115956	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	○	○	○	○	○	○	○	(95)
		18–NR	586460	61	5.5	○	●	○	17154	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	○	(96)
S–EHR	Sweden	00–95	170368	62	10.4	○	●	○	3859	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	●	(97)
T–NHIRD	Taiwan	18–NR	88377	61	NR	○	●	○	1041	●	●	○	○	○	○	○	○	○	●	○	○	○	○	●	●	○	○	○	○	○	○	○	(98)
		Participants:	19307781						AF events:	536702																							
		Total participants:	**20420175**						**Total AF events:**	**576602**																							

Table 2 legend: AF – atrial fibrillation, HDL – high–density lipoprotein cholesterol, LDL – low–density lipoprotein cholesterol, ● – yes, ○ – no. Cohort abbreviations: WHI–OS – Women's Health Initiative Observational Study, COSM – Cohort of Swedish Men, NPMS – Niigata preventive medicine study, SMC – Swedish Mammography Cohort, DCHS – Diet Cancer and Health study, MPP – Malmö Preventive Project, ARIC – Atherosclerosis Risk in Communities, CHS – Cardiovascular Health Study, MDCS – Malmö Diet and Cancer study, GPPS – Göteborg Primary Prevention Study, IPHS – Ibaraki prefectural health study, WHS – Women's Health Study, NorPD – Norwegian Prescription Database, TS – Tromsø Study, FHS – Framingham Heart Study, MCS – Malmö Cardiovascular Screening, AGES – Age, Gene and Environment–Reykjavik study, RS – Rotterdam Study , CCHS – Copenhagen City Heart Study, HABC – Health, Aging, and Body Composition, BHS – Busselton Health Study, MESA – Multi–Ethnic Study of Atherosclerosis, CIRCS – Circulatory Risk in Communities Study, S–HS – Stockholm Health Screening cohort , OCS – Oslo Cardiovascular Survey, TSS – The Suita Study, L85PS – Leiden 85–Plus Study, SHIP – Study of Health in Pomerania, HCUP – Healthcare Cost and Utilization Project, D–EHR – Denmark Electronic Health Record cohort, S–EHR – Sweden Electronic Health Record cohort, T–NHIRD – Taiwan National Health Insurance Research Database.