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ORIGINAL RESEARCH

Global Burden of Atrial Fibrillation and Flutter by National Income: Results From the Global Burden of Disease 2019 Database

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BACKGROUND: Atrial fibrillation (AF) and atrial flutter (AFL) are common conditions that can lead to significant morbidity and death. We aimed to understand the distribution and disparities of the global burden of AF/AFL as well as the underlying risk factors.

METHODS AND RESULTS: Data on the AF/AFL burden from the Global Burden of Disease data set were analyzed for the years 1990 to 2019, with countries grouped into low, lower-middle, upper-middle, and high national income classes according to World Bank categories. Data were supplemented with World Health Organization and World Bank information. The prevalence of AF/AFL has more than doubled (+120.7%) since 1990 in all income groups, though with a larger increment in middle-income countries (+146.6% in lower-middle- and +145.2% in upper-middle-income countries). In absolute numbers, 63.4% of AF/AFL cases originate from upper-middle-income countries, although the relative prevalence is highest in high-income countries. Prevalence of AF/AFL appears to be correlated with medical doctor rate and life expectancy. The most relevant AF/AFL risk factors are unevenly distributed among income classes, with elevated blood pressure as the only risk factor that becomes less common with increasing income. The development of these risk factors differed over time.

CONCLUSIONS: The global burden of AF/AFL is increasing in all income groups and is more pronounced in middle-income countries, with further growth to be expected. Underdiagnosis of AF/AFL in low- and middle-income countries may contribute to lower reported prevalence. The risk factor distribution varies between income groups.

Key Words: atrial fibrillation ■ atrial flutter ■ epidemiology ■ Global Burden of Disease 2019 database ■ risk factors

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common cardiac arrhythmias, which can lead to conditions such as stroke and heart failure. They are associated with increased health care costs, morbidity, and death.[1–3] Several risk factors for AF/AFL are known; some are modifiable such as arterial hypertension, obesity, or alcohol consumption, while other risk factors such as age or ethnicity cannot be altered. The risk of AF increases with age and risk factor burden.

The Global Burden of Disease (GBD) database in combination with World Health Organization (WHO) and World Bank data provides unique information to understand AF/AFL prevalence trends and underlying risk factor burden by income status at the global level. Previous analyses of AF/AFL from this database have shown an increase in global AF/AFL prevalence with differences between geographic regions and sociodemographic index.[4–6] Recently, 2 analyses on AF/AFL of the GBD 2019 data set on regional burden and risk

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RESEARCH PERSPECTIVE

What Is New?

- The global burden of atrial fibrillation and atrial flutter is increasing worldwide with differences depending on national income.

What Questions Should Be Addressed Next?

- Factors that contribute to the income-dependency of atrial fibrillation and flutter need to be investigated in more depth in order to address potential inequities.
- Causes of the increasing atrial fibrillation and atrial flutter prevalence, in particular modifiable risk factors, should be identified to reduce the global morbidity burden of these common arrhythmias.

Nonstandard Abbreviations and Acronyms

AFL	atrial flutter
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
GBD	Global Burden of Disease
INVICTUS	Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
WHO	World Health Organization

factor profile have been published.[7,8] While racial and income inequalities have been shown to be related to AF/AFL risk factor profiles, prevalence, management, and outcomes within study cohorts or health systems,[9–11] evidence regarding these disparities on a global level is lacking. Such differential knowledge on the distribution of global AF/AFL burden and disparities could augment the understanding of this heterogeneous condition and possibly guide targeted preventive, diagnostic, and therapeutic strategies in the future.

We aimed to understand the distribution and disparities of the global burden of AF/AFL as well as their underlying risk factors as possible reasons for the observed inequalities.

METHODS

The GBD database is a freely accessible resource delivered by the Institute of Health Metrics and Evaluation of the University of Washington. The GBD's goal is to improve the understanding of global diseases and their causes. The study was designed in compliance with the Guidelines for Accurate and Transparent Health Estimates Reporting recommendations. Extensive descriptions of the methodology of the GBD 2019 data set are available in the manuscript and appendix of a systematic analysis by the GBD 2019 Diseases and Injuries Collaborators.[12] In the following, we briefly summarize the most important aspects of this methodology. The underlying primary data are collected by an international collaborative network to which >9000 researchers from >160 countries contribute.[13] Most primary data are gathered by collaborating external organizations. Methods to collect such primary data include but are not limited to censuses, interviews, scientific literature, health care records and claims, and measurement of biometric data.[14,15] In total, >86 000 sources were used in the GBD 2019 data set.[12] The update cycles of these collected data depend on the primary sources. After collection, these primary data are then processed by the Institute of Health Metrics and Evaluation.[14] The metadata and, if publicly available, the primary data sets are catalogued on the Global Health Data Exchange data page.[13] Disability-adjusted life years (DALYs) were computed by the addition of years of life lost and years lost to disease specifically for each age-sex-location group, with repeated draws to account for uncertainty. The Healthcare Access and Quality Index has been used to account for variations in health care access. A microsimulation process is used to correct for comorbidities of years lived with disease for each age-sex-location-year group.[12] The cause of death is determined, for example, by administrative data such as vital registration or a so-called *verbal biopsy*, a battery of standardized questionnaires answered by the bereaved relatives to compensate for lacking vital registration.[16] A complete flowchart depicting the input data and 6-step modeling process for the estimation of AF/AFL death can be found on page 237 of Appendix 1 from Vos et al, with detailed descriptions of the methodology on the following pages.[12] The data of more recent years are regularly updated, the most current data set is the 2019 data set used in the present study. Data were extracted from the GBD database[17] for the years 1990 to 2019. Additionally, data from the World Bank Open Data[18] and WHO Global Health Observatory[19] was used for analysis. All data and materials are publicly available at the respective repository of the GBD and World Bank Open Data databases as well as the WHO Global Health

Observatory, and can be accessed at https://vizhub.healthdata.org/gbd-results/, https://data.worldbank.org/, https://apps.who.int/gho/data/node.imr, respectively. As this work is limited to the analysis of existing databases, no institutional review board approval or informed consent was required. All figures except for Figure S1 were produced using matplotlib (https://matplotlib.org) in Python 3.8. Figures 1 through 3 were built using matplotlib's standard *plot* function without additional smoothing.

Countries were grouped into 4 World Bank income classes according to their national income, using the World Bank classification for the fiscal year of 2019. Low-income countries were defined by a gross national income per capita, calculated using the Atlas method, of ≤$995, lower-middle-income countries were defined by a gross national income of $996 to $3895 per capita, upper-middle-income countries were defined by a gross national income of $3896 to $12 055 per capita and high-income countries were defined by a gross national income of $12 055 or higher per capita.[20] See Data S1 and Figure S1 for an overview world map and Table S1 for a list of countries in each income group.

Information about AF/AFL prevalence, DALYs, and deaths, as well as risk factor estimates for AF/AFL, were extracted from the GBD database. These risk factor estimations include the potentially modifiable risk factors high systolic blood pressure, high body mass index (BMI), alcohol use, dietary risks (relevant for AF/AFL risk factor estimations is a diet high in sodium), tobacco use and environmental risk factors (relevant for AF/AFL risk factor estimations is lead exposure) related to AF/AFL.[21]

Information on population size, age structure, life expectancy, and estimates of future developments until 2050 were extracted from the World Bank Open Data database.

Data regarding the medical doctor rate (number of medical doctors per 10 000 inhabitants), average BMI (in kg/m^2, age-standardized), alcohol consumption (measured by total alcohol consumption per capita in liters of pure alcohol in the age group ≥15 years and

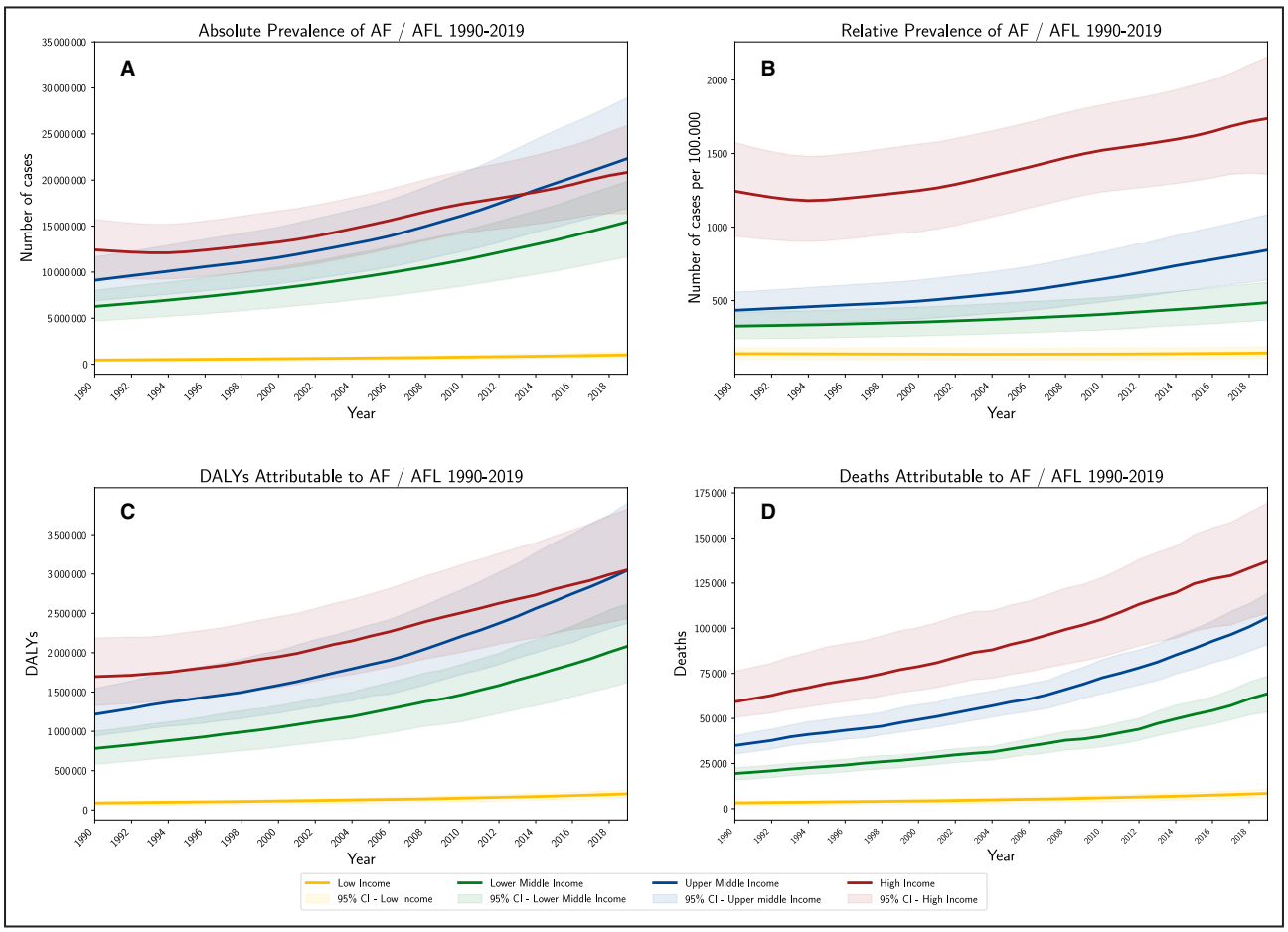

Figure 1. Development of epidemiologic standard measures for AF/AFL from 1990–2019: absolute AF/AFL prevalence (A), relative AF/AFL prevalence (B), absolute number of DALYs attributable to AF/AFL (C), and absolute number of deaths from AF/AFL (D).

AF/AFL indicates atrial fibrillation and flutter; and DALYs, disability-adjusted life years.

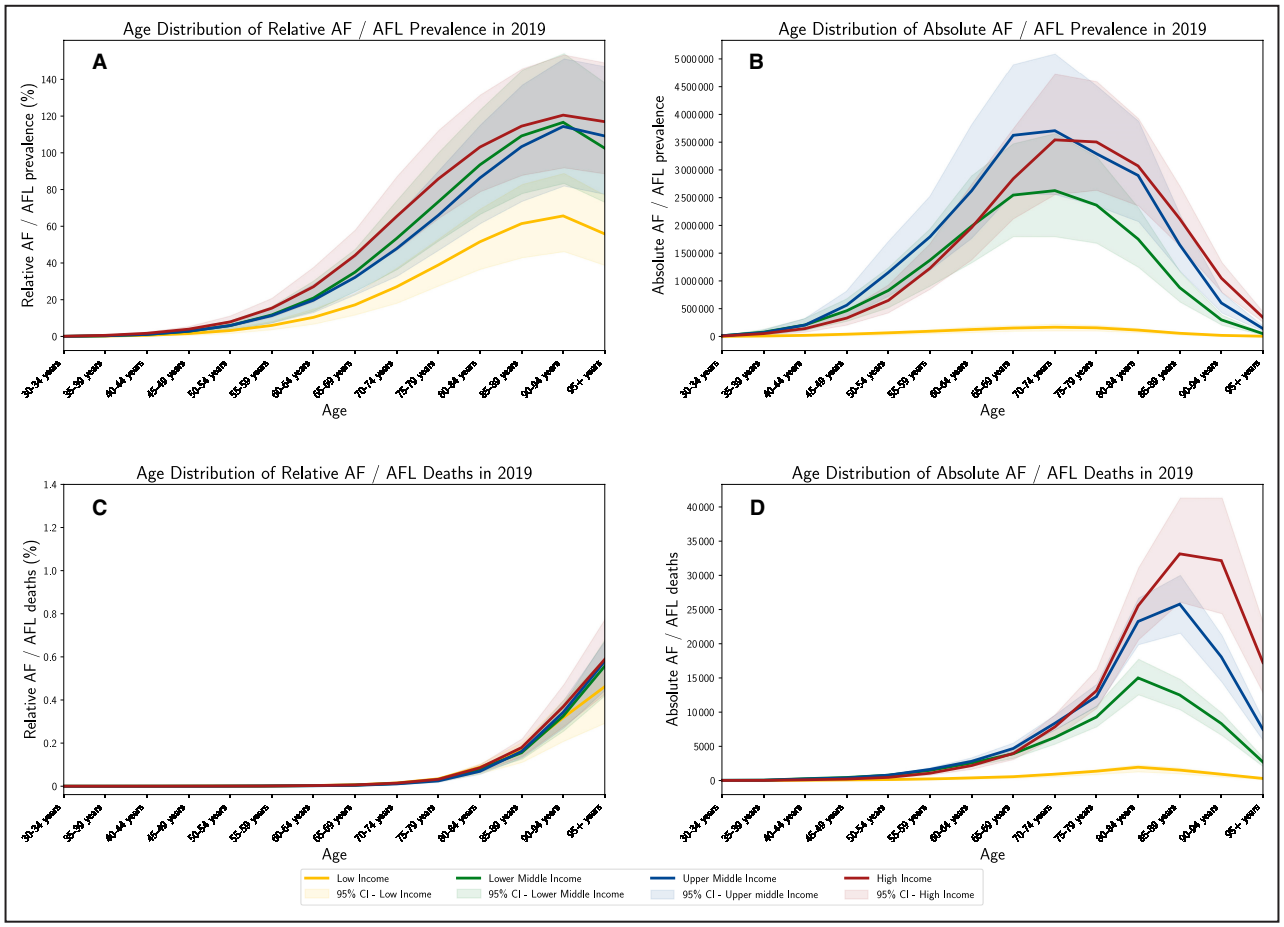

Figure 2. Age distribution of relative (A and C) and absolute (B and D) AF/AFL prevalence (A and B) and deaths (C and D) in 2019.
AF/AFL indicates atrial fibrillation and flutter.

average daily alcohol intake in grams among drinkers), current tobacco use (measured by prevalence of current tobacco use in percentage of adults in a population), insufficient physical activity (defined as percentage of defined population attaining <150 minutes of moderate-intensity physical activity per week, or <75 minutes of vigorous-intensity physical activity per week, or equivalent), raised fasting blood glucose (defined as a fasting blood glucose ≥7.0 mmol/L or on medication; age-standardized) and raised blood pressure (defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg; age-standardized) was extracted from the WHO Global Health Repository. If available, data from 2019 were used to match the data from the GBD database. If there were no data available for 2019, the most recent data were used.

We assessed absolute and relative prevalence of AF/AFL from 1990 to 2019 as well as the DALYS and deaths attributable to AF/AFL in that period. An analysis of sex differences was performed for absolute and relative AF/AFL prevalence. Further, we analyzed the age distribution of AF/AFL prevalence and deaths. Adding data from the WHO and World Bank, we illustrated the correlation between AF/AFL and both life expectancy and rate of medical doctors on the level of individual countries. Information about medical doctor rate for 2019 was available for 83 countries, in contrast to 2018, where information on 131 countries was available. Thus, 2018 was chosen for analysis. Finally, we assessed risk factor profiles, both the attributable risk factor proportions for AF/AFL as well as the general risk factor prevalence in the population and the temporal development. The risk factor estimations from the GBD database were not available for AF/AFL prevalence. Thus, risk factors for AF/AFL DALYs were analyzed.

RESULTS

Absolute and Relative Prevalence, DALYs, and Deaths

The absolute global prevalence of AF/AFL has more than doubled between 1990 and 2019, from worldwide

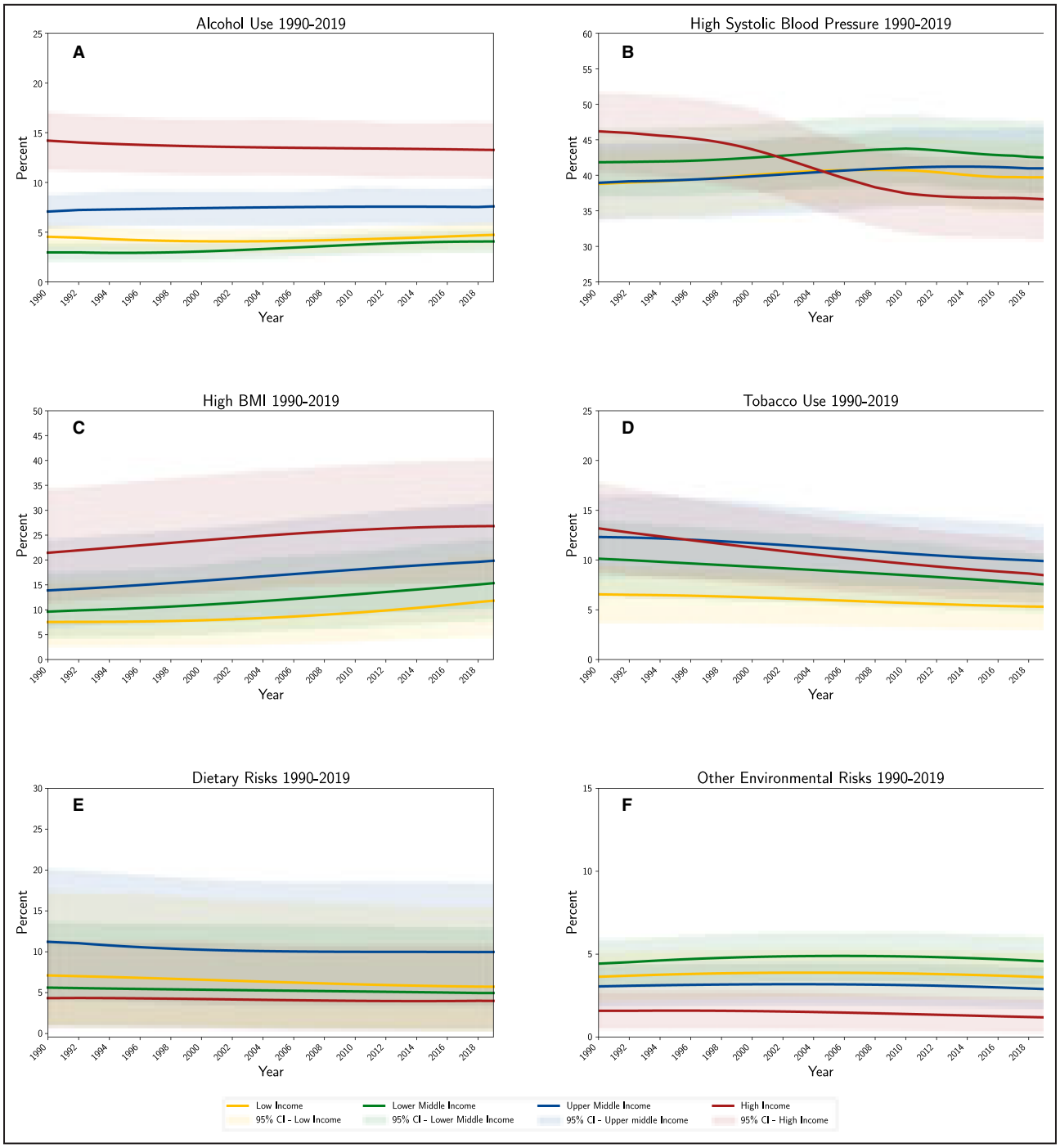

Figure 3. Temporal development of AF/AFL risk factors estimations from the GBD database: high BMI (A), high systolic blood pressure (B), dietary risks (C), tobacco use (D), alcohol use (E), and other environmental risk factors (F).
AF/AFL indicates atrial fibrillation/atrial flutter; BMI, body mass index; and GBD, Global Burden of Disease.

estimates of 28 273 978 AF/AFL cases in 1990 to 59 671 814 cases in 2019. In middle-income countries, the rise in prevalence has been greatest, with an increase of 146.6% in lower-middle-income countries and an increase of 145.2% in upper-middle-income countries. In low-income countries, the prevalence rose by 120.7%. In high-income countries, AF/AFL prevalence has risen by 67.8%. High-income countries had the highest absolute prevalence until 2014. Since then, prevalence in upper-middle-income countries is higher than in high-income countries (Figure 1A). The relative prevalence of AF/AFL is still highest in high-income countries with a prevalence rate of 1738 per 100 000 in 2019. In upper-middle-income countries, relative prevalence

was 844 per 100 000, in lower-middle-income countries 487 per 100 000 and in low-income countries 144 per 100 000 (Figure 1B). The absolute number of DALYs has continuously increased since 1990. This increase was greatest in upper-middle-income countries with the number of DALYs attributable to AF/AFL in upper-middle-income countries (+150.4%) almost reaching the numbers of high-income countries (+80.0%) in 2019. In lower-middle-income countries, the number of DALYs has increased by 166.2% since 1990, and by 129.4% in low-income countries (Figure 1C). In contrast to prevalence, the absolute number of AF/AFL-related deaths continues to be highest in high-income countries. It increased by 131.3% between 1990 and 2019. Deaths due to AF/AFL have risen by 202.3% in upper-middle-income countries and by 227.4% in lower-middle-income countries. In low-income countries, the number of deaths increased by 162.3% (Figure 1D). This increase of absolute and relative prevalence in upper-middle-income countries was largely driven by women in an analysis of sex differences (Data S2 and Figure S2).

Age Distribution of Absolute and Relative AF/AFL Prevalence and Deaths

Both AF/AFL prevalence and deaths are strongly age dependent. The age-specific relative prevalence increases with age, reaching its climax in the age group of 90 to 94 years and slightly decreasing in the age group ≥95 years for all income groups. The difference of age-specific relative prevalence in low-income countries compared with the other 3 income groups is less than for the overall relative AF/AFL prevalence (Figure 2A). The age group of ≥65 years makes up for 73.0% of global absolute AF/AFL prevalence: 79.0% of AF/AFL cases in high-income countries, 71.2% in upper-middle-income countries, 68.0% in lower-middle-income countries, and 65.5% in low-income countries occur in this age group. The climax of absolute prevalence differs between income groups. In high-income countries, the highest absolute prevalence of AF/AFL is observed among 75- to 79-year-old individuals, whereas in upper-middle-, lower-middle-, and low-income countries the highest absolute prevalence is reached in the age group 70 to 74 years. Until the age group of 70 to 74 years, the highest absolute prevalence is reached by upper-middle-income countries, whereas high-income countries are leading in the absolute prevalence in the age group of 75 to 79 years and onward. Until the age of 60 to 64 years, the absolute prevalence in lower-middle-income countries is higher than in high-income countries (Figure 2B). The age-specific death rate continuously increases with age, with comparatively small differences between income groups (Figure 2C). As with prevalence, the absolute number of deaths related to AF/AFL was strongly age-dependent, with a shift to older age groups compared with prevalence. The highest number of deaths occurred in the age group 85 to 89 years in high- and upper-middle-income countries and in the age group 80 to 84 in lower-middle- and low-income countries. The age group ≥65 years is most burdened with deaths related to AF/AFL. Of all deaths related to AF/AFL, 97.0% occur above the age of 65 in high-income countries, 94.4% in upper-middle-income countries, 91.1% in lower-middle-income countries, and 89.2% in low-income countries (Figure 2D).

Development of Population Characteristics

Both the size of the total population and the population aged ≥65 years has increased since 1990. Estimations until 2050 project further a growth in global total and elderly population. A sharp increase in absolute numbers of individuals aged ≥65 years is estimated for middle-income countries (Data S3 and Figure S3).

Life Expectancy and AF/AFL Prevalence

Data on life expectancy at birth and AF/AFL prevalence for 2019 was available for 188 countries. On a country-level basis, a common ascent between life expectancy and AF/AFL prevalence per 100 000 can be observed, with the highest life expectancies and AF/AFL prevalence occurring in high-income countries (Figure 4A; Table S2).

Medical Doctors and AF/AFL Prevalence

Data on medical doctor rate and AF/AFL prevalence for 2018 were available for 131 countries. A corresponding increase between medical doctor rate per 100 000 and AF prevalence per 100 000 on the level of individual countries could be observed (Figure 4B; Table S2).

AF/AFL Prevalence and Modifiable Risk Factors

Distribution of AF/FL Risk Factor Estimations Within Income Groups

The modifiable risk factor estimates as given by the GBD do not add up to 100% of total AF/AFL risk. High systolic blood pressure is the most important of these risk factors in all income groups, followed by high BMI. With increasing income, the estimated contribution of high systolic blood pressure to overall AF/AFL DALYs decreases from low-income countries to high-income countries, whereas the estimated contribution of high BMI increases. The estimated proportion alcohol use contributes to AF/AFL DALYs is lowest in lower-middle-income countries and highest in high-income

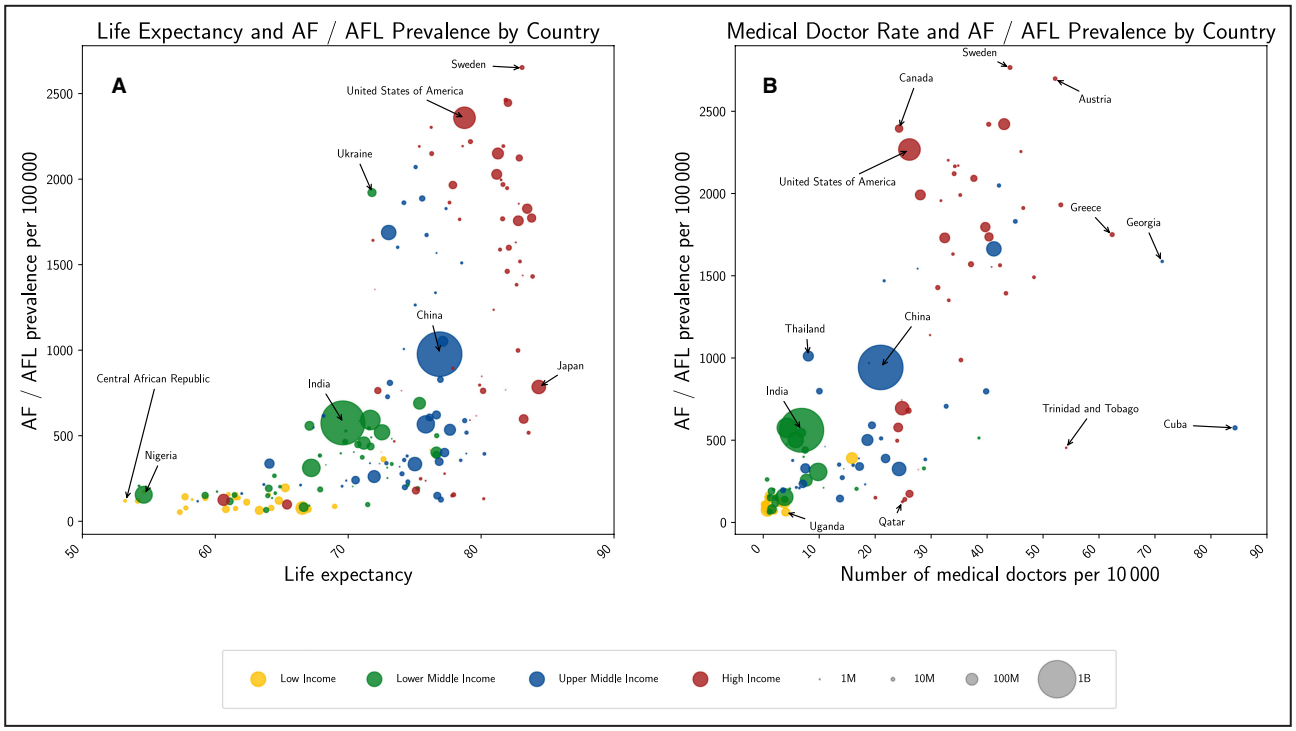

Figure 4. Life expectancy and AF/AFL prevalence by country (A), medical doctor rate and AF/AFL prevalence by country (B). The size of the bubble represents the population size in the respective country.
AF/AFL indicates atrial fibrillation/atrial flutter.

countries. The largest relative share of dietary risks falls to upper-middle-income countries, whereas it is lowest in high-income countries. For tobacco use, the largest relative contribution is estimated in upper-middle-income countries, the lowest contribution in low-income countries. The risk of other environmental risk factors is estimated to be highest in low-income countries and becomes lower with increasing income groups (Figure 5).

Temporal Development of AF/AFL Risk Factor Estimations

The estimated contribution of a high BMI to AF/AFL risk has increased since 1990 for all income groups (Figure 3A). The contribution of high systolic blood pressure to AF/AFL risk has changed over time in all income groups. While its contribution to AF/AFL risk has slightly increased in low-, lower-middle-, and upper-middle-income countries, it has decreased in high-income countries since 1990 from 46.2% to 36.6% (Figure 3B). A slight decrease of the risk contribution of dietary risks to AF/AFL risk can be observed for all income groups (Figure 3C). Tobacco use as a risk factor has decreased in AF/AFL risk contribution for all income classes but is most pronounced in high-income countries, with a reduction from 13.2% to 8.5% (Figure 3D). For alcohol use, there has been a slight reduction in contribution to AF/AFL risk in high-income countries, from 14.2% to 13.3% compared with a slight increase in AF/AFL risk contribution in lower-middle-income countries from 3.0% to 4.7% (Figure 3E). The contribution of other environmental risk factors to AF/AFL risk has changed little between 1990 and 2019 (Figure 3F).

Differences Between Income Groups for General Prevalence of AF/AFL Risk Factors

The prevalence of several risk factors for AF/AFL in the general population was available from the WHO data observatory. Information on age-standardized BMI estimates were available until 2016, on raised blood pressure until 2015, on raised fasting blood glucose until 2014, on alcohol consumption until 2018. Ninety-five percent CIs were not available for alcohol consumption and current tobacco use. For the variable *insufficient physical activity*, only *middle income* was available without further distinguishment into upper- or lower-middle income, the most current available data were from 2016. The prevalence of the modifiable AF/AFL risk factors average BMI, alcohol consumption, and insufficient physical activity in the general population correlated with income. The highest burden was observed in high-income countries and the lowest burden in low-income countries. For the risk factors raised fasting blood glucose and current tobacco use, the risk distribution was not following such a linear trend

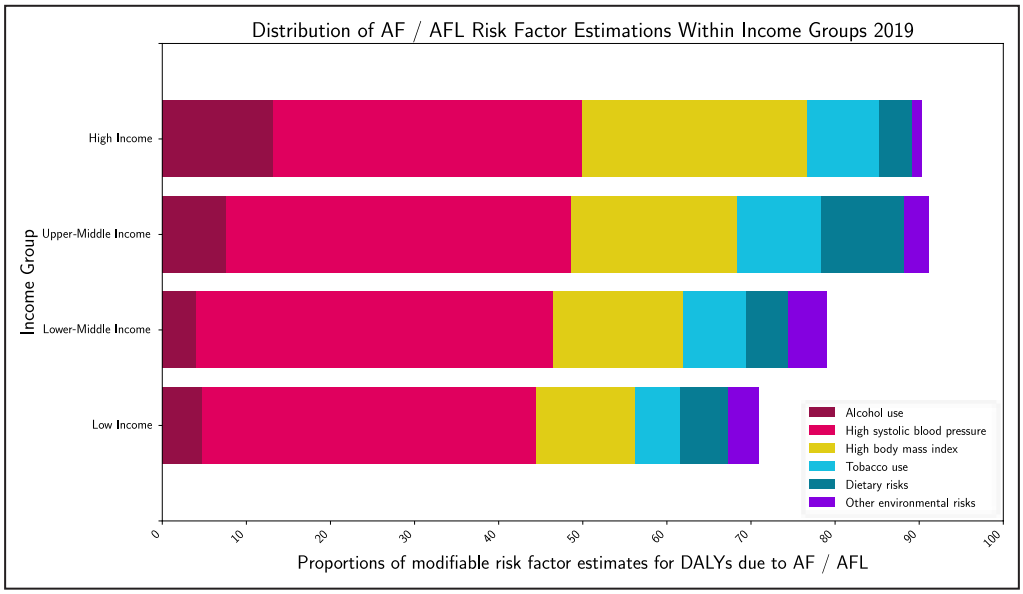

Figure 5. Distribution of the proportion of modifiable risk factor estimates for AF/AFL disability-adjusted life years (DALYs) from the GBD database by income groups.
AF/AFL indicates atrial fibrillation/atrial flutter; and GBD, Global Burden of Disease.

with the highest burden of risk factors in lower-middle-income countries or upper-middle-income countries. Only the percentage of population with raised blood pressure was highest among low-income countries with decreasing burden at increasing income (Figure 6).

DISCUSSION

Main Findings

The prevalence of AF/AFL, DALYs, and deaths consecutively have steadily increased globally and among all income groups between 1990 and 2019. A shift of AF/AFL burden toward middle-income countries can be observed. Collectively, >60% of global AF/AFL cases occurred in middle-income countries in 2019. While relatively seen, AF/AFL prevalence is highest in high-income countries, the absolute burden is greatest in upper-middle-income countries. Whereas the prevalence curve for high-income countries is flattening, the growth in both upper-middle- and lower-middle-income countries is still increasing. This growth is mostly driven by women in these income groups. In 2019, most DALYs still come from high-income countries, though the yearly increase in middle-income countries is greater, and there were almost as many DALYs caused by AF/AFL in upper-middle-income countries as in high-income countries in 2019. For deaths, differences between income groups have been more stable over time with an overall increase. Further, differences in age distribution can be observed with a tendency of AF/AFL cases occurring in younger individuals in middle- and low-income countries and in older individuals in high-income countries. Even more pronounced age differences between income groups can be observed for deaths of AF/AFL, with deaths occurring at higher ages with increasing income.

The reasons for these observations are complex. National income groups are defined by economic factors, but there are further characteristics that differ between income groups. Some are related to income, such as socioeconomic status and health care infrastructure, others are independent, such as geographic and thus also racial differences. The most obvious explanation for the absolute increase of AF/AFL prevalence in middle-income countries is the surge in population size. Lower-middle- and upper-middle-income countries together accounted for 75% of the global population in 2019 (Data S3). In low- and lower-middle-income countries, further population growth is expected until 2050, whereas it is estimated that population size remains mostly unchanged in upper-middle- and high-income countries. This increase in population size is due to increased birth rates but also by an increased life expectancy, which permits the development of AF/AFL at older age. An association between life expectancy at birth and AF/AFL prevalence can be observed on a country level with an exponential trend. Since AF/AFL is typically not an immediately disabling or deadly disease, a reason for the differences between prevalence and both DALYs or death could be a time delay between onset of AF/AFL and disability or death of it. Competing risks of death and a shorter life expectancy might explain a lesser burden of AF/AFL deaths in middle- and low-income countries compared with high-income countries, as death of AF/AFL usually

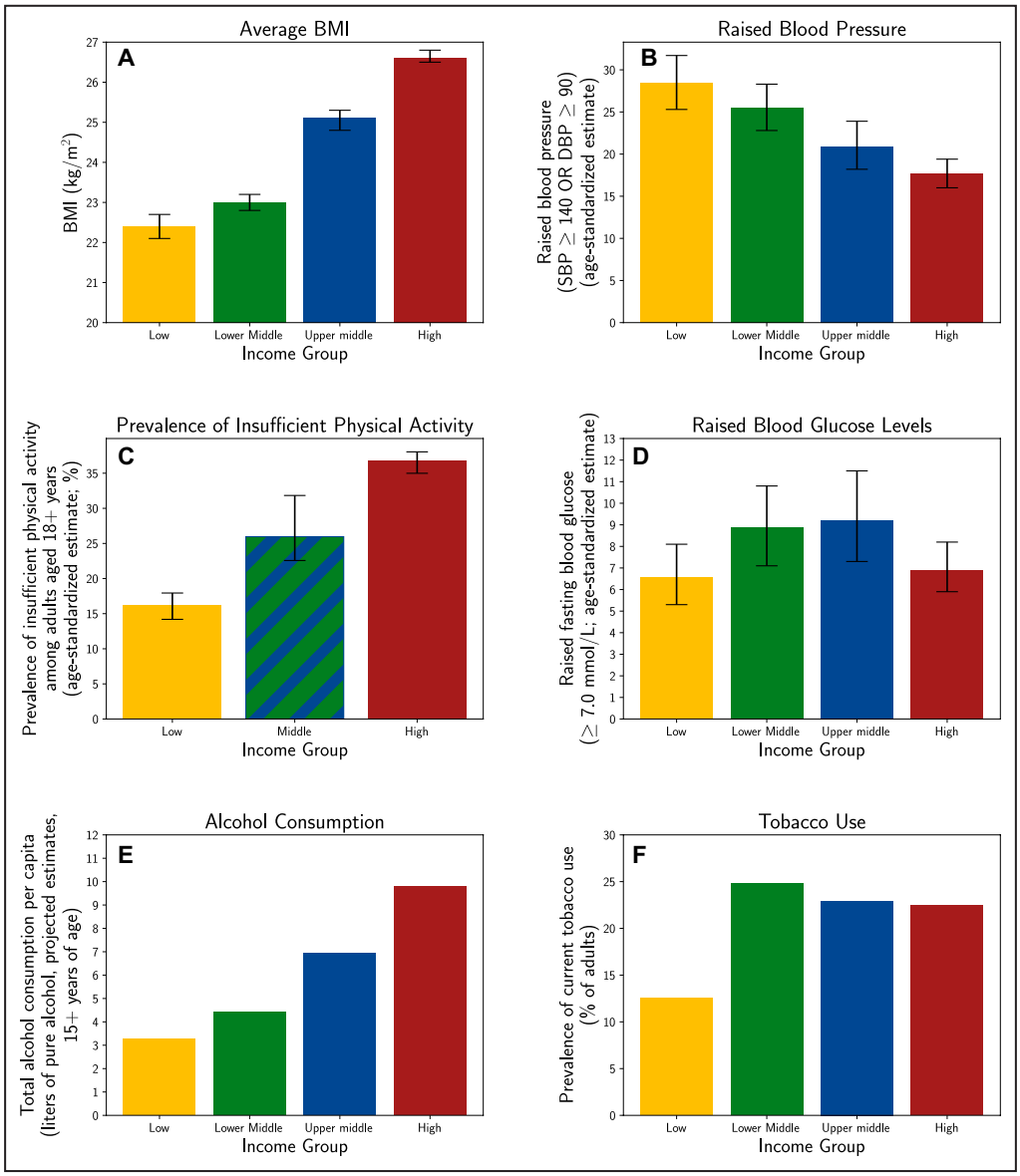

Figure 6. Differences between income groups for the risk factors average BMI (A), raised blood pressure (B), insufficient physical activity (C), raised fasting blood glucose (D), alcohol consumption (E) and current tobacco use (F), data for the general population from the WHO Global Health Repository.

AF/AFL indicates atrial fibrillation and flutter; BMI, body mass index; and WHO, World Health Organization.

occurs in old age. This is underlined by the observation that the age-specific relative AF/AFL prevalence and death rate shows smaller differences between income groups compared with the overall relative AF/AFL prevalence. There appears to be an almost linear trend between the rate of medical doctors and AF/AFL prevalence. This observation indicates a potential underdiagnosis of AF/AFL in countries with restricted health care resources.

There is significant heterogeneity in AF/AFL risk factors and individual characteristics between income groups. Besides age, there are several important and modifiable AF risk factors that vary among income groups, following different trends. Risk factors such as BMI, alcohol consumption, and insufficient physical activity show a clear trend toward higher rates in high-income countries. Raised fasting blood glucose and current tobacco use have the highest rates in middle-income countries, as previously described.[22] Of the risk factors examined here, raised blood pressure is less prevalent with increasing income, which is a comparatively new trend. Temporal analyses show that the prevalence of raised blood pressure was highest in high-income countries in 1990 but started to decrease

for high- and upper-middle-income countries, an effect that could be attributable to increased preventive efforts. The use of antihypertensive medication in high-income countries has increased in the past decades with improving blood pressure control in the population.[23,24] This could not be observed for raised fasting blood glucose, where an increase in all income groups has been observed since 1990, though with almost parallel, steep increases in upper-middle-, lower-middle-, and low-income countries and a lesser increase in high-income countries. The differences among risk factor prevalence between income groups are reflected in the distribution of risk factor estimates from the GBD database. Here, high systolic blood pressure is the leading modifiable risk factor in all income groups, though with an increasingly smaller proportion with increasing income. An antagonistic trend could be observed for the second most important risk factor, high BMI.

Risk Factor Modification and AF/AFL Prevention

The modifiability of risk factors highlights the importance of prevention. Decreasing rates of hypertension in high- and upper-middle-income countries are suggesting a successful treatment and promising similar successes for other countries that adopt treatment strategies for hypertension. Possible reasons for the absence of such positive treatment effects are numerous and hard to determine. They include access to medication (which may be due to medication cost or health care infrastructure) but also factors such as disease awareness, medication adherence, and refusal of modern medicine in some regions. The treatment of other risk factors such as high BMI and alcohol and tobacco use often are more challenging and more expensive than simple pharmacologic treatment of hypertension, though some have been suggested to be cost effective.[25–27]

Underrepresentation and Heterogeneity of Global AF/AFL Patients

The main burden of global AF/AFL prevalence lies on middle-income countries, but the current research of AF/AFL does not reflect this. From a global perspective, most AF/AFL patients are underrepresented in AF research, and their characteristics, from ethnicity to comorbidities, may be significantly different from those individuals who have typically been examined by researchers in the past. Of all papers published on AF from 1945 to 2018, 56% come from 7 high-income countries. The United States (high-income country) alone makes up for 25.9% of all papers. Japan (high-income country) contributed 8.0%, and China (upper-middle-income country) 7% of papers. South and Latin America as well as Africa were almost not represented.[28] In large AF clinical trials, which are mostly located in high-income countries, non-White ethnicities are often underrepresented compared with the entire countries' population or ethnicity is not reported.[29–31] In the ASSERT trial (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), participants with European ethnicity had a higher risk of AF compared with Black Africans, Chinese, and Japanese participants.[32] Differences in clinical complications between ethnicities have been observed, such as a higher stroke risk in Asians even at a low CHA_2DS_2-VASc score[33] or higher rates of heart failure in Africans.[34] Hypertension may increase the risk for both bleeding and thromboembolic events in anticoagulated patients[35–37]; thus the safety profile of anticoagulants might differ in countries with higher rates of hypertension than reflected in most studies. Though the 4 large direct oral anticoagulant approval studies each had participants from 40 to 46 countries, enrollment is not representative for the global AF/AFL population.[38–41] In the ENGAGE-AF TIMI 48 (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial, for example, 62.4% of patients were recruited in high-income countries, 28.2% in upper-middle-income countries, 9.3% in lower-middle-income countries and none in low-income countries.[41] The rate and quality of antithrombotic therapy is higher in high-income countries compared with the rest of the world.[34,42] Rheumatic heart disease was present in 2.2% of North American (high-income countries) AF patients but up to 31.5% in Indian (lower-middle-income country) patients in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial.[34] Treatment of these patients is particularly challenging since rheumatic fever may lead to mitral stenosis and thus valvular AF. Patients with valvular AF have been excluded from most stroke risk stratification and anticoagulation trials in the past,[38–41] and it has been suggested that they may have a higher risk of thromboembolism.[43] The recent INVICTUS study (Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) has shown a higher rate of a composite cardiovascular event end point for rivaroxaban compared with vitamin K antagonists.[44]

In sum, there is a significant global heterogeneity between patients with AF/AFL. Due to significant underrepresentation of low- and middle-income countries in AF/AFL research, what is known about the manifestation and treatment of AF/AFL relates predominantly to patients in high-income countries. It is not well understood to what extent this evidence can be generalized for and transferred to patients with AF/AFL in low-, lower-middle-, and upper-middle-income countries, even though this group makes up the majority of global patients with AF/AFL.

LIMITATIONS AND STRENGTHS

There are several limitations to this study. First, data from 3 different databases (GBD database, WHO data repository, World Bank database) was used and joined. Each of these databases uses different approaches and methodology to generate its data and has its own limitations. The limitations of the GBD database have been previously described elsewhere.[12,45,46] In brief, the availability, quality, and quantity of primary data varies greatly between regions depending on the existence and quality of the respective data sources and are fraught with uncertainties and inconsistencies, which is reflected in the large CIs. As far as it is assessable, the primary data often consist of random samplings and extrapolations, which may cause distortions and significant variability. In the absence of primary data, the GBD collaborators have used estimation models to provide this comprehensive data set. To our knowledge, there are limited attempts to externally validate these estimations with other data sets or estimations.[47] The quality of all estimations, such as future trends or underlying risk factors relies on the respective statistical models that have been used and need to be assessed with caution for their uncertainties and potential errors. The analysis of underlying risk factors is limited to those factors that are included in the GBD database. Several important known risk factors for AF/AFL are missing. Among them are, for example, systolic or diastolic heart failure, valvular disease, sleep apnea, or thyroid disease. Also, rheumatic fever and subsequent rheumatic heart disease are not analyzed as underlying risk factors in the GBD risk factor estimation, though it is a common risk for AF/AFL with important therapeutic consequences. As discussed above, AF/AFL as an often-intermittent condition usually is underdiagnosed, in particular in countries with less diagnostic resources. Some of the primary data used in this databank relies on diagnoses assigned by the routine health care. The GBD data are observational and thus susceptible to many biases and confounders, and challenges in the interpretation of such results like reverse causality need to be taken into consideration. Also, countries were grouped according to national income. We cannot discriminate a significant proportion of confounding or reverse causality, as these countries differ not only in income but also in other aspects that could be relevant in this setting, such as socioeconomic status, health care infrastructure, and racial differences. Therefore, it should not be assumed that national income is causal for the incidence of AF/AFL, but rather that it correlates with several potentially causal factors.

Strengths include the possibility to compare global trends for a variety of AF/AFL measures over a time span of 3 decades as well as their underlying risk factors. This extensive data source permits to gather a deeper understanding of the past developments and show up disparities in the present situation. Even at the acknowledgement of the numerous limitations of the GBD database, it remains the most comprehensive data set available for public research. Together with estimations of the development of the global population, a trend for the development of the global burden of AF/AFL in the future can be surmised, though more complex modeling is necessary to support these projections with more robust data.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1–S3
Tables S1–S2
Figures S1–S3

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