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The burden of hypercholesterolemia and ischemic heart disease in an ageing world

Angela Pirillo [a,1], Giuseppe Danilo Norata [b,*,2]

[a] Center for the Study of Atherosclerosis, E. Bassini Hospital, Cinisello Balsamo, Milan, Italy
[b] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

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ABSTRACT

Despite a general improvement in global health conditions in the last decades, cardiovascular diseases (CVDs) are still the first global cause of death and disability worldwide, with ischemic heart disease (IHD) being responsible for half of CVD deaths. Hypercholesterolemia is a major causal risk factor for IHD. Although the availability of effective cholesterol-lowering drugs largely increased in the last few years, we are still facing disparities in the awareness of dyslipidaemia as a CVD-associated risk factor and therefore in health expenditure among different world areas. Although no significant changes have been reported globally in the levels of plasma cholesterol in the last three decades, relevant differences among world areas according to their economic status can be observed. Only high-income countries have experienced an improvement in plasma lipid profile which translated into a substantial decrease in the deaths and disabilities due to IHD, whereas countries in other income groups showed no reduction or even an increase. As expected, most of the deaths for IHD attributable to high LDL-C occur in people aged 60 years and above, although significant differences can be observed according to income. Altogether these observations suggest the need for measures to reduce the gap in treating hypercholesterolemia among income groups, with special attention to women and older people.

1. Introduction

Over the past three decades, we have witnessed an overall improvement in global health, although significant differences between the major regions of the world still exist. Cardiovascular disease (CVD) remained the leading cause of death and disability worldwide in 2019 accounting for more than 18,5 million deaths (Fig. 1A) [1], with ischemic heart disease (IHD) accounting for half of global CVD deaths (Fig. 1) [1]. Lifestyle changes combined with the rapid ageing of the population have contributed to an increase in the number of people who are more susceptible to CVD. The availability of novel drugs for the treatment of cardiovascular disease has greatly improved survival after an acute event [2]. However, while some patients recover fully, others remain in a state of partial or total disability, a problem that is even more important in the elderly. These issues contribute to increasing the economic burden on health systems. Among risk factors unequivocally linked to CVD, and particularly to IHD, some can be modified and controlled by interventions, including dyslipidaemias, high blood pressure, diabetes, obesity, diet, and smoking.

In this work, we discuss how the profile of subjects with elevated cholesterol levels, a causal factor involved in IHD [3], changed worldwide in the last decades, with a focus on how gender and age differently impact the risk of IHD attributable to high plasma LDL-C levels according to the economic status of different world areas, based on the most recent available epidemiological data.

2. Data source and definitions

Data source. We took advantage of publicly available data from two global databases:

1) the Global Burden of Disease (GBD, https://www.healthdata.org/gbd), which provides data on mortality and disability across countries, sex, age, and years. From this database, we extracted data on age-standardized (where applicable) death rates and numbers, disability-adjusted life of years (DALYs) rates and numbers, and

* Correspondence to: Department of Pharmacological and Biomolecular Sciences, Università Degli Studi di Milano, Milan, Italy.
E-mail address: danilo.norata@unimi.it (G.D. Norata).
[1] https://orcid.org/0000-0002-2948-6257
[2] https://orcid.org/0000-0002-6081-1257

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summary exposure values (SEV) related to high LDL-C from 1990 to 2019.

2) the NCD Risk Factor Collaboration (NCD-RisC, https://ncdrisc.org/), which provides data on major cardiometabolic risk factors for 200 countries. From this database, we extracted data on total cholesterol, high-density lipoprotein cholesterol (HDL-C), and non-HDL-C expressed in mmol/L in men and women from 1980 to 2018.

Definitions. High LDL-C is defined as the LDL-C concentration that exceeds the theoretical minimum risk exposure level, which is 1.3 mmol/L (50 mg/dL), as determined by a previous study [4]. Summary exposure value (SEV) is the measure of a population's exposure to a risk factor that takes into account the extent of exposure by risk level and the severity of that risk's contribution to disease burden. SEV is 0% when no excess risk for a population exists and 100% when the population is at the highest level of risk. A decline in SEV indicates reduced exposure to the specified risk factor, whereas an increase in SEV indicates increased exposure. The income level classification of single countries (low, lower middle, upper middle, and high) by the World Bank is based on the gross national income per capita in United States dollars (https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html).

3. Dyslipidaemia as a modifiable CV risk factor

Among the modifiable risk factors for CVD, dyslipidaemias play a fundamental role. Genetic, epidemiologic, and clinical studies have established a causal association between elevated levels of LDL-C and an increased risk of atherosclerotic CVD (ASCVD) [3,5]. Clinical and genetic studies have shown that reducing LDL-C lowers the risk of CV events, independently of the mechanism by which such reduction is achieved [3]. Furthermore, the greater the reduction in LDL-C, the greater the clinical benefit. The treatment of hypercholesterolemia is much easier today than it was a decade ago because, in addition to statins, new therapeutic approaches are available that have expanded the extent of lipid-lowering that can be achieved [6].

It is important to emphasise that lowering LDL-C to very low levels does not eliminate cardiovascular risk. All apolipoprotein B (apoB)-containing lipoproteins are atherogenic; they include not only LDL particles but also remnant particles and lipoprotein(a) (Lp(a)), all of which contribute to atherogenesis [3,7] and residual lipid-related cardiovascular risk beyond LDL-C levels. Indeed, remnant particles, deriving from the intravascular metabolism of larger intestinal and hepatic lipoproteins (i.e. chylomicrons and VLDL, respectively) may be retained in the intima, [8–10]. In addition, elevated levels of Lp(a), a lipoprotein consisting of an LDL particle covalently bound to apolipoprotein(a), represent an independent risk factor for ASCVD [11–14]. The overall level of these atherogenic lipoproteins can be better captured by assessing non-HDL-C levels, which provide a measure of the cholesterol levels in all apoB-containing lipoproteins. Of note, non-HDL-C levels may provide relevant information on the residual CV risk even in subjects with very low LDL-C [15].

While current guidelines for the management of dyslipidaemias promote LDL-C levels as the primary goal for all CVD risk categories, apoB and non-HDL-C are proposed as secondary goals [16]. However, evidence is accumulating suggesting non-HDL-C levels as a key parameter for the assessment of CV risk. A large risk-evaluation and modelling study using data from 398,846 individuals belonging to 38 cohorts showed that, along with a continuous association of non-HDL-C levels with cardiovascular disease both in men and women, determining non-HDL-C levels can improve the individual long-term risk assessment and profile the potential benefit of early lipid-lowering intervention [17]. Interestingly, this study suggests that elevated levels of non-HDL-C predict long-term CV risk, in particular at a young age (<45 years), both

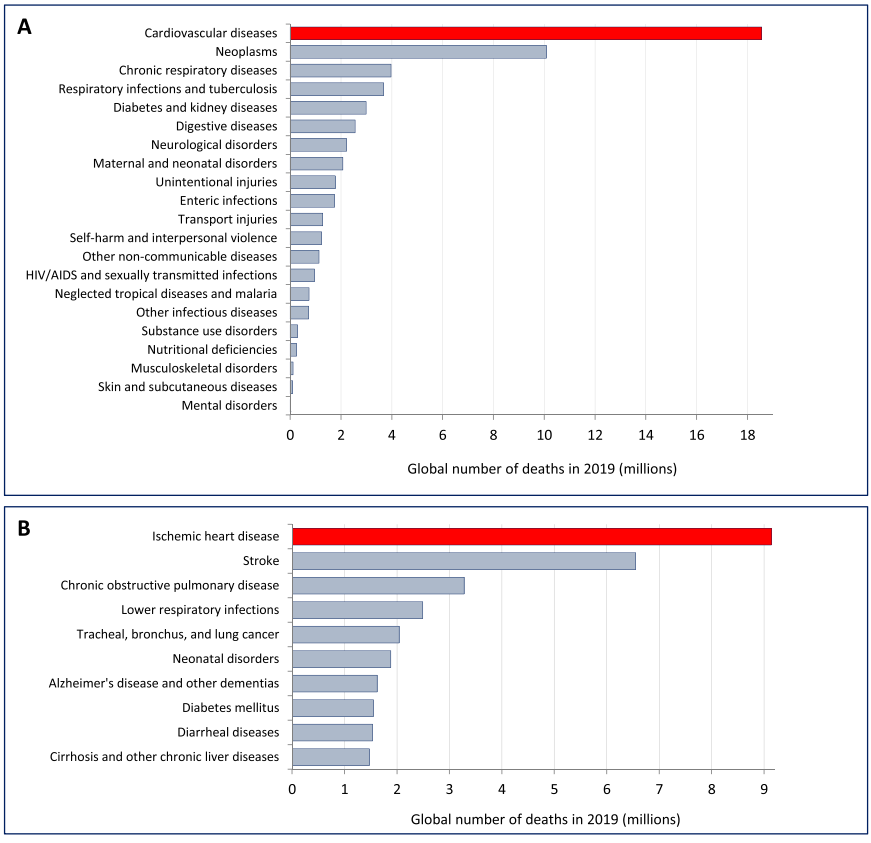

Fig. 1. Global leading causes of death in 2019, in both sexes and all ages. (A) Level 2 causes include 21 disease and injury aggregates, such as cardiovascular diseases; (B) level 3 includes specific causes such as ischemic heart disease and stroke. Bars represent the number of deaths in million.

in men and women, potentially resulting from lifetime exposure to increased levels of pro-atherogenic particles [17].

4. Global changes in plasma cholesterol levels in the last four decades

Globally, total cholesterol and non-HDL-C mean levels remained similar in the last four decades both in men and women (Figs. 2 and 3) [18]. However, significant differences among world areas according to their economic status can be observed (Fig. 2). High-income countries have experienced a reduction in total cholesterol levels both in men and women (Fig. 2, panels A and B), largely driven by the significant reduction in non-HDL-C (~0.7 mmol/L, ~17% reduction compared with 1980 for both men and women) (Fig. 3). Such reductions in non-HDL-C, however, were not observed in other income groups (Fig. 3). The upper middle-income group showed unchanged levels of both total cholesterol and non-HDL-C in both sexes; conversely, lower middle- and low-income groups showed increases in non-HDL-C over 4 decades both in men (+8.2% and 15.3%, respectively) and women (+10.1% and 19.2%, respectively) (Fig. 3). Of note, HDL-C levels were globally unchanged in men, with even small reductions observed in the lower middle- and low-income groups; women showed a global 0.1 mmol/L increase in HDL-C, driven by increases in the high- and upper middle-income groups (Supplementary Figure 1).

Since the last four decades have been characterized by marked changes in the developmental and economic status of many countries as well as in the availability of drugs for the control of hypercholesterolemia, we have analysed trends in lipid parameters stratifying per decade and income. The high-income group had a constant reduction in total cholesterol and non-HDL-C in the last 4 decades (Fig. 4), especially starting from 1990, likely due to an increase in the use of statins. In the other groups, different trends were observed. In the low-income and lower middle-income groups, the levels of non-HDL-C increased in all the decades considered, both in men and women, with a trend that slowed down over the years (Fig. 4). The upper middle-income group, after a small increase in the period 1980–1990, showed a trend reversal, both in men and women (Fig. 4). Trends for HDL-C levels differ between men and women; overall, men showed a reduction in HDL-C levels in all analysed decades, except in the high-income group (Supplementary Figure 2); conversely, women show more favourable trends.

5. Ischemic heart disease attributable to high LDL-C

Globally, CVD accounted for more than 18,5 million deaths in 2019 (32.8% of all deaths), with an age-standardized death rate of 239.9 per 100,000 people, which is essentially unchanged compared with 1990, when a death rate of 225.6 was recorded [1]. This observation underlines the substantial impact of cardiovascular diseases even in an era in which the availability of drugs for the treatment of heart disease has largely increased compared with 1990. In 2019, IHD was the first cause of death globally, accounting for 16.0% of total deaths (compared with 12.2% in 1990) and was responsible for half of the global deaths for CVD [1]. An additional parameter that can provide an estimate of the burden of a disease is the disability-adjusted life year (DALY), which is the sum of years lost due to premature death and years lived with disability. A total of 172 million DALYs due to IHD were estimated globally in 2019, with a DALY rate of 2.116 (compared with 2.972 in 1990) [1]. Of note, globally IHD was the second leading cause of DALY in 2019 after neonatal disorders, whereas it ranked four in 1990 [19].

Metabolic risk factors accounted for 88% of deaths by IHD (7.526.949 out of 8.542.367) [1]. Among them, exposure to elevated levels of LDL-C plays a relevant causal role: ~44% of the global deaths by IHD can be attributed to high LDL-C, independently of the income group (Fig. 5). It is worth noting that 77% of deaths for IHD attributable to high LDL-C are registered in the upper middle- and lower middle-income groups (Fig. 5A). Indeed, the lowest death rate for IHD attributable to high LDL-C in 2019 was recorded in the high-income group (Fig. 5B). Similar findings were observed in DALY numbers and rates (Supplementary Figure 3).

The availability of lipid-lowering drugs in the last decades has substantially improved the possibility of effectively managing dyslipidaemias and further reducing the cardiovascular risk; the armamentarium of therapies is currently further enriching with promising additional effective drugs [20]. This observation contributes to explaining the

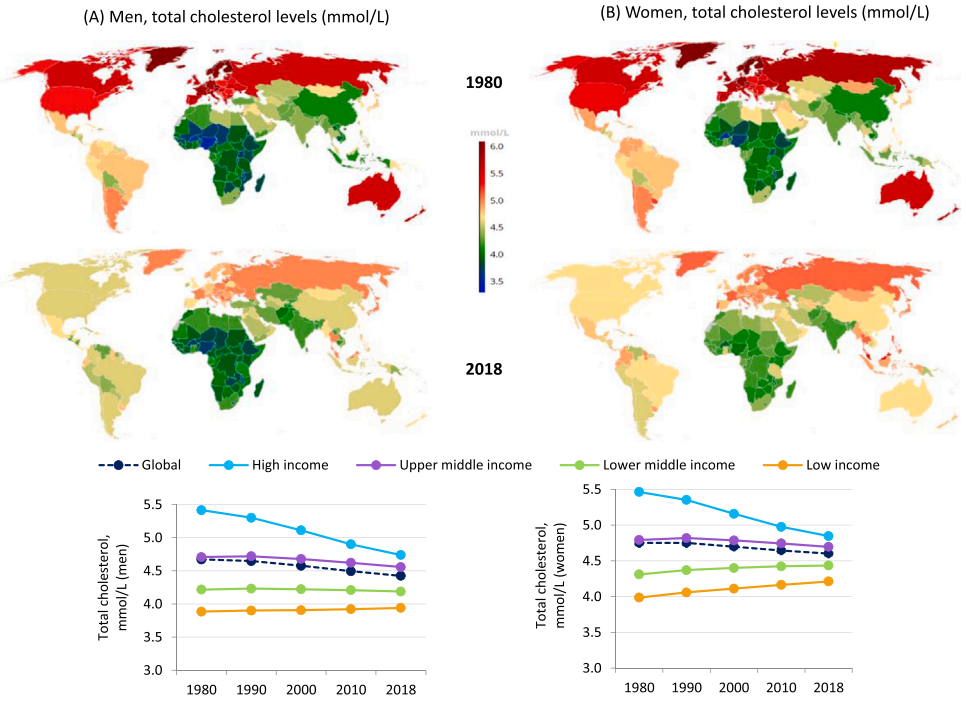

Fig. 2. Levels of total cholesterol in men and women. Total cholesterol levels from 1980 to 2018 were obtained from https://ncdrisc.org/. Maps represent age-standardized estimates of total cholesterol levels in 1980 and 2018 in men (A) and women (B) aged 18 years and older.

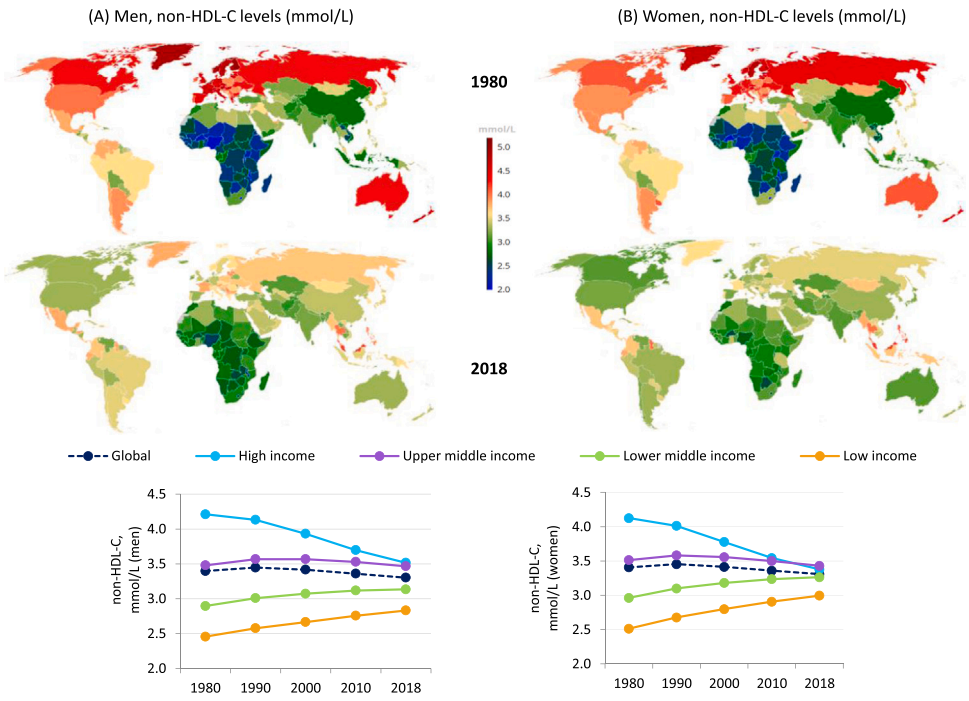

Fig. 3. Levels of non-HDL-C in men and women. Non-HDL-C levels from 1980 to 2018 were obtained from https://ncdrisc.org/. Maps represent age-standardized estimates of non-HDL-C levels in 1980 and 2018 in men (A) and women (B) aged 18 years and older. Non-HDL-C: non-high-density lipoprotein cholesterol.

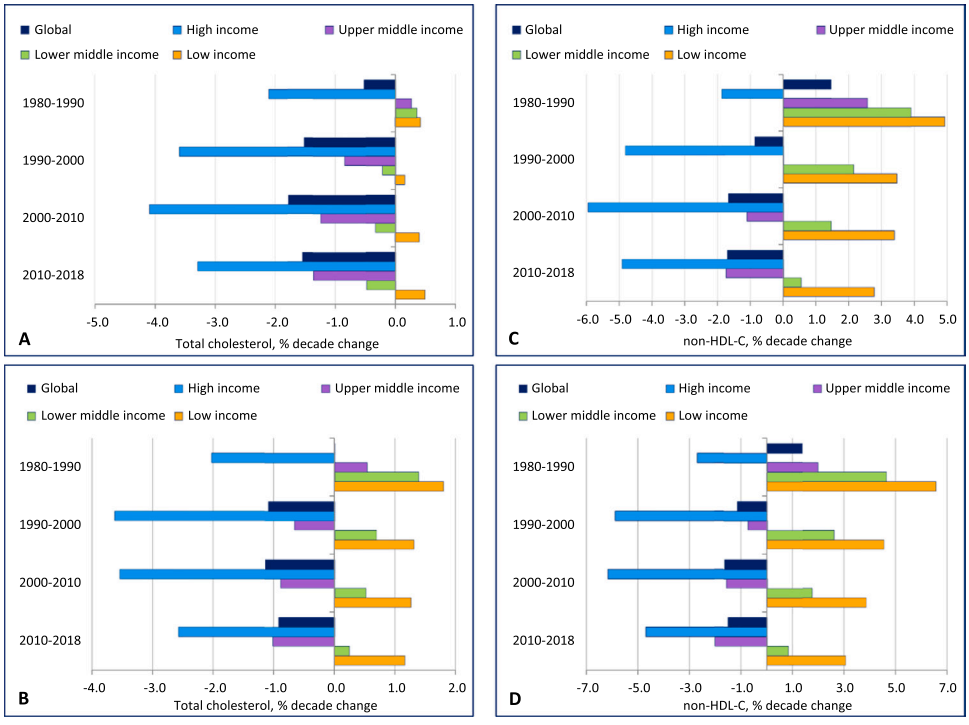

Fig. 4. Percent changes in total cholesterol and non-HDL-C by decade. Percent changes in total cholesterol and non-HDL-C were calculated based on the levels in the selected decades in men (A, C) and women (B, D).

global reduction in death rates for IHD attributable to high LDL-C (−36.3% compared with 1990) (Fig. 6A). However, a deeper analysis of death rate curves over time according to the income groups provides a different picture. Overall, in 2019 the lowest mortality for IHD attributable to high LDL-C was observed in the high-income group and the highest in the lower middle-income group (Fig. 6A). This observation may be indicative of significantly different access to lipid-lowering therapies, as well as substantial disparities in health expenditure among different income groups [21].

Accordingly, in 2019 the high-income group showed a substantial reduction in age-standardized death rate for IHD attributable to high LDL-C compared with 1990 (64%) (Fig. 6A); a more modest reduction was observed in the upper middle-income group (25.9%), minimal in the lower middle (12.7%), or even absent in the low-income group

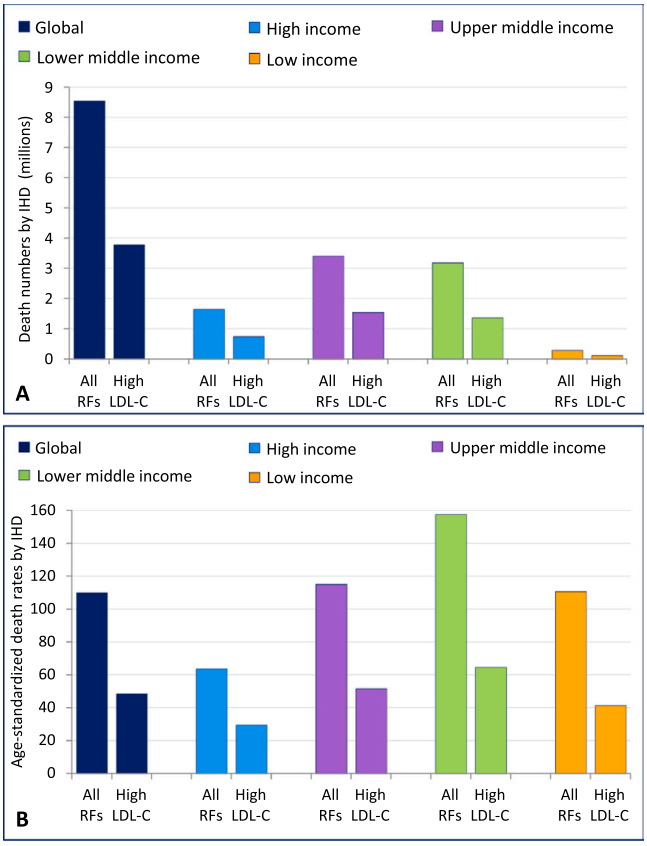

Fig. 5. Ischemic heart disease attributable to high LDL-C. Death numbers (A) and age-standardized death rates per 100,000 people (B) by ischemic heart disease attributable to all risk factors or high LDL-C in 2019 in both sexes, by income.
IHD: ischemic heart disease; RFs: risk factors; LDL-C: low-density lipoprotein cholesterol.

(Fig. 6A). Globally, the reduction in age-standardized death rate for IHD attributable to high LDL-C was similar in men and women (35.1% and 38.1%, respectively) (Fig. 6, panels B and C). When analysed by income levels, relevant differences were observed. In the high-income group, both men and women showed similar percent reductions (64.4% and 65.1%, respectively) compared with 1990; in 2019, women from this group had the lowest age-standardized death rate (Fig. 4). The upper middle-income group showed modest reductions in both sexes, with 22.3% and 29.4% reductions in men and women, respectively; in the lower middle-income group, women showed an 18.8% reduction compared with a modest 5.9% reduction in men; no changes were observed in the low-income group (Fig. 6B and C). Of note, in 2019 the lower middle-income group showed the highest age-standardized death rate for IHD attributable to high LDL-C in both men and women; women in this income group show the highest age-standardized death rate over the whole period of observation (Fig. 6, panels B and C). Of note, men show higher death rates than women in all income groups. Similar results were obtained with age-standardized DALY rates (Supplementary Figure 4).

When analysed according to decades, we observed substantial important and comparable reductions in the high-income group in the first two decades (Fig. 6D); in the third decade the reduction, although present, was considerably reduced; these trends were comparable in men and women (Fig. 6, panels E and F). For the other income groups, men experienced a reduction in the last decade (2010–2019), whereas women from the upper middle- and lower middle-income groups showed reductions also in the previous decades (Fig. 6, panels E and F).

6. The burden of exposure to high LDL-C

Then, we estimated whether the exposure to high LDL-C has changed throughout the decades by evaluating the summary exposure value (SEV) for high LDL-C. The global burden of exposure to high LDL-C appears to be unchanged in the last three decades; only the high-income group showed a reduction in SEV to high LDL-C, which is in line with the reduction in the death rate for IHD attributable to this risk factor (Fig. 7A). The reduction in SEV was similar in men and women from the high-income group (−26% and −23%, respectively) (Fig. 7, panels B and C). Of note, the high-income group had the highest SEV for high LDL-C in 1990 and, despite the reduction, it remains the highest compared with all other income groups (Fig. 7A). It is worth noting that important differences among high-income country subgroups can be observed, with high-income North America showing a substantial SEV reduction (−51%), in contrast with a more modest reduction in Western Europe (−16%) and even an increase in the high-income Asia-Pacific region (Fig. 7D). High-income countries have experienced the largest reduction in SEV for high LDL-C in the decade 1990–2000 (−15.6%), while in the last decade, the SEV for high LDL-C is almost unchanged (−2.1%) both in men and women (Fig. 7E).

The other income groups showed overall modest increases in SEV for high LDL-C (3–9%) ((Fig. 7, panels A-C). Altogether these data suggest that hypercholesterolemia still represents a relevant cardiovascular risk factor both in higher-income countries and in lower economies.

7. Relevance of high-LDL for IHD in an ageing world

The major non-modifiable risk factor for cardiovascular diseases is age: both age-related physiological changes and the burden of lifelong exposure to multiple cardiovascular risk factors increase the susceptibility to cardiovascular events. The world population is rapidly ageing, and, for the first time in history, most people can expect to live into their sixties and beyond (Fig. 8 A). Many high-income countries already have a large proportion of the older-age population, with people aged 60 years and above representing 24% of the whole population (compared with 16.9% in 1990) (Fig. 8B), while many low- and middle-income countries are still relatively young. The latest projections by the United Nations suggest that the population aged 60 and above could grow to around 2.1 billion in 2050 and 3.1 billion in 2100 (Fig. 8 A); in all income groups, an increase in the proportion of people aged 60 and above is expected, although with different trends (Fig. 8B) [22].

It is worth noting that, regardless of the world area where they live, the first cause of death in older people is CVD; more in detail, IHD is the first cause of CVD death in all income groups except low-income countries, where it is the second cause of death after stroke [19]. In all groups, high LDL-C represents the second major risk factor for IHD, after high blood pressure [19].

Deaths for IHD attributable to high LDL-C occur mostly in people aged 60–89 years (62.6%), with a death rate that is about 3 times higher than that of the previous age group (Fig. 8C). The global death number for IHD attributable to high LDL-C is increased over the last 3 decades among people aged 60–89 years, with different trends among income levels (Fig. 8A). The high-income group, which experienced a 7.3% increase in the number of people aged 60 + in the last 3 decades, showed a decrease in the number of deaths by IHD attributable to high LDL-C, with a substantial reduction in the death rate (−64,8%) (Fig. 8A and B). In contrast, the death rates were unchanged in the upper middle and lower middle groups, in which significant and persistent increases in the number of deaths for IHD attributable to high LDL-C were recorded (Fig. 8, panels A and B). Of note, the upper middle-income group experienced a 7.5% increase in the population aged 60 + years, with the highest absolute increase (165.943.845 in 1990 and 400.259.656 in 2019) [22]. No substantial changes were observed in the low-income group, that, however, in 2019 had a death rate for IHD attributable to high LDL-C higher than that observed in the high-income group for this

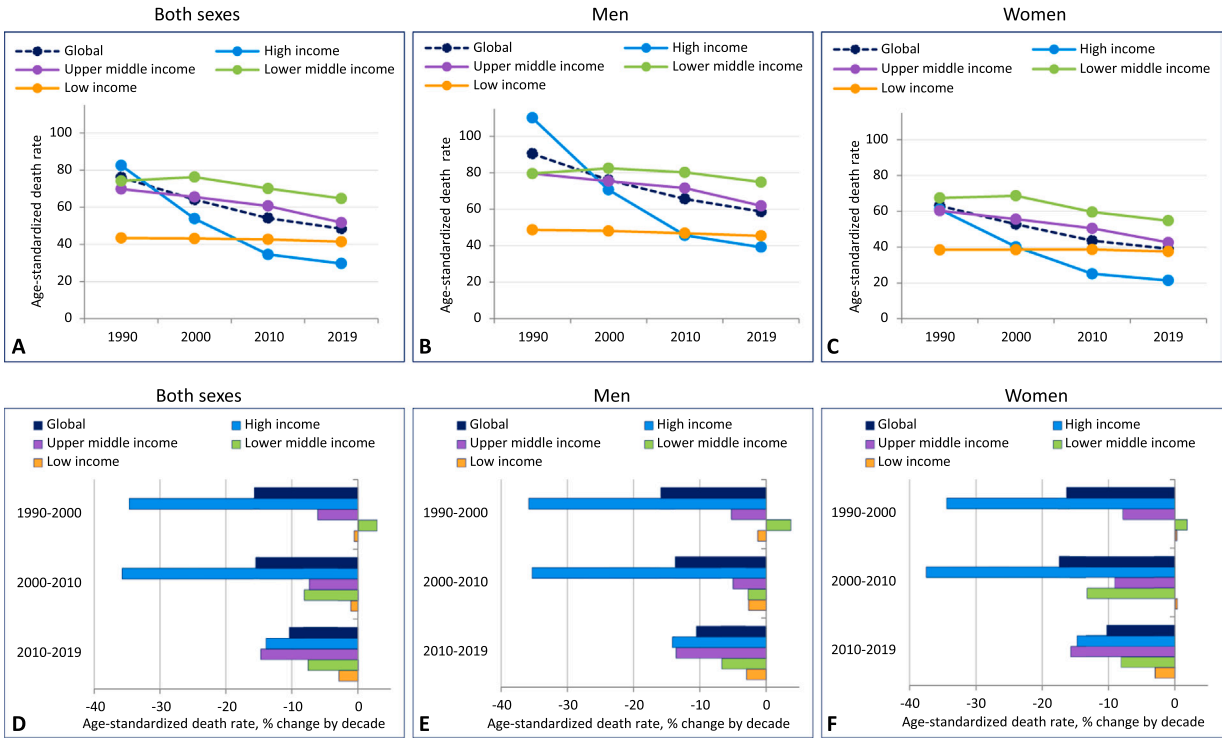

Fig. 6. Age-standardized death rates by ischemic heart attributable to high LDL-C. (A-C), death rates by IHD attributable to high LDL-C from 1990 to 2019 in both sexes (A), men (B), and women (C) by income. (D-F), percent change in age-standardized death rates by IHD attributable to high LDL-C by decade, by income in both sexes (D), men (E), and women (F).
IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol.

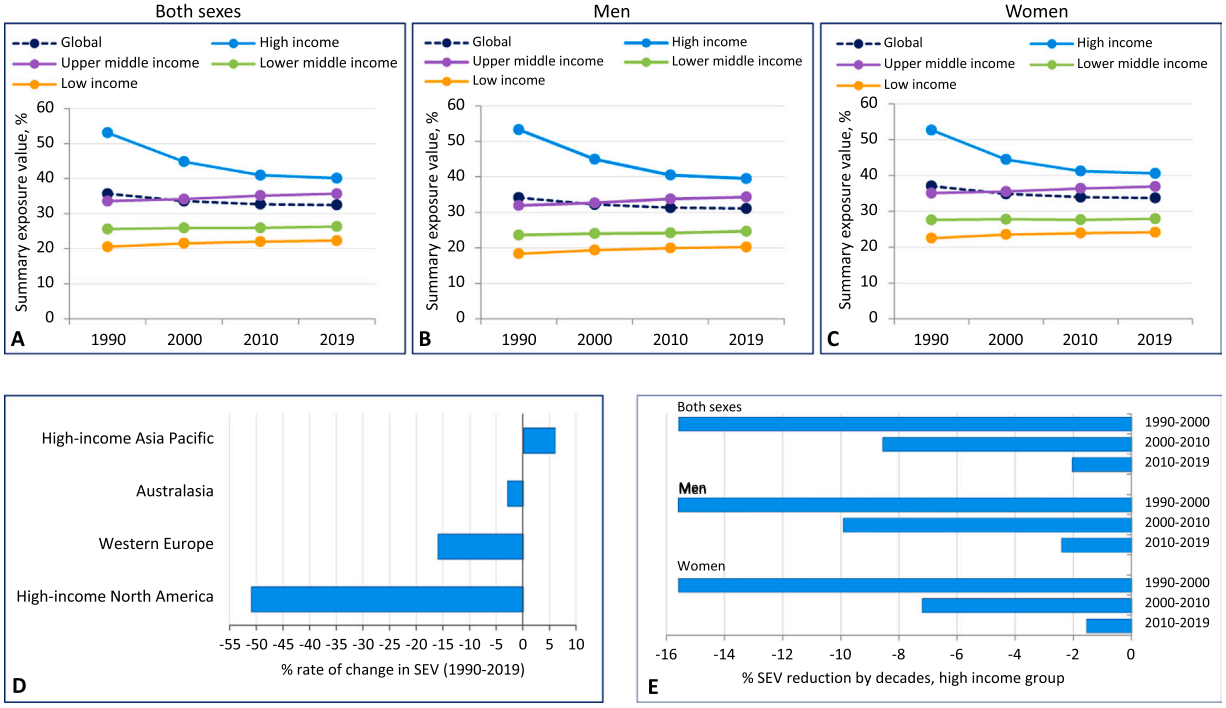

Fig. 7. Summary exposure value to high LDL-C. (A-C), summary exposure value (SEV) from 1990 to 2019 in both sexes (A), men (B), and women (C). A decline in SEV indicates reduced exposure to the specified risk factor, whereas an increase in SEV indicates increased exposure. (D), % rate of change in SEV to high LDL-C in high-income country subgroups from 1990 to 2019 in both sexes. (E), % rate of change in SEV to high LDL-C by decades in the high-income group in both sexes, men, and women. SEV: summary exposure value.

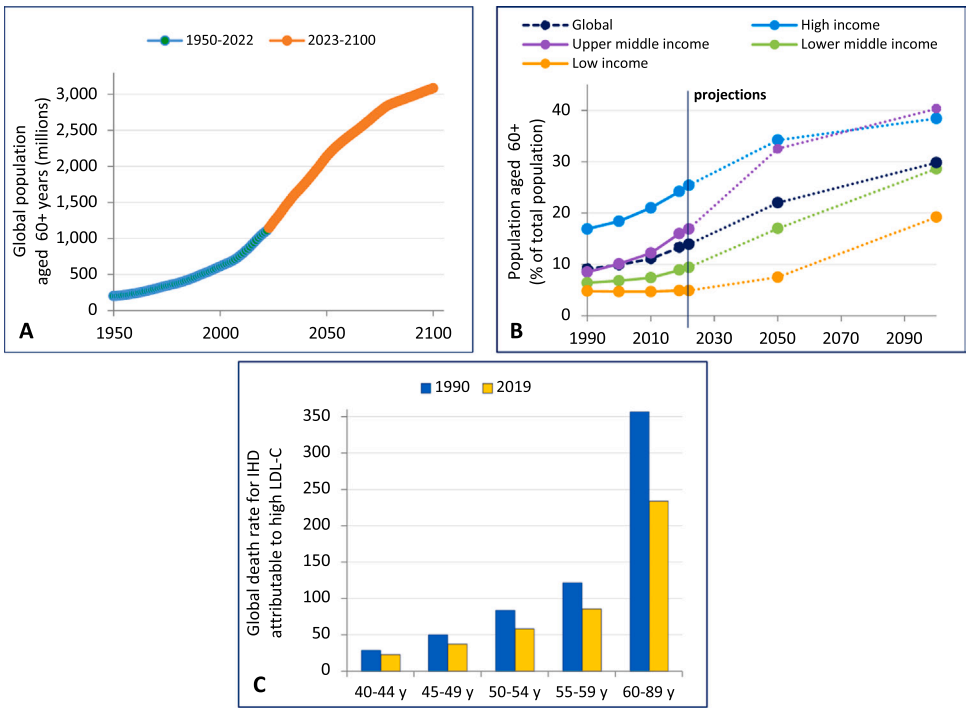

Fig. 8. (A) Population aged 60 years and above; global population estimates, 1950–2022, and projections, 2023–2100. Data were obtained from the United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition [22]. (B) Percentage of population aged 60 years and above by income groups, estimates 1990–2022 and projections 2023–2100. (C) Global death rate by IHD attributable to high LDL-C in 2019, by age range.

age range. Similar trends are obtained when considering DALY numbers and rates (Fig. 8, panels C and D); of note, the absolute numbers are very high, which raises a relevant issue concerning the aspect of disability in older people.

Globally, women outnumber men at older ages [23]. Thus, we analysed the death rates for IHD attributable to high LDL-C in men and

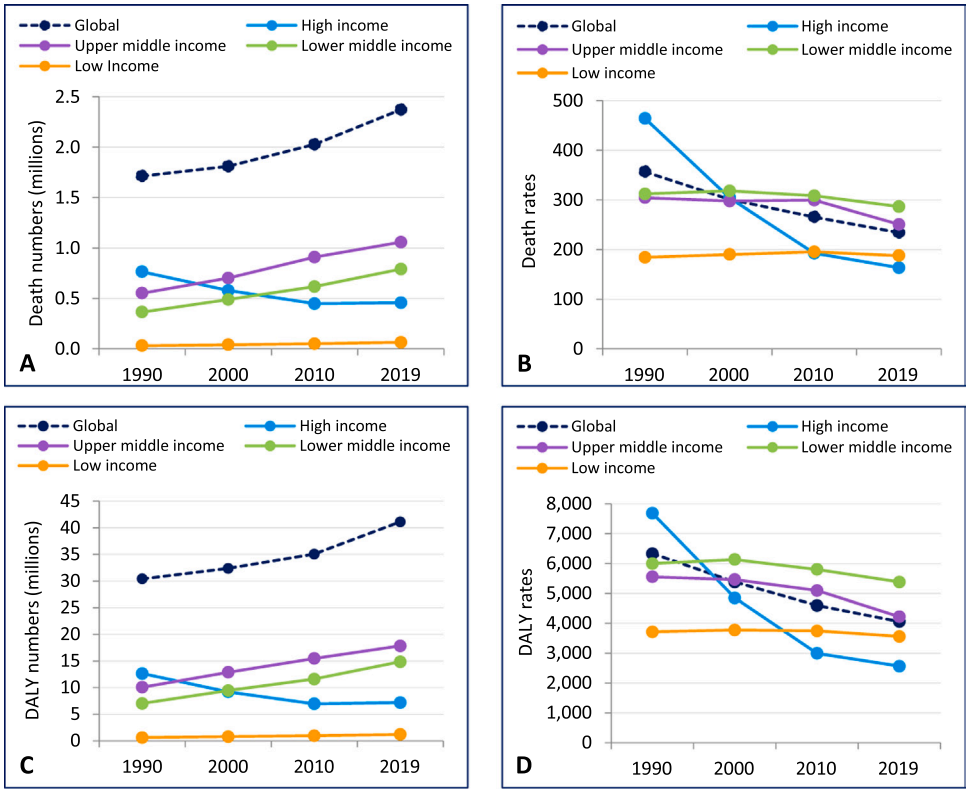

Fig. 9. Death numbers (A) and death rates per 100,000 people (B) by IHD attributable to high LDL-C in people aged 60–89 years from 1990 to 2019, by income. DALY numbers (C) and DALY rates per 100,000 people (D) by IHD attributable to high LDL-C in people aged 60–89 years from 1990 to 2019, by income. IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; DALY: disability-adjusted life year.

women aged 60–89 in 1990 and 2019 (Supplementary Figure 5A). Overall, trends are similar to those reported in the age-standardized analysis, with the number being higher, as expected, both in men and women. In the high-income group, the reduction in age-standardized death rate was similar in men and women (~65%), while other income groups showed more modest or even no reduction. Interestingly, in 2019 women aged 60–89 years from the low-income group showed a death rate higher than those from the high-income group. Similar results were obtained for DALY rates (Supplementary Figure 5B)..

8. Discussion

The most updated available data establish that IHD attributable to high LDL-C remains a relevant global cause of death and disability despite improvements in the pharmacological options to treat dyslipidaemias. The main reason for this is the global increase in life expectancy, which expands the number of subjects aged 60 + years exposed to high LDL-C.

Significant differences exist, however, among different world regions according to their income status. In the high-income group, the use of cholesterol-lowering drugs over the past 30 years has significantly reduced the incidence of CV events attributable to elevated plasma cholesterol levels, as also proved by the reduced plasma levels of non-HDL-C. These reductions were not observed in other income groups, which could depend on several factors. First, health expenditure as a percentage of gross domestic product (GDP) is substantially different among different income groups, with the high-income group spending 12.49% of its GDP in 2019 on medical health, a percentage that is 2–3 times higher than that spent by the other income groups [24]. Of note, government priority to health increased in richer countries, and declined in poorer; a significant group of lower-income countries face severe health financing limits, which slow their progress towards health security and universal health coverage [25]. The pattern of health spending by disease varies considerably among different income groups, with middle-income countries spending a greater share on non-communicable diseases than low-income countries (29% and 13%, respectively) [25]. Regarding lipid-lowering strategies, a recent study reported substantial disparities in the use of statins between high and low/middle-income countries [26]. Despite a global increase in statin use (+24.7% in 2020 compared with 2015), in 2020 statin utilization was seven times higher in high-income countries than in low/middle-income countries [26]. In low/middle-income countries (which account for 68% of the global population of middle-aged and older adults and 55% of CVD deaths worldwide), statin use is still very low [26]. The availability of low-cost generic statins in low/middle-income countries likely would increase access and adherence to therapy. It is worth noting that during the COVID-19 pandemic, a global reduction in the use of statins has been observed, and some low/middle-income countries have experienced the most dramatic declines [26].

Another relevant issue when considering populations from low/middle-income areas is the lower awareness of the burden of hypercholesterolemia and its clinical consequences. An analysis using a pooled dataset of nationally representative, population-based surveys including 129,040 individuals from 35 low/middle-income countries showed that, among individuals with hypercholesterolemia, less than 1 out of every 3 had been treated and less than 1 in 5 had achieved controlled lipid values [27]. This analysis also showed a high heterogeneity across countries, with the Americas, the Eastern Mediterranean, and European regions showing a higher level of access to hypercholesterolemia care than Africa, Southeast Asia, and the Western Pacific regions [27]. Since the increasing burden of hypercholesterolemia and related CVD raises a considerable threat to public health, increasing the ability of community health workers to address CVD prevention through screening programmes conducted locally (consisting of screening, referral to community health clinics, and follow-up) would provide a tool for the early identification, treatment, and prevention of CVD also in lower-income countries. Projects to apply this protocol are planned in poor sub-Saharan African rural and urban communities to mitigate the rising burden of non-communicable diseases, including CVD [28].

8.1. Is IHD risk attributable to high LDL-C equal in men and women?

In 2019 CVD deaths in women represented 48% of all CVD deaths, with IHD being the most important cause of CVD mortality in women worldwide. Despite that, data on the prevalence of risk factors and their association with CVD in women are much less than in men, especially in low- and middle-income countries. The diagnosis of CVD is often delayed, and treatment is less optimal for women compared with men; overall, women experience disparities in the distribution of wealth, income, and access to resources, which results in reduced health and quality of life, which contributes to a lower health status compared with men [29]. The major consequence is the lesser prevention and treatment of CVD in women in all age groups.

Young women exhibit a significantly lower rate of coronary events compared with age-matched men; however, menopause and loss of oestrogen are associated with relevant unfavourable changes in lipid profile and vascular function, resulting in an increased risk of experiencing myocardial infarction and stroke [30]. However, although globally women exhibit lower rates of death and disability compared with men, in the age range 60–89 years the number and rates of deaths and DALY are significantly high also in women.

An analysis of data from the PURE (Prospective Urban Rural Epidemiological) study, which enrolled participants from the general population from 21 high-income, middle-income, and low-income countries and followed them up for approximately 10 years, showed that, despite having a more favourable CV risk profile than men (especially at younger ages), women and men have similar CVD risk factors and the magnitude of association with CVD for most risk factors is similar, which emphasises the importance of similar approaches for the prevention of CVD in both sexes [31]. In agreement with this observation, a meta-analysis of data from 22 statin trials showed that the reductions in major CV events per 1 mmol/L LDL-C reduction were similar in men and women [32]. Considering the substantial burden of CVD cardiovascular disease in both developed and developing countries, the widespread availability of generic statins may represent an effective tool to prevent CVD among women as well as men.

8.2. Does the increase in the elderly population translate into an increased burden of high lifetime LDL-C levels and CVD?

Age is a major, non-modifiable risk factor for CVD, which takes into account the influence of lifetime exposure to a CV risk factor, such as elevated levels of LDL-C. Population ageing is a global phenomenon affecting all regions in the world. In 2019, one in 11 people in the world was aged 65 and over (9%, 703 million people); by 2050, the number of older people is projected to be one in six people (16%, 1.5 billion) [23], with two-thirds of the population aged 60 years and over be going to reside in lower and middle-income countries. Some regions have experienced the fastest population ageing so far, including Eastern and South-Eastern Asia and Latin America and the Caribbean, followed by Europe and North America [23]; projections indicate that, by 2050, one in every four persons in Europe and Northern America could be aged 65 years or over [23]. Population ageing is expected to have a great impact in large countries such as India and China (currently accounting for one-third of the world population), in which the number of individuals aged 60 and above was almost triplicated from 1990 (India: 55.699.472 in 1990 and 137.530.811 in 2019; China: 93.668.505 in 1990 and 249.933.523 in 2019) [22]; the already-aged countries of Western Europe will likely increase their older population at a significantly lower extent [22]. These observations suggest that an increase over time in age-related pathological conditions such as IHD and stroke will

contribute to raising the burden of CVD worldwide.

We must acknowledge some limitations of this work. First, the GBD presents modelled estimates. Thus, when data are not available, the results depend on the validity of the out-of-sample modelling. Even if data are available, they may not have been obtained using the preferred case definition or measurement method. In addition, the large number of different data sources with many potential sources of bias, combined with missing data for location or years, can affect the analyses. Overall, more data sources are available from high-income countries, while important information on disease burden is missing or unavailable in many countries, especially in low- and middle-income countries, which may affect the quality and representativeness of the data. In addition, total cholesterol and HDL-C may have been measured using different methods, and not all studies may have participated in a lipid standardisation or quality control programme.

It should be noted that "high LDL-C" is defined in GBD as the LDL-C concentration that exceeds the theoretical minimum risk exposure value, which is 1.3 mmol/L (50 mg/dL). However, this threshold, which may be difficult to translate to the general population, is derived from the observation that individuals with LDL-C levels < 50 mg/dL ($<$1.3 mmol/L) have a much lower risk of major cardiovascular and coronary events than individuals with LDL-C levels between 50 and 70 mg/dL [33], suggesting that this may be a threshold below which the risk attributable to LDL-C remains minimal. It is also worth noting that the contribution of other atherogenic lipoproteins besides LDL is not taken into account, which may influence the results in some areas where the prevalence of obesity and diabetes has increased substantially in recent decades [34,35].

9. Conclusion

Despite research has made possible the development of a large number of drugs that can efficiently control dyslipidaemias [6,36], IHD attributable to high levels of plasma cholesterol continues to cause mortality and morbidity worldwide. However, while high-income countries went through significant improvements, low- and middle-income countries have experienced changes in their lifestyle which contributed to the increased prevalence of some metabolic risk factors playing causal roles in IHD. Overall, the need for non-optimal cholesterol level control become a relevant issue for East and Southeast Asia and Pacific island nations [37,38]. Low/middle-income countries are now facing an increasing burden of CVD with an excessive lack of awareness and applicable recommendations in resource-limited settings. Thus, on the one hand, high-income countries must continue to control the burden of hypercholesterolemia, on the other hand, lower-income countries need dedicated measures to reduce the gaps in targeting hypercholesterolemia as well as in the identification and treatment of subjects at increased risk. Worldwide, special attention should be paid to women and older people, two often neglected categories in the prevention of CVDs.

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CRediT authorship contribution statement

Both authors have participated in Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106814.

References

[1] Global Burden of Disease Collaborative Network, Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: institute for Health Metrics and Evaluation (IHME), 2020 (Available from), ⟨https://vizhub.healthdata.org/gbd-results/⟩.
[2] D.P. Leong, P.G. Joseph, M. McKee, S.S. Anand, K.K. Teo, J.D. Schwalm, S. Yusuf, Reducing the global burden of cardiovascular disease, part 2: prevention and treatment of cardiovascular disease, Circ. Res 121 (6) (2017) 695–710.
[3] B.A. Ference, H.N. Ginsberg, I. Graham, K.K. Ray, C.J. Packard, E. Bruckert, R. A. Hegele, R.M. Krauss, F.J. Raal, H. Schunkert, G.F. Watts, J. Boren, S. Fazio, J. D. Horton, L. Masana, S.J. Nicholls, B.G. Nordestgaard, B. van de Sluis, M. R. Taskinen, L. Tokgozoglu, U. Landmesser, U. Laufs, O. Wiklund, J.K. Stock, M. J. Chapman, A.L. Catapano, Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel, Eur. Heart J. 38 (32) (2017) 2459–2472.
[4] GBD 2019 Risk Factors Collaborators, Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet 396 (10258) (2020) 1223–1249.
[5] J. Boren, M.J. Chapman, R.M. Krauss, C.J. Packard, J.F. Bentzon, C.J. Binder, M. J. Daemen, L.L. Demer, R.A. Hegele, S.J. Nicholls, B.G. Nordestgaard, G.F. Watts, E. Bruckert, S. Fazio, B.A. Ference, I. Graham, J.D. Horton, U. Landmesser, U. Laufs, L. Masana, G. Pasterkamp, F.J. Raal, K.K. Ray, H. Schunkert, M. R. Taskinen, B. van de Sluis, O. Wiklund, L. Tokgozoglu, A.L. Catapano, H. N. Ginsberg, Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel, Eur. Heart J. 41 (24) (2020) 2313–2330.
[6] A. Pirillo, A.L. Catapano, G.D. Norata, Recent insights into low-density lipoprotein metabolism and therapy, Curr. Opin. Clin. Nutr. Metab. Care 24 (2) (2021) 120–126.
[7] J. Boren, K.J. Williams, The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity, Curr. Opin. Lipido 27 (5) (2016) 473–483.
[8] A.B. Jorgensen, R. Frikke-Schmidt, A.S. West, P. Grande, B.G. Nordestgaard, A. Tybjaerg-Hansen, Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction, Eur. Heart J. 34 (24) (2013) 1826–1833.
[9] M. Kaltoft, A. Langsted, B.G. Nordestgaard, Triglycerides and remnant cholesterol associated with risk of aortic valve stenosis: Mendelian randomization in the Copenhagen General Population Study, Eur. Heart J. 41 (24) (2020) 2288–2299.
[10] K. Zhang, X. Qi, F. Zhu, Q. Dong, Z. Gou, F. Wang, L. Xiao, M. Li, L. Chen, Y. Wang, H. Zhang, Y. Sheng, X. Kong, Remnant cholesterol is associated with cardiovascular mortality, Front Cardiovasc Med 9 (2022), 984711.
[11] C. Emerging Risk Factors, S. Erqou, S. Kaptoge, P.L. Perry, E. Di Angelantonio, A. Thompson, I.R. White, S.M. Marcovina, R. Collins, S.G. Thompson, J. Danesh, Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality, JAMA (2009) 412–423.
[12] P.R. Kamstrup, A. Tybjaerg-Hansen, R. Steffensen, B.G. Nordestgaard, Genetically elevated lipoprotein(a) and increased risk of myocardial infarction, JAMA 301 (22) (2009) 2331–2339.
[13] R. Clarke, J.F. Peden, J.C. Hopewell, T. Kyriakou, A. Goel, S.C. Heath, S. Parish, S. Barlera, M.G. Franzosi, S. Rust, D. Bennett, A. Silveira, A. Malarstig, F.R. Green, M. Lathrop, B. Gigante, K. Leander, U. de Faire, U. Seedorf, A. Hamsten, R. Collins, H. Watkins, M. Farrall, Genetic variants associated with Lp(a) lipoprotein level and coronary disease, New Engl. J. Med 361 (26) (2009) 2518–2528.
[14] B.G. Nordestgaard, A. Langsted, Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology, J. Lipid Res 57 (11) (2016) 1953–1975.
[15] C.D.L. Johannesen, M.B. Mortensen, A. Langsted, B.G. Nordestgaard, Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients, J. Am. Coll. Cardiol. 77 (11) (2021) 1439–1450.
[16] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, M. J. Chapman, G.G. De Backer, V. Delgado, B.A. Ference, I.M. Graham, A. Halliday, U. Landmesser, B. Mihaylova, T.R. Pedersen, G. Riccardi, D.J. Richter, M. S. Sabatine, M.R. Taskinen, L. Tokgozoglu, O. Wiklund, ESC Scientific Document Group, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur. Heart J. 41 (1) (2020) 111–188.

[17] F.J. Brunner, C. Waldeyer, F. Ojeda, V. Salomaa, F. Kee, S. Sans, B. Thorand, S. Giampaoli, P. Brambilla, H. Tunstall-Pedoe, M. Moitry, L. Iacoviello, G. Veronesi, G. Grassi, E.B. Mathiesen, S. Soderberg, A. Linneberg, H. Brenner, P. Amouyel, J. Ferrieres, A. Tamosiunas, Y.P. Nikitin, W. Drygas, O. Melander, K.H. Jockel, D. M. Leistner, J.E. Shaw, D.B. Panagiotakos, L.A. Simons, M. Kavousi, R.S. Vasan, R. P.F. Dullaart, S.G. Wannamethee, U. Riserus, S. Shea, J.A. de Lemos, T. Omland, K. Kuulasmaa, U. Landmesser, S. Blankenberg, C. Multinational, Cardiovascular Risk, Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium, Lancet 394 (10215) (2019) 2173–2183.
[18] http://www.ncdrisc.org/index.html.
[19] https://vizhub.healthdata.org/gbd-compare/.
[20] D. Preiss, J.A. Tobert, G.K. Hovingh, C. Reith, Lipid-modifying agents, from statins to PCSK9 inhibitors: JACC focus seminar, J. Am. Coll. Cardiol. 75 (16) (2020) 1945–1955.
[21] M. Lotfaliany, S. Akbarpour, N. Zafari, M.A. Mansournia, S. Asgari, F. Azizi, F. Hadaegh, D. Khalili, Health expenditure or cardiometabolic risk factors? A further explanation of the wide gap in cardiometabolic mortality between worldwide countries: an ecological study (World Bank Income Group), Int J. Endocrinol. Metab. 16 (3) (2018), e59946.
[22] United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition.
[23] United Nations Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022: Summary of Results. UN DESA/POP/2022/TR/NO. 3.
[24] https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?locations=XD-XT-XN-XM.
[25] World Health Organization (WHO). Global spending on health: Weathering the storm; 2020.
[26] J.S. Guadamuz, A. Shooshtari, D.M. Qato, Global, regional and national trends in statin utilisation in high-income and low/middle-income countries, 2015-2020, BMJ Open 12 (9) (2022), e061350.
[27] M.E. Marcus, C. Ebert, P. Geldsetzer, M. Theilmann, B.W. Bicaba, G. Andall-Brereton, P. Bovet, F. Farzadfar, M. Singh Gurung, C. Houehanou, M.R. Malekpour, J.S. Martins, S.S. Moghaddam, E. Mohammadi, B. Norov, S. Quesnel-Crooks, R. Wong-McClure, J.I. Davies, M.A. Hlatky, R. Atun, T.W. Barnighausen, L. M. Jaacks, J. Manne-Goehler, S. Vollmer, Unmet need for hypercholesterolemia care in 35 low- and middle-income countries: a cross-sectional study of nationally representative surveys, PLoS Med. 18 (10) (2021), e1003841.
[28] K. Okop, P. Delobelle, E.V. Lambert, H. Getachew, R. Howe, K. Kedir, J.B. Niyibizi, C. Bavuma, S. Kasenda, A.C. Crampin, A.C. King, T. Puoane, N.S. Levitt, Implementing and evaluating community health worker-led cardiovascular disease risk screening intervention in sub-saharan Africa communities: a participatory implementation research protocol, Int. J. Environ. Res. Public Health 20 (1) (2022).
[29] S. Stringhini, C. Carmeli, M. Jokela, M. Avendano, P. Muennig, F. Guida, F. Ricceri, A. d'Errico, H. Barros, M. Bochud, M. Chadeau-Hyam, F. Clavel-Chapelon, G. Costa, C. Delpierre, S. Fraga, M. Goldberg, G.G. Giles, V. Krogh, M. Kelly-Irving, R. Layte, A.M. Lasserre, M.G. Marmot, M. Preisig, M.J. Shipley, P. Vollenweider, M. Zins, I. Kawachi, A. Steptoe, J.P. Mackenbach, P. Vineis, M. Kivimaki, L. consortium, Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women, Lancet 389 (10075) (2017) 1229–1237.
[30] P. Anagnostis, I. Lambrinoudaki, J.C. Stevenson, D.G. Goulis, Menopause-associated risk of cardiovascular disease, Endocr. Connect 11 (4) (2022).
[31] M. Walli-Attaei, A. Rosengren, S. Rangarajan, Y. Breet, S. Abdul-Razak, W. A. Sharief, K.F. Alhabib, A. Avezum, J. Chifamba, R. Diaz, R. Gupta, B. Hu, R. Iqbal, R. Ismail, R. Kelishadi, R. Khatib, X. Lang, S. Li, P. Lopez-Jaramillo, V. Mohan, A. Oguz, L.M. Palileo-Villanueva, K. Poltyn-Zaradna, S.P. R, L.V.M. Pinnaka, P. Seron, K. Teo, S.T. Verghese, A. Wielgosz, K. Yeates, R. Yusuf, S.S. Anand, S. Yusuf, P. investigators, Metabolic, behavioural, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study, Lancet 400 (10355) (2022) 811–821.
[32] C. Cholesterol Treatment Trialists, J. Fulcher, R. O'Connell, M. Voysey, J. Emberson, L. Blackwell, B. Mihaylova, J. Simes, R. Collins, A. Kirby, H. Colhoun, E. Braunwald, J. La Rosa, T.R. Pedersen, A. Tonkin, B. Davis, P. Sleight, M. G. Franzosi, C. Baigent, A. Keech, Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials, Lancet 385 (9976) (2015) 1397–1405.
[33] S.M. Boekholdt, G.K. Hovingh, S. Mora, B.J. Arsenault, P. Amarenco, T. R. Pedersen, J.C. LaRosa, D.D. Waters, D.A. DeMicco, R.J. Simes, A.C. Keech, D. Colquhoun, G.A. Hitman, D.J. Betteridge, M.B. Clearfield, J.R. Downs, H. M. Colhoun, A.M. Gotto Jr., P.M. Ridker, S.M. Grundy, J.J. Kastelein, Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials, J. Am. Coll. Cardiol. 64 (5) (2014) 485–494.
[34] I.D.F. Diabetes Atlas 2021, 10th edition https://diabetesatlas.org/atlas/tenth-edition/.
[35] M. Bluher, Obesity: global epidemiology and pathogenesis, Nat. Rev. Endocrinol. 15 (5) (2019) 288–298.
[36] A. Pirillo, G.D. Norata, A.L. Catapano, LDL-cholesterol-lowering therapy, Handb. Exp. Pharm. 270 (2022) 73–101.
[37] NCD Risk Factor Collaboration (NCD-RisC), Factor Collaboration. Repositioning of the global epicentre of non-optimal cholesterol, Nature 582 (7810) (2020) 73–77.
[38] A. Pirillo, G.D. Norata, A.L. Catapano, Worldwide changes in total cholesterol and non-HDL-cholesterol trends indicate where the challenges are for the coming years, Clin. Chem. 67 (1) (2021) 30–32.