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Metabolic risks remain a serious threat to cardiovascular disease: findings from the Global Burden of Disease Study 2019

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Abstract

Metabolic factors are major and controllable risk factors for cardiovascular diseases (CVD), and few studies have described this burden. We aim to assess it from 1990 to 2019 and predict the trends through 2034. Global Burden of Disease (GBD) provides data on sex, age, and socio-demographic index (SDI) levels. Numbers, age-standardized death rates (ASDR) and estimated annual percentage change (EAPC) were used. Future trends were estimated by NORDPRED model. The deaths cases of metabolic-related CVD increased from 8.61 million (95% UI: 7.91–9.29) to 13.71 million (95% UI: 12.24–14.94) globally. The ASDR continued to decline globally (EAPC = −1.36). The burden was heavier in male and middle-aged people and elderly people. CVD-related ASDR caused by high systolic blood pressure (SBP) had a downward trend globally (EAPC = −1.45), while trends of high body mass index (BMI) (EAPC = 1.29, 1.97, 0.92) and fasting plasma glucose (FPG) (EAPC = 0.95, 1.08, 0.46) were increasing in the middle, low-middle, and low SDI regions, respectively. Compared to 2015–2019, cumulative deaths will increase by 27.85% from 2030 to 2034, while ASDR will decrease 10.47%. The metabolic-related CVD burden remained high globally and deaths will continue to rise in the future. Men, middle-aged and elderly people were focus of concern. High SBP was globally well-managed over the past 30 years, but the CVD burden due to high BMI and FPG remained high. Exceptional initiatives are needed to regarding interventions targeting high BMI and FPG in middle and lower SDI regions.

Keywords Cardiovascular disease · Metabolic risk factors · Socio-demographic index · Death · Global Burden of Disease Study · Prediction

Abbreviations

CVD	Cardiovascular disease
SDI	Socio-demographic index
GBD	Global Burden of Disease
DALYs	Disability-adjusted life years
YLLs	Years of life lost
YLDs	Years of life lived with disability
ASR	Age-standard rates
ASDR	Age-standard death rates
CRA	Comparative risk assessment
EAPC	Estimated annual percentage change
UI	Uncertainty interval
CI	Confidence interval
SBP	Systolic blood pressure
LDL-C	Low-density lipoprotein cholesterol
FPG	Fasting plasma glucose
BMI	Body mass index
GHDx	Global Health Data Exchange
IHD	Ischemic heart disease
AFF	Atrial fibrillation and flutter
CM-MC	Cardiomyopathy and myocarditis
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes

Introduction

Cardiovascular disease (CVD), as the main reason of death and disability globally, accounting for 46% of the world's NCD-related deaths, is a major obstacle to sustainable human development [1–4]. With global urbanization and industrialization as well as a shift in lifestyle, we are confronting a large metabolic wave, whose prevalence has

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steadily increased in many countries and regions [5, 6]. As a risk factor of CVD, metabolic risk factors became the largest contributor to the burden of CVD, illustrating that in-depth knowledge is necessary to facilitate subsequent prevention and control efforts [7].

Currently, there are many studies exploring the burden of CVD and its classifications [8–10]. There are also some studies have focused on risk factors such as high body mass index (BMI), high fasting plasma glucose (FPG), diet risks, to examine the global burden of disease due to certain important risk factors [11–13]. In addition, there was some researches that combines risk factors with disease, such as studies on the burden of CVD due to risk factors such as smoking and diet [14, 15]. Metabolic risks are the leading cause of CVD. However, few studies have examined the CVD burden attributable to metabolic risk factors and the categorization (including high BMI, high FPG, high systolic blood pressure (SBP), high low-density lipoprotein cholesterol (LDL-c) and kidney dysfunction) delicately worldwide. Consequently, using the data reported in the GBD 2019, the purpose of this study is (1) to describe the status of the burden of metabolic risks contributed to CVD (1990–2019) at global as well as SDI regions levels; (2) to observe the trend of CVD caused by specific metabolic risk factors including high systolic blood pressure (high SBP), high low-density lipoprotein cholesterol (high LDL-c), high fasting plasma glucose (high FPG), high body mass index (high BMI), and kidney dysfunction worldwide, and compare the difference of burden between developing countries and developed counties; (3) to predict future CVD trends (2020–2034) caused by metabolic risk factors.

Methods

Data sources

Previous study had reported detailed methodologies for estimating the burden of GBD 2019 diseases [16]. Information on metabolic-attributed CVD deaths number, disability-adjusted life years (DALYs), and age-standard rates (ASRs), by location, age, sex, and socio-demographic index (SDI) was extracted from the 1990 to 2019 GBD database (http://ghdx.healthdata.org/gbd-results-tool). Our study design was based on Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) [17].

Definitions

According to GBD comparative risk assessment framework, metabolic risk factors were defined as high SBP, high BMI, high FPG, high LDL-c, and kidney dysfunction. The total CVD cases assessed in this study are mainly composed of 11 diseases including IHD, stroke, hypertensive heart disease (HHD), rheumatic heart disease (RHD), non-rheumatic valvular heart disease, cardiomyopathy and myocarditis, atrial fibrillation and flutter (AFF), aortic aneurysm, peripheral artery disease (PAD), endocarditis, other cardiovascular and circulatory diseases [18]. The detailed diagnosis and confirmation of CVD have been described in previous studies [7, 18]. IHD was consisted of myocardial infarction (MI), chronic stable angina, chronic IHD, and heart failure caused of IHD. MI was defined according to the Fourth Universal Definition of Myocardial Infarction and was adjusted to include out-of-hospital sudden cardiac death. Stable angina was defined according to the Rose Angina Questionnaire. Stroke was defined according to the World Health Organization definition. HHD was defined as symptomatic heart failure due to the direct and long-term effects of hypertension. PAD was defined by an ankle brachial index under 0.9 or with a claudication symptom. Cardiomyopathy was characterized as symptomatic heart failure resulting from primary myocardial disease or exposure to myocardial toxins. Myocarditis was defined as a transient and time-limited state caused by myocardial inflammation. AFF was defined by the image of electrocardiogram. Endocarditis and RHD were defined by their clinical diagnosis. The GBD cause of death analysis is based on vital records with medical certification. Data on death about CVD were estimated by coded to the International Classification of Disease (ICD) system or household mortality surveys.

In the GBD 2019, the SDI, a summary indicator that provides a quantitative assessment of the socio-demographic development level in a particular country or territory ranges from 0 to 1 and is calculated using various demographic factors [19]. For example, the 0 represents the minimum income per capita, lowest educational achievement, and highest total fertility rate recorded among all GBD regions between 1990 and 2019. GBD regions and countries are divided into five SDI levels from low to high (low SDI; low-middle SDI; middle SDI; high-middle SDI; high SDI).

The DALYs were calculated basing on data of age-specific mortality in the GBD 2019, YLLs due to premature mortality caused by metabolic-attributed CVD, and YLDs to take into account both short-term and long-term health losses and assign a weight to each based on the severity of the disability. The techniques used for estimating DALYs in the GBD modeling strategies have been detailed in earlier studies [3, 16].

Statistical analysis

The deaths number or DALYs, ASRs, and estimated annual percentage change (EAPC) with a 95% confidence interval (CI) or 95% uncertainty interval (UI) were applied to assess the CVD burden due to risk factors

related metabolism. The calculation formula and method of ASR have been explained in previous studies [20]. The EAPC is a commonly used metric to summarize and track the trend of ASR over a specific time period. According to the liner regression model: $y = \beta x + \alpha + \varepsilon$, where y denotes the ln(ASR), x denotes the year (1990–2019), the EAPC was computed utilizing the formula $100 \times (\exp(\beta) - 1)$, and the 95%CI was calculated by the model [20]. Therefore, we adopted ASR and EAPC-ASR to reflect changing diseases and tendencies in a specific period. Likewise, the death-related indicators mentioned above were also used to assess gender differences in the CVD burden due to metabolic risk factors.

To explore the metabolic-related CVD burden in different age groups, we further divided the ages from 15 to 94 into four age groups [6]. We summed the CVD deaths numbers (caused by metabolic risk factors) of four age groups in the same years. The proportion of each age group were calculated to reflect the specific age groups with CVD burden due to metabolic risk factors. We also used the percent change of death cases to reflect the changes with different age groups. The percent changes of death cases were based on the data of 1990 and 2019, and specific calculation formula has been described in previous study detailly [6]. In addition, considering that SDI grade has a significant impact on CVD burden, Pearson correlation coefficients were utilized to estimate the relationship between SDI and CVD burden and any trends. A 2-sided P value <0.05 was considered statistically significant.

We used the NORDPRED age-period-cohort model and the power-five link function to project the death numbers and mortality from 2020 to 2034 by sex worldwide. The NORDPRED software package, developed and implemented in R, has been validated and optimized by many studies [21–23]. The measured variable of death numbers and mortality was modeled by using a power-5 link function, which input variables such as age groups, calendar period, and birth cohort [24]. In our study, we analyzed the death numbers and mortality data of metabolic-attributed CVD worldwide for 5 years (1990–1994, 1995–1999, … , and 2015–2019) and the 5-year age groups. The prediction of metabolic-attributed CVD was conducted in the 5 years (2020–2024, 2025–2029, 2030–2034). The GBD forecast primarily combined the Global Population Forecasts data and age-standard metabolic-attributed CVD 1990–2019 deaths data.

All statistical analysis was conducted with the R program (Version 4.3.0, R core team) and two-tailed p value lower than 0.05 was deemed statistically significant.

Results

Global and regional burden of CVD due to metabolic risks

73.85% of CVD death cases (95% UI: 68.57–78.55) and 74.01% of DALY numbers (95% UI: 69.52–78.11) were contributed to metabolic risk factors. From 1990 to 2019, the CVD-related due to metabolic risk factors total cases of four indicators all significantly increased (death, DALYs, YLL, and YLD) (Table 1; Table S1a–c; Fig. 1A). Globally, the CVD deaths increased steadily from 8.61 million (95% UI: 7.91–9.29) in 1990 to 13.71 million (95% UI: 12.24–14.94) in 2019 (Table 1). Except the high SDI, metabolic-attributed CVD death cases were in a downward trend, the other 4 SDI regions were in an upward trend from 1990 to 2019. However, the number of deaths in high SDI regions ended the previous downward trend in 2013 and showed an alarming reversal, which is vigilant (Fig. 1B).

Global ASRs of CVD attributable to metabolic risk factors for four indicators gradually declined from 1990 to 2019 (Table 1; Table S1a–c). The ASDR declined from 252.93 (95% UI: 229.98–274.62) per 100,000 in 1990 to 176.06 (95% UI: 156.18–192.44) per 100,000 in 2019 worldwide (Table 1). The ASR for four indicators consistently declined, especially in high and middle-high SDI (Table 1; Table S1a–c; Fig. 1C). However, based on region-specific data, 3 specific regions showed rises in ASDR: Central Asia, Oceania, and Southern Sub-Saharan Africa (Fig. 1C, D). In 204 countries and territories, an extremely high ASDR was found in Uzbekistan (741.87 [95% UI: 634.29–852.28] per 100,000), while Japan with 49.55 [95% UI: 40.54–56.36] per 100,000 population had the lowest ASDRs in 2019 (Fig. 1E). Despite the ASDRs were on the decline in most regions, Uzbekistan (EAPC = 2.75 [95% CI: 2.11–3.40]) and Tajikistan (EAPC = 2.08 [95% CI: 1.84–2.33]) experienced relatively rapid increases (Fig. 1F). The results of DALY in 204 countries and territories showed that the ASR of DALY ranged from 1620.47 (95%UI: 1460.11–1744.70) in Japan to 20,181.50 (95%UI: 16,678.86–23,957.75) in Solomon Islands. The ASR of DALY in 168 countries had decreasing trends, and only 3 countries (Lesotho, Uzbekistan, Philippines) had the EAPC > 2 (Figure S1).

The death burden from stroke and IHD due to metabolic risk factors is higher in middle and high-middle SDI regions, and there is a tendency to shift from higher SDI to lower SDI regions. Surprisingly, the burden of death from atrial fibrillation and flutter (AFF) and cardiomyopathy and myocarditis (CM-MC) are higher in

Table 1 The death cases and age-standardized death rates from cardiovascular disease due to metabolic risk factors in 1990 and 2019, and their temporal trends from 1990 to 2019

Characteristics	Number of deaths (no. × 10^3) (95% UI)		ASDR per 100,000 (95% UI)		EAPC of ASDR (95% CI)
	1990	2019	1990	2019	1990–2019
Global	8610.10 (7912.19, 9294.28)	13,707.28 (12,241.26, 14,937.45)	252.93 (229.98, 274.62)	176.06 (156.18, 192.44)	−1.36 (−1.40, −1.31)
Sex					
Men	4269.22 (3929.52, 4617.85)	7134.69 (6408.19, 7800.9)	283.34 (259.38, 307.28)	205.33 (183.06, 224.75)	−1.17 (−1.2, −1.14)
Women	4340.88 (3904.07, 4737.6)	6572.58 (5728.97, 7367.3)	225.66 (201.21, 247.05)	149.86 (130.67, 167.96)	−1.56 (−1.62, −1.5)
Socio-demographic index					
Low	437.78 (380.95, 499.48)	895.55 (792.58, 1002.23)	221.67 (191.56, 254.97)	203.10 (178.72, 227.57)	−0.32 (−0.39, −0.26)
Low-middle	1124.75 (1010.1, 1249.53)	2515.19 (2245.94, 2782.83)	226.30 (201.96, 253.85)	207.90 (184.1, 230.26)	−0.30 (−0.35, −0.26)
Middle	2056.05 (1864.99, 2261.29)	4489.24 (3996.12, 4915.69)	249.86 (224.56, 277.01)	209.84 (185.6, 230.89)	−0.47 (−0.54, −0.40)
High-middle	2798.75 (2572.38, 3018.35)	3826.49 (3404.87, 4199.87)	306.69 (278.03, 333.28)	194.37 (172.18, 213.42)	−1.84 (−2.02, −1.66)
High	2188.26 (1985.55, 2357.1)	1973.06 (1689.06, 2195.10)	210.12 (189.71, 226.54)	91.59 (80.15, 100.98)	−3.20 (−3.37, −3.02)
Region					
Central Asia	161.41 (147.42, 174.15)	261.09 (233.95, 287.52)	384.75 (349.07, 417.74)	454.00 (402.49, 501.51)	0.27 (−0.12, 0.67)
Central Europe	545.19 (506.04, 582.21)	529.56 (448.93, 600.78)	411.96 (376.84, 442.62)	238.31 (202.43, 269.9)	−2.23 (−2.36, −2.1)
Eastern Europe	1048.95 (961.57, 1127.73)	1217.19 (1056.13, 1348.89)	421.91 (381.80, 457.08)	352.42 (306.05, 390.99)	−1.16 (−1.59, −0.73)
Australasia	46.95 (42.53, 50.77)	43.09 (36.04, 48.63)	209.38 (187.61, 227.34)	76.85 (65.25, 86.11)	−3.89 (−4.09, −3.69)
High-income Asia Pacific	271.20 (244.13, 294.24)	287.53 (226.92, 336.46)	154.10 (136.02, 168.75)	50.86 (41.94, 58.39)	−4.01 (−4.21, −3.81)
High-income North American	750.24 (676.92, 805.89)	740.08 (645.09, 820.00)	206.14 (186.68, 221.35)	108.43 (95.71, 119.24)	−2.61 (−2.8, −2.42)
Southern Latin America	85.78 (76.41, 94.63)	100.23 (89.20, 109.73)	204.38 (180.60, 226.79)	117.51 (104.75, 128.43)	−1.89 (−2.02, −1.76)
Western Europe	1272.89 (1157.18, 1371.48)	1006.66 (851.14, 1118.13)	216.30 (195.70, 233.01)	90.68 (78.26, 99.92)	−3.34 (−3.51, −3.17)
Andean Latin American	23.46 (20.13, 26.94)	47.50 (38.51, 57.91)	127.31 (108.74, 146.52)	88.42 (71.54, 107.69)	−1.11 (−1.35, −0.87)
Caribbean	57.49 (51.73, 63.07)	93.72 (80.19, 107.47)	238.08 (213.95, 261.67)	180.37 (154.10, 206.77)	−0.95 (−1.14, −0.77)
Central Latin American	125.17 (115.11, 134.82)	286.15 (241.85, 332.78)	175.04 (157.80, 190.74)	126.88 (106.39, 147.53)	−1.28 (−1.42, −1.14)
Tropical Latin American	201.43 (186.24, 216.38)	302.02 (269.82, 328.08)	255.64 (232.11, 277.69)	129.39 (115.08, 141.03)	−2.36 (−2.45, −2.28)
North African and Middle East	535.33 (485.34, 586.76)	1058.32 (928.18, 1192.41)	373.25 (333.91, 410.62)	289.71 (253.91, 324.67)	−0.94 (−0.99, −0.90)
South Asia	1023.85 (903.40, 1149.38)	2434.93 (2111.36, 2773.7)	219.29 (192.04, 250.36)	194.90 (166.92, 221.57)	−0.49 (−0.6, −0.39)
East Asia	1584.28 (1364.85, 1832.41)	3369.82 (2853.54, 3877.54)	237.87 (203.55, 273.17)	192.21 (162.71, 221.52)	−0.45 (−0.58, −0.32)
Oceania	6.96 (5.78, 8.4)	18.00 (14.33, 22.4)	265.14 (220.27, 318.50)	283.35 (230.51, 346.43)	0.27 (0.21, 0.32)

Table 1 (continued)

Characteristics	Number of deaths (no. × 10^3) (95% UI)		ASDR per 100,000 (95% UI)		EAPC of ASDR (95% CI)
	1990	2019	1990	2019	1990–2019
Southeast Asia	1023.85 (903.40, 1149.38)	2434.93 (2111.36, 2773.7)	219.29 (192.04, 250.36)	194.90 (166.92, 221.57)	−0.49 (−0.6, −0.39)
Central Sub-Saharan Africa	49.64 (42.07, 58.19)	100.04 (80.87, 121.75)	272.59 (232.44, 315.75)	239.63 (196.59, 289.91)	−0.51 (−0.59, −0.43)
Eastern Sub-Saharan Africa	126.43 (107.57, 144.67)	252.13 (219.42, 284.35)	203.10 (171.72, 233.08)	189.4 0(164.76, 212.83)	−0.27 (−0.30, −0.25)
Southern Sub-Saharan Africa	43.91 (39.27, 48.59)	89.22 (80.63, 97.74)	181.05 (160.40, 201.72)	189.86 (170.42, 208.2)	0.21 (−0.22, 0.64)
Western Sub-Saharan Africa	144.13 (118.59, 176.14)	293.28 (245.82, 340.99)	198.94 (163.29, 242.47)	192.76 (163.21, 221.32)	−0.05 (−0.14, 0.05)

ASDR age-standardized death rate, *EAPC* estimated annual percentage change, *UI* uncertainty interval, *CI* confidence interval

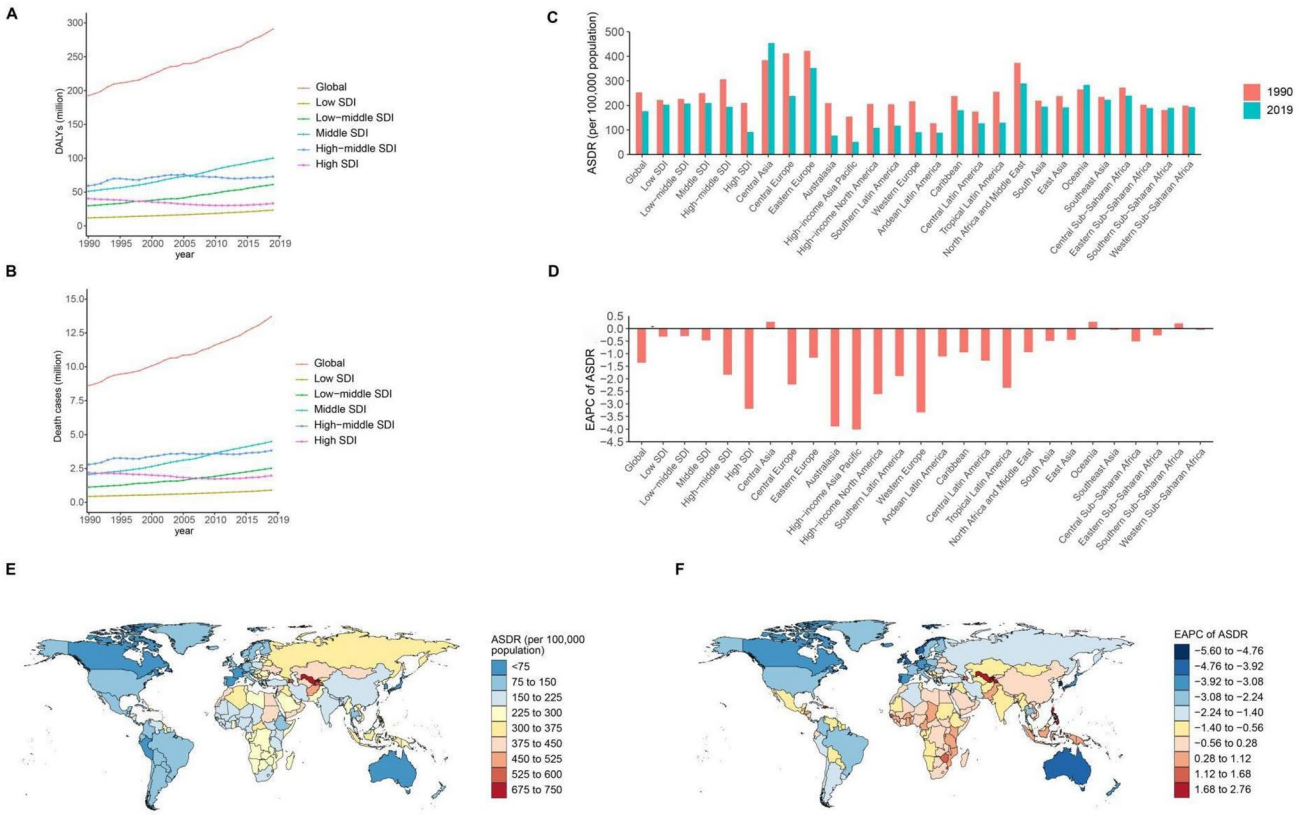

Fig. 1 The burden of CVD attributable to metabolic risk factors from 1990 to 2019. **A** DALYs of CVD attributed to metabolic risk factors globally, and in territories with low to high SDIs regions. **B** Death cases of CVD attributed to metabolic risk factors globally, and in territories with low to high SDIs regions. **C** The ASDRs in 1990 and 2019 globally, in territories with low to high SDIs and in 21 GBD regions. **D** The EAPCs of ASDRs globally, in territories with low to high SDIs and in 21 GBD regions. **E** The ASDRs in 204 countries and territories in 2019. **F** The EAPCs of ASDRs in 204 countries and territories. ASDR, age-standardized death rate; EAPC, estimated annual percentage change (color figure online)

developed countries than in developing countries (Figure S7). Analogously, similar manifestations were found in 204 countries and territories (Figure S8).

Global and regional burden of CVD due to metabolic risks by sex

Globally, the deaths of metabolism-related CVD were 4.27 million (95% UI: 3.93–4.62) in males and 4.34

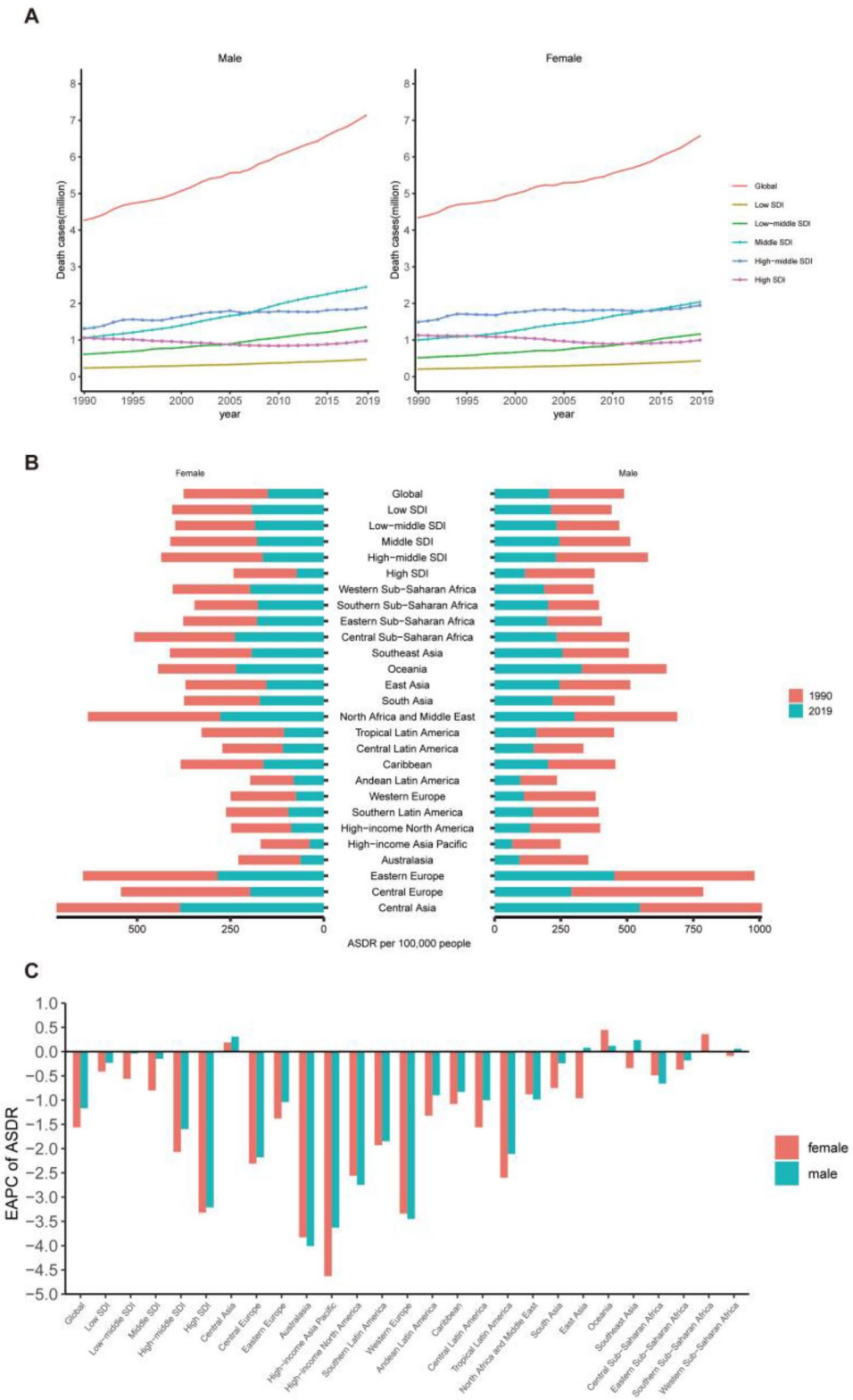

Fig. 2 The burden of CVD attributable to metabolic risk factors by sex from 1990 to 2019. **A** Death cases in males and females globally, and in territories with low to high SDIs. **B** The ASDRs of males and females in 1990 and 2019 globally, in territories with low to high SDIs and in 21 GBD regions. **C** The EAPCs of ASDRs in males and females globally, in territories with low to high SDIs and in 21 GBD regions. ASDR, age-standardized death rate; EAPC, estimated annual percentage change (color figure online)

million (95% UI: 3.90–4.74) in females in 1990, reaching 7.13 million (95% UI: 6.41–7.80) and 6.57 million (95% UI: 5.73–7.37) in 2019 respectively (Table 1; Fig. 2A). Although the ASDR of metabolic-attributed CVD has a downward trend among both females and males, the descending tendency of females was much greater than males worldwide and the gender difference in middle and lower SDI regions are clearly higher than middle-high and high SDI regions. The EAPC showed a decline trend in high SDI and developed countries; while in Oceania, the index of both male and female showed significant upward trend (EAPC = 0.11 [95% CI: 0.07–0.17] in male, EAPC = 0.45 [95% CI: 0.40–0.51] in female), and the index of female in Southeast Asia also shows an increasing trend (EAPC = 0.24 [95% CI: 0.14–0.33]) (Fig. 2B, C). The ASR-DALYs of CVD attributable to metabolic risk factors were also in a decline trend in most regions. Similarly, the Oceania with a higher trend in EAPC of ASR-DALYs among male (EAPC = 0.19, [95% CI: 0.12–0.26]) and female (EAPC = 0.48, [95% CI: 0.39–0.57]) (Figure S2).

Global and regional burden of CVD due to metabolic risks by age groups

The elderly people accounted for the largest proportion both in 1990 and 2019 globally and in high SDI regions. From the high SDI to low SDI, the proportion of young people dying gradually increased. Compared 1990–2019, the proportion of CVD deaths due to metabolic risk factors in the elderly increased significantly, with the largest proportion in both 1990 (65.73%) and 2019 (77.89%) in Western Europe (Fig. 3B). In high SDI regions, the death number at all ages showed a downward trend, while a contrasting trend has been found in middle and lower SDI regions, whose upward trends are apparent in all age groups. Percent changes in death numbers among young people moved in a positive direction as the SDI rises, reflecting the importance attached to youth health in higher SDI regions. Notably, the rising trend of deaths among young people was more pronounced than elderly in Oceania, Western Sub-Saharan Africa (Fig. 3C). There is still some difference in the percentage change in the number of deaths of men and women between the sexes at different ages, and the percentage change in the deaths of men is higher than women, but the difference between men and women in the 45–59 age group is smaller than in other age groups (Figure S3). Similar trends were observed in DALY number of CVD due to metabolic risk factors (Figure S4).

Dominant subtypes of metabolic risks for CVD

CVD deaths attributable to high SBP changes from 6.45 million (95% UI: 5.74–7.15) in 1990 to 9.97 million (95% UI: 8.68–11.21) in 2019 globally, contributing the most to CVD in 5 risk factors related metabolism. The death number of high LDL-c, high FPG, high BMI and kidney dysfunction also showed a clear upward trend globally (Fig. 4A; Table S2). Although the ASDR of high SBP leading to CVD changes from 188.23 per 100,000 population (95% UI: 165.09–210.85) in 1990 to 127.54 (95% UI: 110.59–143.80) in 2019, it is still the most serious metabolic risk factor leading to CVD death in 2019 (Fig. 4B; Table S2). The ASDRs of all 5 metabolic risk factors showed downtrends, the most obvious metabolic risk is high LDL-c globally (EAPC = −1.70 [95% CI: −1.76 to −1.65]). All 5 metabolic risks have declining trends in high-middle and high SDI regions. In middle and lower SDI, the ASDR for high BMI and high PFG performing upward trends. For high BMI, the EAPC of low SDI is 1.29 [95% CI: 1.22–1.36]; the EAPCs were 1.97 [95% CI: 1.93–2.01] in low-middle SDI and 0.92 [95% CI: 0.87–0.96] in middle SDI. For high FPG, 1.08 of EAPC (95% CI: 0.98–1.18) was found in low-middle SDI, followed by 0.95(95% CI: 0.86–1.04) in low SDI and 0.46 (95% CI: 0.25–0.66) in middle SDI regions (Fig. 4C; Table S2). For the ASR-DALYS of all 5 metabolic risk factors, they were also in the downtrends, the most obvious metabolic risk was high LDL-c globally (EAPC = −1.46 [95% CI: −1.51 to −1.41]) (Table S3). The high BMI and high FPG showed in upward trends in low, low-middle, and middle SDI (Figure S5).

The burden of CVD due to 5 subtypes of metabolic risks in 204 countries is shown in Figure S9, the ASDRs of EAPC for 4 metabolic risk factors except high BMI were on the rise in Uzbekistan, while the EAPC of all these metabolic risk factors was on a downward trend in developed countries. More details of the global and regional burden of CVD due to metabolic risks by sex and age are shown in Figures S10 and S11. The ASDRs of CVD death due to metabolic risk factors are higher in male than in female worldwide (Figure S10B). Male has the most outstanding upward trend of high FPG and high BMI in low-middle SDI (Figure S10C). The proportion of CVD deaths due to high BMI was most pronounced among the youth population with a proportion of 25.44%, illustrating high BMI accounts for a decreasing proportion of deaths from CVD as age rises. Additionally, the high SBP had a rising trend with age growth (Figure S11C).

Correlations between the SDI and ASRs

The metabolic-attributed CVD death burden is in a downward trend when the SDI value is above 0.7 (high-middle

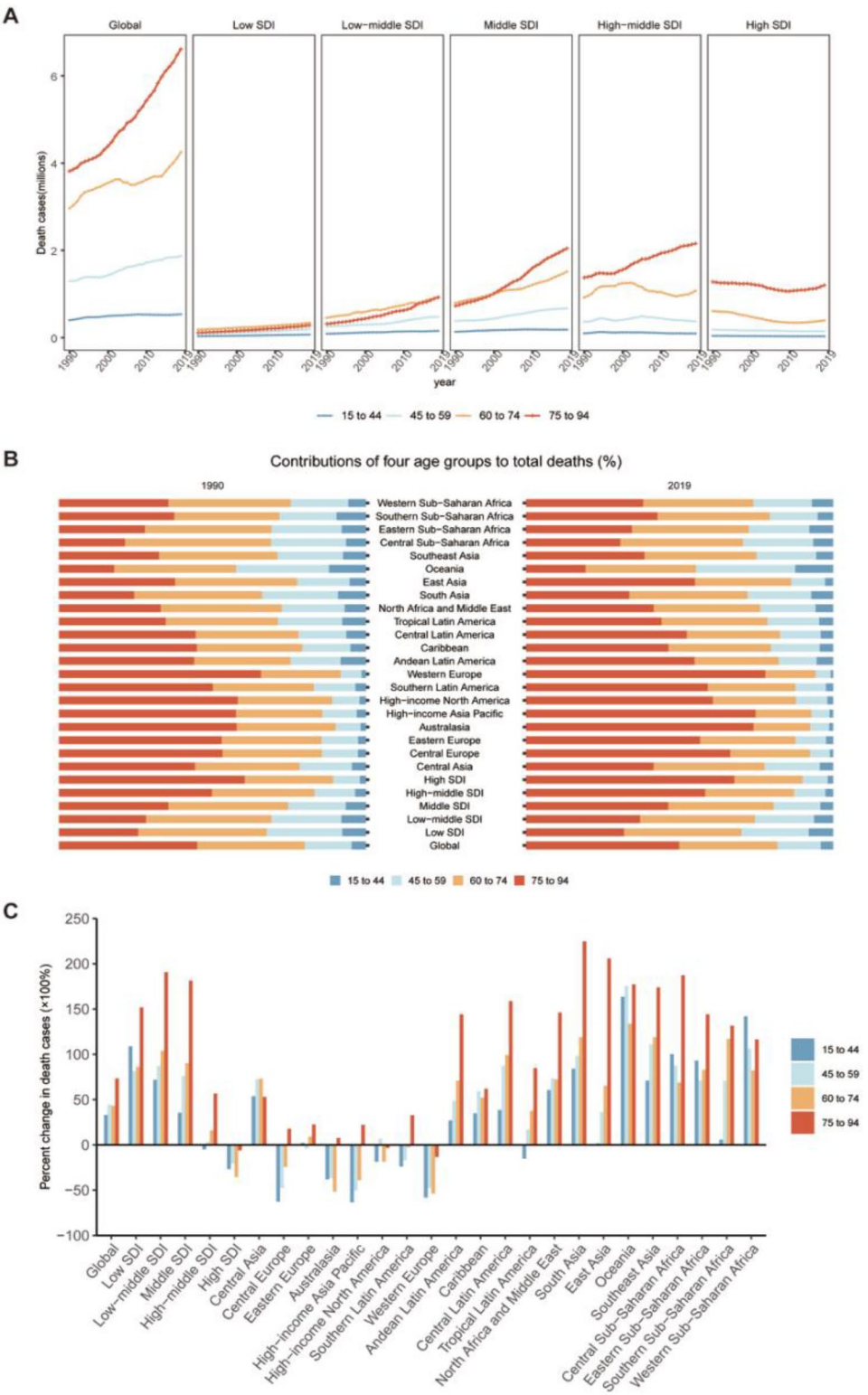

Fig. 3 The burden of CVD attributable to metabolic risk factors by age groups from 1990 to 2019. **A** The death cases in four age groups (15–44 years, 45–59 years, 60–74 years, and 75–94 years) globally and in territories with low to high SDIs. **B** The four age groups as percentages of total deaths globally, in territories with low to high SDIs and in 21 GBD regions in 1990 and 2019. **C** The percent changes of deaths in four age groups between 1990 and 2019 globally and in territories with low to high SDIs. SDI, socio-demographic index (color figure online)

SDI), while rising steadily when SDI below 0.7 in 2019. Similar trends are found in four subtypes of metabolic risks (high BMI, high LDL-c, high FPG and kidney dysfunction), but only the ASR of high SBP-attributed CVD

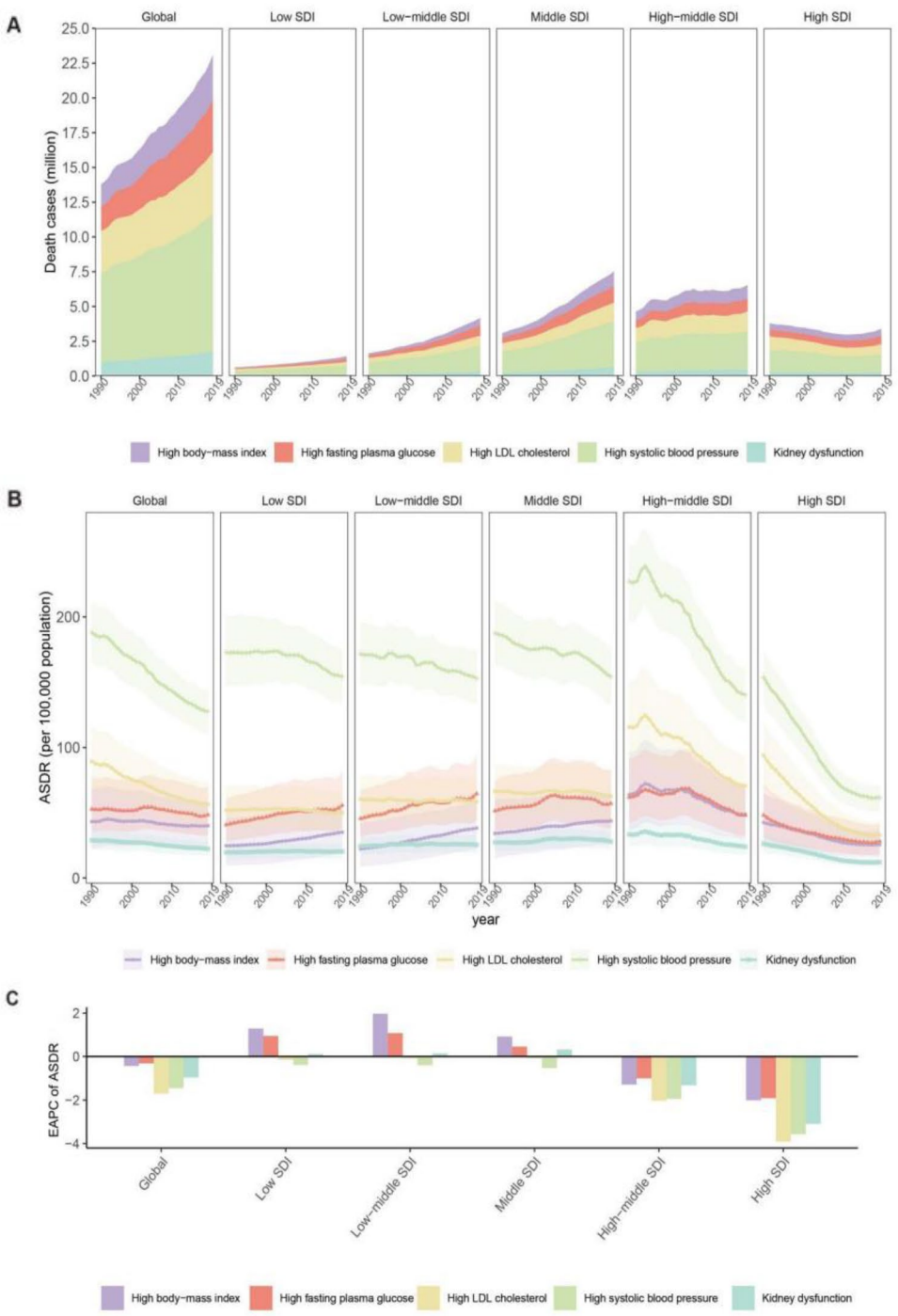

Fig. 4 The burden of CVD caused by metabolic risk factors classification from 1990 to 2019. **A** The death cases globally and in territories with low to high SDIs. **B** The ASDRs globally and in territories with low to high SDIs. **C** The EAPCs of ASDRs globally and in territories with low to high SDIs. ASDR, age-standardized death rate; EAPC, estimated annual percentage change (color figure online)

is keeping a steady trend when the SDI value is below 0.7 (Figure S6).

Prediction of death numbers and mortality of metabolic-attributed CVD

The metabolic-related CVD deaths were cumulative 90.93 million from 2030–2034, an increase of 27.85% compared with 2015–2019, and the discrepancies in deaths by sex has widened (Fig. 5A). The ASDR of metabolic-attributed CVD has a downward trend (157.63 per 100,000 population globally in 2030–2034), decreasing 10.47% compared with 2015–2019 and male (182.09 per 100,000 population) and female (135.31 per 100,000 population). (Fig. 5B). For specific metabolic risk factors, the number of deaths from CVD due to the five metabolic risk factors remained an upward trend between 1990 and 2019 and is expected to continue to rise between 2020 and 2034, while ASDR is on the decline

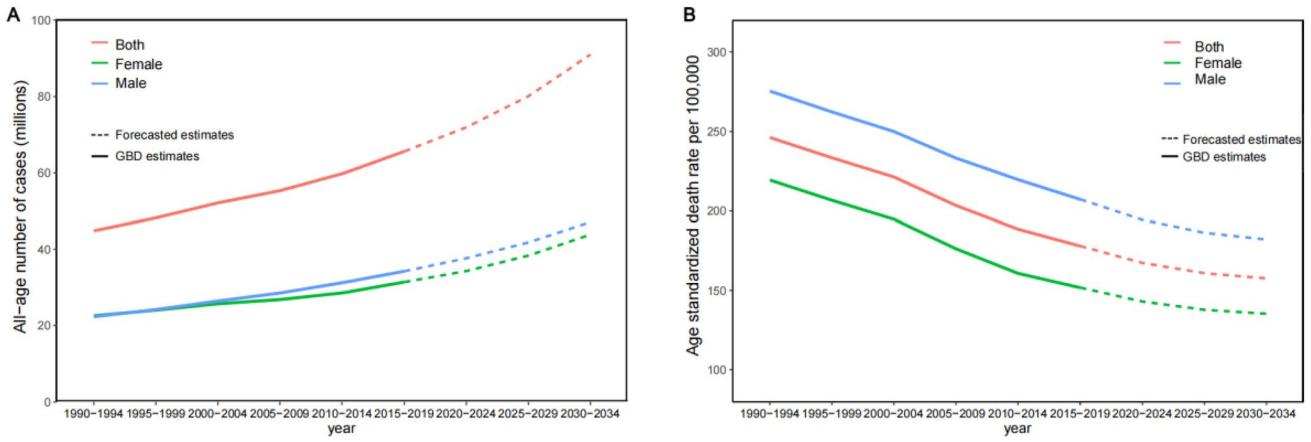

Fig. 5 Prediction of death cases and age-standardized (world) death rates of CVD attributable to metabolic risk factors: the solid lines indicate the observed values (1990–2019) and the dotted lines are the predicted values (2020–2034). **A** The death number of CVD attributable to metabolic risk factors globally. **B** The ASDRs of CVD attributable to metabolic risk factors globally. ASDR, age-standardized death rate (color figure online)

between 2020 and 2034, where the trends for high BMI and high FPG plateau over this period (Figure S12).

Discussion

We found that the global CVD burden continues to be high as the death and DALY number due to metabolic risk factors show a rising trend from 1990 to 2019, while the ASDR and ASR-DALY shows clear decreasing trend globally, which indicate that population growth may have contributed to the increase in the absolute number of death and DALY. The deaths are expected to maintain a continuous upward trend from 2020–2034 globally, but the ASDR of metabolic-attributed CVD is on a downward trend in the future. The CVD burden caused by metabolic risk factors differs by sex and is higher in male than in female; it is highest among middle-aged people and elderly people. High SBP remained the most essential metabolic risk factor contributing to CVD, while had a downward trend globally and in different SDI regions. High LDL-c was the secondary metabolic risk leading to CVD. High BMI and high FPG burden showed a clear increasing trend in the middle and lower SDI regions.

The number of CVD deaths and DALY due to metabolic risk factors increased globally between 1990 and 2019, but there were some differences between different regions. The death and DALY number for CVD due to metabolic risk factors are still increasing in developing countries, but declining in developed countries. For example, after decades of implementation and promotion of prevention strategies and measures, the CVD burden has improved significantly in developed countries [25]. Conversely, as industrialization, urbanization, and globalization progress, the lifestyles of people in developing countries are moving closer to those of Western countries, while the corresponding prevention and control capacity is relatively weak, leading to an increased CVD burden due to metabolic risk factors in developing countries [26, 27]. Developing countries should take measures to address this situation.

Globally, the CVD burden due to metabolic risks is higher in male than female, is highest among middle-aged people and elderly people. This can be explained by the difference genetic mechanisms in different gender. The phenomenon that inequality between male and female are more obvious in middle and lower SDI regions may be explain by the smaller gap of physical activities and smoking behavior between male and female in high-middle and higher SDI regions, and more possible causes need more research to explore [28–30]. In addition, middle-aged and elderly people are more probably to develop CVD attributed to metabolic risk factors and there was a greater CVD burden caused by metabolic risk factors. Global age composition has shown an aging trend over the last few decades, which is closely linked to advances in global medical care and population growth [6]. For subtypes of metabolic risks, the burden of high BMI is greater in young people than in other age groups, which is an important and widespread public health problem, and measures to address obesity are the most cost-effective way to prevent CVD in young people, particularly in high SDI regions [31].

The ASDR and ASR-DALYs of CVD burden due to SBP was on the downward trends not only in developed counties but also in developing countries, which illustrates that efforts devoted to high SBP management over the past decades have been remarkably fruitful globally. The International Society of Hypertension (ISH) developed the ISH2020 International Hypertension Practice Guidelines for worldwide applicability, and proposed basic standards for underdeveloped regions

and optimal standards for developed regions are provided by ISH2020 [32]. Global report on hypertension by WHO notes that hypertension detection, treatment and control have improved in most countries. Treatment coverage—the proportion of hypertensive adults aged 30–70 years with hypertension taking hypertension medication—increased from 22% in 1990 to 42% in 2019 globally [33]. For example, constructive guidelines, such as the guidelines for the CVD prevention in clinical practice and the management guidelines for the high SBP adults have enabled European health systems to achieve cure rates of up to 80% and control rates of 60% for high SBP [29]. In China, although the burden of high SBP remains high, awareness and control of high SBP have increased significantly, being two and three times higher, respectively, than in 2002 [34]. The use of two anti-hypertensive drugs is 40% and 50%, respectively, in developed countries, and in low- and middle-income countries, the drug use increased three times in 2019 compared to 2009 [35].

Although there is a downward trend in CVD burden due to high LDL-c globally, the gap between developed and developing countries is still apparent. Research in the field of high LDL-c has made breakthroughs in countries and regions at different development levels, and guidelines for the prevention of CVD in most countries recommend that lipid-lowering drugs should be taken by high-risk groups [36–38]. However, the CVD burden due to high LDL-c has a significant downward trend in developed countries, while the trend in developing countries is not obvious. For example, the use of statins (LDL-c-lowering drugs) is 70% in developed countries [32]. But the awareness of high LDL-c is low in China, where less than half of primary care facilities have access to statins, and in India, the prescription rate for statins is still much lower than in economically developed countries such as North America and Europe [39, 40].

Our result showed that the CVD burden due to high BMI showed downward trends in developed countries, but still clearly upward trends in developing countries. Developed countries increasingly recognizing the benefits of weight loss, and the guidelines provided recommendations for weight management in people with obesity combined with CVD, behavioral interventions, pharmacological and surgical treatments are recommended for the purpose of weight loss [41, 42]. However, the use of weight-loss medications remains conservative in many low- and middle-income countries because of the limited availability and safety concerns, and cardiovascular physicians in many developing countries are still not sufficiently involved in the management of weight loss in patients with CVD or high risk of CVD [43].

Similarly to high BMI, the high FPG attributed to CVD burden was decreasing in developed countries, but increasing in developing countries. The European Society of Cardiology (ESC) and the European Society for the Study of Diabetes (EASD) jointly published three editions of the guideline "Diabetes, Prediabetes and Cardiovascular Disease" in 2007, 2013, and 2019, respectively, which provide guidance and recommendations for the management of European with diabetes or at risk of diabetes (prediabetes) and for the prevention and treatment of CVD [44–46]. However, data from 49 developing countries show that insulin use among essential patients was only 42.2% in 2016, and the proportion of patients receiving diabetes-related education is low, although doctors have a good understanding of hyperglycemia, but rarely enough time for patients [47].

Although some progress has been made in the diagnosis and management of metabolic risk factors, unhealthy lifestyles, one of the main causes of metabolic risks, remain prevalent globally [48]. The World Health Organization reports that global physical activity levels have not improved since 2001. More than a quarter of the global population has an insufficient level of physical activity and physical inactivity levels are twice as high in high-income countries compared to low-income countries [49]. In addition, a global dietary survey counts the population's intake of each food group and scores it according to its healthiness, producing a "Healthy Eating Index" ranging from 0 to 100. In 2018, the global Healthy Eating Index was 41.5, which is far from reaching the standard of healthy eating patterns recommended by the Dietary Guidelines [50]. Guidelines have recommended that healthy lifestyles are primary means of secondary prevention of CVD, which is more accessible and cost-effective [51, 52]. And further lifestyle improvement strategies and measures should be adopted to reduce CVD burden from metabolic risk factors.

To our knowledge, this study is one of the most detailed studies to date on the global CVD burden due to metabolic risk factors, not only analyzing and predicting the burden of CVD due to total metabolic risk factors, but also providing a detailed description of the distribution and difference of 5 metabolic risk factors in different SDI regions. However, it still has limitations. First, data collected in different regions may vary greatly, which inevitably result in some bias in the estimates. Second, other metabolic risk factors for CVD, such as metabolic fatty liver disease, and some non-modifiable risk factors, such as heredity and genetics, also contribute to some CVD burden but are not addressed in this study. Third, the data included in this paper are up to 2019 and the trends in health, overweight and obesity, and cardiovascular disease in children and adults may change after 2020 due to the COVID-19 pandemic.

Conclusions

The burden of CVD due to metabolic risk remains high globally from 1990 to 2019, and the deaths will continue to rise in a 15-year period (2020–2034). Men, middle-aged, and elderly people being the main targets of concern. Although the CVD burden due to high SBP had a downward trend globally, it remained the most essential metabolic risk factor contributing to CVD and still needed to control. In high SDI regions, more targeted measures should be taken to prevent a rebound of the downward trend. In middle and lower SDI regions measures should be taken as soon as possible to curb the rapid upward trend of the CVD burden caused by high BMI and high FPG.

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Author contributions Runhong Li and Jinang Shao: Designed the study, Software, Formal analysis, Writing—review and editing. Chengxiang Hu, Tong Xu, Jin Zhou, Jiaqi Zhang, Xiaoting Fan, Wenhui Zhou, and Rong Huang: Literature search, Review and editing. Qitong Liu, Mengying Han and Ning Ning: Review and editing. Lina Jin and Yanan Ma: Conceptualization, Review and editing, Supervision, Resources. Runhong Li and Jinang Shao contributed equally as the co-first author of this article. Lina Jin and Yanan Ma contributed equally as the corresponding co-author.

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Data availability Our data was extracted from the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool).

Declarations

Conflict of interest The authors disclose no conflicts.

Human and animal rights The study did not include any human participants or performed animals.

Informed consent A waiver of informed consent was reviewed and approved by the Washington University Institutional Review Committee, since GBD 2019 used de-identified and aggregated data.

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