National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants


Summary

Background Data for trends in serum cholesterol are needed to understand the effects of its dietary, lifestyle, and pharmacological determinants; set intervention priorities; and evaluate national programmes. Previous analyses of trends in serum cholesterol were limited to a few countries, with no consistent and comparable global analysis. We estimated worldwide trends in population mean serum total cholesterol.

Methods We estimated trends and their uncertainties for adults 25 years and older in 199 countries and territories. We obtained data from published and unpublished health examination surveys and epidemiological studies (321 country-years and 3·0 million participants). For each sex, we used a Bayesian hierarchical model to estimate mean total cholesterol by age, country, and year, accounting for whether a study was nationally representative.

Findings In 2008, age-standardised mean total cholesterol worldwide was 4·64 mmol/L (95% uncertainty interval 4·51–4·76) for men and 4·76 mmol/L (4·62–4·91) for women. Globally, mean total cholesterol changed little between 1980 and 2008, falling by less than 0·1 mmol/L per decade in men and women. Total cholesterol fell in the high-income region consisting of Australasia, North America, and western Europe, and in central and eastern Europe; the regional declines were about 0·2 mmol/L per decade for both sexes, with posterior probabilities of these being true declines 0·99 or greater. Mean total cholesterol increased in east and southeast Asia and Pacific by 0·08 mmol/L per decade (−0·06 to 0·22, posterior probability=0·86) in men and 0·09 mmol/L per decade (−0·07 to 0·26, posterior probability=0·86) in women. Despite converging trends, serum total cholesterol in 2008 was highest in the high-income region consisting of Australasia, North America, and western Europe; the regional mean was 5·24 mmol/L (5·08–5·39) for men and 5·23 mmol/L (5·03–5·43) for women. It was lowest in sub-Saharan Africa at 4·08 mmol/L (3·82–4·34) for men and 4·27 mmol/L (3·99–4·56) for women.

Interpretation Nutritional policies and pharmacological interventions should be used to accelerate improvements in total cholesterol in regions with decline and to curb or prevent the rise in Asian populations and elsewhere. Population-based surveillance of cholesterol needs to be improved in low-income and middle-income countries.

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Introduction Raised serum total cholesterol is an important cardiovascular risk factor, which causes an estimated 4·4 million deaths every year worldwide. Variations in diet, especially consumption of animal-based versus plant-based fats, adiposity, and use of drugs to lower cholesterol have led to differences in serum cholesterol concentrations across populations and over time.

Reliable population-based data for cholesterol trends are needed to assess the effects of diet, adiposity, and statin use; guide priority setting; and evaluate programmes. Investigators of the MONICA Project and other studies have analysed trends in serum cholesterol in specific communities and recorded changes as large as 0·7 mmol/L per decade. Less is known about national trends, in high-income or developing countries. Previous comparative cross-population analyses were based on a small number of data sources, used data that might not have been population based, did not explicitly address missing data for whole countries or for older ages, combined data from nationally representative surveys with subnational and community studies without distinguishing them, and did not quantify uncertainty. Our aim was to estimate trends in cholesterol by country, and to systematically quantify uncertainty.

Methods Study design We estimated 1980–2008 trends in mean serum total cholesterol and their uncertainties, by sex, for 199 countries...
and territories in 21 subregions of the Global Burden of Diseases, Injuries, and Risk Factors study, which are grouped into seven merged regions (webappendix p 16). Although LDL cholesterol, ratio of total to HDL cholesterol, and specific apolipoproteins might be better indicators of cardiovascular risk,1,4,30 our primary analysis was based on total cholesterol because our search of published studies showed that population-based data for lipoproteins and apolipoproteins were available in very few countries. We used mean total cholesterol, instead of the prevalence of hypercholesterolaemia, because the association with cardiovascular outcomes is linear in commonly observed ranges.1,4

Our analysis included two steps: (1) identification of data sources, and accessing and extracting data; and (2) application of a statistical model to estimate trends in total cholesterol by country and sex. We analysed the uncertainty in the estimates, taking into account sampling uncertainty and uncertainty from statistical modelling.

Data identification, access, and extraction

We obtained data from health examination surveys and community studies with anonymised data available to Collaborating Group members; multicentre studies; a review of published articles; and unpublished data identified through the WHO Global InfoBase (figure 1 and webappendix pp 2–3).

Collaborating Group members analysed anonymised data from health examination surveys and epidemiological studies. Mean total cholesterol was calculated by sex and age group, incorporating appropriate sample weights when applicable. We identified data sources by searching Medline and Embase for articles published between January, 1980, and July, 2009, with no language restriction. Webappendix pp 2–3 and figure 1 provide detailed information about search strategy, exclusion criteria, and the number of articles identified and retained. In brief, studies were included if they were from a representative sample, including from a national, subnational, or community population, and, following the recommendation of the Adult Treatment Panel III,30 if blood samples were fasting.

We contacted the authors of published studies that had not reported total cholesterol by age and sex and invited them to join the Collaborating Group and to provide age-stratified and sex-stratified data with a standardised data request form. We also used the WHO Global InfoBase to obtain age-stratified and sex-stratified data from sources for which stratified data were not available in the original published article.

![Flow diagram for data identification and access](Image)
We identified additional data sources through personal communications with researchers, including inquiries about additional data from authors of published studies. We also searched the WHO Global InfoBase for additional data sources. This process led to data from multicentre studies (eg, the MONICA Project), published government reports, published sources not identified in our review, and unpublished data. These data were used only if information about study population and measurement methods were available.

We identified duplicate sources of data by comparing studies that were from the same population-year (eg, when data from one of the MONICA Project or other multicentre study sites were reported separately, or when a national survey available to Collaborating Group members was also reported in a publication), and we used the source with most detail.

Data stratified by age and sex were extracted into standard data extraction files. Extracted data included age-stratified and sex-stratified total cholesterol mean and SD; sample sizes, standard errors, and confidence intervals; survey population and sampling strategy; and selected other study characteristics (webappendix pp 17–29). Importantly, for each data source we recorded whether the data were national (separated into weighted and unweighted), subnational (covered multiple communities, provinces, or states), or were from individual communities (denoted as coverage hereafter); and whether the study population was rural, urban, or both (webappendix pp 17–29). This information was used to account for potential bias and additional uncertainty in data sources that were not representative of their national populations.

**Statistical analysis**

Despite our extensive data access, many country-years were without data or without nationally representative data, because in most countries risk factor surveys are not undertaken every year. Further, because of measurement difficulties, fewer health surveys measure serum cholesterol than other risks such as blood pressure and body-mass index (BMI). Some sources with data covered only some age or sex groups, or only rural or urban populations. We developed a statistical model to estimate mean total cholesterol over time, by age group, sex, and country. We did all analyses by sex, because lipid concentrations and trends can differ in men and women.21,22

We used a Bayesian hierarchical model to make estimates for each age-country-year unit; the estimates were informed by data from that unit itself, if available, and by data from other units. Specific model features, and their motivations, are described briefly below. Webappendix pp 4–15 provides complete details about the statistical model and about model validation and testing.

We used a hierarchical model in which levels and trends of total cholesterol in countries were, in turn, nested in subregional, regional, and global levels and trends. The hierarchical model borrows information across countries, subregions, and regions, appropriately compromising between (overly) uncertain within-unit estimates and (overly) simplified aggregate cross-unit estimates. It borrows information to a greater degree when data are non-existent or non-informative (ie, have large uncertainty), and to a lesser degree in data-rich countries, subregions, and regions.

Trends over time were modelled as non-linear, consisting of a linear trend plus a smooth non-linear trend, at all levels. Both components were modelled hierarchically. Time varying country-level covariates informed the estimates. The covariates, described elsewhere,23 were national income (Ln per-head gross domestic product in 1990 international dollars), urbanisation (proportion of population that lived in urban areas), and national availability of multiple food types. To reduce the effect of fluctuations of covariates between years and to reflect potentially cumulative associations, we used a weighted average of the past 10 years, with progressively smaller weights in the more distant past.

Subnational and community studies might be undertaken in areas with low or high cholesterol and hence might differ systematically from national studies. They might also have larger variation than nationally representative studies. Our model included offsets for subnational and community data, and additional variance components for subnational and community data and for national data without sample weights. These variance components were estimated empirically and allowed national data with sample weights to have a stronger effect on estimates than other sources. Lipid profiles might differ systematically between rural and urban populations, with the difference depending on the country’s extent of urbanisation. Therefore, our model also accounted for differences between study-level and country-level urbanisation.

Mean total cholesterol might be non-linearly associated with age, and the age association might flatten or even decrease in older ages. The age association of total cholesterol might vary across countries, and generally rises steeply when mean cholesterol is high. Therefore, we used a cubic spline age model, with parameters estimated as a function of total cholesterol at a baseline age.

Mean total cholesterol was estimated from the model for 5–10-year age groups, by country and year, for adults 25 years and older. Subregional and regional estimates for every year were calculated as population-weighted averages of the constituent country estimates by age group and sex. For presentation, age-specific estimates for each country or region and year were age-standardised to the WHO reference population.22

We quantified the following sources of uncertainty (webappendix pp 4–15): sampling uncertainty of original data sources; uncertainty associated with fluctuations between years in national data, because of unmeasured study design and quality factors (eg, national data from the USA and Singapore in webappendix pp 89–284) or...
because some had not used sample weights; additional uncertainty associated with data sources that were not national, because of subgroup variation within each country; and uncertainty due to use of a model to estimate mean total cholesterol by age group, country, and year when data were missing.

We fitted the Bayesian model with the Markov chain Monte Carlo (MCMC) algorithm and obtained samples from the posterior distribution of model parameters, which were in turn used to obtain the posterior distribution of mean total cholesterol for each age, country, and year, reflecting all the above sources of uncertainty (webappendix pp 4–15). The uncertainty intervals represent the 2·5–97·5 percentiles of the posterior distribution of estimated mean total cholesterol. Change was estimated as linear trend over the 28 years of analysis in each MCMC iteration, and is reported as per decade. We also report the posterior probability that an estimated increase or decrease corresponds to a truly increasing or decreasing trend, referred to simply as posterior probability. The posterior probability is not a p value; the posterior probability would be 0·50 in a country or region in which an increase is statistically indistinguishable from a decrease, and larger posterior probability indicates more certainty.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Writing and Global Analysis Group had access to all data sources and has responsibility for the contents of the report and the decision to submit for publication.

Results
Our analysis included 321 country-years of data for serum total cholesterol with 3·0 million participants (figure 1). 166 country-years were from 24 high-income countries and 155 from 66 low-income and middle-income countries, showing the global gap in lipids surveillance, even relative to blood pressure and BMI.31,33 High-income Asia-Pacific, North America, and western Europe had the most data per country (webappendix pp 39–41). Japan had 20 years of national data since 1980, and the USA had 7 years. We could not identify any population-based data for more than 100 countries. Sub-Saharan Africa, Latin America and Caribbean, and central and southeast Asia had the largest proportion of countries without data. About 40% of all data and two-thirds of all national data were from the 2000s (webappendix pp 42–43). One in five countries had time-series data for total cholesterol.

Figure 2: Trends in age-standardised mean total cholesterol by region between 1980 and 2008 for men (A) and women (B)
Webappendix pp 44-46 shows trends by subregion and webappendix pp 54-88 trends by country. The solid line represents the posterior mean and the shaded area the 95% uncertainty interval.
Articles

(website pp 89–284), compared with about 40% for male and female systolic blood pressure (SBP) and male BMI, and about 60% for female BMI; one of 21 subregions (central Africa) had no data for total cholesterol whereas SBP and BMI had time-series data for all subregions.31,33

National surveys contributed about a third of all data, subnational studies 12%, and community studies the remainder (website pp 42–43). In the statistical model, total cholesterol in subnational and community studies differed by an average of about 0·05 mmol/L from nationally representative ones (website p 37). Unweighted national, subnational, and community studies had larger variation than did the national ones (data not shown), but the differences were smaller than for SBP.11 Therefore, studies other than weighted national ones were essentially unbiased and had only modestly larger variance.

Globally, mean total cholesterol changed little between 1980 and 2008, decreasing by less than 0·1 mmol/L per decade in men and women (posterior probabilities of the small observed decrease being a true decline were 0·97 for men and 0·92 for women; figure 2). In 2008, global age-standardised mean total cholesterol was 4·64 mmol/L (95% uncertainty interval 4·51–4·76) for men and 4·76 mmol/L (4·62–4·91) for women. Women had higher total cholesterol than did men in most low-income and middle-income subregions, although differences between sexes were barely distinguishable (figure 2).

Total cholesterol decreased in the high-income region consisting of Australasia, North America, and western Europe by 0·19 mmol/L per decade (0·11–0·28) for men and 0·21 mmol/L per decade (0·11–0·31) for women (posterior probability >0·999 for both sexes; figure 2). Australasia had a steeper decrease than did western Europe and North America (website pp 44–46). By contrast, high-income Asia-Pacific had a moderate rise (0·01–1 mmol/L per decade), with a posterior probability of 0·92 for women and 0·98 for men (website pp 44–46). Mean total cholesterol also decreased in the combined region of central and eastern Europe and central Asia, by 0·23 mmol/L per decade (0·07–0·40, posterior probability=0·99) for men and 0·24 mmol/L per decade (0·06–0·43, posterior probability=0·99) for women. By contrast with these regions, mean total cholesterol rose in the populous regions of east and southeast Asia and Pacific (figure 2). We noted little evidence of change in total cholesterol in Latin America and Caribbean, north Africa and Middle East, south Asia, and sub-Saharan Africa; this finding might be partly because there were few historical data in these regions.

Total cholesterol might have decreased in more than 165 countries for either sex with varying degrees of uncertainty. Of these, men in 11 countries and women in eight had posterior probabilities of being true declines of 0·975 or greater (website pp 285–287). Of these countries, Czech Republic, New Zealand, Finland, Sweden, Malta, and the UK had decreases of 0·3 mmol/L or more per decade for one or both sexes. Total cholesterol might have increased in about 30 countries, with posterior probabilities of 0·80 or higher in China, Thailand, and Japan for both sexes. Specifically, male and female total cholesterol in Japan increased by 0·13–0·15 mmol/L per decade, with posterior probabilities greater than 0·98. Other countries with fairly large increases were mainly in east and southeast Asia and Oceania (website pp 285–287). The correlation between mean total cholesterol in 1980 and its change between 1980 and 2008 was −0·57 mmol/L, indicating a worldwide convergence. As a result of these trends, the differences between countries with the highest and lowest total cholesterol decreased from 2·22 mmol/L in 1980 to 1·90 mmol/L in 2008 for men, and from 1·89 mmol/L to 1·70 mmol/L for women.

The lowest serum total cholesterol concentration throughout the analysis period was less than 4 mmol/L in men in several African countries; the highest concentrations were more than 6 mmol/L in men and women in the 1980s in western Europe and New Zealand (figure appendix). Despite converging trends, total cholesterol in 2008 remained highest in the region consisting of Australasia, North America, and western Europe with a mean of 5·24 mmol/L (5·08–5·39) for men and 5·23 (5·03–5·43) for women, and lowest in sub-Saharan Africa at 4·08 mmol/L (3·82–4·34) for men and 4·27 mmol/L (3·99–4·56) for women. In high-income regions, western Europe and Australasia had higher means than did North America (figure appendix, and website pp 44–46). With few exceptions, the 25 countries with the lowest worldwide total cholesterol for both sexes in 2008 were in sub-Saharan Africa, some less than 4·0 mmol/L for men and around 4·0 mmol/L for women. Countries with the highest serum total cholesterol were mostly in western Europe, with mean concentrations around 5·5 mmol/L for both sexes (figure appendix). However, some countries with recent data, including Japan, Seychelles, and Singapore, had cholesterol concentrations that approached western European values, and were greater than Canada, Sweden, and USA (figure appendix, and website pp 47–53).

Although the 1980–2008 trends are uncertain in low-income and middle-income regions, in high-income subregions we detected cross-country differences (website pp 54–88). Notably, in high-income Asia-Pacific, Singapore had a unique trend, with decreasing total cholesterol in the 1980s, which is consistent with a previous study, but the decrease ended for men and reversed for women; South Korea had almost no rise in total cholesterol, which is consistent with maintaining a diet low in saturated fats; and Japan had a rise, mostly before the mid-1990s, which might be due to higher dietary saturated fats.5,27 As a result, whereas total cholesterol in Japan was similar to that in South Korea in 1980,
concentrations in Japanese men and women were higher by 0.3–0.4 mmol/L in 2008. In western Europe, men in some Nordic countries (eg, Finland and Sweden) started with high total cholesterol in 1980 and values fell steeply, surpassing countries such as Germany and Italy that had lower total cholesterol in 1980 but decreased more slowly.

**Discussion**

Findings from our systematic analysis of worldwide serum total cholesterol have shown that the global average changed little between 1980 and 2008. This apparent lack of change stems from opposite trends in Australasia, North America, and Europe, where serum total cholesterol decreased from high concentrations, and in east and southeast Asia and Pacific, where it rose from low concentrations. Such polarised trends are arguably the most salient feature of this risk factor, especially relative to adiposity, which has increased in most regions. Total cholesterol concentrations had a noticeable age association, peaking at around 50–60 years. We did not detect differences in trends and regional patterns between younger and older age groups, although the slopes might have differed (detailed results available from authors on request). Full investigation of trends by age group should use an age-cohort model because there could be changes by birth cohort—eg, when new treatments become available.

The strengths and innovations of this study include analysis of long-term trends; use of substantially more data than previous analyses; the Bayesian hierarchical model to estimate mean total cholesterol; incorporation of non-linear age associations and time trends; incorporation of study coverage as offset and variance components in the statistical model; and systematic quantitative analysis and reporting of uncertainty. Coverage-specific offsets and variances allowed our estimates to use all available data and to follow data from nationally representative studies more closely than other sources. Further, the coverage-specific variance components are larger for less representative data sources, resulting in larger uncertainty when we did not have nationally representative data, propagating through the Bayesian model into our uncertainty intervals, thereby representing the true availability of information.

Our model did well in external predictive validity tests. Specifically, in each of five separate model runs, 10% of studies were excluded. The model was then used to predict the excluded values. The 95% uncertainty intervals of model predictions included 95–96% of excluded study means for the two sexes. Our model also had good predictive validity by region (covering 92–100% of excluded study means) and age group (90–99%), and at different income and urbanisation levels (89–99%). When we excluded all data for some countries (ie, created the appearance of no data when data were available), the uncertainty intervals of model predictions included more than 95% of the known but excluded study means.}

We appended pp 4–15 and 38 provide the detailed designs and results of these tests and additional tests about model performance.

The main limitation of our study is that despite extensive data seeking, many country-years still did not have data, especially in the 1980s, compared with other risk factors such as SBP and BMI. As a consequence of the geographic and temporal patterns of data availability, unlike analyses of SBP and BMI, we did not model time-varying associations with covariates. These interactions were omitted because fewer countries and subregions had time-series data for total cholesterol than for SBP and BMI. As a result, whereas estimated trends in high-income, Asian, and selected other regions and countries were based on time-series data, trend estimates in other countries would have been affected more by covariates. Removal of the interaction terms yielded flatter estimated trends with larger uncertainty intervals, which we regarded as a better reflection of our knowledge on the basis of available data. Further, although we incorporated information about study coverage into our model, other study characteristics (eg, cholesterol measurement method) could also lead to variability across studies. Of the data used in our analysis 86% measured cholesterol with enzymatic methods, 4% with chemical methods, and 10% with mixed or unknown methods. 60% of studies that had used chemical methods were undertaken in the 1980s; even in that decade, they made up only 10% of all studies. Previous comparisons showed that measurements from the two classes of methods are highly correlated and have small differences, around 0.1 mmol/L for most commonly used methods.

The data limitation is partly caused by measurement difficulties, including the need to have fasting samples and standard procedures for blood sample handling and processing; for this reason, we did not include some large health examination surveys (eg, from Ireland, Germany, and UK) and many MONICA Project sites. In a sensitivity analysis, we used an additional 77 country-years of non-fasting data and modified the statistical model to include offset and variance terms for studies of non-fasting cholesterol (data not shown). On average, studies of non-fasting cholesterol had 0.05 mmol/L higher mean and slightly larger variance than did studies that used fasting serum cholesterol. Our results were not sensitive to the inclusion of these new data sources, with median change in estimates of 0.03 mmol/L or less across both sexes and all 29 analysis years. Uncertainty was on average slightly smaller when non-fasting data were included. This finding implies that studies of non-fasting data, which are logistically easier, might be used for population-based surveillance, especially if accompanied by smaller and less frequent studies that allow estimation of the effect of fasting. How fasting duration affects total cholesterol concentrations is and how well non-fasting total cholesterol predicts risk in diverse populations needs to be further investigated, as has been done in cohorts from developed
cost-eff ectiveness and Similarly, as the benefi ts of statins are established in countries, but there is lower coverage of screening drugs are increasingly used in high-income even genetic factors. Statins and other lipid-lowering determinants, and with studies that have assessed total cholesterol in relation to dietary and pharmacological drivers of the polarised worldwide trends. Such a conclusion would be consistent with longitudinal community studies that have assessed trends in dietary fats, adiposity, and, in high-income countries, statin use are the likely drivers of the polarised worldwide trends. Such a conclusion would be consistent with trends in total cholesterol in relation to dietary and pharmacological determinants, and with studies that have assessed trends in dietary fats in specifi c countries and regions.

Our findings, together with cross-sectional dietary studies in Australasia, North America, western Europe, and Asia, raise the question of whether higher serum lipids are an inevitable consequence of economic development, urbanisation, and nutritional transition, to be later offset through uptake of healthier diets and pharmacological interventions. We believe, however, that the same fi nding could create an opportunity to implement specifi c interventions that use financial and regulatory mechanisms to encourage healthy diets, with unsaturated fats, at all levels of economic development. Similarly, as the benefi ts of statins are established in international studies, their cost-effectiveness and feasibility in countries at various levels of economic development should be assessed. More systematic and frequent population-based surveillance of serum cholesterol could also help with priority setting and assessment of such interventions and policies.
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References


