Article

Repositioning of the global epicentre of non-optimal cholesterol

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NCD Risk Factor Collaboration (NCD-RisC)*

High blood cholesterol is typically considered a feature of wealthy western countries[1,2]. However, dietary and behavioural determinants of blood cholesterol are changing rapidly throughout the world[3] and countries are using lipid-lowering medications at varying rates. These changes can have distinct effects on the levels of high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol, which have different effects on human health[4,5]. However, the trends of HDL and non-HDL cholesterol levels over time have not been previously reported in a global analysis. Here we pooled 1,127 population-based studies that measured blood lipids in 102.6 million individuals aged 18 years and older to estimate trends from 1980 to 2018 in mean total, non-HDL and HDL cholesterol levels for 200 countries. Globally, there was little change in total or non-HDL cholesterol from 1980 to 2018. This was a net effect of increases in low- and middle-income countries, especially in east and southeast Asia, and decreases in high-income western countries, especially those in northwestern Europe, and in central and eastern Europe. As a result, countries with the highest level of non-HDL cholesterol—which is a marker of cardiovascular risk—changed from those in western Europe such as Belgium, Finland, Greenland, Iceland, Norway, Sweden, Switzerland and Malta in 1980 to those in Asia and the Pacific, such as Tokelau, Malaysia, The Philippines and Thailand. In 2017, high non-HDL cholesterol was responsible for an estimated 3.9 million (95% credible interval 3.7 million–4.2 million) worldwide deaths, half of which occurred in east, southeast and south Asia. The global repositioning of lipid-related risk, with non-optimal cholesterol shifting from a distinct feature of high-income countries in northwestern Europe, north America and Australasia to one that affects countries in east and southeast Asia and Oceania should motivate the use of population-based policies and personal interventions to improve nutrition and enhance access to treatment throughout the world.

Blood cholesterol is one of the most important risk factors for ischaemic heart disease (IHD) and ischaemic stroke[4–6]. Consistent and comparable information on cholesterol levels and trends in different countries can help to benchmark national performance in addressing non-optimal cholesterol, investigate the reasons behind differential trends and identify countries in which interventions are needed the most.

A previous global analysis[7] reported trends in total cholesterol from 1980 to 2008, but did not analyse important lipid fractions—including HDL and non-HDL cholesterol—that are key to understanding the cardiovascular disease risk associated with non-optimal cholesterol. Dietary and behavioural determinants of cholesterol have changed throughout the world in the past decades, including a worldwide rise in adiposity[8,9], divergent global trends in alcohol use[10], a rise in the intake of animal-source foods in middle-income countries (especially in east Asia)[3,11], and a replacement of saturated fats and trans fats with unsaturated fats in some high-income countries[3,11,12]. There is also considerable variation in how much different countries have adopted lipid-lowering medications[13]. These changes are likely to have influenced cholesterol levels substantially in the decade since the last estimates were made. Furthermore, HDL and non-HDL cholesterol, which have opposite associations with cardiovascular diseases[4,5], respond differently to diet and treatment, and may therefore have different geographical patterns and trends over time[14]. Information on these major lipid fractions, which were not included in the previous global estimates, is essential for priority setting and intervention choice.

Here we pooled 1,127 population-based studies that measured blood lipids in 102.6 million individuals aged 18 years and older (Extended Data Figs. 1, 2 and Supplementary Table 1) and used a Bayesian hierarchical model to estimate trends from 1980 to 2018 in mean total, non-HDL and HDL cholesterol levels for 200 countries. We also estimated the number of deaths caused by IHD and ischaemic stroke that were attributable to high levels of non-HDL cholesterol using information on its hazards from epidemiological studies.

*A list of participants and their affiliations appears in the online version of the paper.

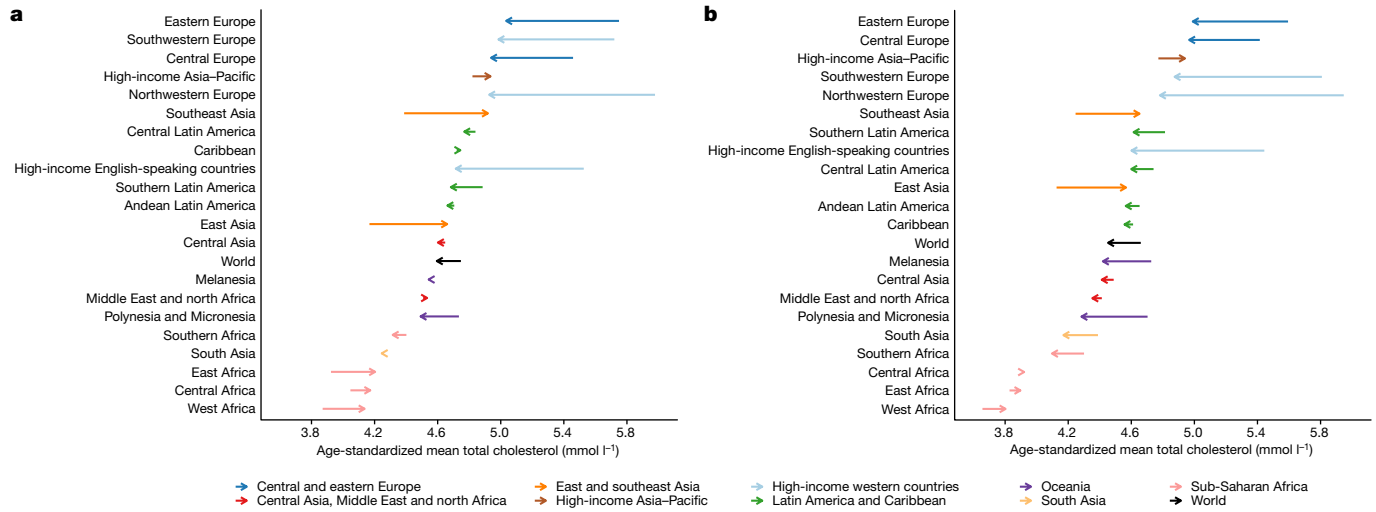

Fig. 1 | Change in age-standardized mean total cholesterol between 1980 and 2018 by region for women and men. a, Age-standardized mean total cholesterol in women. **b**, Age-standardized mean total cholesterol in men. The start of the arrow shows the level in 1980 and the head indicates the level in 2018. See Extended Data Fig. 3 for age-standardized mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

Trends in total cholesterol

In 2018, global age-standardized mean total cholesterol was 4.6 mmol l^{-1} (95% credible interval, 4.5–4.7) for women and 4.5 mmol l^{-1} (4.3–4.6) for men. Global age-standardized mean total cholesterol changed little over these nearly four decades, decreasing by 0.03 mmol l^{-1} per decade (−0.02–0.08) in women and 0.05 mmol l^{-1} per decade (0.00–0.11) in men (posterior probability of the observed declines being true declines = 0.90 for women and 0.98 for men) (Fig. 1). Regionally, total cholesterol decreased the most in high-income western regions and in central and eastern Europe. The decrease was the largest (around 0.3 mmol l^{-1} per decade; posterior probability >0.9999) in northwestern Europe, where mean total cholesterol levels had been the highest in 1980. The decrease in total cholesterol in high-income western regions and central and eastern Europe was largely due to a decline in non-HDL cholesterol (Extended Data Fig. 4), which among women was offset partly by an increase in mean HDL cholesterol levels. Mean total cholesterol changed little in most of the other regions, with the notable exception of east and southeast Asia, where it increased by more than 0.1 mmol l^{-1} per decade in both women and men (posterior probability ≥0.95). The increase in east and southeast Asia was largely due to an increase in non-HDL cholesterol.

Trends in non-HDL and HDL cholesterol

In 2018, global age-standardized mean non-HDL cholesterol was 3.3 mmol l^{-1} (3.2–3.4) for women and 3.3 mmol l^{-1} (3.3–3.4) for men; global age-standardized mean HDL cholesterol was 1.3 mmol l^{-1} (1.2–1.3) for women and 1.1 mmol l^{-1} (1.1–1.2) for men. Global age-standardized mean non-HDL cholesterol remained almost unchanged from 1980 to 2018, decreasing by only 0.02 mmol l^{-1} per decade (−0.02–0.06; posterior probability = 0.80) in women and 0.01 mmol l^{-1} per decade (−0.03–0.06; posterior probability = 0.72) in men. Global age-standardized mean HDL cholesterol remained unchanged for women and decreased slightly for men (by 0.02 mmol l^{-1} per decade, posterior probability = 0.91).

Regionally, non-HDL cholesterol decreased substantially in high-income western regions and central and eastern Europe. The largest decrease occurred in northwestern Europe (>0.3 mmol l^{-1} per decade; posterior probability >0.9999) (Fig. 2). By contrast, it increased in east and southeast Asia, parts of sub-Saharan Africa and Melanesia. The increase was the largest in southeast Asia, increasing by approximately 0.2 mmol l^{-1} per decade (posterior probability >0.9999). Mean HDL cholesterol increased in the high-income Asia–Pacific region, by as much as 0.1 mmol l^{-1} per decade in women (posterior probability >0.9999) but decreased in Melanesia, Polynesia and Micronesia (Extended Data Fig. 3).

Belgium, Finland, Greenland, Iceland, Norway, Sweden, Switzerland and Malta had some of the highest non-HDL cholesterol levels in 1980 (>4.5 mmol l^{-1} in women and >4.7 mmol l^{-1} in men) but experienced some of the largest declines (Figs. 3, 4). At the extreme, mean non-HDL cholesterol declined by around 0.45 mmol l^{-1} per decade or more in Belgian and Icelandic women and men, changing their ranks from being in the top 10 countries in terms of non-HDL cholesterol in 1980 to being ranked in the lower half of the countries in 2018—below countries in southwestern Europe such as France and Italy. The largest increases were found in east Asian countries (for example, China) and southeast Asian countries (for example, Indonesia, Thailand, Malaysia, Cambodia and Lao PDR). In these countries, age-standardized mean non-HDL cholesterol increased by as much as 0.23 mmol l^{-1} per decade. As a result of these opposite trends, countries with the highest age-standardized mean non-HDL cholesterol levels in 2018 were all outside northwestern Europe: Tokelau, Malaysia, The Philippines and Thailand, all of which had mean non-HDL cholesterol around or above 4 mmol l^{-1}. China, which had one of the lowest mean non-HDL cholesterol levels in 1980, reached or surpassed non-HDL cholesterol levels of many high-income western countries in 2018. Sub-Saharan African countries had the lowest mean non-HDL cholesterol in 2018, as low as 2.6 mmol l^{-1} in some countries, as they had in 1980. Not only did high-income countries benefit from decreasing non-HDL cholesterol levels, they had higher mean HDL cholesterol than low- and middle-income countries (Extended Data Fig. 6).

Deaths attributable to non-optimal cholesterol

In 2017, high non-HDL cholesterol was responsible for an estimated 3.9 million (3.7–4.2 million) worldwide deaths from IHD and ischaemic stroke (Fig. 5), accounting for a third of deaths from these causes. From 1990 to 2017, the number of deaths caused by IHD and ischaemic stroke that were attributable to high non-HDL cholesterol increased by around 910,000 globally. This increase was a net result of a large decrease in western countries, from 950,000 (890,000–990,000) to 480,000 (430,000–530,000), and a large increase throughout Asia. In particular, the number of deaths attributable to high non-HDL cholesterol more

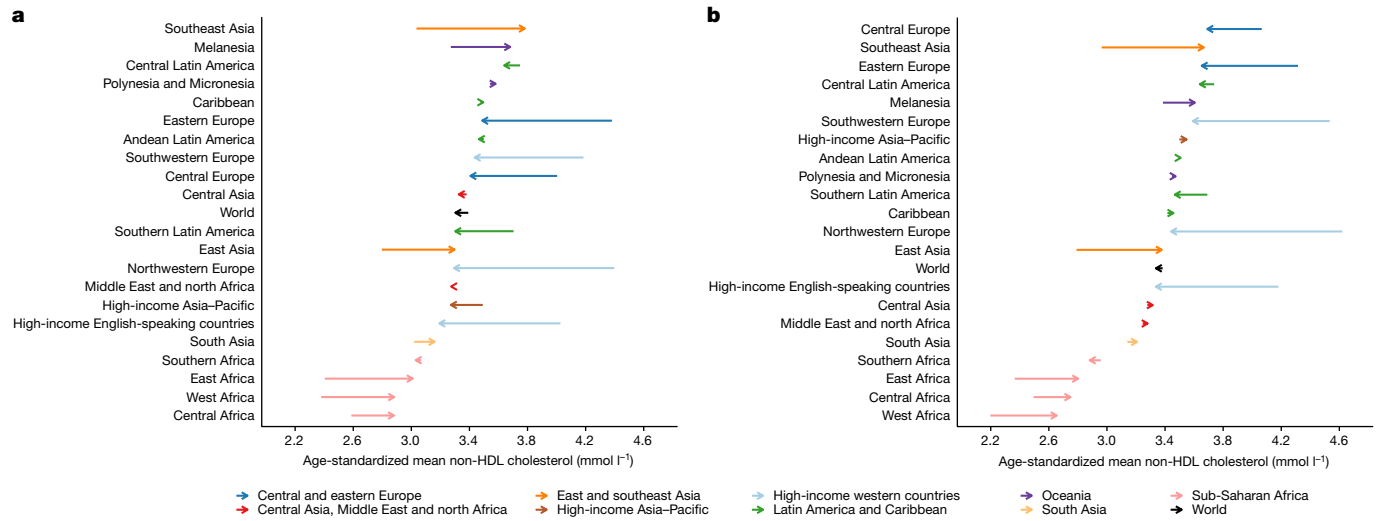

Fig. 2 | Change in age-standardized mean non-HDL cholesterol between 1980 and 2018 by region for women and men. a, Age-standardized mean non-HDL cholesterol in women. **b**, Age-standardized mean non-HDL cholesterol in men. The start of the arrow shows the level in 1980 and the head indicates the level in 2018. See Extended Data Fig. 3 for age-standardized mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

than tripled in east Asia, from 250,000 (230,000–270,000) to 860,000 (770,000–940,000), and more than doubled in southeast Asia, from 110,000 (100,000–120,000) to 310,000 (290,000–330,000). As a result, by 2017 east, southeast and south Asia accounted for half of all deaths attributable to high non-HDL cholesterol, compared with a quarter in 1990.

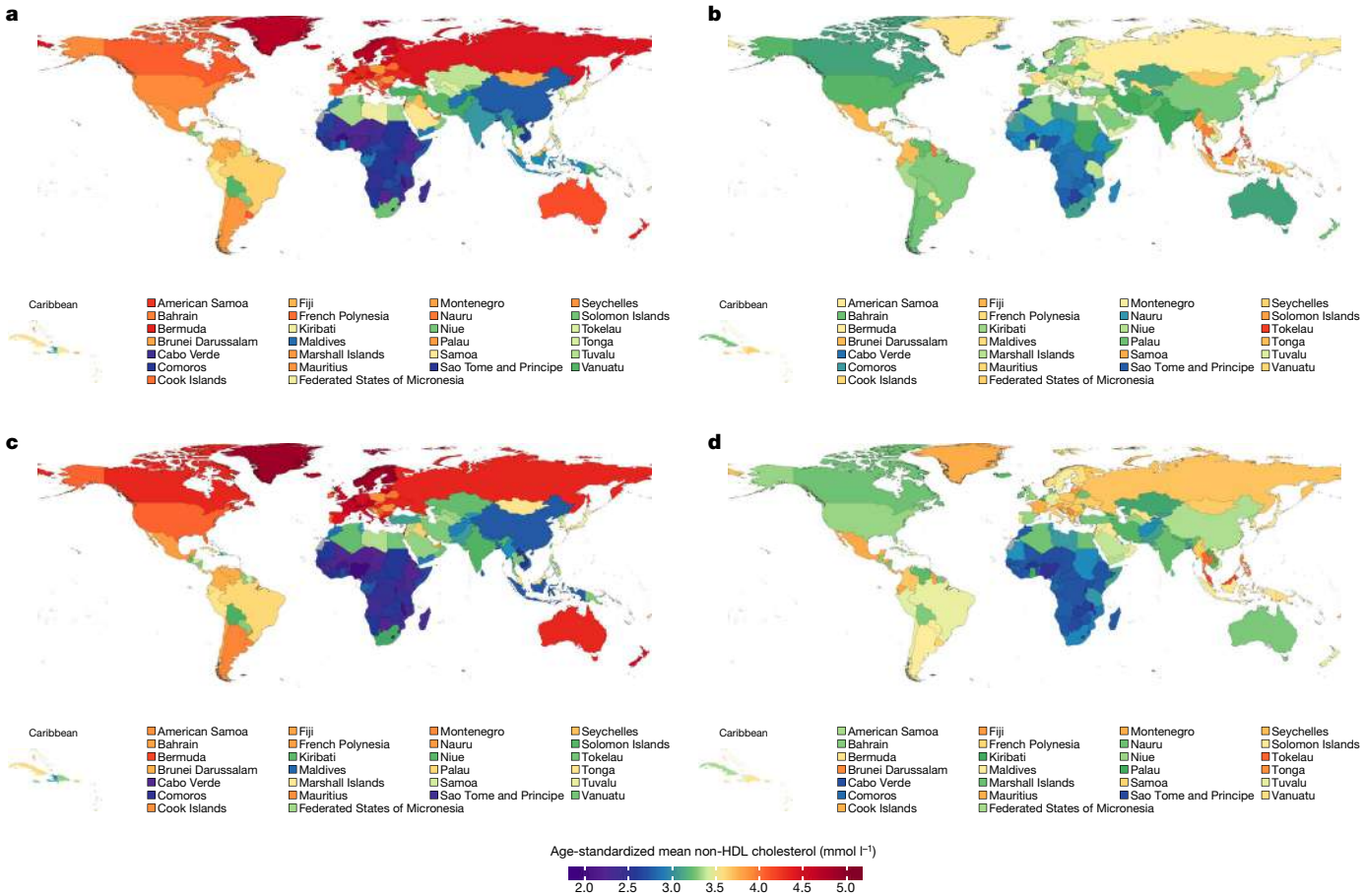

Fig. 3 | Age-standardized mean non-HDL cholesterol by country in 1980 and 2018 for women and men. a, Age-standardized mean non-HDL cholesterol in women in 1980. **b**, Age-standardized mean non-HDL cholesterol in women in 2018. **c**, Age-standardized mean non-HDL cholesterol in men in 1980. **d**, Age-standardized mean non-HDL cholesterol in men in 2018. See Extended Data Fig. 5 for age-standardized mean total cholesterol and Extended Data Fig. 6 for age-standardized mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

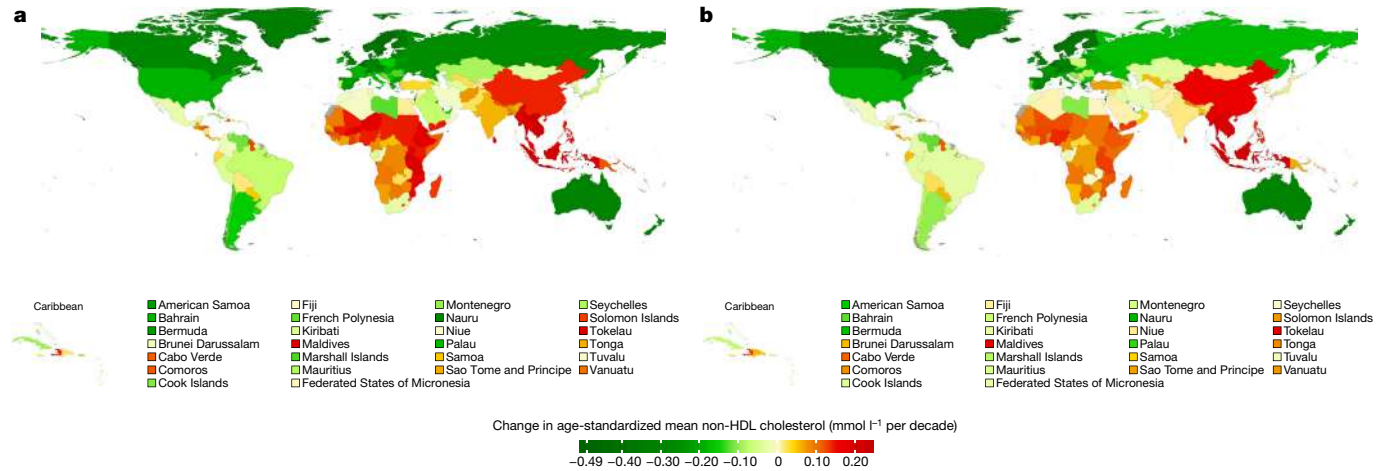

Fig. 4 | Change in age-standardized mean non-HDL cholesterol per decade by country for women and men. a, Change per decade in age-standardized mean non-HDL cholesterol in women. **b**, Change per decade in age-standardized mean non-HDL cholesterol in men. See Extended Data Fig. 7 for change per decade in age-standardized mean total cholesterol and Extended Data Fig. 8 for change per decade in age-standardized mean HDL cholesterol. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

Implications

Our results show that over the past nearly four decades, there has been a major global repositioning of lipid-related risk, with non-optimal cholesterol patterns shifting from being a distinct feature of high-income countries in northwestern Europe, north America and Australasia to one that affects middle-income countries in east and southeast Asia, as well as some countries in Oceania and central Latin America. This transition is especially noticeable for non-HDL cholesterol, which had not been quantified previously in a global analysis. This global repositioning has occurred as a consequence of opposing trends in high-income western countries and in Asia, which has led to some Asian countries having the highest worldwide non-HDL cholesterol levels in 2018.

The decrease in non-HDL cholesterol in western countries started in the 1980s, before statins were widely used[15,16]. This indicates that changes in diet, especially the replacement of saturated with unsaturated fats[3,17–21] and reduction in trans fats[12,17,22], are major contributors to this decline. Nonetheless, the increased use of statins from the late 1990s onwards[15,16], may explain up to one half of the decrease in those countries in which statins are widely used[19,23,24]. In contrast to high-income western countries, the consumption of animal-source foods, refined carbohydrates and palm oil has increased substantially in east and southeast Asia[3,25,26], where statin use remains low[13,27]. For example, the Pearson correlation coefficient between the change in non-HDL cholesterol and the change in a multi-dimensional score of animal-source foods and sugar[3] was 0.69 for women and 0.67 for men using data from high-income western countries and countries in east and southeast Asia, the two regions that experienced the largest decrease and increase, respectively, in non-HDL cholesterol levels. Finally, changes in diet, especially a decrease in carbohydrate and an increase in fat intake[28–31], may have contributed to the large increase in HDL cholesterol observed in the high-income Asia–Pacific region, where there was little increase in overweight and obesity relative to other regions[8,9]. By contrast, the large increase in diabetes[32] and adiposity[8] in Oceania may have contributed to the decrease in HDL cholesterol in this region. The Pearson correlation coefficient between the change in HDL cholesterol and the change in body-mass index[8] was −0.87 for women and −0.69 for men using countries in the high-income Asia–Pacific region and Oceania, the two regions that had the largest increase and decrease, respectively, in HDL cholesterol; the Pearson correlation coefficient for the change in HDL cholesterol and change in diabetes prevalence[32] was −0.84 for women and −0.69 for men. In the same regions, the Pearson correlation coefficient between the change in non-HDL cholesterol and the change in body-mass index[8] was 0.77 for women and 0.62 for men; for the change in non-HDL cholesterol and the change in diabetes prevalence[32], the Pearson correlation coefficient was 0.54 for women and 0.40 for men.

Although it has previously been documented that the prevalence of adiposity[8,9], diabetes[32] and high blood pressure[33] is now higher in low- and middle-income countries than in high-income countries, higher cholesterol is commonly considered to be a feature of affluent western nations[1,2]. We show that, when focusing on non-HDL cholesterol,

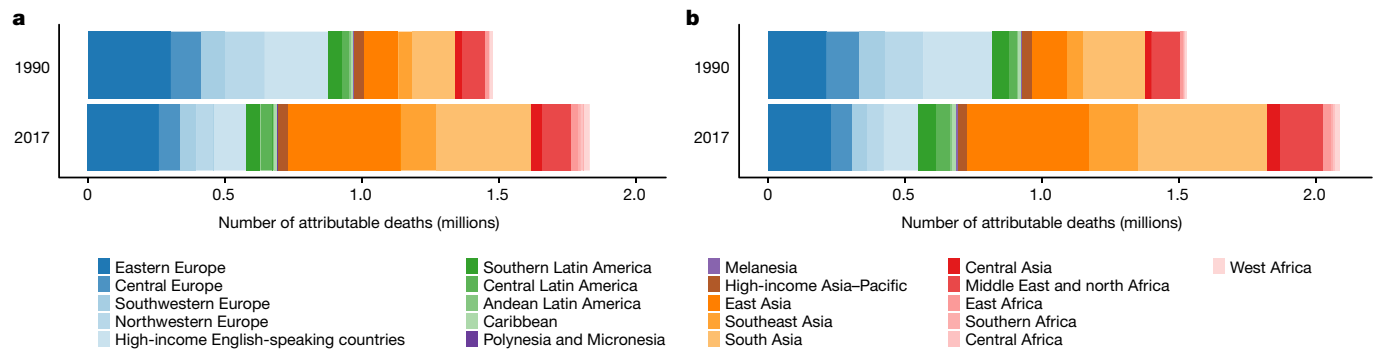

Fig. 5 | Deaths from IHD and ischaemic stroke attributable to high non-HDL cholesterol by region in 1990 and 2017 for women and men. a, Deaths in women attributable to high non-HDL cholesterol. **b**, Deaths in men attributable to high non-HDL cholesterol.

middle-income countries have emerged as the new global epicentre of non-optimal cholesterol as they did for other major cardiovascular disease risk factors, indicating that there is no such a thing as a western risk factor. At the same time, the populations of high-income countries would also benefit from further lowering non-HDL cholesterol. Therefore, population-based policies and personal interventions to improve nutrition and enhance treatment are now needed in all countries, especially as a part of the movement towards universal health coverage.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2338-1.

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Methods

Our aim was to estimate trends in mean total, HDL and non-HDL cholesterol for 200 countries and territories (Supplementary Table 2). We used non-HDL cholesterol rather than low-density lipoprotein (LDL) cholesterol because most studies in our analysis had measured total cholesterol and HDL cholesterol, from which non-HDL cholesterol can be calculated through subtraction. By contrast, LDL cholesterol was directly measured in only around 14% of studies. When LDL cholesterol is not directly measured, its calculation requires data on triglycerides, which were available in approximately 64% of the studies. Furthermore, the most-commonly used estimation method—that is, the Friedewald equation—can be inaccurate, particularly at high levels of triglycerides[34]. Non-HDL and LDL cholesterol were highly correlated (Pearson correlation coefficient = 0.94) in studies with data on both variables (Extended Data Fig. 9), because LDL cholesterol constitutes most of non-HDL cholesterol. Furthermore, non-HDL cholesterol predicts IHD risk at least as well as LDL cholesterol[5,35], and can be measured at a lower cost than LDL cholesterol, which is relevant for how widely it can be used in low- and middle-income countries. Although non-HDL cholesterol is now commonly used in clinical guidelines[36–38], LDL cholesterol continues to be a key target for treatment[36,37], possibly because the interpretation of non-HDL cholesterol is more complex than LDL cholesterol alone. Specifically, an increase in non-HDL cholesterol could be due to the increase in LDL cholesterol or very-low-density lipoprotein cholesterol[39]. Furthermore, there is some evidence that triglyceride levels are high in Asian populations, compared to levels seen in high-income western countries[40]. Therefore, data on non-HDL cholesterol can motivate dietary interventions to both reduce LDL cholesterol (for example, reducing saturated and trans fat intake) and triglyceride levels (for example, reducing refined carbohydrates and increasing omega-3 fatty acids) as well as treatments that lower LDL cholesterol (statins), alongside those that lower triglycerides (for example, fibrates).

Data sources

We used a database of population-based data on cardiometabolic risk factors collated by the NCD Risk Factor Collaboration (NCD-RisC), a worldwide network of health researchers and practitioners that systematically monitors the worldwide trends and variations in non-communicable disease (NCD) risk factors. The database was collated through multiple routes for identifying and accessing data. We accessed publicly available population-based multi-country and national measurement surveys (for example, Demographic and Health Surveys and surveys identified through the Inter-University Consortium for Political and Social Research and European Health Interview & Health Examination Surveys Database). We requested, via the World Health Organization (WHO) and its regional and country offices, from ministries of health and other national health and statistical agencies to identify and access population-based surveys. Requests were also sent via the World Heart Federation to its national partners. We made a similar request to the co-authors of an earlier pooled analysis of cardiometabolic risk factors[7,41–43], and invited the co-authors of the analysis to reanalyse data from their studies and join NCD-RisC. Finally, to identify major sources that were not accessed through the above routes, we searched and reviewed published studies as described in the Supplementary Information and invited all eligible studies to join NCD-RisC.

For each data source, we recorded the available information about the study population, start year and duration of measurement, sampling approach and measurement methods. The information about study population was used to establish that each data source was population-based, and to assess whether it covered the whole country, multiple subnational regions or one or a small number of communities, and whether it was rural, urban or combined.

We carefully checked all data sources in terms of how they met our inclusion and exclusion criteria listed below. We identified duplicate data sources by comparing studies from the same country and year. Additionally, all NCD-RisC members are asked periodically to review the list of sources from their country, to suggest additional sources not in the database, and to verify that the included data meet the inclusion criteria listed below and are not duplicates. The NCD-RisC database is continuously updated through the above routes and through regular contact with NCD-RisC members.

Anonymized individual record data from sources included in NCD-RisC were reanalysed according to a common protocol. Within each survey, we included participants aged 18 years and older who were not pregnant. We removed participants with implausible total cholesterol levels (defined as total cholesterol levels of <1.75 mmol l^{-1} or >20 mmol l^{-1}, or total cholesterol values that were lower than HDL cholesterol values) (<0.05% of all participants with total cholesterol measurements) or HDL cholesterol levels (defined as HDL cholesterol levels of <0.4 mmol l^{-1} or >5 mmol l^{-1}, or total cholesterol values that were lower than HDL cholesterol values) (<0.15% of all participants with HDL cholesterol measurements). When data on LDL cholesterol were also available, we removed individuals for whom the sum of LDL and HDL cholesterol level surpassed total cholesterol level by more than is plausible based on the limits to errors in their measurement (following the CDC Cholesterol Reference Method Laboratory Network (CRMLN) standards, these errors were set at 8.9% for total cholesterol, 13% for HDL cholesterol and 12% for LDL cholesterol) (<0.06% of all participants with total cholesterol and HDL cholesterol measurements)[44–46].

We calculated mean total cholesterol, mean HDL cholesterol and mean non-HDL cholesterol, and associated standard errors and sample sizes, by sex and age group (18–19 years, 20–29 years, followed by 10-year age groups and 80+ years). All analyses incorporated appropriate sample weights and complex survey design in calculating age–sex-specific means when applicable. To ensure summaries were prepared according to the study protocol, computer code was provided to NCD-RisC members who requested assistance. All submitted data were checked independently by at least two researchers. Questions and clarifications were discussed with NCD-RisC members and resolved before the data were incorporated in the database.

Finally, we obtained data not accessed through the above routes by extracting data from published reports of all additional national health surveys identified through the above-described strategies, as well as eight sites of the WHO Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project that were not deposited in the MONICA Data Centre. Data were extracted from published reports only when reported by sex and in age groups no wider than 20 years. We also used data from a previous pooling study[7] when such data did not overlap with those accessed through the above routes.

Data inclusion and exclusion

Data sources were included in NCD-RisC database if: (1) measured data on total, LDL, HDL cholesterol and/or triglycerides were available; (2) study participants were 10 years of age or older; (3) data were collected using a probabilistic sampling method with a defined sampling frame; (4) data were from population samples at the national, subnational (covering one or more subnational regions, more than three urban communities or more than five rural communities) or community (one or a small number of communities) level; (5) data were collected in or after 1950; and (6) data were from the countries and territories listed in Supplementary Table 2.

We excluded all data sources that included only hypercholesterolaemia or dyslipidaemia diagnosis history or medication status without measurement of cholesterol levels. We also excluded data sources on population subgroups for which the lipid profile may differ systematically from the general population, including: (1) studies that had included or excluded people on the basis of their health status or

cardiovascular risk; (2) studies for which the participants were only from ethnic minorities; (3) studies that had recruited only specific educational, occupational or socioeconomic subgroups, with the exception noted below; and (4) studies that had recruited participants through health facilities, with the exception noted below.

We used school-based data in countries and for age–sex groups, for which secondary school enrolment was 70% or higher. We used data for which the sampling frame was health insurance schemes in countries in which at least 80% of the population was insured. Finally, we used data collected through general practice and primary-care systems in high-income and central European countries with universal insurance, because contact with the primary-care systems tends to be as good as or better than response rates for population-based surveys. We used data sources regardless of fasting status, because the differences between fasting and non-fasting measurements are negligible for total, non-HDL and HDL cholesterol[39], and therefore non-fasting lipid profiles are now widely endorsed for the estimation of cardiovascular risk[36,37].

Data used in the analysis

For this paper, we used data from the NCD-RisC database for years 1980 to 2018 and individuals aged 18 years and older. A list of the data sources that we used in this analysis and their characteristics is provided in Supplementary Table 1. The data comprised 1,127 population-based measurement surveys and studies that included measurements of blood lipids on 102.6 million participants aged 18 years and older. We had at least one data source for 161 of the 200 countries that we made estimates for, covering 92.4% of the world's population in 2018 (Extended Data Fig. 1); and at least two data sources for 104 countries (87.5% of the world population). Of these 1,127 sources, 409 (36.3%) sampled from national populations, 250 (22.2%) covered one or more subnational regions, and the remaining 468 (41.5%) were from one or a small number of communities. Regionally, data availability ranged from around 2 data sources per country in sub-Saharan Africa to approximately 35 sources per country in the high-income Asia–Pacific region. In total, 454 data sources (40.3%) were from years before 2000 and the remaining 673 (59.7%) were collected from 2001 onwards.

Adjusting for the differences in mean cholesterol between portable device and laboratory measurements

In 112 (10%) of the 1,127 data sources used in our analysis (11.5% and 5.8% of age–sex-specific data points for total and HDL cholesterol, respectively) lipids were measured using a portable device. Some portable devices have narrower analytical ranges than laboratory methods, which results in truncations of blood cholesterol data that are outside their range (Supplementary Table 3). This may in turn affect the population mean. Although cholesterol concentrations that fall outside the analytical range are displayed as 'high' (above the measurement range) or 'low' (below the measurement range) by these devices, different surveys record and code cholesterol concentrations outside the analytical range in different ways, for example using 'too low', 'too high' and 'error' codes; assigning the minimum or maximum value to individuals whose cholesterol was below or above the analytical range, respectively; setting values outside the analytical range to missing; and so on. We used an approach that treated surveys with such data consistently.

Specifically, we first dropped all participants with cholesterol levels below and at the minimum, and at and above the maximum, values of the analytical range of each portable device before calculating the mean cholesterol (Supplementary Table 3). We then developed conversion regressions to adjust the mean cholesterol levels measured using a portable device (calculated over the restricted range, Supplementary Table 3) to the levels expected using laboratory measurements. The dependent variable in each regression was mean total, non-HDL or HDL cholesterol for the full range, and the main independent variable was mean total, non-HDL or HDL cholesterol over the above-mentioned restricted cholesterol range of the portable devices. The regression coefficients were estimated from data sources for which lipids were measured in a laboratory, and thus had the full range of measurement and could be used to calculate both dependent and independent variables. When estimating the regression coefficients, we constructed the dependent variable using the full data, and the independent variable by dropping the values outside the above-mentioned restricted cholesterol range of each device, mimicking those that would be expected if a portable device had been used. Separate models were developed according to the specific range of the different portable devices. All regressions included terms for age and sex, as well as interactions between predictors and age and sex, based on the Bayesian information criterion[47]. The regressions for mean non-HDL cholesterol also included mean total cholesterol and mean HDL cholesterol because non-HDL cholesterol is calculated from total cholesterol and HDL cholesterol. We excluded data points for which there were fewer than 25 individuals for the purpose of estimating the coefficients of these regressions. All sources of uncertainty in the conversion—including the sampling uncertainty of the original data, the uncertainty of the regression coefficients and residuals—were carried forward by using repeated draws from their respective distributions. The regression coefficients and number of data points used to estimate the coefficients are shown in Supplementary Table 4.

Statistical analysis

We used a statistical model to estimate mean total, non-HDL and HDL cholesterol by country, year, sex and age using all of the available data. The model is described in detail in a statistical paper and related substantive papers[8,32,33,48]; the computer code is available at http://www.ncdrisc.org/. In summary, we organized countries into 21 regions, mainly based on geography and national income; these regions were further aggregated into 9 'super-regions' (Supplementary Table 2). The model had a hierarchical structure in which estimates for each country and year were informed by its own data, if available, and by data from other years in the same country and from other countries, especially countries in the same region or super-region with data for similar time periods. The extent to which estimates for each country-year are influenced by data from other years and other countries depends on whether the country has data, the sample size of data, whether or not they are national, and the within-country and within-region data variability. The model incorporated nonlinear time trends comprising linear terms and a second-order random walk. The age association of blood lipids was modelled using a cubic spline to allow nonlinear age patterns, which might vary across countries. The model accounted for the possibility that blood lipids in subnational and community samples might systematically differ from nationally representative ones; and/or have larger variation. These features were implemented by including data-driven fixed-effect and random-effect terms for subnational and community data. The fixed effects adjust for systematic differences between subnational or community studies and national studies. The random effects allow national data to have larger influence on the estimates than subnational or community data with similar sample sizes. The model also accounted for rural–urban differences in blood lipids, through the use of data-driven fixed effects for rural-only and urban-only studies. These rural and urban effects were weighted by the difference between study-level and country-level urbanization in the year in which the study was done. The proportion of the national population living in urban areas was also included as a predictor (covariate) in the model. The model for mean non-HDL and HDL cholesterol also used age-standardized mean total cholesterol as a covariate.

We fitted the statistical model with the Markov chain Monte Carlo (MCMC) algorithm, and obtained 5,000 post-burn-in samples from the posterior distribution of model parameters, which were in turn used to obtain the posterior distributions of mean total, non-HDL and HDL cholesterol. We calculated average change in mean total, HDL and non-HDL cholesterol across the 39 years of analysis (reported as change

per decade). Age-standardized estimates were generated by taking weighted averages of age–sex-specific estimates, using the WHO standard population. Estimates for regions and the world were calculated as population-weighted averages of the constituent country estimates by age group and sex. The reported credible intervals represent the 2.5–97.5th percentiles of the posterior distributions. We also report the posterior probability that an estimated increase or decrease represents a truly increasing or decreasing trend as opposed to a chance observation. We performed all analyses by sex, because blood lipids levels and trends are different in men and women.

Validation of statistical model

We tested how well our statistical model predicts missing data, known as external predictive validity, in two different tests. In the first test, we held out all data from 10% of countries with data (that is, created the appearance of countries with no data where we actually had data). The countries for which the data were withheld were randomly selected from the following three groups: data rich (5 or more data sources, with at least one data source after the year 2000), data poor (1 data source) and average data availability (2–4 data sources). In the second test, we assessed other patterns of missing data by holding out 10% of our data sources, again from a mix of data-rich, data-poor and average-data countries, as defined above. For a given country, we either held out a random half of the data of a country or all of the 2000–2018 data of the country to determine, respectively, how well we filled in the gaps for countries with intermittent data and how well we estimated in countries without recent data. In both tests, we then fitted the model to the remaining 90% of the countries (test 1) or data sources (test 2) and made estimates of the held-out observations. We repeated each test five times, holding out a different subset of data in each repetition. In both tests, we calculated the differences between the held-out data and the estimates. We also calculated the 95% credible intervals of the estimates; in a model with good external predictive validity, 95% of held-out values would be included in the 95% credible intervals.

Our statistical model performed well in the external validation tests, that is, in estimating mean cholesterol when data were missing. The estimates of mean total, non-HDL and HDL cholesterol were unbiased, as evidenced with median errors that were very close to zero globally for every outcome and test, and less than ±0.30 mmol l^{-1} in every subset of withheld data except for women in the high-income Asia–Pacific region in test 1 for non-HDL cholesterol (median error 0.47 mmol l^{-1}) and men in south Asia in test 2 for non-HDL cholesterol (median error −0.33 mmol l^{-1}) (Supplementary Table 5). The 95% credible intervals of estimated means covered 83–92% and 75–83% of true data globally in the first and second tests, respectively. In subsets, coverage ranged from 47% to 100%, but was mostly greater than 75%, with coverage generally lower in test 2 than test 1. Median absolute errors ranged from 0.07 to 0.23 mmol l^{-1} globally for different outcomes and sexes, and were no more than 0.45 mmol l^{-1} in all subsets of withheld data, except for women in the high-income Asia–Pacific region for non-HDL cholesterol in test 1 (median absolute error 0.47 mmol l^{-1}).

Calculation of the number of deaths attributable to high cholesterol

We estimated the number of deaths from IHD and ischaemic stroke attributable to high non-HDL cholesterol. For each country, year, sex and age group, we first calculated the population attributable fractions—that is, the proportion of deaths from IHD and ischaemic stroke that would have been prevented if non-HDL cholesterol levels were at an optimal level (defined as a mean of 1.8–2.2 mmol l^{-1}) in the population[6,49]. For these calculations, we used age-specific relative risks from meta-analyses of prospective cohort studies[4,5,50]. The number of IHD and ischaemic stroke deaths attributable to high non-HDL cholesterol was calculated for each country–year–age–sex group by multiplying the cause-specific population attributable fractions by the cause-specific deaths from the Global Burden of Disease study in 1990 and 2017 (the earliest and latest years with cause-specific mortality data).

Strengths and limitations

The strengths of our study include its scope in making consistent and comparable estimates of trends in blood cholesterol and its cardiovascular disease mortality burden, over almost four decades for all of the countries in the world, including global estimates of non-HDL and HDL cholesterol. We used a large amount of population-based data, which came from countries in which 92% of the global adult population lives. We used only data from studies that had measured blood lipids to avoid bias in self-reported data. Data were analysed according to a consistent protocol, and the characteristics and quality of data from each country were rigorously verified through repeated checks by NCD-RisC members. We pooled data using a statistical model that took into account the epidemiological features of cholesterol, including nonlinear time trends and age associations. Our statistical model used all available data while giving more weight to national data than to subnational and community sources.

Similar to all global analyses, our study is affected by some limitations. Despite our extensive efforts to identify and access worldwide population-based data, some countries had no or few data sources, especially those in sub-Saharan Africa, the Caribbean, central Asia and Melanesia. Estimates for these countries relied mostly or entirely on the statistical model, which shares information across countries and regions through its hierarchy. Data scarcity is reflected in wider uncertainty intervals of our estimates for these countries and regions, highlighting the need for national NCD-oriented surveillance. The distribution of lipids measured in a population using a portable device, which was used in 10% of our studies, may be truncated and may therefore affect the population mean. To overcome this issue, we developed conversion regressions to adjust mean cholesterol levels measured using a portable device to the levels expected in laboratory measurements; the conversion regressions used for this purpose had good predictive accuracy. Although most studies had measured cholesterol in serum samples, around 7% had used plasma samples. As cholesterol measured in plasma and serum samples differ[51] by only about 3%, adjusting for plasma-serum differences would have little effect on our results, as seen in a previous analysis[14]. Although methods to measure total and HDL cholesterol have evolved over time, since the 1950s there have been systematic efforts to standardize lipid measurements that have resulted in increased comparability between different methods. In our analysis, 90% of studies measured lipids in a laboratory; of these studies more than 60% for total cholesterol and more than 70% for HDL cholesterol participated in a lipid standardization programme or quality control scheme. We did not analyse emerging lipid markers such as apolipoprotein B and apolipoprotein A-I, because they are neither commonly measured in population-based health surveys, nor routinely used in clinical practice[36].

Comparison with other studies

There are no global analyses on trends in lipid fractions for comparison with our results. Our findings for total cholesterol were largely consistent with the only other previous analysis[7], but we estimated a larger decrease in mean total cholesterol in high-income western countries and central Europe, and a larger increase in southeast Asia, because we had an additional decade of data compared with the earlier global analysis. Therefore, although the highest mean total cholesterol levels reported previously[7], for 2008, were still in high-income western countries, we estimated that in 2018 total cholesterol was equally high or higher in southeast Asia. Our findings on mean total cholesterol trends are also largely consistent with previous multi- and single-country reports[14,15,17–21,52–73]. Differences from previous studies—for example, in Italy[61], Lithuania[63], the Netherlands[65], Russian Federation[69] and in some countries that participated in the MONICA Project[52]—mostly arise

because our study covered a longer period and used a larger number of data sources. Studies[15,18,54,63,66,70,74–77] that have reported trends in lipid fractions for a period longer than 15 years have found changes in non-HDL cholesterol (or in LDL cholesterol for some studies) that were consistent with our results.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

Estimates of mean total, non-HDL and HDL cholesterol by country, year and sex are available at http://www.ncdrisc.org/. Input data from publicly available sources can also be downloaded from http://www.ncdrisc.org/. For other data sources, contact information for data providers can be obtained from http://www.ncdrisc.org/.

Code availability

The computer code for the Bayesian hierarchical model used in this work is available at http://www.ncdrisc.org/.

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Author contributions M.E. and G.D. designed the study and oversaw research. C.T., B.Z., H.B. and R.C.L. led the data collection. The other authors contributed to study design; and collected, reanalysed, checked and pooled data. C.T. analysed pooled data and prepared results. C.T., E.G. and M.E. wrote the first draft of the manuscript with input from the other authors.

Competing interests M.E. reports a charitable grant from the AstraZeneca Young Health Programme, and personal fees from Prudential, Scor and Third Bridge, outside the submitted work. The other authors declare no competing interests.

Additional information

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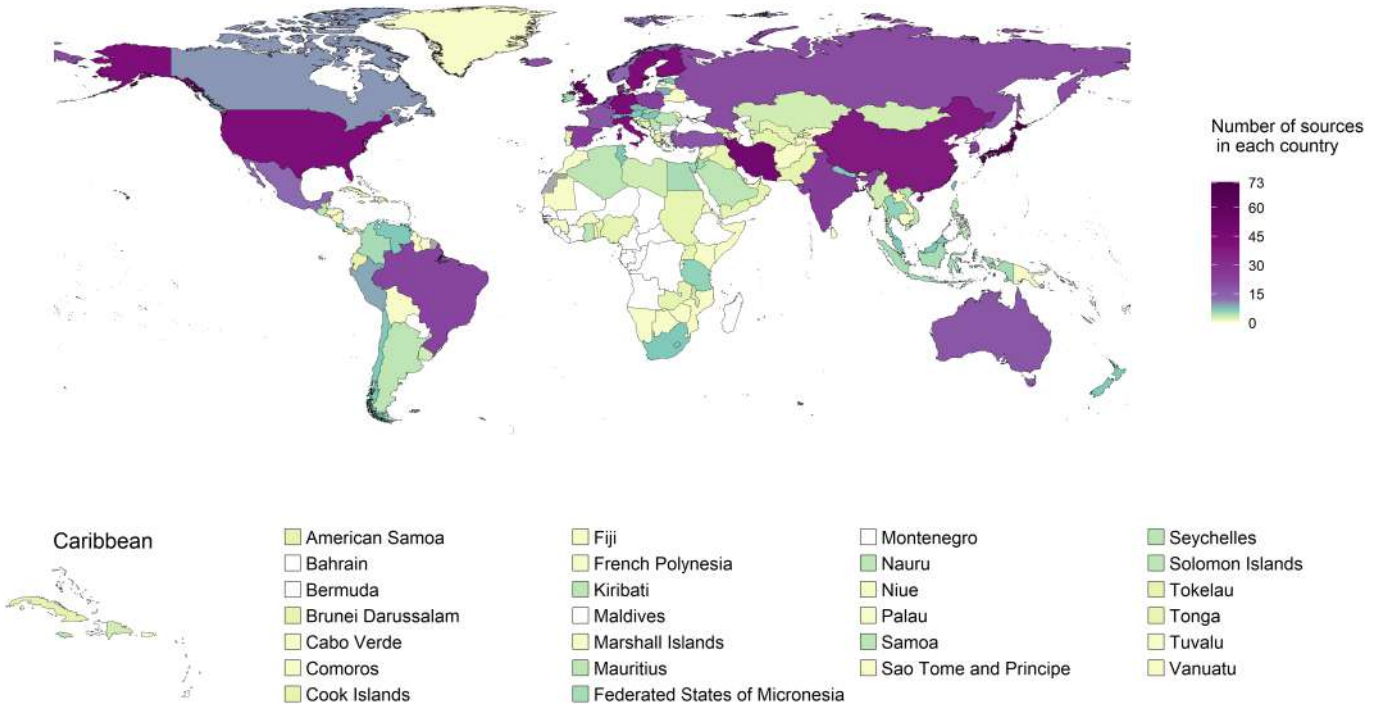
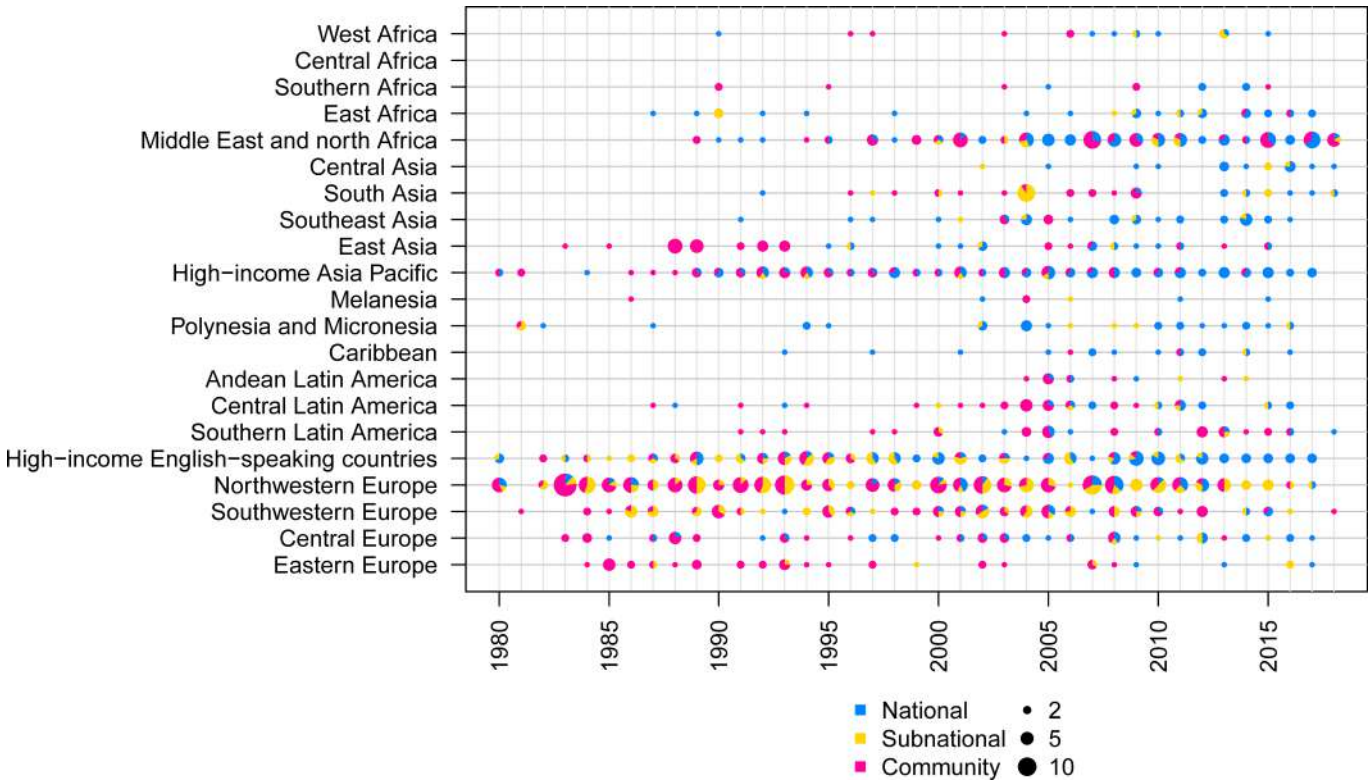
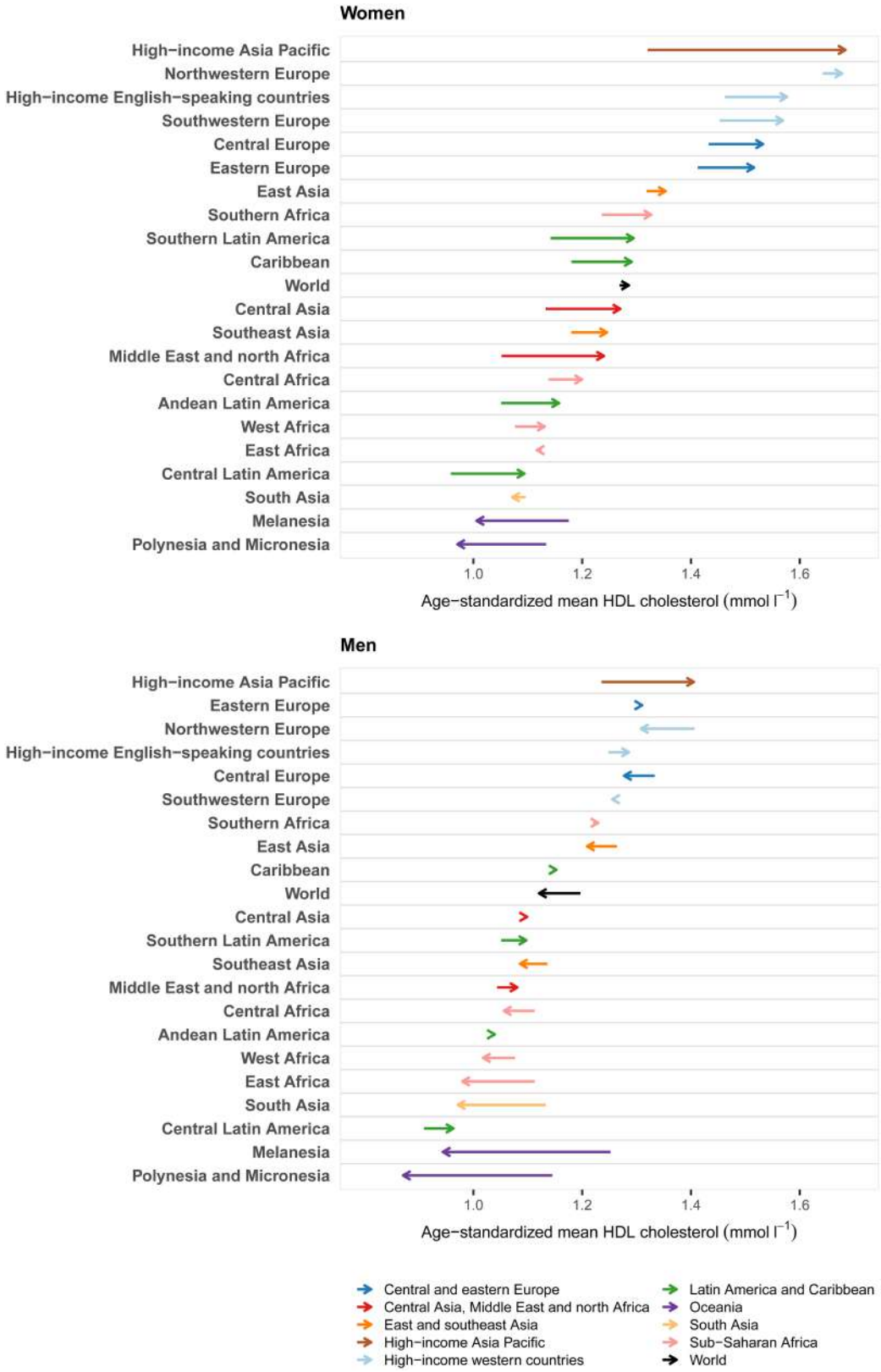


Extended Data Fig. 1 | Number of data sources by country. The colour indicates the number of data sources for each country used in the analysis. Countries and territories that were not included in the analysis are coloured in grey.

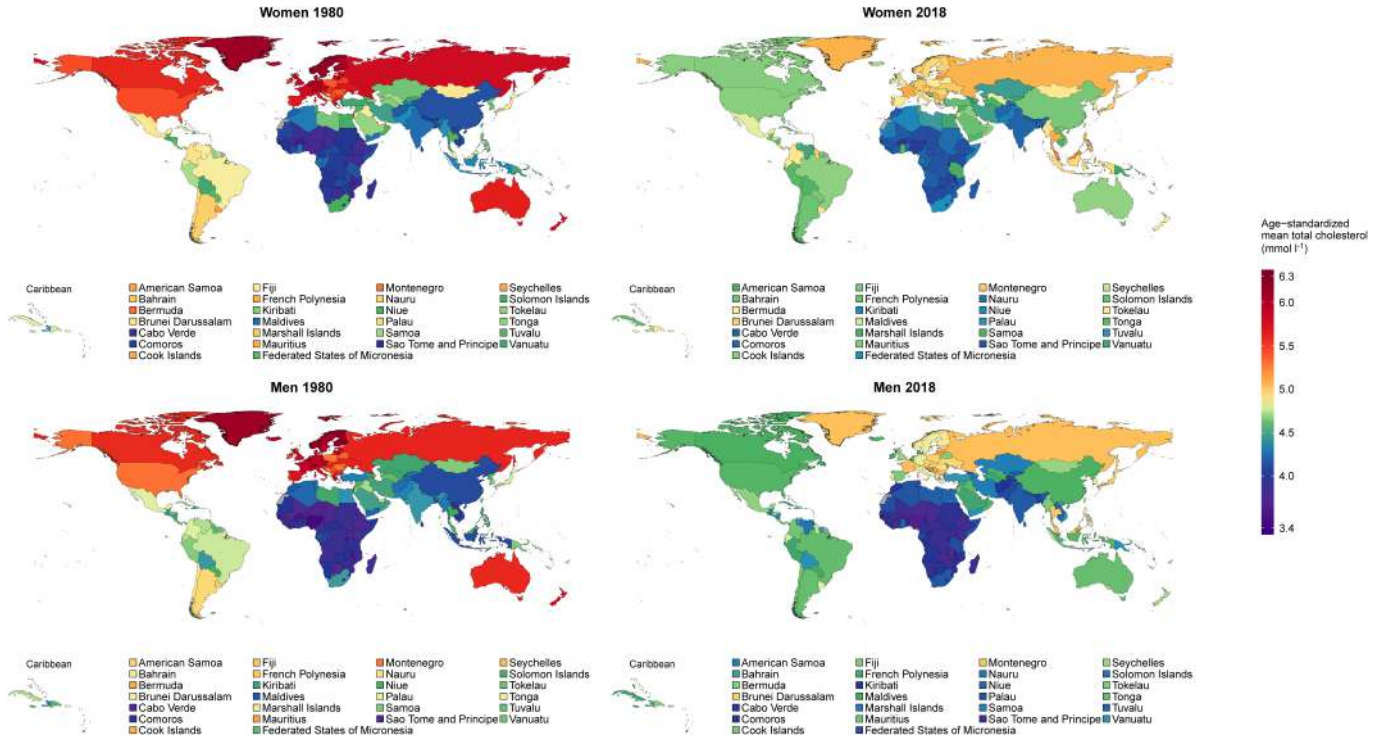


Extended Data Fig. 2 | Number of data sources by region and year. The size of each circle shows the number of data sources for each region and year, and the colours indicate the relative size of national, subnational and community data sources.

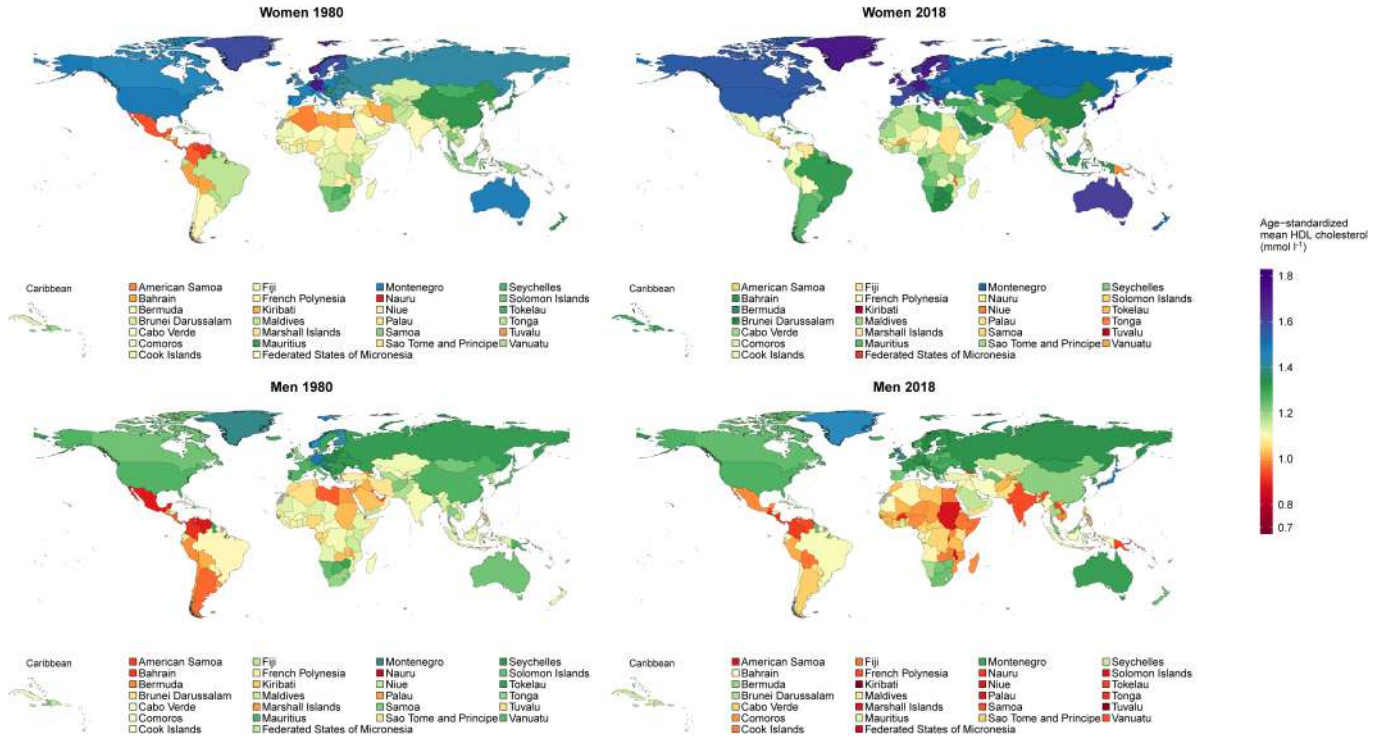


Extended Data Fig. 3 | Change in age-standardized mean HDL cholesterol between 1980 and 2018 by region for women and men. The start of the arrow shows the level in 1980 and the head shows the level in 2018. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

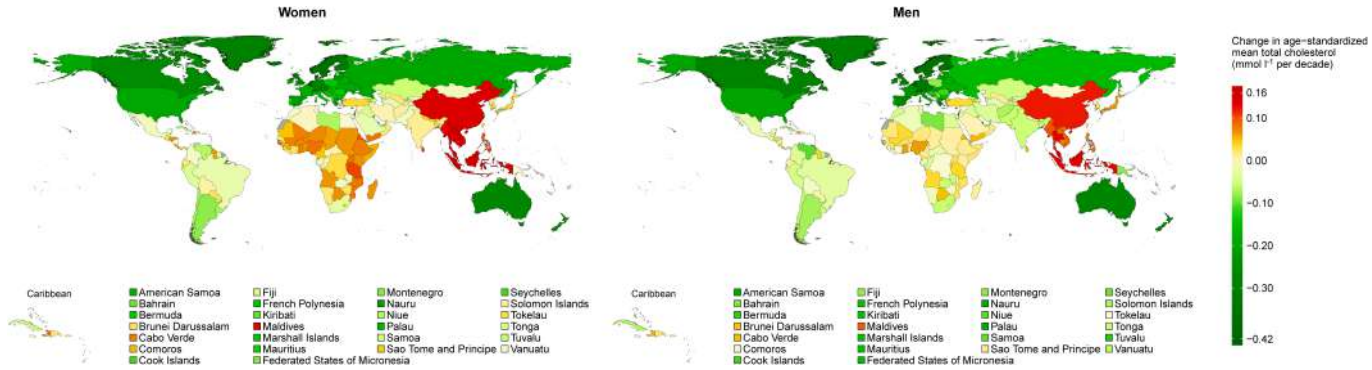
Extended Data Fig. 4 | Change in age-standardized mean HDL and non-HDL cholesterol between 1980 and 2018 by region for women and men. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.



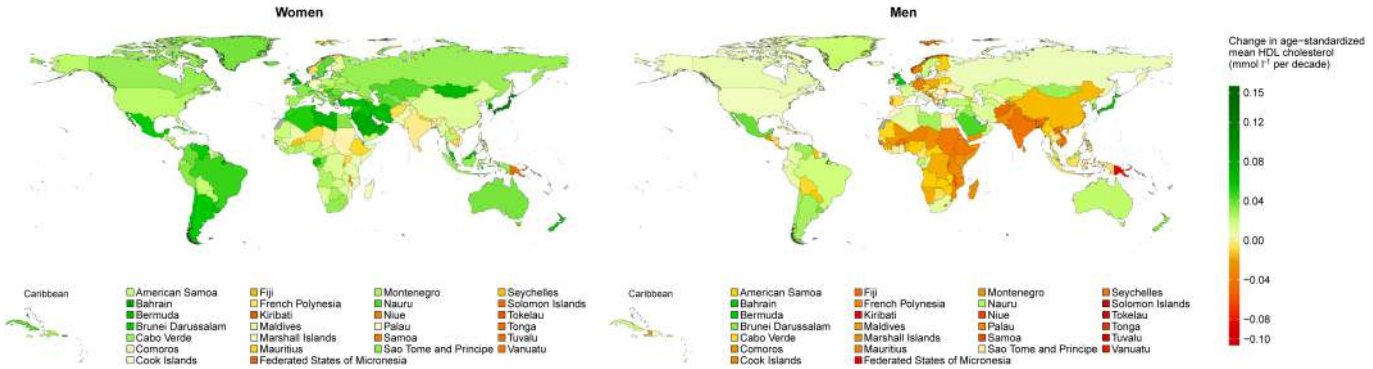
Extended Data Fig. 5 | Age-standardized mean total cholesterol by country in 1980 and 2018 for women and men. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.



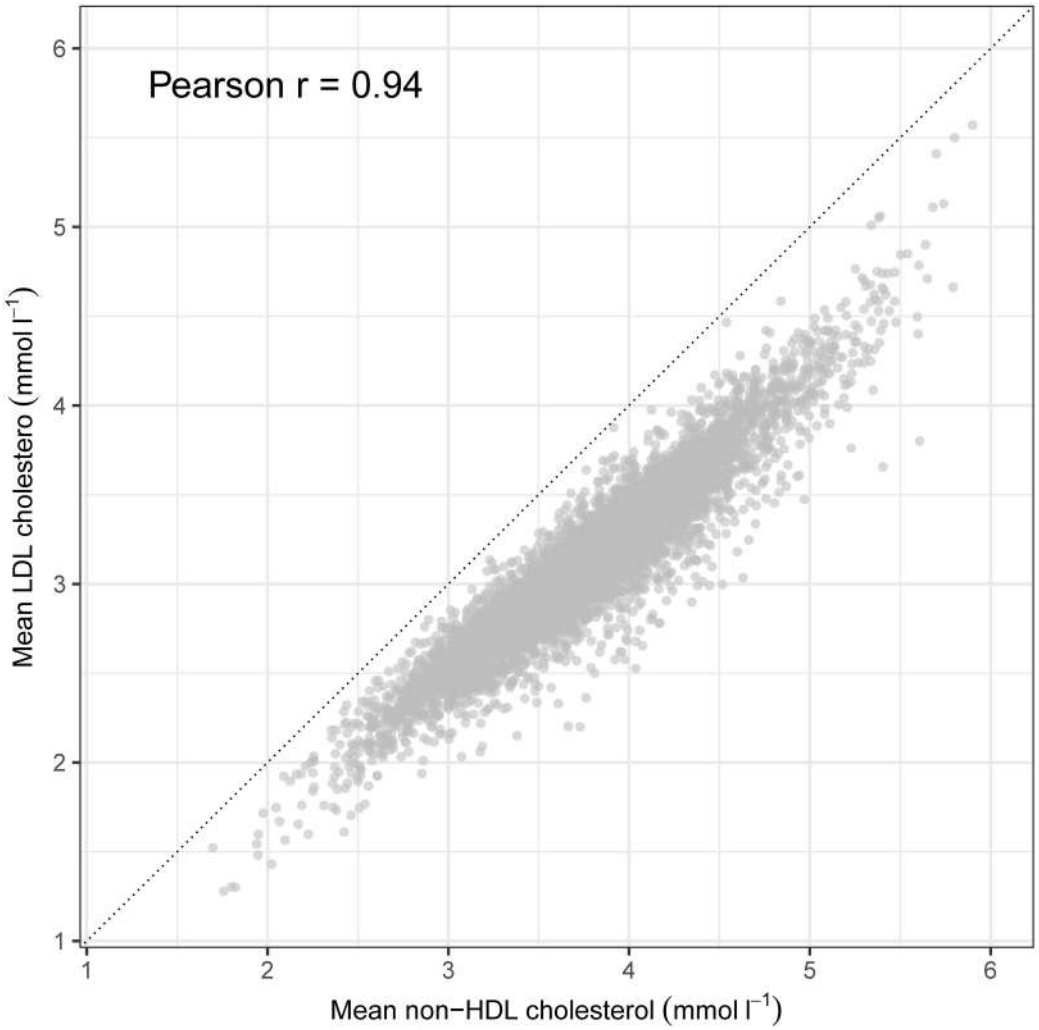
Extended Data Fig. 6 | Age-standardized mean HDL cholesterol by country in 1980 and 2018 for women and men. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.



Extended Data Fig. 7 | Change per decade in age-standardized mean total cholesterol by country for women and men. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.



Extended Data Fig. 8 | Change per decade in age-standardized mean HDL cholesterol by country for women and men. One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.



Extended Data Fig. 9 | The association between mean LDL and non-HDL cholesterol in studies that measured lipids in a laboratory that had data for both variables. Each data point is one study–age–sex group (n = 6,864). One mmol l^{-1} is equivalent to 38.61 mg dl^{-1}.

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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☒	☐	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
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☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Processing of secondary data was conducted using the statistical software R (version 3.6.0).
Data analysis	All analyses were conducting using the statistical software R (version 3.6.0). The code for estimation of mean risk factor trends is available at www.ncdrisc.org.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

This is a data-pooling study that brings together more than 1000 disparate data sources and uses a Bayesian hierarchical model to estimate population risk factor trends. Estimates of mean total, non-HDL and HDL cholesterol by country, year, and sex will be available from www.ncdrisc.org upon the publication of the paper. Some of the input data sources are publicly available, for which we will add links in the final version of the paper. Others are the property of specific research groups and agencies, for which we will provide contact information.

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☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	We pooled and re-analysed population-based data that had measured blood lipids in adults to estimate trends in mean total, non-HDL and HDL cholesterol from 1980 to 2018 for 200 countries and territories, using a Bayesian hierarchical model.
Research sample	We pooled data from 1,127 population-based studies of blood lipids conducted in 161 countries, with measurement of blood lipids in over 102 million adults aged 18 years and older. Studies were representative of a national, subnational or community population.
Sampling strategy	We included data collected using a probabilistic sampling method with a defined sampling frame. We therefore included studies with simple random and complex survey designs but excluded convenience samples.
Data collection	We used data on measured blood lipids to calculate mean total, non-HDL and HDL cholesterol. We excluded self-reported data.
Timing	We pooled data collected from 1980 to 2018. We also included national studies for the 3 years prior to 1980 (n=1), assigning them to 1980, so that they can inform the estimates in countries with slightly earlier national data.
Data exclusions	We excluded all data sources that included only hypercholesterolemia or dyslipidaemia diagnosis history or medication status without measurement of cholesterol levels. We also excluded data sources on population subgroups whose lipid profile may differ systematically from the general population, including: • studies that had included or excluded people based on their health status or cardiovascular risk; • studies whose participants were only ethnic minorities; • specific educational, occupational, or socioeconomic subgroups, with the exception noted below; • those recruited through health facilities, with the exception noted below. We used school-based data in countries, and in age-sex groups, where secondary school enrollment was 70% or higher. We used data whose sampling frame was health insurance schemes in countries where at least 80% of the population were insured. Finally, we used data collected through general practice and primary care systems in high-income and central European countries with universal insurance, because contact with the primary care systems tends to be as good as or better than response rates for population-based surveys. Our exclusion criteria were established at the initiation of the study to ensure all data were representative.
Non-participation	Our inclusion/exclusion criteria were designed to ensure participants of the surveys included were representative of the general population from which each sample was drawn.
Randomization	Our study is descriptive, and we did not carry out experiments.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging