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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ESTIMATING THE PREVALENCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN STROKE AND TRANSITORY ISCHEMIC ATTACK POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract.

Background/Objectives: Familial hypercholesterolemia (FH) is a common inherited disorder characterized by lifelong elevation of LDL-cholesterol. While FH prevalence is well described in coronary populations, its contribution to cerebrovascular disease is less clear. This study aims to address this gap by systematically reviewing and synthesizing available evidence to estimate the prevalence of FH in patients with ischemic stroke or transitory ischemic attack overall and across key subgroups. **Methods:** This systematic review included original observational studies, with data on stroke and FH. The protocol was registered in PROSPERO with the ID CRD420251162340. Two reviewers independently screened records, extracted study characteristics and assessed risk of bias. **Results:** Four studies involving 389272 stroke/transient ischemic attack (TIA) patients (2083 with FH) met eligibility criteria. The pooled prevalence of FH was 0.96% (95% CI 0.11–7.63), with significant between-study heterogeneity ($I^2 = 95.3\%$, $\tau^2 = 1.7139$, $p < 0.0001$). Among patients with large artery atherosclerosis (LAA) strokes, FH prevalence was 2.89% (95% CI 0.05–63.28%), also with highheterogeneity ($I^2 = 93.9\%$, $\tau^2 = 2.4854$, $p < 0.0001$).

Conclusions: The evidence linking FH to stroke remains limited and highly heterogeneous, preventing firm quantitative conclusions. However, the available studies offer preliminary signals that FH may have relevance beyond cardiology and should be considered in discussions of cerebrovascular risk. Given the small number of studies and their methodological variability, further research with standardized diagnostic criteria and larger, well-designed cohorts is needed to clarify this relationship and to determine whether improved detection and management of FH in stroke populations could help reduce the broader burden of atherosclerotic disease.

Key words. Familial hypercholesterolemia, stroke, transient ischemic attack, prevalence, epidemiology.

Introduction.

Stroke remains a leading cause of death and disability in the world, second after ischemic heart disease, with 11.9 million incident cases and 7.3 million deaths in 2021 and a substantial, persisting global burden of disability adjusted life years (160.5 million) [1]. Stroke risk is driven by classical modifiable factors such as hypertension, diabetes, smoking, and air pollution as well as lipid disorders [2-4]. Elevated low-density lipoprotein (LDL) levels are considered as a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) [5]. One of the genetical causes of LDL elevation is familial hypercholesterolemia (FH).

Familial hypercholesterolemia is considered to be the most prevalent autosomal dominant disorders globally, with a prevalence rate of 1:311 in the general population and increases 10-fold among patients with ischemic heart disease [6,7]. It is mainly caused by loss of function mutations in low-density lipoprotein receptor (LDR), additionally less often by mutations in apolipoprotein B (APOB) genes and proprotein convertase subtilin/kexin type 9 (PCSK9) genes [8-11]. The following mutations predisposes one to a life-long impairment of the hepatic clearance of LDL. As a result, a cumulative exposure of atherogenic levels of LDL-C will take place several decades in advance in comparison with those with normal levels [12]. Coronary arteries tend to demonstrate the consequences earliest. Without any interference with management approaches, a predisposition towards a drastically increased risk of pre-term myocardial infarction (MI) and coronary-related deaths would be observed in individuals with heterozygous forms of this clinical condition (HeFH) [13]. In contrast, homozygous forms of this clinical condition (HoFH), a relatively rare but more severe form with a prevalence of 1:300000 would lead to severe major adverse cardiac events (MACE) prior reaching the first decade of life [14]. Consequently, the vast majority of FH literature and clinical guidelines have focused on the prevention of coronary heart disease (CHD). Despite this, FH remains substantially underdiagnosed and undertreated globally, a gap emphasized by recent consensus and guidance statements [15,16].

While the role of coronary risk remains fairly well understood and demarcated with a measurable degree of precision, stroke risk among individuals with FH remains a debated issue. Stroke is a heterogeneous syndrome rather than a single disease entity. Ischemic stroke, accounting for the majority of cases, can arise from large artery atherosclerosis, cardioembolism, small vessel occlusion, or other determined etiologies [17,18]. Large artery atherosclerosis (LAA) is a stroke subtype driven by atherothrombotic plaque formation, which is primarily caused by dyslipidemia in conjunction with hypertension, inflammation, and endothelial dysfunction [19]. Although recent data in large-scale prospective FH registries, such as the Norwegian FH registry, the Copenhagen General Population Study, SAFEHEART registry and Simon-Broom Register, report stroke incidence rates not comparable with the general population, most of them are disease-based designed to characterize patients who already have FH, track management, and capture cardiovascular outcomes [20-28]. However, in studies before the statin therapy period, individuals with heterozygous FH faced a substantially higher stroke risk (OR of 7.658; 95% CI: 6.059–9.678) compared to the general population, a risk that was significantly reduced to an OR of 0.251 (95% CI: 0.176–0.358) following the widespread adoption of statins [29].

This fact tends to lead towards a series of fundamental questions regarding the relation of FH with stroke. The analyses in registers often combined all stroke phenotypes, potentially masking the specific association between FH and atherosclerosis-driven stroke like LAA. Moreover, the burden of familial hypercholesterolemia in stroke patients could not be estimated through data from such registries due to selection, referral, and survivorship biases. Therefore, a different approach is necessary to understand the burden of familial hypercholesterolemia in stroke.

Our study aims to estimate the prevalence of familial hypercholesterolemia in patients with ischemic stroke or transitory ischemic attack (TIA). We conducted a systematic review and meta-analysis to estimate the prevalence of FH among patients with stroke or TIA, overall and in key subgroups.

Materials and Methods.

Registration and Search strategy:

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) [30]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the ID CRD420251162340. We included PubMed/MEDLINE, Embase and Cochrane Library as the search databases for our systematic review. Searches included all studies prior to October 7, 2025, MeSH terms or Emtree terms and general keywords depending on the database were used. Detailed information regarding the search strategy is presented in Table A1.

Two reviewers (M.K. and B.A.) were assigned for the primary screening of titles, abstracts and keywords. The process of primary review was blinded for the reviewers. In conflict situations a third reviewer (A.M.) was assigned to resolve the conflict. Full texts of potentially relevant studies were then assessed by the same process with assessing the eligibility of studies.

Eligibility criteria:

We included original observational studies, with data on stroke and familial hypercholesterolemia. Studies were eligible if they met the following criteria: (1) enrolled individuals with clinically diagnosed ischemic stroke or TIA; (2) reported sufficient data to compute the overall prevalence and for subgroups; (3) ascertained FH using a recognized approach like genetic testing (NGS), Dutch Lipid Clinic Network (DLCN), Simon Broome (SB), MEDPED, or LDL-C > 90th percentile in proband [31-34]. We excluded case reports, reviews, editorials, conference abstracts without extractable data, studies with a sample size below fifty and interventional studies lacking baseline prevalence data. When overlapping populations occurred, we retained the most relevant study, hence the latest and with full data.

Data extraction:

Two reviewers (M.K. and A.M.) independently extracted data using the pre-designed form. First author, publication

Table 1. *Studies included in the systematic review and their general characteristics.*

Study	Enrollment period	Population	Age (years)	Diagnostic criteria	Sample size, N	FH cases, N	Female patients, N (%)	FH in females, N (%)	LAA patients, N (%)	FH cases in LAA, N
Li et al. [36] (2024) China	2015 - 2018	IS/TIA	62.25	1. NGS (LDLR and EPHX2); 2. SB	10428	24	3291 (31.6%)	8 (33.3%)	2999 (28.8%)	24
Abumoawad et al. [37] (2023) USA	2019	AIS	-	ICD code	377669	2039	173789 (46%)	1040 (51%)	-	-
Tung et al. [38] (2021) Taiwan	2018 - 2019	IS/TIA	-	1. LDL-C > 90th percentile in proband; 2. NGS (LDLR, APOB, and PCSK9)	121	6	38 (31.4%)	0 (0%)	27 (22.3%)	4
Toell et al. [39] (2017) Austria	2014 - 2016	IS/TIA	69.3	DLCNA	1054	14	446 (42.3%)	7 (50%)	191 (18.1%)	3

Note: IS – ischemic stroke, TIA – Transitory ischemic attack, AIS – Acute ischemic stroke, NGS – New-generation sequencing, SB- Simon Broome, DLCN - Dutch lipid clinic network, ICD - International Classification of Diseases, LDL-C – Low-density lipoprotein cholesterol, LDL-R - Low-density lipoprotein receptor gene, APOB - Apolipoprotein B gene, PCSK9 - Proprotein convertase subtilisin/kexin type 9 gene, EPHX2 - Epoxide hydrolase 2 gene, LAA – Large-artery atherosclerosis, FH – Familial hypercholesterolemia.

Table 2. *Risk of bias assessment.*

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall
Tung et al. [38]	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Li et al. [36]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Abumoawad et al. [37]	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	High
Toell et al. [39]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

Note: Yes = low risk for that item; No = high risk for that item. Q1 – Target population, Q2 – Sampling frame, Q3 – Random selection, Q4 – Non-response bias, Q5 – Data collection direct, Q6 – Case definition, Q7 – Validity of study instrument, Q8 – Same mode of data collection, Q9 – Prevalence period, Q10 – Calculation and reporting.

year, country, enrollment period, population type, mean age, diagnostic criteria, sample size, female frequency, LAA frequency, FH cases in sample, female and LAA were extracted as variables. The detailed characteristics can be found in Table 1. Frequencies were calculated manually when only percentages were given.

Risk of bias assessment:

We used the tool developed by Hoy et al. for assessing the risk of bias [35]. The tool included 11 items and was reviewed by two reviewers (A.M. and M.K.) independently with recourse to a third reviewer (B.A.) when needed. Items 1–4 cover external validity (representativeness of the target population, sampling frame, selection method/census, and non-response), and items 5–10 address internal validity (direct data collection, acceptable case definition, reliability/validation of measurement, uniform data-collection mode, appropriateness of prevalence period, and correct use of numerators/denominators). We classified the overall risk (item 11) as moderate when 2–3 items were high risk or when any single selection-domain item (items 1-4) was high risk, and high when ≥4 items were high risk or when ≥2 selection-domain items were high risk.

Statistical analysis:

The prevalence rates for the groups of interest were calculated with: Prevalence = (Number of FH cases / Population) * 100. We synthesized study-specific prevalence of FH using random-effects meta-analysis, prespecified due to anticipated clinical and methodological heterogeneity. Proportions were logit-transformed and pooled with inverse-variance weighting. Between-study variance (τ^2) was estimated by restricted maximum likelihood (REML), and Hartung–Knapp adjustments were applied for random-effects confidence intervals. For zero-cell strata, a continuity correction of 0.5 was added to all studies. Pooled effects and 95% CIs were transformed back to the raw scale and reported as percent prevalence.

Statistical heterogeneity was evaluated with Cochran's Q, I^2, and τ^2. Subgroup analysis was performed on LAA and sex, also on random-effects model. Small-study effects were explored visually with funnel plots of logit-transformed prevalence versus its standard error. Formal Egger's test could not be performed due to the limited number of included studies. We performed sensitivity analysis by leave-one-out method, iteratively refitting the random-effects model after omitting each study.

We investigated potential sources of between-study heterogeneity in the pooled prevalence estimates using univariate meta-regression analysis. The independent variables assessed included mean patient age, proportion of female participants, sample size, diagnostic criteria, and risk of bias. Categorical covariates (diagnostic criteria and risk of bias) were converted to dummy variables for analysis. We applied mixed-effects models to logit-transformed proportions, utilizing the DerSimonian-Laird estimator for heterogeneity (τ^2). The Hartung-Knapp adjustment was employed to refine confidence intervals and calculate the R^2 statistic.

Results.

Study selection and characteristics:

Our search strategy identified 196 records (Figure 1). After the removal of duplicates and ineligible publications, only 4 studies were included in the final systematic review with a total sample of 389272 patients and 2083 FH patients (Table 1). DNA-based criteria were used as the primary method in one study, where a secondary diagnostic with SB criteria followed the genetic testing [36]. Another study collected data from a register utilizing ICD codes, noting that the diagnostic criteria may vary [37]. A third study employed a clinical approach alongside an additional secondary diagnostic based on DNA criteria [38]. Finally, the last study relied only on DLCNA criteria [39].

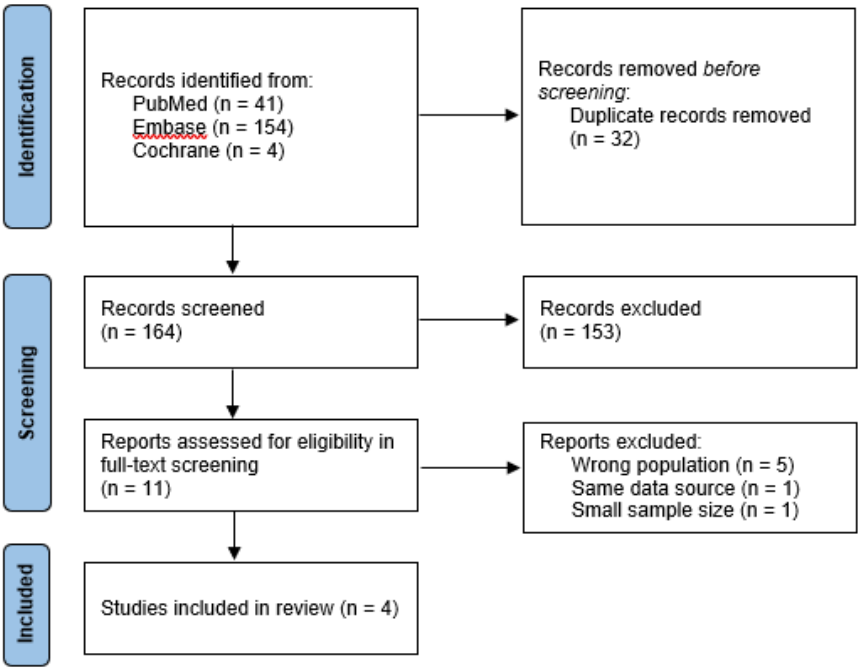

Figure 1. *Study selection PRISMA flow diagram.*

Risk of bias in studies:

All studies were subjected to a risk of bias assessment to establish their risk in determining the prevalence of FH in the stroke population across all ages (Table 2). Two studies had high risk of bias, while the other two were moderate.

Results of prevalence synthesis:

Table 3 summarizes the unweighted prevalence rates reported across four studies. There was substantial heterogeneity in the reported overall prevalence, spanning from a low of 0.23% to a high of 4.96%. While one study demonstrated absence of FH cases in females, the other 3 studies reported slightly higher prevalence in females compared to males. Hence, the range varied from 0% to 1.57% in females and 0.22% to 7.23% in males. The general crude prevalence from the total population of 389272 patients was 0.54%, while the crude prevalence in males and females had values of 0.49% and 0.59% respectively.

Notably, in studies that stratified for stroke etiology, the prevalence was consistently higher among patients with LAA. For example, Tung et al. observed an overall prevalence of 4.96%, which rose to 14.81% specifically within the LAA subgroup. Similarly, Li et al. noted a nearly four-fold increase in the LAA cohort (0.80%) compared to the general stroke population (0.23%). The crude prevalence of FH in LAA patients resulted in 0.96%.

Results of meta-analysis:

The pooled random-effects prevalence of FH among patients with stroke was 0.96% (95% CI 0.11–7.63%), with significant between-study heterogeneity (I^2 = 95.3%, τ^2 = 1.7139, p < 0.0001) (Figure 2). Individual study prevalence estimates ranged from 0.23% in the largest population-based cohort (Li et al., 2024) to 4.96% in a small single-center study (Tung et al., 2021). The weighting of studies in the random-effects model was balanced (range 23.7–26%). After exclusion of the study with non-reliable diagnostical criteria, the pooled prevalence across three remaining studies (N = 11603) increased to 1.18% (95% CI 0.02–38.26%), with persistent high heterogeneity (I^2 = 96.8%, τ^2 = 2.4291, p < 0.0001) (Figure 3).

Visual inspection of the funnel plot of logit-transformed prevalence versus standard error showed asymmetry and a wide scattering of study estimates, suggesting potential small-study effects (Figure 4). Several studies fall outside the 95% pseudo-confidence limits, visually confirming significant between-study heterogeneity.

Among patients with large-artery atherosclerotic stroke (N = 3217; three studies), the random-effects pooled prevalence of FH was 2.89% (95% CI 0.05–63.28%) (Figure 5). Study-specific prevalences were 1.57% [39], 14.81% [38], and 0.80% [36]. Between-study heterogeneity remained high (I^2 = 93.9%, τ^2 = 2.4854, p < 0.0001).

All four studies provided sex-stratified data (Figure 6). Among females (N = 177564), the pooled prevalence was 0.67% (95% CI 0.17–2.56%; I^2 = 79.1%, τ^2 = 0.6144, p = 0.0025). Among males (N = 211708), the prevalence was higher with a value of 1% (95% CI 0.09–10.54%; I^2 = 95.3%, τ^2 = 2.2511, p < 0.0001). The combined pooled prevalence across sexes was 0.84% (95% CI 0.31–2.23%; I^2 = 92.8%, τ^2 = 1.2891, p < 0.0001) with no significant difference between groups (χ^2 = 0.22, df = 1, p = 0.6418).

Table 3. *FH prevalence in studies.*

Study	General prevalence, (%)	Prevalence in females, (%)	Prevalence in males, (%)	Prevalence in LAA patients, (%)	Δ relative percent change in LAA
Li et al. [36]	0.23	0.24	0.22	0.80	+247.83%
Abumoawad et al. [37]	0.54	0.60	0.49	-	-
Tung et al. [38]	4.96	0	7.23	14.81	+198.59%
Toell et al. [39]	1.33	1.57	1.15	1.57	+18.05%

Note: LAA – Large-artery atherosclerosis.

Table 4. *Leave-one-out sensitivity analysis of pooled FH prevalence among patients with stroke.*

Omitted study	Pooled prevalence	Δ absolute pp	Δ relative percentage	I^2 after omitting
Li et al. [36]	1.52%	+0.56 pp	+59%	95.6%
Abumoawad et al. [37]	1.18 %	+0.22 pp	+23.4%	96.8%
Tung et al. [38]	0.55%	-0.40 pp	-42.3%	93.3%
Toell et al. [39]	0.86%	-0.1 pp	-10.1%	96.1%

Note: pp – percentage points.

Table 5. *Meta-regression analyses.*

Independent variable	No. of studies	Beta coefficient (95% CI)	P value	R^2 (%)
Age	2	NA	NA	NA
Sex	4	-2.69 (-55.63 to 50.24)	0.85	0.00
Diagnostic criteria	4	NA	0.95	0.00
Sample size	4	0.00 (-0.00 to 0.00)	0.69	0.00
Risk of bias	4	NA	0.54	0.00

Note: 95% CI, 95% confidence interval; NA, not applicable; No. of Studies, number of studies with observations for the indicated variable; R2, between-study heterogeneity accounted for by the indicated variable and adjusted with the Hartung-Knapp modification

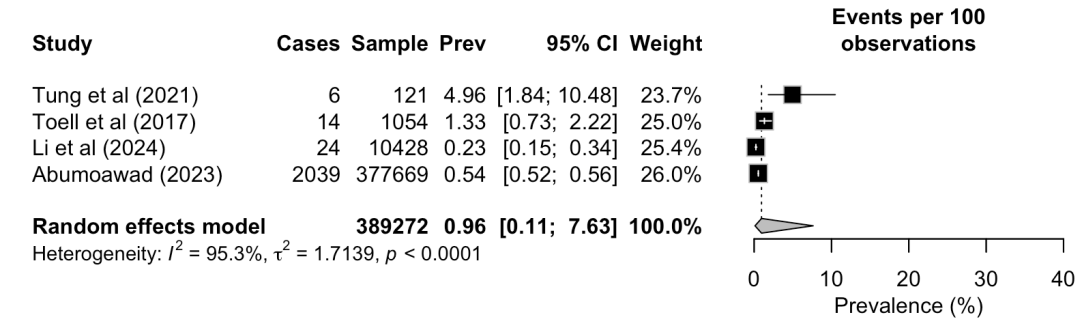

Figure 2. *Forest plot of FH prevalence in stroke patients across all studies [36-39].*

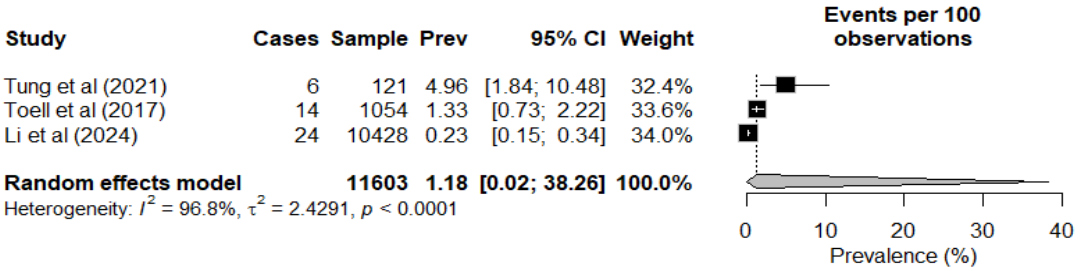

Figure 3. *Pooled prevalence restricted to studies with strict criteria [36,38,39].*

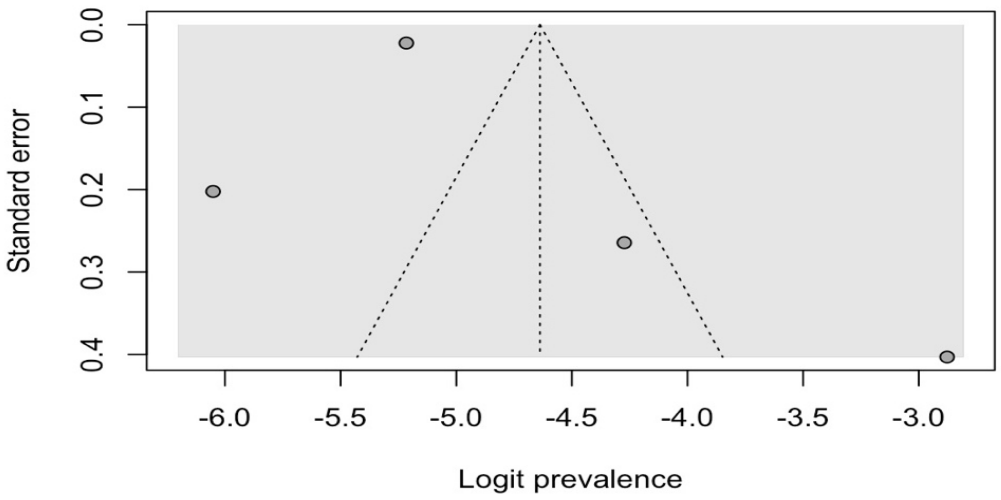

Figure 4. *Funnel plot of logit-transformed prevalence against standard error for assessment of small-study effects.*

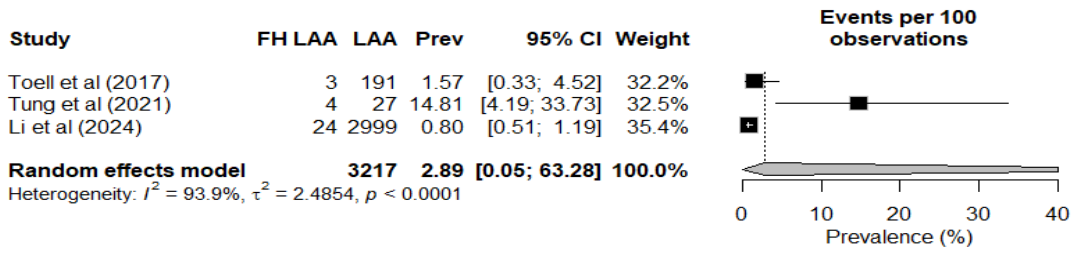

Figure 5. *Subgroup analysis for large-artery atherosclerosis stroke patients [36,38,39].*

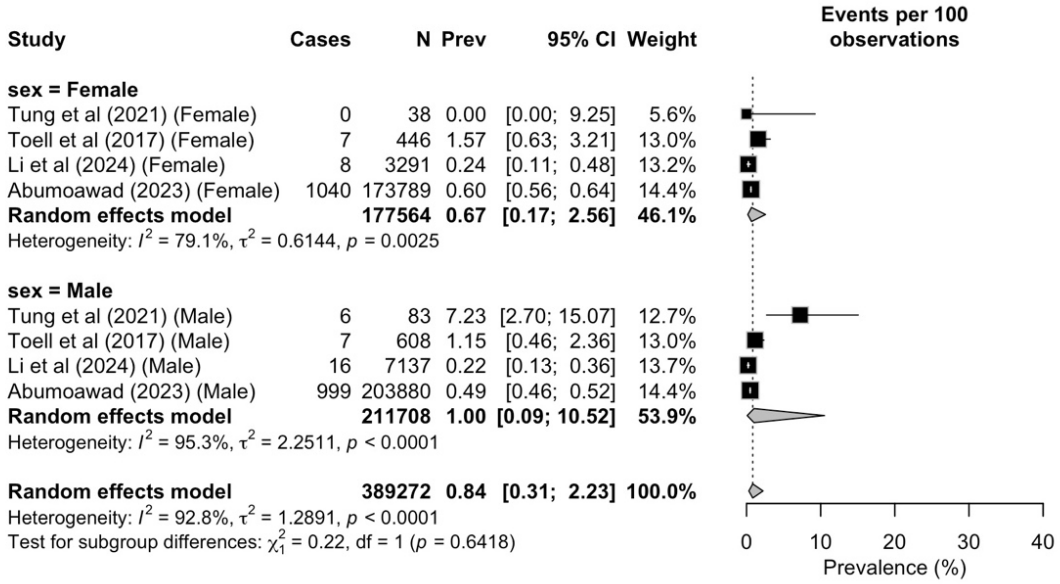

Figure 6. *Sex-stratified pooled prevalence of FH among stroke patients [36-39].*

Table A1. *Search strategy for Embase.*

Search #	Keyword or phrase	Results found
#1	'ischemic stroke' OR 'ischemic stroke'/exp	149539
#2	'familial hypercholesterolemia' OR 'familial hypercholesterolemia'/exp	18376
#3	'transient ischemic attack' OR 'transient ischemic attack'/exp	59025
#4	'prevalence' OR 'prevalence'/exp OR 'incidence' OR 'incidence'/exp OR 'epidemiology' OR 'epidemiology'/exp	7504620
#5	#1 OR #3	196170
#6	#5 AND #2	266
#7	#6 AND #4	151

Sensitivity analysis:

In the leave-one-out analyses the overall pooled prevalence varied between 0.55% and 1.52%, while the heterogeneity remained high (I^2 = 93.3-96.8%) (Table 4). Omitting Tung et al. caused the highest relative percentage reduction of -42.3% (Δ absolute pp = 0.4 pp). In contrast, the highest rise in pooled prevalence of +59% (Δ absolute pp = 0.56 pp) occurred when Li et al. was omitted.

Meta-regression analysis

We conducted linear regression analyses to determine whether age, sex, diagnostic criteria, sample size, or risk of study bias may have influenced the overall pooled prevalence of FH in stroke. Due to missing data, meta-regression for mean age could not be performed. None of the variables were not determined to have a significant effect on the overall pooled prevalence. However, these results should be interpreted with caution given the small number of studies included in the analysis (n=4).

Discussion.

Our systematic review and meta-analysis aimed to estimate the prevalence of FH in patients with IS/TIA and revealed a substantial heterogeneity in FH prevalence, ranging from 0.23% to 4.96% with a pooled prevalence of 0.96% (95% CI: 0.11% to 7.63) from our data from four observational studies, comprising a total of 389272 patients. This variation is largely attributable to the difference in diagnostic criteria used in the studies, ranging from strict SB and DLCN to administrative ICD coding and LDL thresholds with NGS. A total crude prevalence of 0.54% results from the general population of 389272 patients from 4 studies. The finding from the sensitivity analysis that restricted the data to studies with strict diagnostic criteria yielded a more focused, albeit still heterogeneous, pooled prevalence of 1.18%. We propose that the true FH prevalence in a strictly-defined stroke cohort is likely in the range of 0.55% to 1.52%, as reflected by our leave-one-out sensitivity analysis. Therefore, this percentage appears to be higher than the expected prevalence of 0.3-0.4% in the general population [6,40]. In addition, when the looser definition of the phenotype has been used, a substantially higher percentage of stroke subjects exhibited indicative features of Familial Hypercholesterolemia. For example, in the study by Toell et al. a further 10% were considered as “possible” FH subjects when applying the DLCN Criteria 3-5 point scoring system, corresponding altogether to the total potential fraction of 11.5% among ischemic stroke subjects [39]. These observations point towards the fact that although the actual prevalence among stroke subjects seems to remain below 5% at most, Familial Hypercholesterolemia clearly represents a significantly elevated risk factor among ischemic stroke subjects.

A notable finding from available evidence from our review is the suggestion of a potential phenotype-specific association.

Although the high heterogeneity and wide confidence intervals precluded a precise pooled prevalence estimate for the LAA subgroup (2.89%, 95% CI 0.05–63.28%, $I^2 = 93.9\%$,), individual studies consistently signalled higher FH rates in this phenotype compared to the general stroke population. For instance, Tung et al. reported a nearly threefold increase in FH prevalence within the LAA subgroup compared to the general stroke population (14.81% vs. 4.96%), while Li et al. observed a similar trend (0.80% vs. 0.23%) [36,38]. These findings reinforce the lifelong elevated LDL-C in patients with FH contributes to stroke primarily through accelerated atherosclerosis of large vessels rather than cardioembolism or small vessel occlusion. Some small studies demonstrated the higher prevalence of small vessel disease in FH patients [41]. Furthermore, the prevalence was notably higher in younger populations and those with premature cardiovascular events, as evidenced by Toell et al., who identified significant familial lipid abnormalities in young stroke cohorts [39]. A similar pattern was observed in an older study [42].

These observations both support and extend previous studies related to the prevalence of FH within specific at-risk populations. Historically, FH has been most clearly identified in association with "premature" coronary disease. For example, the 2019 meta-analysis conducted by Kramer et al. among multiple studies observed a combined prevalence of 4.7% for FH among the broader ACS population, increasing to 7.3% among individuals ≤ 60 years and 13.7% among individuals ≤ 45 years [43]. In other words, 1 in 21 individuals among the total ACS population has FH. Moreover, among the youngest individuals suffering from ACS, the prevalence jumps to 1 in 7. In contrast to the relative preponderance of younger subjects among the total ACS population, the stroke patient population tends to be disproportionately elder and encompasses multiple etiologies such as atherothrombotic stroke, cardioembolic stroke, and stroke due to small vessel disease. As such, the absolute percentage of FH subjects tends to decrease. In fact, our present finding does suggest that the prevalence of FH among individuals suffering stroke appears less than among the ACS group.

Our review indicates that FH is frequently undiagnosed prior to the stroke event. Toell et al. noted that stroke was the first clinical manifestation of disease in 71.4% of FH patients [39]. Although we had no data to conduct a subgroup analysis by age, when Toell at al. included the younger stroke patient population (men < 55 years and women < 60 years), the rates became more similar among the patient population with coronary disease [39]. In the younger stroke patient population studied, 3.1% presented with definite and probable FH and 13.1% presented with possible FH. This again reflects the correlation observed among the ACS patient population where the risk of underlying FH strongly correlates with the patient's age. This suggests a dilution effect in older populations, consistent with the view of FH as a driver of premature vascular aging. Our subgroup analysis demonstrated a higher pooled prevalence of FH and higher numbers of stroke patients in men compared to women, which should be interpreted cautiously due to the high heterogeneity and non-significance of difference. The general difference can be explained by behavioral risk factors, which facilitates the event risk occurrence [4,44,45].

These findings suggest that patients presenting with ischemic stroke, especially those with a relatively younger age or evidence of atherosclerosis, should be evaluated for possible FH. Recurrent events were common among FH patients. Tung et al. observed that 50% of FH carriers had a prior history of cerebrovascular or coronary artery disease, suggesting that FH contributes to a cumulative burden of vascular injury [38]. Currently stroke prevention efforts focus on immediate causes such as anticoagulation in atrial fibrillation or intensive blood pressure control, and hyperlipidemia is treated as a modifiable risk factor, not always understanding its origin. Identifying FH cases is crucial because it enables aggressive lipid-lowering therapy and cascade family screening, which can prevent future vascular events. Although the European Atherosclerosis Society (EAS) and the American Heart Association (AHA) advocate for opportunistic FH screening in patients with premature or unexplained ASCVD, the strongest recommendations are for the young MI patients. Our data supports extending this paradigm to ischemic stroke patients, especially those under 60 or with carotid artery disease. The EAS Familial Hypercholesterolemia Studies Collaboration and other experts have called for systematic strategies to improve FH case-finding, including integrating FH detection into routine care for ASCVD patients and even population-based cholesterol screening in youth [46-48]. We recommend active screening for FH, specifically in patients presenting with Large Artery Atherosclerosis (LAA) stroke or premature stroke (<60 years). Our data indicates that FH-related stroke is distinctively characterized by an atherosclerotic phenotype, with significantly higher prevalence in the LAA subgroup (2.89%) and evidence of increased carotid intima-media thickness in FH carriers. Identifying these patients is crucial for initiating cascade screening [38].

This study appears to be the first systematic review focusing specifically on the prevalence of FH among stroke patients. One of the advantages of our analysis is the thorough incorporation of studies applying both clinical and molecular diagnostic criteria for FH. This made possible the comparison and interpretation of the outcome across the spectrum of diagnostic tools chosen. This review encompassed international studies (European, Asian, and other patient sources), increasing the generalizability of our results.

We also acknowledge the limitations of our study. First, the number of studies and total sample size for stroke-specific FH prevalence was limited. Second, there was substantial heterogeneity between studies, a major source is the high variation in diagnostic criteria for FH used across studies. For example, in the genetic testing, not all genetic variants were assessed, hence there is a chance of missing cases. The use of different diagnostic criteria limits the generalization to any single clinical setting, but confirms the presence of FH across different detection modalities. Another important limitation is that stroke cohorts were mainly composed of older adults, in whom diagnosing FH can be challenging. Older patients are more likely to be on lipid-lowering therapy or have other comorbidities affecting LDL levels, potentially lowering their LDL levels at presentation and underdiagnosing of FH. A critical limitation of our systematic review is the lack of uniform

data on pre-stroke statin use. Statin therapy significantly alters lipid profiles, potentially masking the clinical diagnosis of FH in studies relying on phenotypic scores (e.g., DLCNA). Lipid-lowering therapy is a cornerstone of ischemic stroke prevention, and its unmeasured variance across cohorts may influence prevalence estimates [49]. A major limitation of this review is the unequal weight of the included evidence. Approximately 97.6% of the identified FH cases (2039/2083) originated from a single nationwide registry study (Abumoawad et al.) utilizing ICD codes [37]. This introduces a significant skew, as ICD coding often underestimates prevalence compared to active clinical screening. The survival bias could paradoxically lower FH prevalence relative to what might have been if patients had not been succumbed to coronary disease earlier [50]. Unpublished data or ongoing registry findings could further inform the prevalence estimate and add data for future meta-analysis.

Conclusion.

The current evidence base examining familial hypercholesterolemia in the context of stroke remains limited, heterogeneous, and methodologically diverse. Although our review suggests a potential association between FH and stroke, the substantial variability across the few available studies prevents requires cautious interpretations. Rather than interpreting the estimate as definitive, these findings should be viewed as preliminary signals indicating that FH may play a role outside the traditional cardiology setting and merits consideration when evaluating cerebrovascular risk.

Given the scarcity and inconsistency of existing research, future studies using standardized diagnostic criteria, larger sample sizes, and more rigorous methodological designs are needed to clarify the relationship between FH and stroke. Strengthening the evidence base will be essential for determining whether systematic screening, improved recognition, and targeted management of FH in stroke populations could contribute to reducing the broader burden of atherosclerotic disease.

Author Contributions.

Conceptualization, K.D., B.A., F.I. and M.K.; methodology, D.D., A.M. and I.B.; software, D.D.; validation, M.K. and B.A.; formal analysis, D.D., F.I., A.M. and S.L.; data curation, K.D., I.B. and S.L.; writing—original draft preparation, D.D.; writing—review and editing, K.D., M.K., B.A., F.I., I.B., S.L. and A.M.; visualization, D.D.; supervision, K.D., B.A. and M.K; funding acquisition, K.D. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement.

The study did not involve humans or animals; it is a systematic review of previously published literature.

Informed Consent Statement.

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Data Availability Statement.

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest.

The authors declare no conflicts of interest.

Abbreviations.

The following abbreviations are used in this manuscript:

ASCVD	Atherosclerotic Cardiovascular Disease
IHD	Ischemic Heart Disease
FH	Familial Hypercholesterolemia
LDL	Low-Density Lipoprotein
ACS	Acute Coronary Syndrome
NGS	Next-Generation Sequencing
TIA	Transitory Ischemic Attack
MEDPED	Make Early Diagnosis to Prevent Early Deaths
SB	Simon Broome
DLCN	Dutch Lipid Clinic Network
MI	Myocardial Infarction
ICD	International Classification of Diseases
LDL-R	Low-Density Lipoprotein Receptor Gene
APOB	Apolipoprotein B Gene
EPHX2	Epoxide Hydrolase 2 Gene
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9 Gene
LAA	Large-Artery Atherosclerosis
PCSK9	Proprotein Convertase Subtilin/Kexin Type 9
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
MACE	Major Adverse Cardiac Events
CHD	Coronary Heart Disease

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