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Original Article

Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990–2017: results from the Global Burden of Disease Study 2017

Haijiang Dai [1,2†], Quanyu Zhang[3†], Arsalan Abu Much [4,5†], Elad Maor[4,5], Amit Segev[4,5], Roy Beinart [4,5], Salim Adawi[6,7], Yao Lu[2,8*], Nicola Luigi Bragazzi [1*], and Jianhong Wu[1]

[1]Laboratory for Industrial and Applied Mathematics, Centre for Disease Modelling, Department of Mathematics and Statistics, York University, 4700 Keele Street, Toronto, ON M3J 1P3, Canada; [2]Department of Cardiology, The Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha 410013, China; [3]Department of Cardiology, General Hospital of Northern Theater Command, Shenyang, China; [4]Leviev Heart Center, Sheba Medical Center, Tel HaShomer, Israel; [5]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [6]Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, Haifa, Israel; [7]The Ruth and Bruce Rappaport Faculty of Medicine, Technion Israel Institute of Medicine, Haifa, Israel; and [8]Center of Clinical Pharmacology, The Third Xiangya Hospital, Central South University, Changsha, China

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Aims To estimate the prevalence, incidence, mortality, and risk factors for atrial fibrillation (AF) in 195 countries and territories from 1990 to 2017.

Methods and results Following the methodologies used in the Global Burden of Disease Study 2017, the prevalence, incidence, and mortality of AF were analysed by age, sex, year, socio-demographic index (SDI), and location. The percentage contributions of major risk factors to age-standardized AF deaths were measured by population attributable fractions. In 2017, there were 37.57 million [95% uncertainty interval (UI) 32.55–42.59] prevalent cases and 3.05 million (95% UI 2.61–3.51) incident cases of AF globally, contributing to 287 241 (95% UI 276 355–304 759) deaths. The age-standardized rates of prevalent cases, incident cases, and deaths of AF in 2017 and their temporal trends from 1990 to 2017 varied significantly by SDI quintile and location. High systolic blood pressure was the leading risk factor for AF age-standardized deaths [34.3% (95% UI 27.4–41.5)] in 2017, followed by high body mass index [20.7% (95% UI 11.5–32.2)] and alcohol use [9.4% (95% UI 7.0–12.2)].

Conclusion Our study has systematically and globally assessed the temporal trends of AF, which remains a major public heath challenge. Although AF mainly occurred in developed countries, the unfavourable trend in countries with lower SDI also deserves particular attention. More effective prevention and treatment strategies aimed at counteracting the increase in AF burden should be established in some countries.

Keywords Atrial fibrillation • Prevalence • Incidence • Mortality • Risk factor

* Corresponding author. Tel: 86-731-88618319, Fax: 86-731-88618319, Email: luyao0719@hotmail.com (Y.L.); Tel: (416) 736-5243, Fax: (416) 736-5698, Email: robertobragazzi@gmail.com (N.L.B.)
† The first three authors contributed equally to the study.

Introduction

Atrial fibrillation (AF) represents the most commonly diagnosed cardiac arrhythmias in the general population. Atrial fibrillation is a serious public health concern, in that it imposes a severe clinical burden in terms of increased risk of developing stroke, systemic embolism, and heart failure.[1,2] From a clinical standpoint, AF represents a highly heterogeneous group of diseases, with a great variety of symptoms and range of severity, which makes the estimate of AF particularly challenging. In 2010, the global number of individuals suffering from AF was computed to be approximately 33.5 million, with increasing incidence and prevalence trends since the nineties.[3] These estimations are expected to further increase in future and are projected to reach 12.1 million people in the USA by 2050 and 17.9 million people in Europe by 2060.[4,5] The reasons and factors underlying such increases have yet to be elucidated, and included population ageing, improved survival, and enhanced detection, among others. As such, a considerable increment in the consumption of health care resources and costs due to morbidity and mortality is expected.[6] At the same time, serious efforts has been deployed in the field of clinical cardiology that have led to a paradigm shift in the diagnosis and management of AF, which has markedly influenced the natural history of the disease. For instance, the introduction of novel oral anticoagulants has resulted in significantly improved survival and decreased morbidity rates among AF patients compared to traditional therapy.[7,8]

However, in the existing scholarly literature, there is a dearth of data concerning the global burden of AF. In order to better inform cardiology policies and guidelines according to the current body of evidence and to monitor the effectiveness of the therapeutics, global reliable, and accurate estimates of AF and their temporal trends are urgently needed. Therefore, in the present study, we aimed to evaluate such trends in terms of global, regional, and national prevalence, incidence, mortality, and risk factors of AF.

Methods

Data sources

This study is part of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, which is designed to provide comprehensive and systematic estimations for 359 diseases and injuries; 282 causes of death; and 84 behavioural, environmental, and occupational, and metabolic risk factors. The detailed methods used for GBD 2017 have been published elsewhere.[9–12] In the present study, data for the burden of AF were extracted through a query tool from the website of the Institute for Health Metrics and Evaluation (IHME) (http://ghdx.healthdata.org/gbd-results-tool, accessed July 30, 2020). Detailed information about original data sources used for the estimations of AF can be found on the GBD 2017 Data Input Sources Tool website (http://ghdx.healthdata.org/gbd-2017/data-input-sources, accessed July 30, 2020). Since GBD 2017 used de-identified, aggregated data, a waiver of informed consent was reviewed and approved by the University of Washington Institutional Review Board.

Definitions

Atrial fibrillation was identified using the International Classification of Diseases and Injuries (ICD-9 and ICD-10). All cardiovascular diseases coded as 427.3–427.32 in the ICD-9 and I48–I48.92 in the ICD-10 were considered as AF in the study.[10] Consistent with previous GBD studies, the diagnosis of AF required an electrocardiogram demonstrating and included atrial flutter.[3]

Socio-demographic index (SDI) was a composite indicator used to assess the development status for each location-year.[9–12] It was made up of the geometric mean of three common indicators: the lag distributed income per capita, mean educational achievement for those aged 15 years or older, and total fertility rate under 25 years. SDI ranged from 0 to 1, where 0 represents the theoretical minimum level of development, whereas 1 represents the theoretical maximum level of development. SDI quintiles were determined using the country-level estimates of SDI, excluding countries with populations of less than 1 million.[10] Based on SDI quintiles, 195 countries and territories were categorized into five country groups: low SDI, low-middle SDI, middle SDI, high-middle SDI, and high SDI.[10]

Risk factors were selected with the following criteria: sufficient evidence of causation with AF, availability of exposure data, and potential for modification.[12] In GBD 2017, six risk factors, i.e., high systolic blood pressure, high body mass index, alcohol use, smoking, a diet high in sodium, and lead exposure, were considered to cause AF deaths. Details on definitions of these risk factors and methods for quantifying the percentage contributions of these risk factors to AF deaths have been published elsewhere.[12]

Statistical analyses

We used counts, age-standardized rates per 100 000 people, and percentage change, with 95% uncertainty intervals (UIs) to quantify the burden of AF. Prevalence, incidence, and deaths were metrics used to measure the burden of AF in the study; they were reported by sex, age, SDI, year (1990–2017), and location, including 21 GBD regions consisted of 195 countries and territories. In more detail, the AF-associated death rate was statistically estimated and modelled, utilizing an integrated, multi-parameter approach informed by the combinations of various country-level covariates achieving statistical significance.[11] External validity was employed to refine the models and produce a final ensemble model.[11] Indeed, usually, AF does not directly cause death but rather causes disorders (such as heart failure or stroke) that indirectly lead to an increased mortality risk. Therefore, since the crude case fatality rate among AF patients was not a suitable metric, mortality rate attributable to AF was preferred. Age-standardized rate was calculated by standardization to the global age structure, and it was considered necessary when comparing the populations from different locations or for the sample population over time.[13] Uncertainty intervals were calculated from 1000 draw-level estimates for each parameter. The 95% UIs were defined as the 25th and 975th values of the ordered 1000 estimates. The percentage contributions of major risk factors to age-standardized AF deaths were estimated using population attributable fractions, which represent the proportions of age-standardized AF deaths that would be reduced if the exposure to a risk factor in the past were reduced to an ideal exposure scenario.[12] Population attributable fractions were computed using relative risks computed based on meta-regression of published studies.[12] For all analyses, a 95% UI, excluding 0, was considered to be statistically significant.

Results

Burden of atrial fibrillation in 2017

In 2017, there were 37.57 million (95% UI 32.55–42.59) prevalent cases and 3.05 million (95% UI 2.61–3.51) incident cases of AF globally (Supplementary material online, *Table S1*). The age-standardized

prevalence and incidence rates of AF were 481.5 (95% UI 416.5–546.2) per 100 000 people and 38.2 (95% UI 32.6–43.9) per 100 000 people, respectively. Atrial fibrillation contributed to 287 241 (95% UI 276 355–304 759) deaths globally in 2017. The age-standardized mortality rate of AF was 4.0 (95% UI 3.9–4.2) per 100 000 people.

By sex, more incident cases of AF occurred in males [1.59 million (95% UI 1.35–1.82)] over females [1.46 million (95% UI 1.24–1.68)], with a higher age-standardized incidence rate of AF was observed in males [42.5 (95% UI 36.3–49.0)] than in females [34.2 (95% UI 29.1–39.4)]. Similar results were also found for prevalent cases of AF (Supplementary material online, *Table S1*). Conversely, more deaths of AF were seen in females [177,270 (95% UI 170 925–183 825)] than in males [109 971 (95% UI 98 219–124 963)] in 2017. The age-standardized mortality rate was 3.9 (95% UI 3.5–4.4) per 100 000 people in males and 4.1 (95% UI 3.9–4.2) per 100 000 people in females.

Age-specific counts and rates of prevalent cases, incident cases, and deaths of AF by sex in 2017 were shown in *Figure 1*. The age-specific prevalence and mortality rates of AF increased with increasing age in both sexes. However, declined incidence rates were observed from the ages of 80–84 years in both sexes. The counts of AF prevalent cases peaked at the ages of 75–79 years in both sexes, and the counts were higher in males than in females in age groups of <80 years, whereas the counts were lower in males than in females in age groups of ≥80 years. The counts of AF incident cases peaked at the ages of 65–69 years in both sexes, and until the ages of 75–79 years, the counts were higher in males than in females in the same age group. The counts of AF deaths peaked at the ages of 85–89 years in both sexes, and from the ages of 70–74 years, the counts were higher in females than in males in the same age group.

By SDI quintile, in 2017, the age-standardized rates of prevalent cases, incident cases, and deaths of AF tended to be higher in countries with higher SDI (Supplementary material online, *Table S1*). Across the 21 GBD regions, the highest age-standardized prevalence rates of AF in 2017 were seen in the high-income North America [871.0 (95% UI 762.2–978.7) per 100 000 people] and Australasia [799.5 (95% UI 688.2–916.8) per 100 000 people] (except Greenland, all are in countries in the high SDI quintile). Similar results were also found for the age-standardized incidence rates of AF. The two countries with the highest age-standardized prevalence rates of AF were New Zealand [915.4 (95% UI 811.2–1027.4) per 100 000 people] and USA [899.9 (95% UI 789.0–1010.9) per 100 000 people]; they also have the highest age-standardized incidence rates: USA [78.0 (95% UI 67.8–88.7) per 100 000 people] and New Zealand [74.2 (95% UI 64.7–84.4) per 100 000 people; *Figure 2* and Supplementary material online, *Table S1*]. The highest age-standardized mortality rate of AF across the 21 GBD regions was observed in Australasia [6.6 (95% UI 5.8–7.2) per 100 000 people; Supplementary material online, *Table S1*]. Notably, despite the lowest age-standardized rates of prevalent cases, incident cases, and deaths of AF were mainly observed in countries in the low SDI quintile (Supplementary material online, *Table S1*), high-income Asia Pacific region had the lowest age-standardized rates of prevalent cases [238.4 (95% UI 209.2–270.1) per 100 000 people], incident cases [16.2 (95% UI 13.8–18.4) per 100 000 people], and deaths [2.4 (95% UI 2.2–2.7) per 100 000 people] among all the GBD regions.

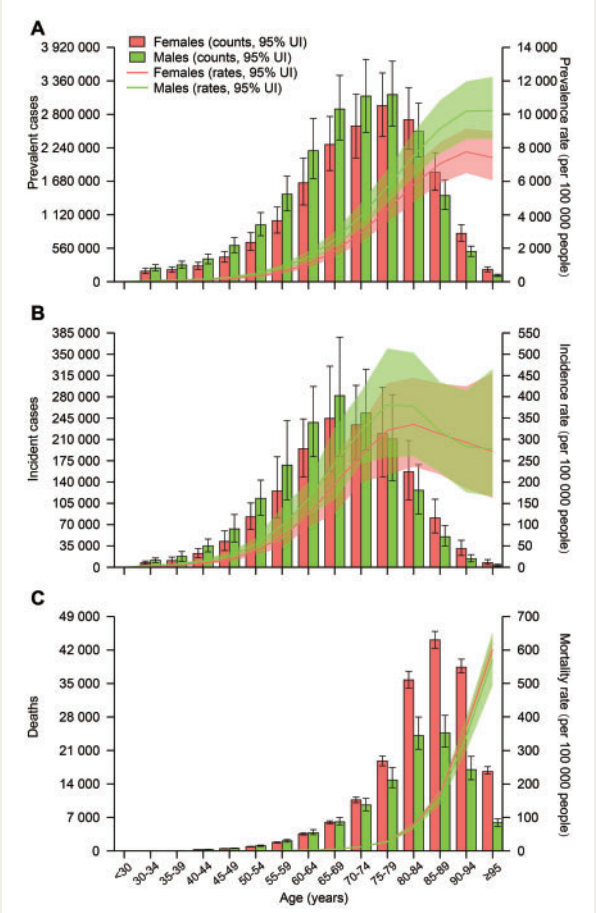

Figure 1 Age-specific counts and rates of prevalent cases (*A*), incident cases (*B*), and deaths (*C*) of atrial fibrillation by sex, 2017. Error bars and shading represent 95% uncertainty intervals.

Trends in the burden of atrial fibrillation from 1990 to 2017

Compared with 1990, the counts of AF prevalent cases in 2017 increased from about 19.14 million (95% UI 16.44–21.92) to 37.57 million (95% UI 32.55–42.59)—an increase of around 18.43 million cases. The counts of AF incident cases increased from more than 1.59 million (95% UI 1.35–1.85) to 3.05 million (95% UI 2.61–3.51)—an increase of around 1.45 million cases. The counts of AF deaths have more than doubled [113 389 (95% UI 107 769–120 755) in 1990 to 287 241 (95% UI 276 355–304 759) in 2017]. Nevertheless, the age-standardized mortality rates of AF remained stable between 1990 and 2017, and the age-standardized prevalence and incidence rates have decreased by -5.1% (95% UI -6.2 to -3.8) and -4.3% (95% UI -5.4 to -3.1), respectively (Supplementary material online, *Table S1*).

The temporal trends in the age-standardized rates of prevalent cases, incident cases, and deaths of AF varied significantly by SDI quintile (Supplementary material online, *Table S1* and *Figure S1*; *Figure 3*). From 1990 to 2017, the countries in the high SDI quintile had declined percentage changes in age-standardized rates of prevalent

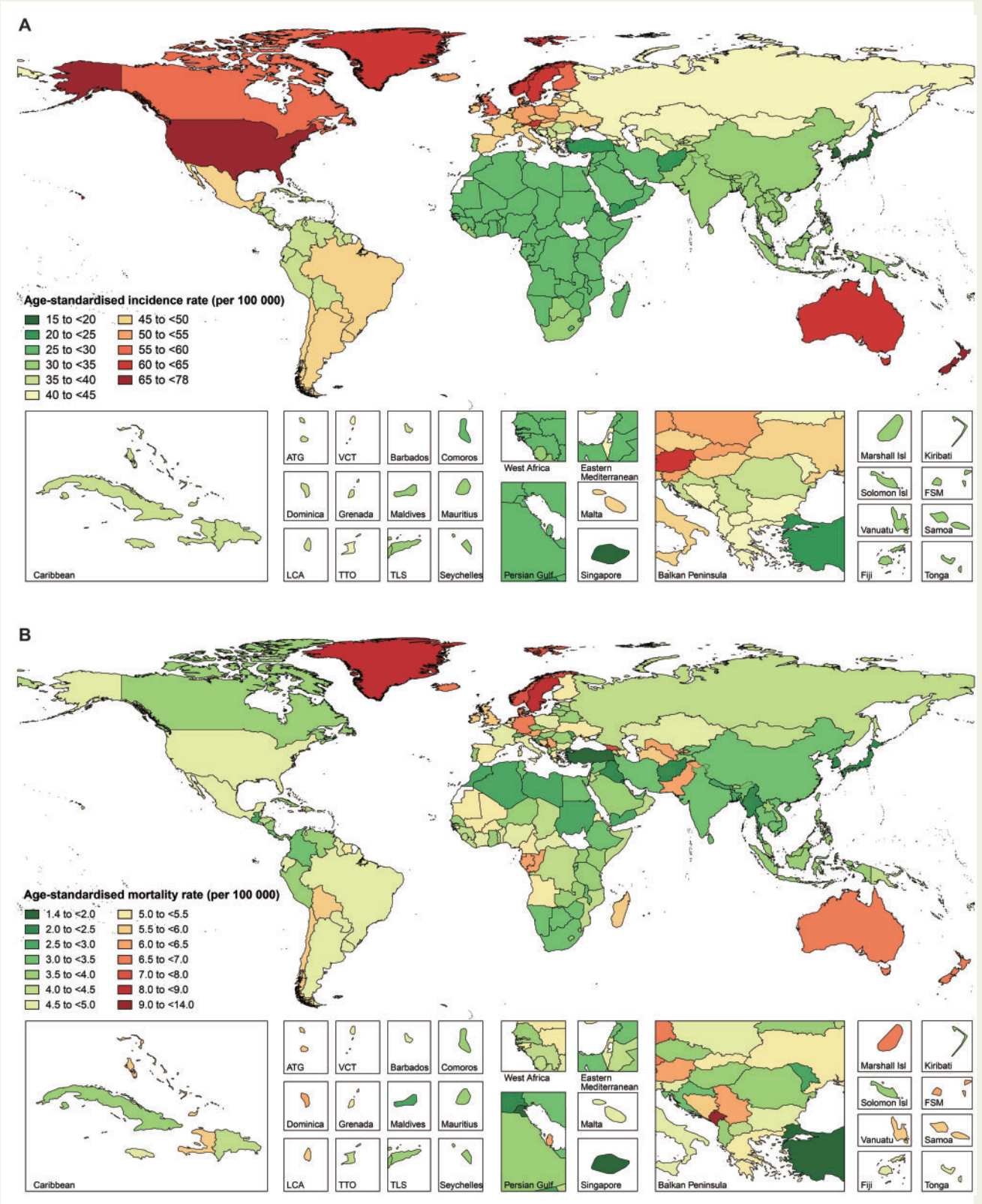

Figure 2 Age-standardized incidence (*A*) and mortality (*B*) rates of atrial fibrillation across 195 countries and territories for both sexes combined, 2017. ATG, Antigua and Barbuda; FSM, Federated States of Micronesia; Isl, Islands; LCA, Saint Lucia; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines.

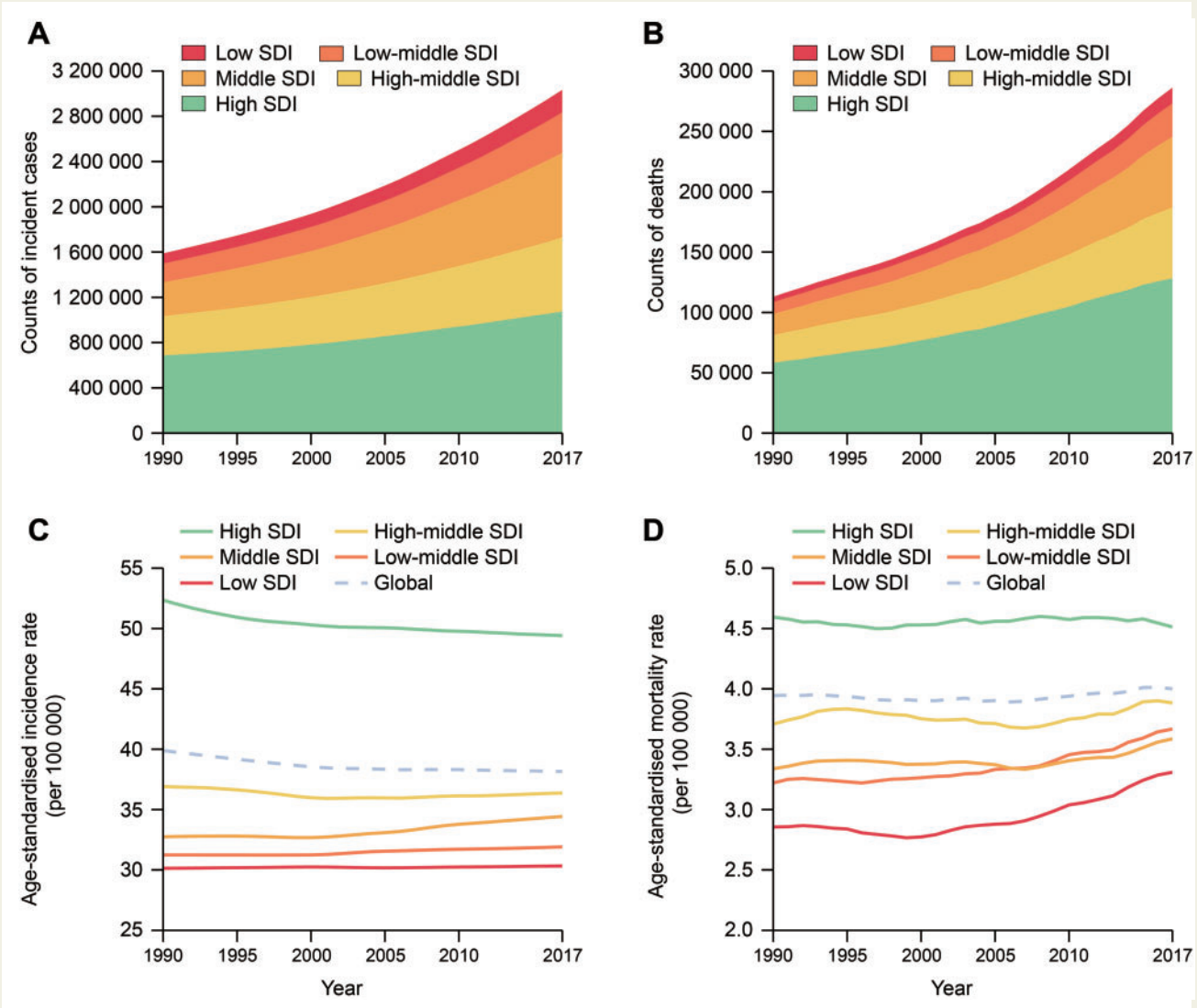

Figure 3 Temporal trends in counts and age-standardized rates of atrial fibrillation incident cases and deaths by socio-demographic index quintile for both sexes combined, 1990–2017. (*A*) Trends in counts of atrial fibrillation incident cases by socio-demographic index quintile, 1990–2017. (*B*) Trends in counts of atrial fibrillation deaths by socio-demographic index quintile, 1990–2017. (*C*) Trends in age-standardized incidence rates of atrial fibrillation by socio-demographic index quintile, 1990–2017. (*D*) Trends in age-standardized mortality rates of atrial fibrillation by socio-demographic index quintile, 1990–2017. AF, atrial fibrillation; SDI, socio-demographic index.

cases, incident cases, and deaths of AF, whereas the countries in the middle SDI quintile experienced the largest increase in age-standardized prevalence [4.9% (95% UI 4.2–5.6)] and incidence [5.1% (95% UI 4.3–5.9)] rates. By SDI quintile, the countries with lower SDI tended to have greater percentage increases in age-standardized mortality rates of AF; the greatest percentage increase was seen in countries in the low SDI quintile [15.9% (95% UI 7.7–26.9)].

Risk factors for atrial fibrillation

High systolic blood pressure was the leading risk factor for AF age-standardized deaths [34.3% (95% UI 27.4–41.5)] in 2017 for both sexes combined, followed by high body mass index [20.7% (95% UI 11.5–32.2)] and alcohol use [9.4% (95% UI 7.0–12.2)]. The percentage contributions of major risk factors to AF age-standardized deaths by sex and SDI in 2017 were presented in *Figure 4* and Supplementary material online, *Table S2*. For high systolic blood pressure and high body mass index, the percentage contributions were higher in females than in males, whereas the percentage contributions of alcohol use, smoking, and lead exposure were higher in males than in females.

Across SDI quintiles, the percentage contributions of high body mass index, and alcohol use to AF age-standardized deaths tended to increase with increasing SDI in both sexes in 2017 (*Figure 4* and Supplementary material online, *Table S2*). Conversely, the percentage contributions of lead exposure to AF age-standardized deaths decreased with increasing SDI in both sexes. In addition, the largest percentage contributions of smoking to AF age-standardized deaths were seen in countries in the high-middle SDI quintile for males

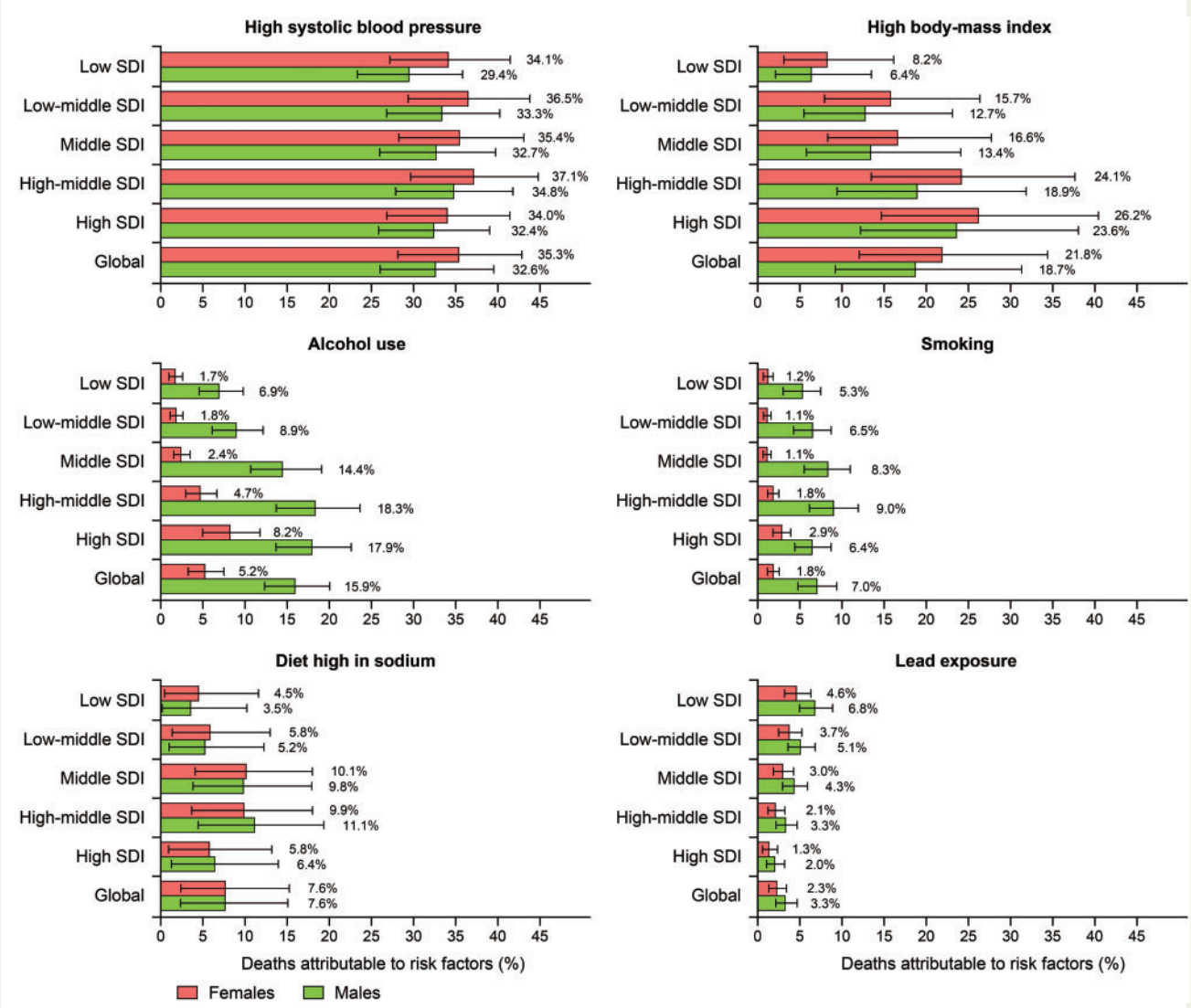

Figure 4 Percentage contributions of major risk factors to atrial fibrillation age-standardized deaths by sex and socio-demographic index quintile, 2017. Error bars and shading represent 95% uncertainty intervals. SDI, socio-demographic index.

[9.0% (95% UI 6.1–11.9)] and in countries in the high SDI quintile for females [2.9% (95% UI 1.8–3.9)]. For diet high in sodium, the countries in the middle SDI and high-middle SDI quintiles had relatively higher percentage contributions to AF age-standardized deaths in both sexes. From 1990 to 2017, globally, there were downward trends in the percentage contributions of high systolic blood pressure, alcohol use, and smoking to AF age-standardized deaths in both sexes, but upward trends for high body mass index, a diet high in sodium, and lead exposure in both sexes (Supplementary material online, *Table S2*).

Discussion

The present study has thoroughly investigated the global, regional, and national prevalence, incidence, mortality, and risk factors for AF from 1990 to 2017. We estimated that in 2017, 37.57 million (95% UI 32.55–42.59) individuals lived with AF and 3.05 million (95% UI 2.61–3.51) new AF cases occurred globally. The absolute numbers of AF prevalent and incident cases have almost doubled from 1990 to 2017, contrasting with declined changes in age-standardized prevalence and incidence rates. The exact causes for the trends are unknown but may be partly driven by population growth and aging. In addition, there is a growing body of evidence that in the last decades, thanks to the introduction of new advanced technologies for screening patients at risk of AF, more and more asymptomatic AF have been uncovered, which may also affect the findings presented in our study.[14] Other explanations could be an increased awareness of AF, a change in the coding shifting from the ICD-9 to the ICD-10, as well as a change in coding practices by physicians. On the other hand, not all treatments of AF are equally effective and there is an urgent need to develop more proper approaches.

We found that more females than males died of AF in 2017, while an opposite result could be detected in terms of AF-related incidence. The gap in outcomes of AF between males and females is a well-known fact from previously published studies.[15,16] Females with AF were more likely symptomatic, with relatively more severe symptoms, and associated with higher risks of cardiovascular diseases and mortality when compared with males. According to a meta-analysis of 30 cohort studies including over 4 million participants, AF is a stronger risk factor for heart failure, stroke, cardiovascular, and all-cause mortality in females compared with males.[17] Another important aspect which could contribute to this gap is that women were found to be less treated by electrical cardioversion and catheter-ablation as a rhythm control strategy despite a higher incidence rate of symptomatic episodes of AF.[18]

Age is a major risk factor in the development of AF. As shown in our study, both the prevalence and incidence rates of AF peaked in the elderly. However, we should note that AF-related mortality increased sharply in the elderly, which suggests that despite achievements in the field of modern medicine, there is still room for improvement in the management of AF, especially in the elderly. From the year 1990s, studies showed that AF patients benefitted from anticoagulation. The 'European AF Trial'[19] and the 'Veterans Affairs Stroke Prevention in Nonrheumatic AF'[20] clarified the benefits of anticoagulation on AF complications. The average age of patients was relatively young in the two studies. Increased risk of haemorrhages was found with increasing age, leading to doctors' hesitation in anticoagulation treatment of elderly patients.[21] Although more and more studies supported anticoagulation in elder patients (>80 years),[22,23] results from present studies reflect that in real-world clinical work, the effort was ineffective to some extent. More studies balancing haemorrhage and thrombus on the antithrombotic program for the elderly AF patients are still needed, as well as individualized treatment is needed for the antithrombotic program of the elderly.

In the present study, age-standardized rates of prevalent cases, incident cases, and deaths of AF tended to be higher in developed countries, while the lowest rates were observed in low SDI countries and some Asian countries such as Japan. These findings are consistent with previous studies.[3,24] Currently available evidence reveals that AF might be related to various aetiological factors, including adverse stressors, structural heart disease, endocrine system disease, and genetic factors.[25] Regions with high-risk factors of AF may experience higher levels of prevalent cases, incident cases, and deaths. Other studies showed that different areas can have diverse risk factors.[26] For instance, hypertension is the most common risk factor for AF worldwide, but nearly one-third of AF patients suffer from rheumatic heart disease in India. The present study showed that high systolic blood pressure, high body mass and alcohol use were AF risk factors, representing unhealthy lifestyles particularly widespread in high SDI countries. Thus, targeted interventions in different SDI country groups should be taken into consideration in future works.

Trends in risk factors of AF from 1990 to 2017 deserve our further attention. There were downward trends in the percentage contributions of high systolic blood pressure, alcohol use, and smoking to AF age-standardized deaths in both sexes, but upward trends for high body mass index, a diet high in sodium, and lead exposure. This trend was procyclical with respect to the decreased trends in alcohol use and smoking exposure.[12] Furthermore, deaths attributable to obesity increased by 71.7% in the analysis of global risk factors in GBD. High exposure of low-level environmental lead has been generally overlooked, but, in the last decade, are getting more and more attention, with available evidence showing that an increase of the lead concentration in blood can be associated with increased cardiovascular disease mortality.[27] Lead, a heavy metal, is one of the most abundant xenobiotics on earth, and both experimental and observational epidemiological studies have found a correlation between low-level lead exposure and cardiovascular disease and hypertension.[28] In particular, according to a recently published study,[27] recruiting 14 289 adults in the USA, an increase in the blood concentration of lead from 0.048 μmol/L to 0.324 μmol/L resulted in a higher all-cause mortality, cardiovascular disease, and ischaemic heart disease mortality, with population attributable fractions computed at 18.0%, 28.7%, and 37.4%, respectively. However, the relationship between lead exposure and electrocardiographic conduction abnormalities has been less studied.[29] A cohort sampled from the USA 'Normative Aging Study' has been prospectively studied, with low-level lead exposure resulting in a higher risk of developing QT and JT prolongation.[29] These abnormalities could be the result of a complex gene–environment interplay: some variants of genes involved in the iron metabolism could confer, indeed, an increased risk.[30]

Keeping into account all these factors' trends, the counts of AF deaths in the present study have more than doubled from 1990 to 2017. This could be due to temporal changes in various risk factors and demographic characteristics all over the world. In conclusion, the rising AF burden represents a global public health concern: healthcare decision- and policy-makers could utilize the findings of the current study to devise targeted, specific preventative programs, properly allocating resources, and monitoring their effectiveness.

Strengths and limitations

Despite the present study partly confirms well-known risk factors for AF, as arising from high-quality surveys, including the Framingham Heart, the Rotterdam and the 'Atherosclerosis Risk in Communities' (ARIC) studies, these large epidemiological investigations are limited to European and North-American populations. As mentioned by Rahman *et al.*,[31] accurate and reliable global estimates were lacking. The present study was aimed at filling in this gap in knowledge, providing rigorous estimations at the global level, relying on a statistically robust methodological framework. Furthermore, besides informing all relevant stakeholders, this investigation has enabled to uncover overlooked risk factors, such as low-level lead exposure, thus prompting further research in the field.

Our study is not without any limitations. The major shortcoming that should be acknowledged is represented by the use of ICD codes for extracting AF cases. Even though this is a common method to generate very large databases and combine data from different countries, there is the possibility that AF cases may have been over- or under-estimated. Furthermore, another limitation is given by the potential underestimation of asymptomatic AF cases. According to a systematic review of AF screening amongst the general population using electrocardiography or pulse palpation, the incidence of previously undiagnosed AF was 1.4% in adults aged ≥65 years.[32] Even though we acknowledge that enhanced detection over time may have reduced the underestimation rate, we did not explicitly account for this correction. This warrants further high-quality investigations

targeting specific populations. Furthermore, different subsets of AF exist, such as paroxysmal, persistent, or permanent, whereas most studies fail to acknowledge such complexity, considering AF as a mere binary entity, based on its presence or absence among recruited cohorts. Despite we recognize that some subtypes, such as paroxysmal AF, may have been uncovered by technological achievements and diagnostic improvements, thus explaining an absolute increase in AF cases, we could not stratify according to different clinical subtypes. In addition, we were not able to account for some risk factors like high fasting blood glucose, because they were omitted in the GBD database, due to their uncertain causality.[33] Moreover, the present data analysis is based on published studies and has not been adjusted for potential publication bias, in that we did not make any effort to retrieve unpublished sources.

Conclusions

Our study has systematically and globally assessed the temporal trends of AF, which remains a major public health challenge. Considering the high incidence of AF, particularly in developed countries, physicians in high-burden areas should be aware of the scale of the disease to provide a timely and effective response. Additionally, AF-related mortality increased significantly in countries with lower SDI from 1990 to 2017, suggesting the current preventative approaches should be reoriented, and more effective prevention and treatment strategies aimed at counteracting the increase in AF burden should be adopted in some countries.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article were derived from sources in the public domain: Institute for Health Metrics and Evaluation (IHME), at http://ghdx.healthdata.org/gbd-results-tool.

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Conflict of interest: none declared.

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