

Disease Burden of Hypercholesterolemia in Adults Aged 60 Years and Older, 1990-2021: Trend Analysis and Model Prediction Globally and in China Postprint

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Abstract

Background Hypercholesterolemia is an independent risk factor for atherosclerotic cardiovascular disease and exerts a substantial impact on the health of elderly populations. However, current research evidence regarding the disease burden of hypercholesterolemia in elderly populations remains relatively insufficient and requires urgent supplementation.

Objective To analyze the disease burden of hypercholesterolemia and its changing trends in global and Chinese elderly populations from 1990 to 2021, providing a reference basis for optimizing health resource allocation and precisely formulating prevention and control strategies.

Methods Data on deaths and disability-adjusted life years (DALYs) related to “High LDL cholesterol” among populations aged ≥ 60 years were extracted from the Global Burden of Disease (GBD) 2021 database for the global population, China, and five Socio-demographic Index (SDI) regions. Joinpoint regression analysis was employed to examine temporal trends in age-standardized mortality rates (ASMR) and age-standardized DALY rates (ASDR). A three-factor decomposition analysis method was utilized to quantify the relative impacts of population aging, population growth, and epidemiological changes on burden variations. A Bayesian age-period-cohort model was applied to project trends in the number of deaths and DALYs from 2022 to 2035.

Results In 2021, the number of deaths from hypercholesterolemia in the global and Chinese elderly populations was 2.7791 million and 692,000, respectively, representing increases of 50.34% and 252.34% compared with 1990; DALYs were 50.2261 million person-years and 12.1701 million person-years, respectively, representing increases of 46.62% and 200.96% compared with 1990. From 1990

to 2021, both ASMR and ASDR for hypercholesterolemia in the global elderly population demonstrated overall decreasing trends (AAPCASM r =-1.65%, 95%CI=-1.81%~-1.48%, P <0.001; AAPCASD r =-1.51%, 95%CI=-1.67%~-1.36%, P <0.001). In contrast, trends in ASMR and ASDR for the Chinese elderly population remained relatively stable (P =0.089, 0.388), while ASMR in Chinese elderly males showed an overall upward trend, increasing by an average of 0.71% annually (95%CI=0.31%~1.11%, P <0.001). In 2021, the number of deaths, DALYs, age-standardized mortality rates, and age-standardized DALY rates from hypercholesterolemia in global and Chinese elderly males were all higher than those in the corresponding female populations. Except for high-SDI regions, all other SDI regions experienced varying degrees of increase in the number of deaths and DALYs from hypercholesterolemia in the elderly population in 2021 compared with 1990. Additionally, in 2021, the age group with the highest proportion of deaths from hypercholesterolemia in both global (463,100 deaths, 16.66%) and Chinese (128,300 deaths, 18.54%) elderly populations was the 80-84 years group. Three-factor decomposition analysis revealed that population growth was the primary influencing factor for increased disease burden across all regions. Bayesian age-period-cohort model predictions indicated that the disease burden of hypercholesterolemia in global and Chinese elderly populations will continue to rise from 2022 to 2035; by 2035, the number of deaths and DALYs from hypercholesterolemia in the global elderly population will increase by 42.67% and 41.20%, respectively, compared with 2021, while in China they will increase by 82.76% and 72.18%, respectively.

Conclusion The disease burden of hypercholesterolemia in global and Chinese elderly populations is substantial and is expected to continue intensifying. Therefore, it is necessary to curb the increasing related disease burden by raising public health awareness, further optimizing health resource allocation, and strengthening the research and development of novel lipid-lowering drugs.

Full Text

Disease Burden of Hypercholesterolemia among Individuals Aged 60 and Above Globally and in China from 1990 to 2021: Trend Analysis and Model-based Projection

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Abstract

Background: Hypercholesterolemia is an independent risk factor for atherosclerotic cardiovascular diseases, exerting a profound impact on the health of the elderly. However, evidence regarding the disease burden of hypercholesterolemia in the elderly remains limited and requires further elucidation.

Objective: To analyze the disease burden and temporal trends of hypercholesterolemia among the elderly globally and in China from 1990 to 2021, thereby providing a reference for optimizing health resource allocation and precisely formulating management strategies.

Methods: Data on deaths and disability-adjusted life years (DALYs) of “High LDL cholesterol” in individuals aged ≥ 60 years globally, in China, and across five sociodemographic index (SDI) regions were collected from the Global Burden of Disease (GBD) 2021 database. Joinpoint regression was used to analyze temporal trends in age-standardized mortality rate (ASMR) and DALYs rate (ASDR). A three-factor decomposition method was used to quantify the relative impacts of population aging, population growth, and epidemiological changes on the burden. The Bayesian age-period-cohort model was employed to predict the number of deaths and DALYs from 2022 to 2035.

Results: In 2021, hypercholesterolemia-related deaths among the elderly population totaled 2,779,100 globally and 692,000 in China, representing increases of 50.34% and 252.34% from 1990, respectively; DALYs were 50,226,100 and 12,170,100 person-years, up by 46.62% and 200.96%, respectively. Globally, both ASMR and ASDR for elderly hypercholesterolemia showed decreasing trends overall (AAPC_{ASMR} = -1.65%, 95%CI = -1.81% to -1.48%, $P < 0.001$; AAPC_{ASDR} = -1.51%, 95%CI = -1.67% to -1.36%, $P < 0.001$) from 1990 to 2021, whereas they remained relatively stable in China ($P = 0.089$, 0.388). Notably, ASMR among elderly males in China showed an overall upward trend, increasing by 0.71% annually (95%CI = 0.31% to 1.11%, $P < 0.001$). In 2021, elderly males globally and in China exhibited higher numbers of deaths and DALYs, as well as higher ASMR and ASDR, than elderly females. Except for the high-SDI region, the number of deaths and DALYs from hypercholesterolemia in the total elderly population in other SDI regions in 2021 increased to varying degrees compared with 1990. Furthermore, the 80-84 years age group accounted for the largest proportion of deaths both globally (463,100 cases, 16.66%) and in China (128,300 cases, 18.54%) in 2021. Decomposition analysis

revealed that population growth was the primary driver of increasing disease burden across all regions. The Bayesian age-period-cohort model indicated that the disease burden of hypercholesterolemia among the elderly population will continue to rise globally and in China from 2022 to 2035. By 2035, the number of deaths and DALYs from hypercholesterolemia in the global elderly population are expected to increase by 42.67% and 41.20%, respectively, compared with 2021, while in China they are projected to increase by 82.76% and 72.18%, respectively.

Conclusion: The disease burden of hypercholesterolemia among the elderly is substantial both globally and in China, and is expected to grow steadily. To effectively mitigate this escalating burden, it is imperative to enhance public health consciousness, refine the allocation of health resources, and strengthen the research and development of novel lipid-lowering medications.

Keywords: Hypercholesterolemia; Older adults; Low-density lipoprotein cholesterol; Epidemiology; Disease burden; Prediction model

Introduction

Hypercholesterolemia is a dyslipidemia disorder characterized by abnormally elevated levels of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) in the blood [1]. It has been established as an independent risk factor for major cardiovascular and cerebrovascular diseases such as hypertension, ischemic heart disease, and ischemic stroke [1-2]. Specifically, LDL-C has been shown to enhance the pro-atherosclerotic effects of serum TC and triglycerides (TG), thereby increasing the risk of atherosclerotic cardiovascular disease (ASCVD) [2]. Dyslipidemia is closely associated with multiple factors including age, lifestyle, genetics, and environment [3]. As the body ages, there is a significant synergistic effect between aging and metabolic disease risk [4-5]. It is projected that by around 2035, China's population aged 60 and above will exceed 400 million, accounting for over 30% of the total population, which means the burden of metabolic diseases will become increasingly severe [6]. Furthermore, during rapid urbanization, behavioral risk factors such as dietary structure transformation and reduced physical activity further increase the risk of hypercholesterolemia among China's elderly population [7-8].

A 2020-2022 study revealed that the awareness, treatment, and control rates of dyslipidemia among Chinese residents aged 18 and above were only 11.7%, 10.1%, and 4.8%, respectively [9], all significantly lower than those in developed countries. Given China's large population base, insufficient public health awareness, and lack of systematic prevention and control measures, the disease burden associated with dyslipidemia may continue to increase. Clarifying the disease burden provides a scientific basis for determining health priorities, research funding priorities, and optimizing health resource allocation [10]. However, current research evidence on the disease burden of hypercholesterolemia in the elderly

population remains relatively scarce. Therefore, this study aims to systematically analyze the disease burden characteristics of hypercholesterolemia among individuals aged ≥ 60 years globally and in China from 1990 to 2021 based on the latest Global Burden of Disease (GBD) data, and to predict future epidemiological trends using a Bayesian age-period-cohort (BAPC) model [12] to help identify high-risk populations and prevention gaps, thereby providing references for differential allocation of health resources and precise formulation and implementation of management strategies.

Methods

Data Sources

All data used in this study were extracted from the GBD 2021 database (<https://vizhub.healthdata.org/gbd-results/>), which provides data covering 371 diseases, 88 risk factors, and 288 causes of death across 204 countries and regions [12-13]. Hypercholesterolemia was defined using “High LDL cholesterol” [13].

The Sociodemographic Index (SDI) is a comprehensive socio-demographic evaluation indicator developed by the GBD Collaborators based on per capita income, average education level, and total fertility rate rankings, ranging from 0 to 1, with higher values indicating higher levels of socio-demographic development [14]. The GBD Collaborators categorized 204 countries/regions into five SDI regions based on SDI values: low (<0.466), low-middle (0.466-0.619), middle (0.620-0.712), high-middle (0.713-0.810), and high (>0.810). China's SDI in 2021 was 0.722, placing it in the high-middle SDI region [15]. This study extracted death and disability-adjusted life years (DALYs) data related to “High LDL cholesterol” for individuals aged ≥ 60 years in China, globally, and across the five SDI regions from 1990 to 2021 from the GBD 2021 database. The specific operations to obtain data through the GBD Results Tool [16] were as follows: select “Risk factor” under “GBD Estimate,” check “Deaths” and “DALYs” under “Measure,” select “Number” and “Rate” under “Metric,” choose “High LDL cholesterol” under “Risk,” select “All causes” under “Cause,” select “Global,” “China,” and all five SDI regions under “Location,” select all age groups from “60-64 years” to “95+ years” in 5-year intervals under “Age,” choose “Female,” “Male,” and “Both” under “Sex,” select all years from 1990 to 2021 under “Year,” and finally click “Download” to retrieve the data.

Statistical Analysis

First, based on the GBD 2021 standard population, we estimated the number of deaths, DALYs, age-standardized mortality rate (ASMR), age-standardized DALYs rate (ASDR), and their 95% confidence intervals (CI) for hypercholesterolemia among the total, female, and male elderly populations aged ≥ 60 years globally and in China [15-16]. Second, Joinpoint regression models were used to calculate the annual percent change (APC) and average annual percent change

(AAPC) of age-standardized rates to assess trends in disease burden, with the maximum number of joinpoints set at 5. An APC/AAPC with a 95%CI lower limit >0 indicated an upward trend, an upper limit <0 indicated a downward trend, and a CI containing 0 indicated a relatively stable trend [15]. We employed the decomposition analysis method proposed by Das Gupta to quantify the relative impacts of three factors—population aging, population growth, and epidemiological changes—on the changes in hypercholesterolemia disease burden among the elderly population, with the sum of the contributions of these three factors within the same region equaling 100% [15]. Finally, a BAPC model was constructed to predict trends in the number of deaths and DALYs from hypercholesterolemia among the global and Chinese elderly populations from 2022 to 2035. Statistical analysis and graphing were performed using R 4.4.0 and Excel 2021. All hypothesis tests were two-sided, with statistical significance defined as a 95%CI not containing 0 or $P < 0.05$.

Results

Death Burden of Hypercholesterolemia among the Elderly Population Globally and in China

Compared with 1990, the number of hypercholesterolemia-related deaths among the total, female, and male elderly populations in 2021 increased by 50.34%, 38.92%, and 63.49% globally, and by 252.34%, 218.50%, and 288.66% in China, respectively (Table 1). The ASMR for the total elderly population globally decreased from 453.10/100,000 in 1990 to 268.97/100,000 in 2021, with an average annual decline of 1.65% (95%CI = -1.81% to -1.48%, $P < 0.001$). In contrast, China's ASMR for the total elderly population increased from 276.65/100,000 to 305.55/100,000, but the change remained relatively stable ($P = 0.089$). However, ASMR among elderly males in China showed an overall upward trend, increasing by 0.71% annually (95%CI = 0.31% to 1.11%, $P < 0.001$) (Table 1, Figure 1 [Figure 1: see original paper]).

Gender-based subgroup analysis revealed that in 1990, hypercholesterolemia-related deaths among elderly females were higher than among males both globally and in China, but by 2021, male deaths had surpassed female deaths. Moreover, ASMR among males was higher than among females in the corresponding regions in both 1990 and 2021.

Further analysis of hypercholesterolemia death burden across the five SDI regions showed that compared with 1990, only the high-SDI region experienced a decrease in deaths (29.66%) in 2021, while high-middle, middle, low-middle, and low-SDI regions saw increases of 40.33%, 177.55%, 150.26%, and 116.09%, respectively. Additionally, from 1990 to 2021, ASMR for the total elderly population showed overall downward trends in high, high-middle, and middle SDI regions (all $P < 0.001$), while trends remained relatively stable in low-middle and low-SDI regions ($P > 0.05$) (Table 1).

DALYs Burden of Hypercholesterolemia among the Elderly Population Globally and in China

In 2021, DALYs from hypercholesterolemia among the total, female, and male elderly populations were 50,226,100, 23,000,200, and 27,225,900 person-years globally, representing increases of 46.62%, 36.01%, and 56.97% from 1990, respectively. In China, DALYs increased by 200.96%, 170.82%, and 230.50% for the total, female, and male populations, respectively (Table 2). From 1990 to 2021, ASDR for the total elderly population globally showed an overall downward trend (AAPC = -1.51%, 95%CI = -1.67% to -1.36%, $P < 0.001$), while China's ASDR trend remained relatively stable ($P = 0.388$) (Table 2, Figure 1).

Gender subgroup analysis revealed that ASDR for elderly females and males globally and elderly females in China showed overall downward trends from 1990 to 2021, with AAPCs of -1.71% (95%CI = -1.88% to -1.53%, $P < 0.001$), -1.35% (95%CI = -1.50% to -1.19%, $P < 0.001$), and -0.20% (95%CI = -0.37% to -0.03%, $P = 0.022$), respectively. In contrast, ASDR for elderly males in China showed an overall upward trend (AAPC = 0.50%, 95%CI = 0.17% to 0.83%, $P = 0.003$). Additionally, in both 1990 and 2021, DALYs and ASDR among elderly females were lower than among males in the corresponding regions.

Analysis by SDI region indicated that compared with 1990, only the high-SDI region saw a decrease in DALYs (33.48%) in 2021, while high-middle, middle, low-middle, and low-SDI regions experienced increases of 31.35%, 156.57%, 139.98%, and 105.41%, respectively. From 1990 to 2021, ASDR showed overall downward trends in all SDI regions except low-middle SDI (where the change was not statistically significant, $P = 0.717$), with the most pronounced decline in the high-SDI region (AAPC = -3.59%, 95%CI = -3.73% to -3.45%, $P < 0.001$) (Table 2).

Age Differences in Disease Burden of Hypercholesterolemia among the Elderly Population Globally and in China

To analyze differences in death and DALYs burden of hypercholesterolemia across age groups, we examined data in 5-year age intervals. The results showed that in 2021, deaths from hypercholesterolemia in all age groups increased to varying degrees compared with 1990 both globally and in China, with the largest increases observed in the 85-89 years age group globally (175,300 cases) and in China (106,500 cases). The second-largest increases occurred in the 90-94 years age group globally (146,200 cases) and the 80-84 years age group in China (99,700 cases) (Figure 2 [Figure 2: see original paper]A). DALYs also increased across all age groups, with the highest increases globally in the 65-69 years (3,260,000 person-years) and 70-74 years (3,224,500 person-years) age groups, and in China in the 70-74 years (1,503,300 person-years) and 65-69 years (1,463,300 person-years) age groups (Figure 2B).

Analysis of the proportion of disease burden by age group in 2021 revealed that the 80-84 years age group accounted for the highest proportion of deaths both

globally (463,100 cases, 16.66%) and in China (128,300 cases, 18.54%). Globally, the 60-64 years (10,863,700 person-years, 21.63%) and 65-69 years (10,353,100 person-years, 20.61%) age groups had the highest proportions of DALYs, while in China, the 65-69 years (2,433,900 person-years, 20.00%) and 70-74 years (2,347,000 person-years, 19.29%) age groups had the highest proportions (Figure 3 [Figure 3: see original paper]).

By SDI region, the age group with the highest proportion of deaths in 2021 was 85-89 years in the high-SDI region, and 80-84 years in high-middle and middle SDI regions. Low-middle and low-SDI regions showed a trend toward younger ages, with death peaks occurring in the 60-64 years and 65-69 years age groups, respectively. The age group with the highest proportion of DALYs was 60-64 years in high, middle, low-middle, and low SDI regions, and 65-69 years in the high-middle SDI region (Figure 3).

Decomposition Analysis of Increasing Disease Burden of Hypercholesterolemia among the Elderly Population Globally and in China

Compared with 1990, both deaths and DALYs from hypercholesterolemia among the elderly population increased significantly globally, in China, and across high-middle, middle, low-middle, and low SDI regions in 2021. To explore the key influencing factors, we used three-factor decomposition analysis to assess the relative impacts of population aging, population growth, and epidemiological changes on the burden increase in each region. The results showed that population growth was the primary contributor to increased deaths and DALYs globally, with contributions of 208.33% and 221.36%, respectively, while epidemiological changes had a mitigating effect (contributions of -138.74% and -134.77%, respectively) (Figure 4 [Figure 4: see original paper]). In China, population growth was also the main driver of increased deaths and DALYs, with contributions of 76.41% and 88.38%, respectively, followed by population aging (19.88% and 10.95%, respectively). Across different SDI regions, population growth consistently emerged as the predominant factor driving increases in both deaths and DALYs from hypercholesterolemia among the elderly population.

Prediction Analysis of Deaths and DALYs from Hypercholesterolemia among the Elderly Population Globally and in China

BAPC model predictions (Figure 5 [Figure 5: see original paper]) indicate that from 2022 to 2035, the number of deaths and DALYs from hypercholesterolemia among the total, female, and male elderly populations will continue to rise globally and in China. By 2035, deaths and DALYs among the global elderly population are projected to increase by 42.67% and 41.20%, respectively, compared with 2021, while in China they are expected to increase by 82.76% and 72.18%, respectively.

Discussion

This study systematically analyzed the disease burden of hypercholesterolemia defined by high LDL-C among elderly populations globally, in China, and across five SDI regions based on the GBD 2021 database. The results show that although ASMR and ASDR for hypercholesterolemia among the total, female, and male elderly populations globally and ASDR among elderly females in China showed significant downward trends from 1990 to 2021, both the absolute numbers of deaths and DALYs among the total, female, and male elderly populations in 2021 increased substantially compared with 1990 globally and in China. Moreover, ASMR and ASDR among elderly males in China showed significant upward trends from 1990 to 2021. The distribution of disease burden across different SDI regions also exhibited heterogeneity. Decomposition analysis revealed that population growth was the primary factor driving increases in both deaths and DALYs from hypercholesterolemia among the elderly population globally and in China. BAPC model predictions suggest that without effective interventions, deaths and DALYs from hypercholesterolemia among China's elderly population in 2035 will increase by 82.76% and 72.18%, respectively, compared with 2021. Therefore, there is an urgent need to develop and implement effective, comprehensive prevention and control strategies—including early screening and monitoring, pharmacological intervention, and lifestyle management—to curb the escalating epidemiological burden of hypercholesterolemia-related diseases among the elderly population globally and in China.

Age subgroup analysis revealed that the 85-89 years age group showed the largest increase in hypercholesterolemia-related deaths in both global and Chinese elderly populations when comparing 2021 with 1990, while the 80-84 years age group accounted for the highest proportion of deaths in 2021. According to the Seventh National Population Census Bulletin, the proportion of China's population aged 60 and above reached 18.70% in 2020 [17], and the latest data from the National Bureau of Statistics show that by the end of 2024, this population reached 310.31 million, exceeding 300 million for the first time and accounting for 22.0% of the total population [18]. With aging, the proliferation and differentiation capacity of adipose progenitor cells declines, weakening the ability of adipose tissue to store lipids and making lipids more likely to accumulate in the liver and muscle tissue. Mitochondrial function in muscle and liver also weakens, reducing the utilization of free fatty acids and glucose and leading to lipid accumulation in the blood [7]. Previous studies have found that blood LDL-C levels increase with age [19]. On one hand, hepatic LDL receptor expression decreases with age, reducing the clearance efficiency of LDL-C from the blood. On the other hand, decreased activity of cholesterol 7-alpha hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis, reduces the conversion of cholesterol to bile acids and increases the risk of hepatic cholesterol accumulation [19]. High LDL-C is one of the major risk factors for ASCVD in diabetic patients, and China has a large base of elderly diabetic patients with poor glycemic control [15,20]. Insulin resistance promotes the release of free fatty acids and inhibits

lipoprotein lipase activity, leading to accumulation of TG and remnant cholesterol and creating a vicious cycle [21] that further increases mortality risk in elderly patients. Therefore, we recommend early ASCVD risk assessment for elderly populations, particularly those with diabetes, combined with community health education on dietary structure adjustment, smoking cessation, limiting alcohol consumption, and weight management to reduce baseline LDL-C levels.

The Chinese Expert Consensus on Dyslipidemia Management in the Elderly [3] sets target values for LDL-C and non-HDL-C in elderly patients undergoing lipid-lowering therapy according to four risk strata: low/moderate risk, high risk, very high risk, and ultra-high risk. Lifestyle intervention is recommended as the basic approach for managing dyslipidemia in the elderly, including smoking cessation, limiting alcohol intake, reducing saturated fatty acid and cholesterol consumption, increasing intake of fruits, vegetables, fish, and whole grains, and promoting regular aerobic exercise [3]. The recently published Chinese Guidelines for Lipid Management (Primary Care Version 2024) [1] stratifies population ASCVD risk into five levels—low risk, moderate risk, high risk, very high risk, and ultra-high risk—based on ASCVD history, number of risk factors (such as diabetes, hypertension, obesity), and TC or LDL-C levels. The guidelines recommend LDL-C as the primary target for lipid-lowering therapy [1] and provide recommended target values for LDL-C in different ASCVD risk strata, such as <2.6 mmol/L for moderate/high-risk populations.

Research shows that although the prevalence of dyslipidemia in China is lower than in the United States, the awareness rate is only one-third and the treatment rate only one-quarter of those in the US [22]. Urban-rural disparities may further increase regional heterogeneity in dyslipidemia management in China, as rural areas—limited by insufficient medical resources and weak health education—have significantly lower disease control rates than urban areas [23-24]. LU et al. [25] investigated the availability of lipid-lowering medications in 3,041 primary healthcare institutions across 31 provinces in rural China and found that the availability rate of statins was only 49.7%, with village clinics having an even lower rate of 43.7%. These findings suggest that optimizing primary healthcare resource allocation, strengthening health education in rural areas, and improving the accessibility of statins at the primary care level may be key to alleviating China's heavy burden of dyslipidemia.

In addition to statins, commonly used lipid-lowering medications include cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and fibrates [1,26]. A meta-analysis showed that hybutimibe, a domestically developed Class I innovative drug, can effectively reduce LDL-C levels in hypercholesterolemia patients when used alone or in combination with atorvastatin, with good safety profiles [27]. A randomized controlled trial published in the *New England Journal of Medicine* found that alirocumab, a PCSK9 monoclonal antibody, significantly reduced LDL-C levels and the risk of composite cardiovascular endpoint events in acute coronary syndrome patients receiving intensive statin therapy, with favorable safety

outcomes [28]. Furthermore, a Phase II trial published in *The Lancet* in 2025 found that solbinsiran, a small interfering RNA (siRNA) drug targeting hepatocyte angiopoietin-like protein 3 (ANGPTL3) mRNA, significantly reduced LDL-C and apolipoprotein B levels in adults with mixed dyslipidemia receiving statin therapy, though its impact on cardiovascular outcomes and safety requires further investigation [29].

In addition to Western medications, traditional Chinese medicine (TCM) interventions, as an indispensable component of China's healthcare system, have also demonstrated promising lipid-lowering effects [30-31]. For example, studies have found that the Chinese patent medicine Zhibitai, used alone or in combination with atorvastatin, can significantly reduce elevated TG, TC, and LDL-C levels [32], while Xuezhikang not only significantly reduces plasma LDL-C levels in coronary heart disease patients but also exhibits strong anti-inflammatory and antioxidant functions [33]. Additionally, a network meta-analysis by CUI et al. [34] confirmed that heat-sensitive moxibustion can significantly reduce blood TG and LDL-C levels while increasing HDL-C levels in coronary heart disease patients.

However, it is important to note that LDL-C is not always “the lower, the better” [35-36]. For instance, a large cohort study demonstrated a U-shaped association between LDL-C levels and all-cause mortality, where both excessively high and low LDL-C levels were associated with increased all-cause mortality risk [35]. Another study found an inverse association between LDL-C levels and mortality risk in acute myocardial infarction patients (a phenomenon known as the “lipid paradox”) [36], possibly related to higher inflammatory risk in these patients. This suggests that clinicians should pay close attention to inflammatory risk when managing LDL-C levels in acute myocardial infarction patients. Additionally, this study found that the disease burden of hypercholesterolemia among elderly males was generally higher than among females globally and in China, which may be related to more prevalent unhealthy lifestyles such as smoking, alcohol consumption, and high-fat diets among men, as well as weaker health management awareness. It may also be related to estrogen's regulatory effect on LDL-C and its promoting effect on HDL-C [37].

In summary, the current burden of hypercholesterolemia-related deaths and DALYs among the elderly population globally and in China is substantial and is likely to continue escalating over the next decade. There is an urgent need to actively develop and implement effective comprehensive prevention and control strategies, including multi-dimensional measures such as enhanced publicity and health awareness, early screening and monitoring, healthy lifestyle promotion, and pharmacological intervention, to curb the increasing disease burden associated with hypercholesterolemia. Attention should also be paid to gender and age factors. For example, in 2021, the number of deaths, DALYs, ASMR, and ASDR from hypercholesterolemia among elderly males in China were all higher than among females, suggesting that additional attention should be paid to managing behavioral risk factors such as smoking, alcohol consumption, and

high-fat, high-sugar diets in male populations.

This study is the first to systematically reveal the heavy epidemiological burden of hypercholesterolemia among the elderly population globally and in China based on the GBD 2021 database, covering 32 years of data from 1990 to 2021. These findings can provide an important reference basis for formulating corresponding public health policies and making decisions regarding investment in research and development of novel lipid-lowering drugs. However, this study has several limitations: (1) GBD results are derived from mathematical modeling and estimation, which may not be entirely consistent with the true disease burden; (2) the accuracy of BAPC model predictions may be affected by future advances in medical technology; (3) due to data availability limitations, this analysis only covered the disease burden among elderly populations defined by “High LDL cholesterol” and could not analyze the burden attributable to high TC or mixed hyperlipidemia, nor could it examine the disease burden of hypercholesterolemia among elderly populations in different provinces and municipalities in China. Therefore, we hope to collaborate with the Chinese Center for Disease Control and Prevention in the future to further improve the analysis and research on the burden of hypercholesterolemia among China’s elderly population.

Author Contributions

LIU Fan and LI Jiali were responsible for data curation, figure preparation, and initial manuscript drafting. KE Lixin was responsible for data collection and manuscript revision. ZHANG Qiang and CHEN Jiahui were responsible for data verification and manuscript revision. LU Cuncun was responsible for project design, statistical analysis, figure preparation, research supervision, and manuscript revision. ZHAO Xinke was responsible for research supervision, manuscript revision, and funding support.

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