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The Prevalence of Different Genotypic Forms of Familial Hypercholesterolemia in Relation to Race and Ethnicity

Makhabbat S. Bekbossynova[1], Tatyana V. Ivanova-Razumova[1], Aknur S. Kali[1], Aliya I. Sailybayeva[1], Sadyk R. Khamitov[1], Zhansaya O. Oralbekova[1]

[1] *"University Medical Center" Corporate Fund, National Cardiac Surgery Center, Astana, Kazakhstan*

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Corresponding author:
Makhabbat Bekbossynova.
E-mail: cardiacsurgeryres@gmail.com.
ORCID: 0000-0003-2834-617X.

Abstract

In the present study, a systematic literature review was conducted to evaluate the epidemiology of Familial hypercholesterolemia genetic variants according to different ethnic and racial background. Familial hypercholesterolemia (FH) is an inherited disease characterized by severe dyslipidemia and as a result high cardiovascular risk. Lipid profile of this patients distinguishes with increased cholesterol and low-density lipoprotein (LDL) blood levels. Databases PubMed, Web of Science, and Elsevier were searched and only peer-reviewed articles with a large number of contributors and sufficient prevalence and ethnicity data were included. Diagnosis of FH was based on genetic testing or clinical criteria. The results of the study indicate inadequate and untimely diagnosis of FH, resulting in inadequate treatment. To date, only 9% of countries have statistical data on the FH prevalence among their citizens. In order to develop effective prevention strategies for cardiovascular diseases associated with FH, further research is needed to obtain accurate epidemiological data, including the race and ethnicity of patients. This will allow to optimize strategies for reducing the social-economic burden of preventable cardiovascular disease associated with FH.

Keywords: Familial hypercholesterolemia, cardiovascular disease, low-density lipoprotein, genes.

Introduction

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disease associated with elevated levels of total cholesterol and low-density lipoprotein (LDL) in the blood. As a result of dyslipidemia, patients have increased risk of atherosclerotic cardiovascular disease early development. Familial hypercholesterolemia characterized by quite complex genetics. It can be subdivided for two main forms: homozygous (mutation in both alleles, severe clinical prognosis and outcome) and heterozygous (presence of mutation in one allele, more favorable outcome). In this case, depending on the combination of mutations, the presence of monogenic or polygenic nature of the lesion distinguishes true homozygous form, as well as combined and compound heterozygotes. Substantially, all cases of FH are induced by mutations in genes, which encode LDL receptors, proprotein convertase subtelisin/kexin 9, Apo B protein. The reason for the rare autosomal recessive form of familial hypercholesterolemia is LDLR1 gene mutation. LDL receptor gene mutations are responsible for 85-90% of genetically confirmed cases of FH [2]. Currently, more than 4900 variants of the LDLR gene and about 350 variants of the PCSK9 gene have been identified, but the pathogenetic significance of most of them has not been proven [29].

According to the data from epidemiology studies, the prevalence of two genetic forms (homozygous and heterozygous) differs significantly. Homozygous familial hypercholesterolemia (homoFH) is a very rare disease, for a long time the incidence was estimated at 1: 1,200,000 populations, but according to a more in-depth study in some European countries (Netherlands, Italy, Spain) it was re-estimated as 1: 650,000, and then 1: 160 - 300,000 [8].

Heterozygous familial hypercholesterolemia (heFH) is one of the most common genetically determined pathologies in the world. According to recent studies, its prevalence is 1:250 in the United

States [1], 1:192 in Catalan Spain, and at 1: 137 in the Danish population [22].

Most studies suggest that familial hypercholesterolemia remains an inadequately and untimely diagnosed pathology, which consequently leads to untimely and incomplete treatment. With an expected number of about 34 million patients worldwide, less than 1% are currently identified in most countries [9,10]. Only 9% of countries in the world have accurate statistics of FH epidemiology [1]. But until this moment prevalence of FH in dependence to the different ethnic groups is not clearly estimated. Obtaining more accurate epidemiological data, including race and ethnicity of patients, will help to optimize strategies to decrease the burden of preventable cardiovascular diseases (CVD).

Purpose: To develop an understanding of the homo- and heterozygous hypercholesterolemia prevalence according to different racial and ethnic groups, and to identify gaps in its epidemiology and demographic characteristic in order to identify future research directions

Materials and methods

A search for relevant to the study topic publications was performed via PubMed, Web of Science, and Elsevier databases from inception to December 2022 reporting on the prevalence of familial hypercholesterolemia among different ethnic groups.

All peer-reviewed published articles [1] involving more than 100 participants in a study with relevant prevalence and ethnicity were considered suitable for inclusion as illustrated in Figure 1 [2]. For diagnosis of FH one of the following criteria was used: genetic testing, Dutch Lipid Clinic Network clinical criteria, Simon Broome criteria, MEDPED (Make Early Diagnosis to Prevent Early Death).

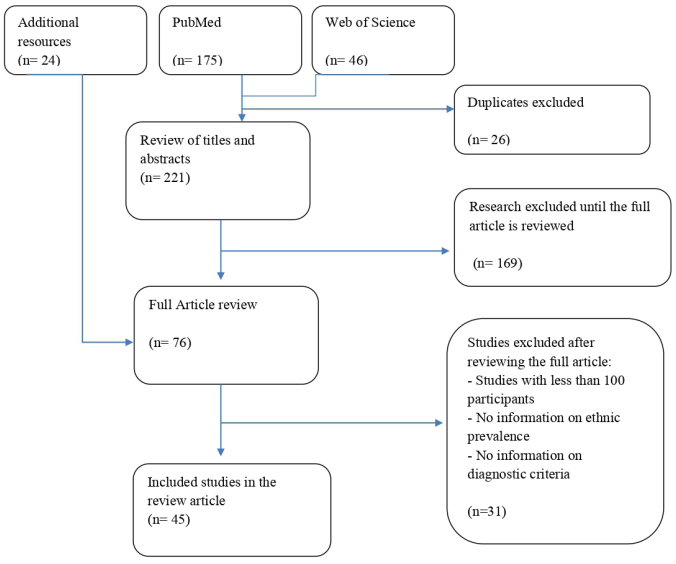

Figure 1 – Study selection flowchart

Studies with unclear methodology for obtaining FH prevalence were excluded.

In the analyzed publications, the epidemiology and prevalence of homozygous familial hypercholesterolemia were evaluated both on the basis of the general population studies and on the basis of Hardy-Weinberg principles calculations. The assessment and analysis of the studies are presented in the Table 1.

Table 1 Assessment and analysis of the studies

Title	Country	Publication year	Data source	Age	Period of participants' inclusion	Diagnostic criteria for FH
ELSA-Brasil study	Brazil	2018	Population study	35-75	Not indicated	DLCN
NHANES study	USA	2016	Population study	>18	1999-2012	DLCN
	USA	2018	Population study	>20	1999-2022	Modified DLCN II
Cape Town Experience	South Africa	2008	Population study	>50	2011-2019	DLCN
YOUNG-MI Registry	USA	2019	Retrospective study	41-50	Not indicated	Not indicated

FH – Familial hypercholesterolemia.
DLCN – Dutch Lipid Clinic Network.

Table 2 Racial and ethnic groups

Region	Ethnic groups
Europe	Danish, Dutch, French, Hispanic, Italian, German, Polish
East Asia	Arabian, Druze, Kurds, Persian, Turks, Jews
Southwest Asia	Chinese, Japanese
Africa	African
North America	Canadian
South America	Brazilian

The following keywords were used in the search: homozygous and heterozygous familial hypercholesterolemia or LDLR or apolipoprotein B or gene mutation, ethnic group or racial and ethnic prevalence. All the racial and ethnic groups are listed in the Table 2.

Results

Over the last decades, a number of studies have demonstrated significant differences in the FH epidemiology not only between countries but also among different ethnic and racial groups. This difference can be determined by several factors: using of different diagnostic criteria [32], differential access to medical care and to genetic testing, differences in screening approaches [11], and differences in the methodology of inclusion of representatives of different ethnic populations, and also due to the "founder effect" in some countries.

To date, almost all studies of the FH prevalence have come from countries on the European continent, North America, East Asia and Australia. This problem is practically unstudied in the African continent, South America, and the Asian region. Moreover, the authors most often studied the prevalence of heterozygous forms, while the demography of homozygous hypercholesterolemia is described in a few papers.

European scientists have pioneered the epidemiology of familial forms. The first large-scale study of the FH prevalence was published in 2012, based on a non-selective Danish population of >69 000 individuals. The prevalence of verified/probable FH was 1:137 [22]. In 2016, the same authors

conducted another study including >98,000 individuals, the prevalence of familial forms of conditional mutations in LDLR and Apo B genes was 1:217 [35]. In other European countries, the prevalence of SHCC was roughly comparable: Poland 1:247 (meta-analysis of 6 studies, 38,900 participants), the Netherlands 1:319, and Germany 1:295 [36, 37, 38]. At the same time, FH was significantly less frequent in the Italian population - 1:526 (for diagnosis the criteria of the Danish lipid clinics were used) [39].

Most of the earlier studies included only Caucasian and Negroid individuals. Several studies, which were later included in meta-analytical projects, investigated the prevalence of FH, including Asian and Hispanic populations. It is noteworthy that there are quite pronounced variations in prevalence values according to different studies, even in ethnically similar populations.

One of the earliest meta-analyses with a broad geography of included studies is the analysis published by Akioymen et al. in 2017. The meta-analysis included 19 cohorts: 9 in Europe, 4 studies from North America, 2 Asian cohorts, 3 studies conducted in the Australian continent and 1 in the African continent [34]. The expected prevalence in each cohort vary from 0.05% to 5.62%. The overall prevalence across the combined population was 0.40% (1:250 individuals, with 95% confidence interval). This analysis has series of limitations: the differences in selected population, design and methods of research, diagnostic criteria for FH. These factors resulted in marked heterogeneity of the included studies.

National Health and Nutrition Examination Surveys (NHANES) study

More recently, in 2020, the results of a large-scale meta-analysis and systematic review on the prevalence of familial forms of hypercholesterolemia in different ethnic groups were published. Meta-analysis consists of thirteen studies, the total number of participants was 1,169,879, and the overall prevalence of FH was 1:303, which is consistent with other authors [7]. The studies included in the meta-analysis predominantly reflected the prevalence of familial forms in a single ethnic group, and only a few studies examined multiple cohorts. Specifically, the National Health and Nutrition Examination Surveys (NHANES) study included members of the following racial groups: non-Hispanic Negroid race, non-Hispanic Caucasoid race, non-Hispanic Mexican-American, and Hispanic. The overall prevalence of familial hypercholesterolemia was 0.40% or 1:250 [1].

ELSA-Brazil study

The ELSA-Brazil study, which included 15,101 Brazilian citizens aged 35-74 years, was based on racial groups such as Negroid, Caucasian and Hispanic. Asian race was excluded due to the small population of this ethnic group in Brazilian territory [23]. The FH overall prevalence was 0.38% or 1:263 [2]. Detailed analyses showed that prevalence of FH increased from 1:417 in the Caucasian cohort, 1:204 among Hispanics to 1:156 in the Negroid cohort. Such high prevalence figures for FH among the Negroid and Hispanic races indicate how underestimated this problem is, both locally and globally.

Pooled data on ethnic prevalence of FH from different studies show higher values among the Negroid race compared to the overall population. In the NHANES study it was 0.46% or 1:249, and 0.64% (1:156) in the ELSA-Brazil study, respectively. At the same time, according to the data of NHANES study, prevalence of FH among individuals with mixed ethnicity and/or race (0.28% or 1:357) was lower than in the general population. The prevalence of FH was also lower in the Caucasian population at 0.25% (1:417) [2].

Cape Town Experience study and YOUNG-MI Registry study

Two studies (Cape Town Experience and YOUNG-MI Registry) have focused on the prevalence of FH by race among so-called "patient" groups. These are cohorts in which participants were recruited among patients in lipid clinics or hospitals, or had high lipid values and/or prior cardiovascular disease. Expectedly, the prevalence of familial forms was higher in these cohorts than in the overall population, while ethnic differences persisted. The overall prevalence of familial heterozygous hypercholesterolemia was 23% [1:4] according to the Cape Town Experience (Cape Town, South Africa, 2008) [4] and 9% or 1:11 according to the YOUNG-MI Registry (USA, 2019) [5]. At the same time, comparison of the two studies results revealed marked differences in the FH prevalence in ethnic groups. In particular, in the Cape Town Experience study, the highest prevalence was observed among Caucasians (32% or 1:3) and Asians (20% or 1:5). YOUNG-MI Registry data showed a high prevalence of this nosology in the Hispanic patient cohort, 14% or 1:5, while in the Asian cohort the values were significantly lower than in the general population, 4.3% or 1:23.

In 2020, the results of another large meta-analysis were published, which included 104 publications and about 11,000,000 patients, respectively, to estimate the prevalence of FH in several subpopulations. Specifically, 44 articles focused on the epidemiology of familial forms in the general population, 28 publications focused on patients with coronary artery disease, 32 studies assessed the prevalence of the FH in patients with early developed coronary heart disease and coronary events, and another 19 articles included patients with severe hyperlipidemia [15]. According to the results of a meta-analysis, in the general population the prevalence of familial hypercholesterolemia was 1:313, while in patient cohorts it was significantly higher: 10 times higher in patients with coronary disease and 20 times in patients with premature cardiovascular events. In the group of patients with severe hypercholesterolemia, the prevalence of familial forms was 23 times higher compared with the whole population [15]. The same meta-analysis compared the prevalence of hypercholesterolemia by ethnicity: Caucasian, Negroid, East Asian and Arab subpopulations.

In contrast to previously reported data in the above meta-analysis, the prevalence of FH in the Asian population was significantly lower than in Europe and North America, 0.19% and 0.32%, respectively. One explanation could be the genetic differentiation of different ethnicities. In addition, the studies by Japanese authors, also included in the meta-analysis, used the criteria for diagnosing CVD developed by the Japanese Atherosclerosis Society in 2012 [16], while most other authors from the Asian region used criteria developed for the Western world, which may affect the validity of the data, since members of the Asian ethnic group traditionally have lower lipid profiles [17].

However, in the patients sub cohorts with coronary pathology and early coronary events, the prevalence of FH among Asian ethnic groups was comparable with that in Europeans and "white" Americans - 3.6% and 5.75%,

respectively [15]. Over the past decades, a significant change in the characteristics of the lipid spectrum in Asian countries, including Japan and China, has been noted, in particular, an increase in the level of total cholesterol, which may be explained by changes in lifestyle [40]. A 2014 study in China using the adapted Danish Lipid Clinics criteria reported a prevalence of FH of 0.28% [42].

In recent decades, there has been a significant change in the demography of inherited diseases and in particular heterozygous and, to a greater extent, homoFH, due to the impact of migration flows on population growth in different regions and the emergence of new sources of mutations.

There are several countries and ethnic groups in the world that are predicted to have a significantly higher incidence of FH. In particular, as a result of the "founder effect" presence, such groups may include French-Canadians, Africans, Christian Lebanese, and ethnic Arabs [1,12]. "Founder effect" in genetics refers to a decrease in gene variability when a new population in a new area is formed by separating a very small group of individuals from a larger population [34].

Other studies

A higher prevalence of FH would also be expected in the Gulf countries (Bahrain, Kuwait, Iraq, Oman, Qatar, Saudi Arabia and the United Arab Emirates), given the greater frequency of closely related individuals. In 1995, a survey of 3212 families in Saudi Arabia was conducted, the percentage of close marriages was 57.7%, with cousins accounting for 28.4% of the couples (26). Almost 10 years later, this study was replicated. 600 women were interviewed, the presence of marriage with cousins was indicated by 30% of respondents, and in parental families this fact was noted by 23% of respondents, i.e. this tradition is preserved to this day [27]. In addition, the previously described "founder effect" is very pronounced in the Gulf countries, reinforced by the high frequency of inbreeding. In particular, Saudi Arabia is home to the mutation of exon 14 of the LDLR gene, which occurs in 40% of the population [28]. Accurate data on the prevalence of FH in Saudi Arabia is not available at the moment, however, according to the Ministry of Health data for 2013, the dyslipidemia prevalence in the population was 8.5% [44]. Regarding FH, there is data from a study conducted in 2018, which included 3224 patients hospitalized for acute coronary syndrome, the prevalence was 3.7% [45]. At the same time, in Israel, another country in the Middle East region, according to the data from 685,314 insured citizens the prevalence of FH was comparable to the European population and compose 1:355. MEDPED criteria were used for diagnosis [41].

Another region in which the FH prevalence is significantly higher than the global rates is South Africa, in particular in 3 ethnic groups - Afrikaners (South Africans of European descent), Jews and South Asian Indians - it is 1:80 [30]. A study by Frederick J. Raal et al on the results of cascade screening in a South African population was published in 2020. The study included 700 subjects, 295 cases (42%) were index cases [32]. The study identified a very interesting ethnic group, 16 dark-skinned Africans, who were not found to have atherosclerosis-associated cardiovascular disease despite long-term exposure to high or extra high levels of LDL and often Lp(a), with a similar incidence of arterial hypertension and diabetes mellitus in non-dark-skinned Africans. This finding is an unexpected phenomenon that requires more detailed study. Ahmad et al. showed an inexplicably higher prevalence of autosomal dominant forms of FH among the non-Hispanic Negroid population. The low prevalence of LDLR gene mutations in the same ethnic group suggests an alternative mechanism of expression of the familial hypercholesterolemia phenotype in the African population [20].

The study of the ethnic peculiarities of the prevalence of FH and variations in its genetic substrate is of rather significant clinical importance, allowing to optimize treatment and diagnostic processes in local populations. In particular, the analysis of the Canadian register of FH, including data of patients from 2008 - 48 people, showed that compared to the world data in the Canadian cohort of patients among the clinical manifestations of the disease was dominated by aortic valve stenosis 47.9% of cases [21].

As in the case of heFH, the prevalence of homozygous forms was also re-evaluated as the results of cohort studies accumulated. In particular, in Denmark it was 1:160 000 [46], in the Netherlands genetically identified forms occurred with a frequency of 1:300 000 [37]. In the Spanish population, the incidence of homozygous FH was 1: 450,000 [47], while in Germany it was significantly lower than the European average of 1: 860,000 [48]. There have been few studies of ethnic aspects of the prevalence of homozygous forms; there are results of studies of a Japanese cohort, where homozygous forms were quite rare with a frequency of 1: 171,167 [49].

Given the need for early diagnosis of familial forms of hypercholesterolemia for the goal of as early as possible initiation of therapy and prevention of the development of significant cardiovascular events, much attention has recently been paid to the study of the epidemiology of FH among children and adolescents. Globally, it is estimated that 20-25% of all cases of FH occur in pediatric population, with 1 child born with this pathology every minute [50,51]. Belay et al. in a study on prescribing statin therapy to pediatric patients, including 885 participants, noted that 92% of the children were of Caucasian race. The general overview of racial differences is illustrated in the Figure 2 in Appendix. These figures reflect differential access to diagnostics and, including cascade screening, in the non-white population [19].

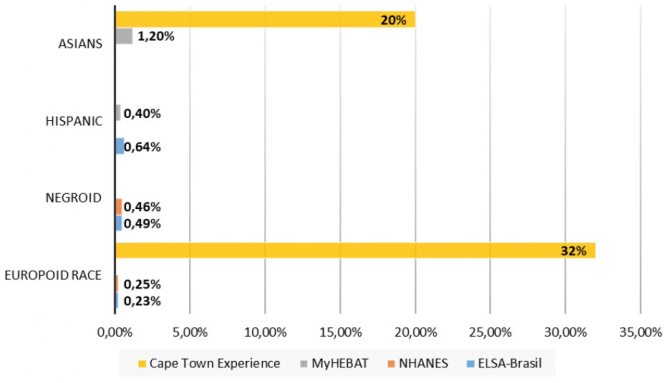

Figure 2 – Familial hypercholesterolemia prevalence by race and ethnicity according to studies

Discussion

Thus, analyzing all of the above, it can be concluded that despite a large number of studies, national screenings, and the development of new approaches, familial hypercholesterolemia remains an underdiagnosed disease. The prevalence of this

pathology in the general population remains unknown in approximately 90% of countries. The European continent is the most studied. According to the data presented, there is considerable variability in the epidemiology of familial forms between different ethnicities and continents. In particular, members of the Negroid race, according to most studies, have a high prevalence of FH. Members of the Asian race have traditionally been less likely to have FH, although there is a trend towards variation in this population as well. There are a number of populations with a very high prevalence of hypercholesterolemia, such as the Gulf States, French Canadians, Afrikaners, etc.

Adequate assessment of the prevalence of FH is difficult, also due to the lack of complete information. Currently available clinical and molecular diagnostic methods have their advantages and disadvantages. In the scoring scales of clinical criteria of FH, lipid arch of the cornea and xanthomatosis of the Achilles tendon have the maximum specific weight. However, according to a genetic cascade screening program conducted in Brazil, among patients with a confirmed gene mutation, these features were detected in only 28.4% and 13.2%, respectively [24]. On the other hand, genetic testing was able to identify the causative mutation in only 20-30% of patients with probable FH, and in 60-80% of patients with confirmed FH [25]. Thus, both clinical and genetic diagnostic methods have significant limitations and lead to underestimation of the real prevalence of FH.

Another difficulty in estimating the true prevalence of FH is the heterogeneity of diagnostic criteria. The criteria used in different countries vary widely. A number of them are based on a point system, such as most widely used in Western countries - Danish Lipid Clinic Criteria. The Simon Broome criteria and the Japanese criteria for the diagnosis of FH are based mainly on such criteria's as clinical manifestations (hypercholesterolemia, tendon xanthomatosis) and a anamnesis of FH and/or early nascence atherosclerosis-associated cardiovascular disease. Such systems as MEDPED take in consideration only cholesterol levels and family history. The described variability of the criteria creates great difficulties in analyzing the results of studies from different countries and consequently including different ethnic cohorts. In addition, the criteria developed so far have been mainly focused on Western countries and therefore cannot be absolutely valid for another ethnic groups. Also, as data from new studies become available, there is a continuous process of revision of diagnostic criteria. For example, in 2020, scientists from Kanazawa University, Japan, conducted a study, according to the results of which, the threshold values of Achilles tendon thickness, after which it can be talked about a probable FH, were changed, the new interval is 7-9 mm (previously more than 9 mm) [18].

The existing problems of underestimating the racial and ethnic prevalence of FH have a number of significant socioeconomic implications. In particular, inequalities in cardiovascular risk evaluation in different ethnic groups; inequalities in access to approved statin therapy, as well as to new lipid-lowering drugs, inefficient allocation of available limited resources (medicines, equipment, human resources), especially in low- and middle-income countries. These facts in turn lead to progressive growth of atherosclerosis-associated cardiovascular diseases and, as a consequence, to increased disability and mortality of working-age adults.

The underestimation of racial and ethnic characteristics of FH is due to several factors, one of which is the so-called "structural racism in medicine" - unequal/ disproportionate involvement of representatives of different ethnic groups in clinical trials [52]. This factor leads to a lower representation of different ethnic groups, especially smaller ethnic groups in large-scale studies and, as a result, a lack of epidemiological data on these groups. In addition, a significant proportion of clinical trials are conducted in high-income countries, given the greater opportunities for their implementation and the a priori assumed reliability of the data obtained, which automatically excludes huge population cohorts from the analysis.

Obtaining reliable data on ethnic and racial differentiation of the prevalence of familial forms of hypercholesterolemia has a number of significant advantages. It is expected to increase the understanding of the pathogenesis of hypercholesterolemia and the burden of this pathology in non-European individuals, strengthen preventive medicine approaches, implement a system of screening, including cascade screening, optimize resource allocation and, as a consequence, improve the survival and quality of life of such patients.

Limitations and Future directions

It is important to take into account the many limitations of this systematic review when evaluating the results. First, the diagnostic standards and procedures applied in the included research vary significantly from one another. This variability makes direct comparisons more difficult and could result in disparities in the reported prevalence of FH across various racial and ethnic groups. Furthermore, the majority of the research included in this review were carried out in high-income nations, which might not fairly represent the world's population, especially in low- and middle-income nations where there is a dearth of information or nonexistence about the incidence of FH. The generalizability of the results is restricted by the absence of data from continents including Africa, South America, and portions of Asia. Additionally, the degree to which genetic testing is relied upon varies greatly throughout studies, and access to this type of testing is frequently restricted by economic and geographic reasons, which may result in underdiagnoses in less affluent areas. Last but not least, because homozygous variants are rarer and there are less studies on them, the review mostly concentrates on heterozygous types of FH.

Expanding research efforts to underrepresented regions, particularly low- and middle-income countries, is crucial to obtaining a more accurate global prevalence of FH. Additionally, future studies should focus not only on heterozygous FH but also on the homozygous forms to better understand the full spectrum of the disease. Standardizing diagnostic criteria and methodologies can help in early identification and management of the condition. All of the gaps in this review should be addressed in future research to provide a more comprehensive understanding of the prevalence of FH across different ethnic and racial groups globally. Overcoming the logistical and financial obstacles in these areas would require cooperation between global research institutes and regional healthcare providers. Lastly, earlier identification and treatment can be made possible by raising public and healthcare professionals' knowledge of FH, which will eventually improve patient outcomes.

Conclusion

To date, FH remains a disease that is underdiagnosed in a timely manner. Data from various studies agree on the overall prevalence of heterozygous forms in the range of 1: 192-303. At the same time, there are significant differences in estimates of the prevalence of FH in Asian, Hispanic, and Negroid populations. Moreover, the data differ with respect to both overall prevalence and patient cohorts. In some populations, such as the Africans, and Lebanese Christians, French Canadians and Gulf region population, where the "founder effect" is strong and the tradition of closely related marriages persists, there is a high incidence of both hetero- and homozygous forms. However, accurate statistics are not available everywhere. Regions such as Central Asian countries remain a white spot on the global map of FH prevalence. Consequently, epidemiological studies with maximum geographical coverage and ensuring equal inclusion of representatives of different ethnic groups are required.

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