



Analysis of Lipid Profile as a Risk Factor for Ischemic Stroke Incidence : A Systematic Review

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ABSTRACT

Background: Ischemic stroke (IS) is a leading cause of death and disability worldwide, with a complex and incompletely understood relationship with lipid parameters. Unlike coronary heart disease, the association between lipids and IS shows heterogeneity across subtypes and populations.

Methods: This systematic review synthesized evidence from 80 sources, including RCT, etc. We focused on studies reporting quantitative associations between lipid profile components and IS incidence, emphasizing statistically significant positive risk factors.

Results: Genetically determined LDL-C showed a modest causal effect on IS (OR 1.09, 95% CI 1.07-1.12) (1), but this was driven entirely by the large artery atherosclerosis (LAA) subtype (OR 0.75 for lower LDL-C) with null effects on cardioembolic and small vessel stroke (3). Observational data confirmed increased IS risk with elevated LDL-C (HR up to 1.74) (20) and non-HDL-C (HR 2.45) (20). HDL-C demonstrated a U-shaped relationship,

with both low (HR 1.29) and very high levels (HR 1.84) increasing risk (4). Lipoprotein(a) [Lp(a)] was a significant observational risk factor (RR 1.29 per 1SD) (7) and for stroke recurrence (OR 1.69) (47), though MR evidence was weaker (1). The triglyceride-glucose (TyG) index (HR up to 2.21) (11) and atherogenic index of plasma (AIP) (HR 1.12) (10) showed strong, significant positive associations. Lp-PLA2 activity was causally linked specifically to LAA stroke (OR 3.25) (15), while oxidized LDL increased both stroke (HR 1.39) and hemorrhagic events (HR 3.61) (14). Omega-3 fatty acids DHA and DPA were protective (HR 0.80 and 0.74, respectively) (12).

Discussion: The LDL-C-IS association is real but weaker than for coronary disease due to subtype heterogeneity. HDL-C is a complex marker where particle functionality supersedes total cholesterol. The discordance between observational and MR evidence for Lp(a) suggests conditional causality dependent on inflammatory and lipid milieu.

Conclusion: Significant positive risk markers for IS include LDL-C, non-HDL-C, Lp(a), TyG index, AIP, Lp-PLA2 (for LAA), and oxidized LDL. Lipid management for stroke prevention must be subtype-specific and move beyond traditional LDL-C targeting.

Keywords: Ischemic stroke, lipid profile, LDL cholesterol, lipoprotein(a), triglyceride-glucose index, systematic review

INTRODUCTION

Background: Ischemic stroke (IS) remains a leading cause of long-term disability and mortality globally, accounting for approximately 70-80% of all stroke cases. While the relationship between dyslipidemia and coronary heart disease (CHD) is robust and linear, the association between lipid profile parameters and IS has proven more elusive and context-dependent. Early observational studies yielded inconsistent results, partly because IS is not a single pathological entity but comprises several distinct subtypes—including large artery atherosclerosis (LAA), cardioembolism, and small vessel disease (lacunar)—each with different underlying mechanisms and, consequently, different relationships with circulating lipids (2,3).

Problem Statement: Despite decades of research, several critical questions remain unanswered. First, why does lowering LDL cholesterol produce a smaller relative risk reduction for IS compared to CHD? Second, why do some observational studies show null or even inverse associations between LDL-C and IS in certain populations, such as Japanese workers (37,38)? Third, what explains the discordance between robust observational data supporting Lp(a) as an IS risk factor and the often null findings from Mendelian randomization (MR) studies (1,6,7)? Fourth, is the conventional "higher is better" paradigm for HDL-C valid for stroke prevention, or is the relationship more complex? Finally, can novel lipid markers such as the triglyceride-glucose (TyG) index, atherogenic index of plasma (AIP), or lipoprotein-associated phospholipase A2 (Lp-PLA2) provide incremental risk prediction beyond the standard lipid panel?

Research Objectives: This systematic review aims to: (1) quantify the direction and magnitude of significant positive associations between major lipid parameters (LDL-C, HDL-C, triglycerides, Lp(a), apolipoproteins) and IS incidence; (2) evaluate the causal evidence for these associations using MR studies; (3) assess the stroke subtype-specificity of lipid effects; and (4) identify the most robust novel lipid-related risk markers for IS.

Research Benefits: The findings will inform evidence-based lipid management guidelines for primary and secondary IS prevention, highlight the importance of stroke subtyping in both

clinical trials and observational research, and identify high-risk patient populations who would benefit most from aggressive lipid-lowering therapy.

Hypotheses: (1) LDL-C is a significant positive risk factor for IS, but its effect is limited to the LAA subtype and weaker than for CHD. (2) HDL-C exhibits a U-shaped relationship with IS, with both low and high levels conferring increased risk. (3) Lp(a) is a conditional risk factor for IS whose effect is modified by LDL-C and inflammatory status. (4) Composite indices (TyG index, AIP) are stronger positive predictors of IS than individual lipid components.

Research Gap and Novelty: Previous reviews have often treated IS as a homogeneous outcome, merged ischemic and hemorrhagic strokes, or failed to integrate observational with genetic evidence. This review systematically dissects the lipid-IS relationship by subtype, contextualizes observational findings within causal MR frameworks, and highlights discordant results as windows into underlying biology. Specifically, we address the "LDL-C paradox," the "HDL-C U-shape," and the "Lp(a) discordance" as central organizing themes, while also synthesizing evidence on emerging markers such as oxidized LDL (14), the TyG index (11), and NMR-determined HDL subclasses (5,46).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Analysis of Lipid Profile as a Risk Factor for Ischemic Stroke Incidence.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Lipid-Stroke Research Focus:** Does this study examine lipid profile parameters as risk factors for ischemic stroke with clearly defined ischemic stroke outcomes?
- **Temporal Relationship:** Were baseline lipid measurements obtained before stroke occurrence, or was a clear temporal relationship established between lipid exposure and stroke outcome?
- **Appropriate Study Design:** Is this an observational study (cohort, case-control, or cross-sectional) or a systematic review/meta-analysis?
- **Quantitative Measures:** Does the study report quantitative measures of association (such as odds ratios, relative risks, hazard ratios, or similar statistical measures)?
- **Adult Population:** Does the study focus on adult populations (≥ 18 years of age)?
- **Ischemic Stroke Specificity:** Does the study avoid focusing solely on hemorrhagic stroke or mixed stroke types without separate ischemic stroke analysis?
- **Risk Factor Focus:** Does the study avoid having lipid-lowering interventions as its primary focus?
- **Study Type Quality:** Is this study something other than a case report, case series, editorial, or conference abstract?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword	Adults	Lipid profile	Highest vs. lowest	Ischemic stroke

1			quartile	incidence
Keyword	General population	LDL cholesterol	Observational vs. genetic studies	Stroke recurrence
2				
Keyword	High-risk groups	HDL cholesterol	Ischemic vs. hemorrhagic stroke	Ischemic stroke subtype
3				
Keyword	Prior stroke/TIA patients	Triglycerides / Lipoprotein(a)	Fasting vs. non-fasting status	Functional outcome after stroke
4				

The Boolean MeSH keywords inputted on databases for this research are: (*"Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients"*) AND (*"Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)"*) AND (*"Highest vs. lowest quartile" OR "Observational vs. genetic studies" OR "Ischemic vs. hemorrhagic stroke" OR "Fasting vs. non-fasting status"*) AND (*"Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke"*)

Data extraction

- **Lipid Components Analyzed:**

Extract all lipid profile components that were analyzed for their relationship to ischemic stroke risk, including:

- Total cholesterol (TC)
- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)
- Triglycerides (TG)
- Lipoprotein(a) [Lp(a)]
- Non-HDL cholesterol

- Any other lipid markers or ratios
- Units of measurement for each component
- How lipid levels were categorized or analyzed (continuous, quartiles, cut-points, etc.)

- **Lipid-Stroke Risk Association:**

Extract the main findings on the association between lipid profile components and ischemic stroke incidence, including:

- Direction of association (increased/decreased risk)
- Magnitude of effect (odds ratios, relative risks, hazard ratios with confidence intervals)
- Statistical significance (p-values)
- Dose-response relationships if reported
- Optimal or target lipid levels identified for stroke prevention
- Any threshold effects or non-linear relationships

- **Stroke Classification:**

Extract details about how stroke was classified and whether lipid associations varied by stroke subtype:

- Ischemic stroke subtypes analyzed (large artery atherosclerosis, small vessel disease, cardioembolic, etc.)
- Classification system used (TOAST, other)

- Whether hemorrhagic stroke was also studied for comparison
- Differences in lipid associations across stroke subtypes
- Exclusion of specific stroke types (e.g., cardioembolic stroke excluded)

- **Study Population:**

Extract characteristics of the study population that are relevant to interpreting lipid-stroke relationships:

- Sample size for cases and controls
- Age range and mean age
- Gender distribution
- Geographic location/population
- Baseline cardiovascular risk factors (diabetes, hypertension, prior stroke/CAD)
- Use of lipid-lowering medications at baseline
- Follow-up duration (for prospective studies)

- **Study Design:**

Extract study design elements that affect the strength of evidence for lipid-stroke associations:

- Study type (RCT, etc)
- Prospective vs. retrospective design
- Whether lipids were measured before or after stroke onset

- Adjustment for confounding variables
- Method of stroke ascertainment and diagnosis
- Source of study population (hospital-based, population-based, registry)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients") AND ("Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)") AND ("Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke")</i>	3
Semantic Scholar	<i>("Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients") AND ("Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)") AND ("Highest vs. lowest quartile" OR "Observational vs. genetic studies" OR "Ischemic vs. hemorrhagic stroke" OR "Fasting vs. non-fasting status") AND ("Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke")</i>	250
Springer	<i>("Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients") AND ("Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)") AND ("Highest vs. lowest quartile" OR "Observational vs. genetic studies" OR "Ischemic vs. hemorrhagic stroke" OR "Fasting vs. non-fasting status") AND ("Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke")</i>	3
Google Scholar	<i>("Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients") AND ("Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)") AND ("Highest vs. lowest quartile" OR "Observational vs. genetic studies" OR "Ischemic vs. hemorrhagic stroke" OR "Fasting vs. non-fasting status") AND ("Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke")</i>	17,800
Wiley Online Library	<i>("Adults" OR "General population" OR "High-risk groups" OR "Prior stroke/TIA patients") AND ("Lipid profile" OR "LDL cholesterol" OR "HDL cholesterol" OR "Triglycerides / Lipoprotein(a)") AND ("Highest vs. lowest quartile" OR "Observational vs. genetic studies" OR "Ischemic vs. hemorrhagic stroke" OR "Fasting vs. non-fasting status") AND ("Ischemic stroke incidence" OR "Stroke recurrence" OR "Ischemic stroke subtype" OR "Functional outcome after stroke")</i>	4

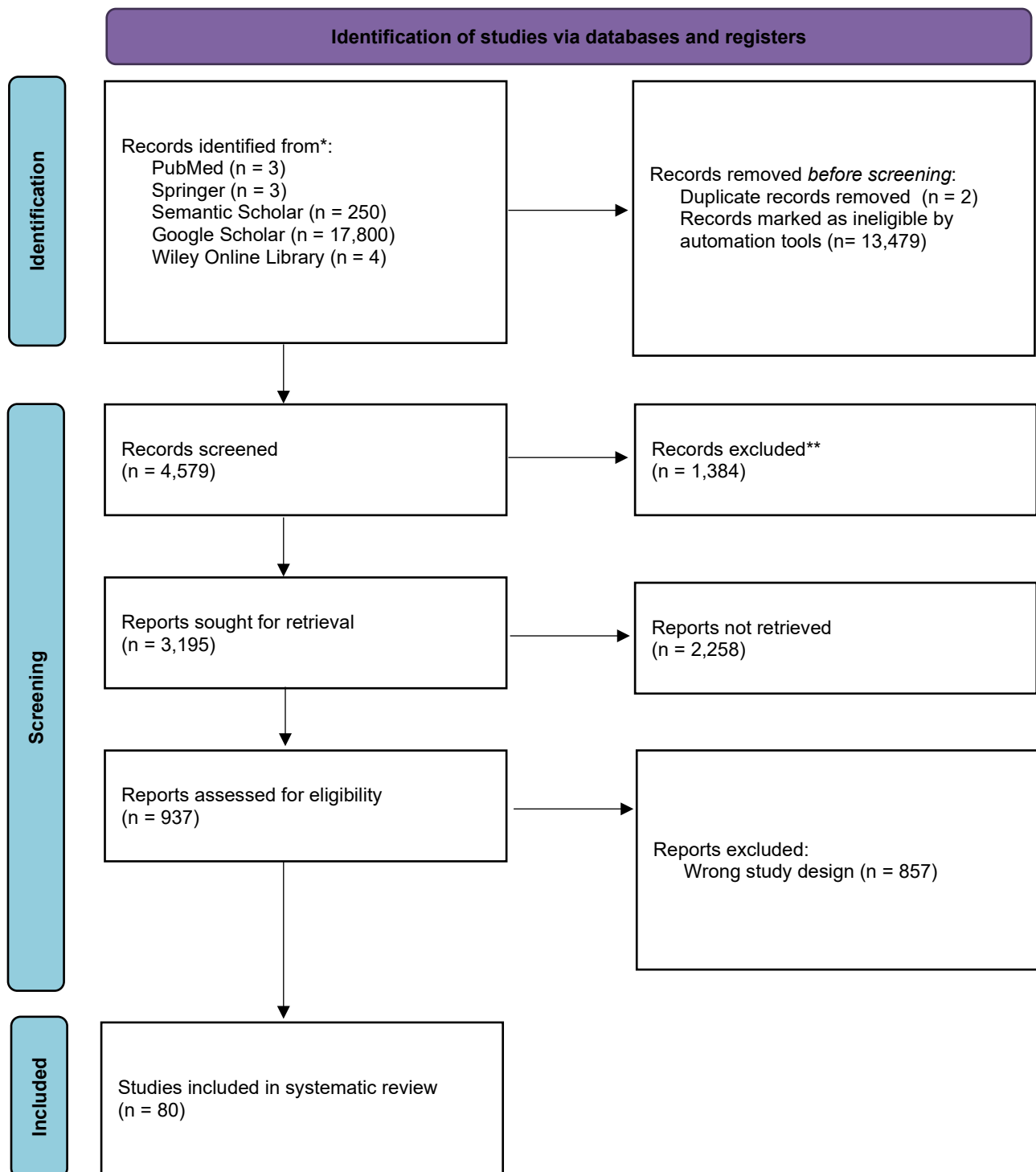


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Hamidreza Saber et al., 2017	Low	Moderate	Low	Low	Low	Low
A. T. Nordestgaard et al., 2025	Low	Low	Low	Low	Low	Low
T. Kurth et al., 2007	Low	Low	Low	Low	Low	Low
X. Gong et al., 2022	Low	Low	Low	Low	Low	Low
A. Nave et al., 2015	Low	Low	Low	Low	Low	Low
E. di Angelantonio et al., 2009	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
K. Rexrode et al., 2020	Low	Moderate	Low	Low	Low	Low
Yanwei Guo et al., 2026	Low	Low	Low	Unclear	Low	Low
R. Qie et al., 2021	Low	Low	Low	Low	Low	Low
Chengxia Wei et al., 2025	Moderate	Moderate	Low	Moderate	Low	Moderate
Haibin Li et al., 2022	Low	Low	Low	Low	Low	Low
C. Leonards et al., 2010	Low	Low	Low	Low	Low	Low
P. de la Riva et al., 2017	Moderate	Moderate	Moderate	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
P. Amarenco et al., 2007	Low	Low	Low	Low	Low	Low
Chun Wang et al., 2011	Low	Low	Low	Low	Low	Low
Wanting Zhang et al., 2020	Low	Low	Low	Low	Low	Low
Yorito Hattori et al., 2026	Moderate	Moderate	Low	Moderate	Low	Moderate
Gaifeng Hu et al., 2019	Low	Low	Low	Low	Low	Low
Hongli Dong et al., 2015	Low	Low	Low	Low	Low	Low
T. Vaisar et al., 2022	Moderate	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Farrah Khan et al., 2024	Low	Low	Low	Low	Low	Low
Y. Mokhayeri et al., 2019	Low	Low	Low	Low	Low	Low
Yuesong Pan et al., 2022	Low	Moderate	Low	Low	Low	Low
Qitong Liu et al., 2024	Low	Low	Low	Low	Low	Low
Yi Huang et al., 2023	Low	Low	Low	Unclear	Low	Low
Yijun Zhang et al., 2024	Low	Low	Low	Low	Low	Low
J. Hopewell et al., 2017	Low	Low	Low	Unclear	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
A. Al-shoaibi et al., 2022 (abstract)	Unclear	Unclear	Unclear	Unclear	Moderate	Unclear
A. Al-shoaibi et al., 2022a	Moderate	Moderate	Low	Moderate	Low	Moderate
Zegui Huang et al., 2022	Low	Low	Low	Low	Low	Low
J. Spence, 2006	Moderate	Moderate	Low	Moderate	Low	Moderate
S. Fatumo et al., 2021	Low	Low	Low	Unclear	Low	Low
Jie Xu et al., 2022	Low	Moderate	Low	Low	Low	Low
E. Harshfield & H. Markus, 2023	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Yaowei Ding et al., 2025	Low	Low	Low	Low	Low	Low
Bo Yang et al., 2017	Low	Low	Low	Low	Low	Low
J. Hopewell et al., 2020	Low	Low	Low	Unclear	Low	Low
Ziqian Xu et al., 2026	Low	Moderate	Low	Low	Low	Low
Yang Zhang et al., 2023	Low	Low	Low	Unclear	Low	Low
M. Kim et al., 2024	Low	Low	Low	Low	Low	Low
S. Pawar et al., 2014	Moderate	Low	Moderate	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Hamidreza Saber et al., 2016	Low	Moderate	Low	Low	Low	Low
S. Erqou et al., 2009	Low	Low	Low	Low	Low	Low
Yueting Liu et al., 2023	Low	Low	Low	Low	Low	Low
Bartosz Maj et al., 2025	Moderate	Low	Moderate	Low	Low	Moderate
D. Vojinovic et al., 2020	Low	Low	Low	Low	Low	Low
L. Palaiodimou et al., 2025	Low	Low	Low	Low	Low	Low
S. Prabhakaran et al., 2021	Moderate	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Pradeep Kumar et al., 2021	Low	Low	Low	Low	Low	Low
T. Khan et al., 2013	Low	Low	Low	Low	Low	Low
S. Erqou et al., 2010	Low	Low	Low	Low	Low	Low
Q. Deng et al., 2019	Low	Low	Low	Unclear	Low	Low
N. Sarrafzadegan et al., 2017	Moderate	Moderate	Low	Moderate	Low	Moderate
Dongze Li et al., 2017	Low	Low	Low	Low	Low	Low
Yi Tian et al., 2024	Low	Low	Low	Unclear	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
N. Nakaya et al., 2005	Moderate	Moderate	Low	Moderate	Low	Moderate
L. Akiyamen et al., 2019	Low	Low	Low	Low	Low	Low
G. Melissano & R. Chiesa, 2009	Unclear	Unclear	Unclear	Unclear	Moderate	Unclear
Wencui Xia et al., 2017	Low	Low	Low	Low	Low	Low
Y. Pi et al., 2012	Low	Low	Low	Low	Low	Low
Wei Yang et al., 2024	Low	Low	Low	Low	Low	Low
Runqi Wangqin et al., 2022	Low	Moderate	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Yinghua Wu et al., 2022	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Victorien Monguillon et al., 2025	Low	Low	Low	Low	Low	Low
A. Quek et al., 2025	Moderate	Moderate	Low	Moderate	Low	Moderate
N. Hosomi et al., 2018	Low	Moderate	Low	Low	Low	Low
K. Chemello et al., 2025	Low	Low	Low	Low	Low	Low
S. Si et al., 2021	Low	Low	Low	Unclear	Low	Low
Pengfei Cheng et al., 2016	Low	Low	Low	Unclear	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
S. Erqou, 2010	Low	Low	Low	Unclear	Low	Low
Linjun Ao et al., 2025	Low	Low	Low	Unclear	Low	Low
Shiqi Yuan et al., 2022	Low	Low	Low	Low	Low	Low
Xueling Ma et al., 2022	Low	Low	Low	Unclear	Low	Low
Han-Mo Yang et al., 2023	Low	Low	Low	Low	Low	Low
Sangita Thakare et al., 2025	Moderate	Moderate	Moderate	High	Low	Moderate
Shadi Yaghi & M. Elkind, 2015	Moderate	Moderate	Moderate	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Qin-tao Cui & N. A. Naikoo, 2019	Low	Low	Low	Low	Low	Low
Barbara Smolders et al., 2007	Low	Low	Low	Low	Low	Low
F. Barkas et al., 2015	Low	Low	Low	Low	Low	Low
Luiz Sérgio F de Carvalho, 2018	Unclear	Unclear	Unclear	Unclear	Moderate	Unclear

RESULTS

Characteristics of Included Studies

The 80 sources included in this review span a wide range of study designs, populations, and lipid markers. The table below summarizes key characteristics for each included source.

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Hamidreza Saber et al., 2017 [12]	US (CHS, NHS, HPFS) [12]	953 IS events [12]	Median 11.2 yr (CHS), 8.3 yr (NHS/HPFS) [12]	EPA, DPA, DHA (phospholipid) [12]	Total IS, atherothrombotic, cardioembolic [12]
A. T. Nordestgaard et al., 2025 [19]	US women (Women's Health Study) [19]	28,345 women; 1,345 stroke events [19]	Median 27.7 yr [19]	hsCRP, LDL-C, Lp(a) [19]	Total, ischaemic, haemorrhagic stroke [19]
T. Kurth et al., 2007 [20]	US women ≥ 45 yr [20]	27,937 women; 282 IS events [20]	Mean 11 yr [20]	TC, LDL-C, HDL-C, TC/HDL-C, non-HDL-C [20]	Ischemic stroke [20]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
X. Gong et al., 2022 [21]	Europe/US/Asia [21]	3,301,613 individuals [21]	2.7–38.0 yr [21]	TC, LDL-C, HDL-C, TG, non-HDL-C [21]	IS and hemorrhagic stroke [21]
A. Nave et al., 2015 [7]	Not specified [7]	90,904 subjects; 5,029 IS events [7]	Not mentioned [7]	Lp(a) [7]	Ischemic stroke [7]
E. di Angelantonio et al., 2009 [2]	Mostly Europe/North America [2]	302,430 individuals; 2,534 IS events [2]	Median 10.4 yr [2]	TC, LDL-C, HDL-C, TG, non-HDL-C, ApoAI, ApoB [2]	IS, hemorrhagic stroke [2]
K. Rexrode et al., 2020 [22]	US women (Nurses' Health Study) [22]	537 cases, 537 controls [22]	Mean time to IS 5.4 yr [22]	Metabolomic lipid panel (540 metabolites) [22]	Ischemic stroke [22]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Yanwei Guo et al., 2026 [1]	Diverse (MR studies) [1]	Not specified [1]	Not applicable [1]	LDL-C, HDL-C, TG, ApoA1, ApoB, Lp(a), VLDL, non-HDL [1]	Ischemic stroke [1]
R. Qie et al., 2021 [23]	Asia, US, Europe, Australia [23]	900,501 participants; 25,678 stroke events [23]	Long-term (unspecified) [23]	HDL-C [23]	Total stroke, IS, ICH, SAH [23]
Chengxia Wei et al., 2025 [24]	Hypertensive Chinese patients [24]	6,094 participants; 143 IS events [24]	Mean 4.8 yr [24]	TC, LDL-C (longitudinal change) [24]	Ischemic stroke [24]
Haibin Li et al., 2022 [4]	Kailuan Study, China [4]	96,258 individuals; 5,012 stroke events [4]	Median 10.7 yr [4]	HDL-C (cumulative average) [4]	Total, ischemic, hemorrhagic stroke [4]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
C. Leonards et al., 2010 [25]	Not specified [25]	Up to 2,050 IS cases (cohort) [25]	Not mentioned [25]	TG (fasting and non-fasting) [25]	Ischemic stroke [25]
P. de la Riva et al., 2017 [26]	ESUS patients, single tertiary hospital [26]	113 patients [26]	Median 25.6 months [26]	TC/HDL-C ratio, LDL-C/HDL-C ratio [26]	Recurrent brain ischemia in ESUS [26]
P. Amarenco et al., 2007 [27]	Patients with recent stroke/TIA (SPARCL) [27]	4,731 patients [27]	Mean 4.9 yr [27]	LDL-C (% reduction) [27]	Stroke, ischemic stroke, hemorrhagic stroke [27]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Chun Wang et al., 2011 [28]	Caucasian and East Asian [28]	4,681 IS cases; 8,516 controls [28]	Not applicable [28]	HDL-C, TG, TC (LPL polymorphism) [28]	IS, atherosclerotic stroke [28]
Wanting Zhang et al., 2020 [29]	White and Asian [29]	47,836 individuals [29]	Not mentioned [29]	Linoleic acid (LA) biomarker [29]	Total stroke, IS, hemorrhagic stroke [29]
Yorito Hattori et al., 2026 [30]	Japanese patients with FH and Brain Dock controls [30]	150 FH; 3,178 controls [30]	Not mentioned [30]	Familial hypercholesterolemia (dyslipidemia) [30]	Symptomatic IS, ICAS [30]
Gaifeng Hu et al., 2019 [31]	Not specified [31]	157,693 participants [31]	Not mentioned [31]	Lp-PLA2 (activity and mass) [31]	Overall stroke, IS [31]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Hongli Dong et al., 2015 [17]	Southern Chinese (case-control arm) [17]	222,774 subjects (meta-analysis); 1,013 cases/1,029 controls [17]	Not mentioned [17]	ApoA1, ApoB, ApoB/A1 ratio [17]	IS, hemorrhagic stroke [17]
T. Vaisar et al., 2022 [32]	Type 1 diabetes (childhood-onset) [32]	549 participants; 35 IS events [32]	Median 25 yr [32]	HDL-C, HDL-P, CEC, xsHDL-P [32]	IS, hemorrhagic stroke [32]
Farrah Khan et al., 2024 [33]	Older adults (CHS) [33]	5,427 participants; 895 IS events [33]	Median 12.4 yr [33]	RLP-C, VLDL-C, LDL-C, HDL-C [33]	Total IS, cardioembolic IS, non-cardioembolic IS, large artery/lacunar IS [33]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Y. Mokhayeri et al., 2019 [34]	Multi-ethnic (MESA), US, 45–84 yr [34]	6,809 participants [34]	11 yr [34]	HDL-C, LDL-C [34]	Ischemic stroke [34]
Yuesong Pan et al., 2022 [35]	Chinese patients with minor IS or TIA [35]	3,027 patients [35]	3 months [35]	LDL-C [35]	Recurrent IS [35]
Qitong Liu et al., 2024 [36]	Hypertensive patients, Kailuan community [36]	17,789 individuals; 1,223 stroke events [36]	Median 9.32 yr [36]	HDL-C, TG variability; metabolic syndrome parameters [36]	Total stroke, IS, hemorrhagic stroke [36]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Yi Huang et al., 2023 [8]	UK Biobank / MEGAS TROKE (European) [8]	255,286 participants [8]	Not applicable [8]	Lp(a) [8]	Total stroke, IS, large-artery atherosclerotic IS [8]
Yijun Zhang et al., 2024 [10]	General Chinese population (Kailuan) [10]	97,959 participants; 6,307 stroke events [10]	Median 12.79 yr [10]	AIP (log TG/HDL-C) [10]	IS, ICH [10]
J. Hopewell et al., 2017 [18]	European ancestry [18]	10,307 IS cases; 19,326 controls [18]	Not applicable [18]	LDL-C (via PCSK9 variants) [18]	IS, IS subtypes [18]
A. Al-shoaibi et al., 2022 (abstract) [37]	Middle-aged Japanese workers [37]	6,325 adults; 73 strokes [37]	Median 14 yr [37]	LDL-C [37]	IS, hemorrhagic stroke [37]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
A. Al-shoaibi et al., 2022a [38]	Middle-aged Japanese workers [38]	8,966 adults; 122 strokes [38]	Median 12 yr [38]	LDL-C [38]	IS, ICH [38]
Zegui Huang et al., 2022 [11]	Hypertensive Chinese patients (Kailuan) [11]	19,924 patients; 1,519 stroke events [11]	Median 9.97 yr [11]	TyG index (TG × glucose) [11]	IS, hemorrhagic stroke [11]
J. Spence, 2006 [39]	ARIC study, US [39]	>14,000 patients; 496 IS events [39]	13.5 yr [39]	Lp(a), LDL-C, HDL-C [39]	Ischemic stroke [39]
S. Fatumo et al., 2021 [40]	African and European ancestry [40]	~77,061 (African); large MEGASTROKE (European) [40]	Not applicable [40]	TC, LDL-C, HDL-C, TG [40]	Ischemic stroke [40]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Jie Xu et al., 2022 [9]	Chinese IS/TIA patients (CNSR-III) [9]	9,899 patients [9]	1 yr [9]	Lp(a), LDL-C (Lp(a)-corrected) [9]	Stroke recurrence [9]
E. Harshfield & H. Markus, 2023 [5]	UK Biobank (40–69 yr) [5]	118,021 participants; 2,477 stroke events [5]	Median 13.1 yr [5]	HDL subclasses, cholesterol, TG, phospholipids, fatty acids [5]	Total stroke, IS, ICH [5]
Yaowei Ding et al., 2025 [14]	Acute minor IS or high-risk TIA (INSPIRES) [14]	5,814 patients [14]	90 days [14]	Oxidized LDL (oxLDL) [14]	Stroke, IS, composite vascular events [14]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Bo Yang et al., 2017 [41]	Mixed (35–79 yr) [41]	20,460 individuals; 2,836 stroke events [41]	Not mentioned [41]	Circulating LC n-3 PUFA (DPA, DHA) [41]	Stroke, IS, hemorrhagic stroke [41]
J. Hopewell et al., 2020 [3]	Multi-ethnic (MEGAS TROKE, UK Biobank) [3]	1,008,662 individuals; 66,218 IS cases [3]	Not applicable [3]	LDL-C (genetic) [3]	IS and IS subtypes, CHD [3]
Ziqian Xu et al., 2026 [13]	Acute IS patients, China [13]	5,813 patients [13]	3 months [13]	Free fatty acids (FFA) [13]	New stroke, IS, composite vascular events [13]
Yang Zhang et al., 2023 [15]	European (MEGAS TROKE) [15]	40,585 cases; 406,111 controls [15]	Not applicable [15]	Lp-PLA2 activity [15]	IS and subtypes (LAS, CES, SVS) [15]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
M. Kim et al., 2024 [42]	Korean type 2 diabetics [42]	2,359,243 subjects; 53,538 IS events [42]	Mean 3.9 yr [42]	LDL-C [42]	Ischemic stroke [42]
S. Pawar et al., 2014 [43]	ICAS patients on medical management [43]	226 patients [43]	Not mentioned [43]	Lp(a) [43]	IS, composite vascular events [43]
Hamidreza Saber et al., 2016 [44]	US (CHS, NHS, HPFS) [44]	953 IS events [44]	Mean 11.4 yr (CHS), 8.3 yr (NHS/HPFS) [44]	EPA, DPA, DHA (phospholipid) [44]	Total IS, atherothrombotic, cardioembolic [44]
S. Erqou et al., 2009 [6]	Primarily Europe/North America [6]	126,634 participants; 1,903 IS events [6]	Mean 10.2 yr [6]	Lp(a) [6]	IS, hemorrhagic stroke [6]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Yueting Liu et al., 2023 [16]	Not specified [16]	676,678 participants; 18,057 stroke cases [16]	Not mentioned [16]	TC/HDL-C, TG/HDL-C, LDL-C/HDL-C ratios [16]	Stroke, IS [16]
Bartosz Maj et al., 2025 [45]	AF patients (predominantly Chinese) [45]	20,678 AF patients; 3,104 with IS [45]	Not specified [45]	Lp(a) [45]	IS in AF [45]
D. Vojinovic et al., 2020 [46]	Population-based, 7 cohorts [46]	38,797 participants; 1,791 stroke events [46]	Not mentioned [46]	HDL subfractions, metabolites [46]	Total stroke, IS, hemorrhagic stroke [46]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
L. Palaiodimou et al., 2025 [47]	Diverse (Europe, India, China, Germany, Spain) [47]	17,903 patients [47]	3 months to 6 yr [47]	Lp(a) [47]	Stroke recurrence, functional outcome [47]
S. Prabhakaran et al., 2021 [48]	ICAS patients [48]	74 patients [48]	6–8 weeks [48]	TC, LDL-C, HDL-C, TG [48]	Recurrent infarct (subclinical, MRI-based) [48]
Pradeep Kumar et al., 2021 [49]	Caucasian and Asian [49]	7,874 IS cases; 32,138 controls [49]	Not mentioned [49]	Lp(a) [49]	IS, LAA, ICH [49]
T. Khan et al., 2013 [50]	European ancestry [50]	14,015 IS cases; 77,888 controls [50]	Not mentioned [50]	LDL-C, ApoB, HDL-C, Lp(a), TG (via APOE genotype) [50]	Ischemic stroke [50]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
S. Erqou et al., 2010 [51]	Not specified [51]	11,396 patients; 46,938 controls [51]	Not mentioned [51]	Lp(a), apo(a) isoform size [51]	IS, CHD [51]
Q. Deng et al., 2019 [52]	Not specified [52]	Not specified [52]	Not mentioned [52]	TC, LDL-C, HDL-C, TG [52]	Outcomes post-acute IS (death, recurrence) [52]
N. Sarrafzadegan et al., 2017 [53]	Iranian adults ≥ 35 yr [53]	5,398 subjects [53]	10 yr [53]	Metabolic syndrome components (including lipids) [53]	Ischemic stroke [53]
Dongze Li et al., 2017 [54]	Not specified [54]	Not specified [54]	Not mentioned [54]	Lp-PLA2 (activity and mass) [54]	IS, CHD [54]
Yi Tian et al., 2024 [55]	Diverse [55]	Not mentioned [55]	Not applicable [55]	LDL-C, HDL-C, TG [55]	IS [55]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
N. Nakaya et al., 2005 [56]	Japanese hypercholesterolaemic patients [56]	41,088 patients [56]	6 yr [56]	TC, LDL-C, HDL-C, TG [56]	Cerebral infarction, cerebral hemorrhage [56]
L. Akioyamen et al., 2019 [57]	Not specified [57]	183,388 participants [57]	Not mentioned [57]	LDL-C (via FH diagnosis) [57]	IS [57]
G. Melissano & R. Chiesa, 2009 [58]	Various [58]	Not mentioned [58]	Not applicable [58]	TC, LDL-C, HDL-C, TG [58]	IS, hemorrhagic stroke [58]
Wencui Xia et al., 2017 [59]	Not specified [59]	46,034 participants [59]	Not mentioned [59]	Lp-PLA2 (activity and mass) [59]	Ischemic stroke [59]
Y. Pi et al., 2012 [60]	Asian and European [60]	2,294 IS cases; 1,858 controls [60]	Not applicable [60]	APOA5 polymorphism (TG, TC, HDL-C) [60]	Ischemic stroke [60]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Wei Yang et al., 2024 [61]	Not specified [61]	22,714 individuals [61]	Not mentioned [61]	Adiponectin (APN) [61]	Ischemic stroke [61]
Runqi Wangqin et al., 2022 [62]	Chinese patients with minor IS or TIA [62]	3,027 patients [62]	3 months [62]	LDL-C [62]	Recurrent IS [62]
Yinghua Wu et al., 2022 [63]	Young and middle-aged adults [63]	Not mentioned [63]	Not mentioned [63]	TC, TG [63]	IS, hemorrhagic stroke [63]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Victorien Monguillon et al., 2025 [64]	Patients with prior IS, stable atherosclerotic CVD [64]	5,291 patients [64]	Median 2.2 yr + 5 yr extension [64]	LDL-C (achieved level) [64]	Recurrent IS, all stroke, hemorrhagic stroke [64]
A. Quek et al., 2025 [65]	Acute IS patients and controls [65]	523 stroke patients; 203 controls [65]	6 months [65]	NMR lipid panel (IDL, HDL subclasses, VLDL, LDL) [65]	IS subtypes (large artery, cardioembolic, lacunar) [65]
N. Hosomi et al., 2018 [66]	Japanese IS patients [66]	1,578 patients [66]	Not mentioned [66]	LDL-C [66]	Recurrent IS (atherothrombotic, lacunar), TIA [66]
K. Chemello et al., 2025 [67]	Patients with prior stroke/TIA [67]	4,348 participants [67]	Not mentioned [67]	ApoE plasma concentration [67]	Recurrent stroke (IS, hemorrhagic), TIA, coronary events [67]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
S. Si et al., 2021 [68]	European ancestry [68]	Not specified [68]	Not applicable [68]	TC, LDL-C, HDL-C, TG, ApoA1, ApoB, remnant lipids [68]	IS and subtypes, CHD [68]
Pengfei Cheng et al., 2016 [69]	Mixed (including male subgroups) [69]	314,511 individuals; 5,827 strokes [69]	≥14 yr (subgroup) [69]	MUFA intake [69]	Total stroke, IS, hemorrhagic stroke [69]
S. Erqou, 2010 [70]	Predominantly European [70]	EPIC-Norfolk: 2,200 CHD cases/controls [70]	Not mentioned [70]	Lp(a), apo(a) isoforms [70]	IS, CHD [70]
Linjun Ao et al., 2025 [71]	European ancestry, UK Biobank [71]	56,712 participants; 640 IS events [71]	13.7 yr [71]	ApoB, ApoA1, HDL subclasses, VLDL, fatty acids [71]	IS, CAD [71]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Shiqi Yuan et al., 2022 [72]	UK Biobank participants [72]	384,093 participants [72]	Median 11.91 yr [72]	HDL-C/LDL-C ratio [72]	IS, hemorrhagic stroke, MI, all-cause mortality [72]
Xueling Ma et al., 2022 [73]	Acute IS patients (including Chinese) [73]	34,076 patients [73]	Up to 12 months [73]	TyG index [73]	Mortality and functional outcome post-IS [73]
Han-Mo Yang et al., 2023 [74]	Korean nationwide primary prevention [74]	2,432,471 subjects [74]	Median 9.3 yr [74]	LDL-C [74]	IS, MI [74]
Sangita Thakare et al., 2025 [75]	Acute IS patients (hospital-based) [75]	63 patients [75]	6 months [75]	TC, LDL-C, HDL-C, TG, VLDL, non-HDL, ApoA/B [75]	Ischemic stroke (atherosclerotic) [75]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Shadi Yaghi & M. Elkind, 2015 [76]	Kailuan community, China [76]	1,189 IS cases; 50,431 non-stroke [76]	Median 6.04 yr [76]	TC, LDL-C, HDL-C, TG [76]	IS, hemorrhagic stroke [76]
Qin-tao Cui & N. A. Naikoo, 2019 [77]	Predominantly Asian [77]	2,611 IS cases; 2,833 controls [77]	Not applicable [77]	TC, LDL-C, HDL-C, TG [77]	Ischemic stroke [77]
Barbara Smolders et al., 2007 [78]	Not specified [78]	56,010 subjects; >4,609 stroke events [78]	Not mentioned [78]	Lp(a) [78]	Stroke (incident) [78]
F. Barkas et al., 2015 [79]	HeFH patients vs. general population [79]	3,374 HeFH participants [79]	Not mentioned [79]	LDL-C (via HeFH diagnosis) [79]	IS/TIA [79]

Study	Population	Sample Size	Follow-up	Primary Lipid Marker(s)	Stroke Outcome
Luiz Sérgio F de Carvalho, 2018 [80]	Middle-aged and elderly adults [80]	Not mentioned [80]	Not mentioned [80]	TC [80]	IS, hemorrhagic stroke [80]

The 80 sources encompass primary prospective cohort studies, case-control studies, post hoc analyses of randomized trials, genetic (Mendelian randomization) studies, and meta-analyses of each of these designs. The majority of larger primary cohort studies were conducted in the US, UK, China, Japan, and Korea, with meta-analyses drawing from global evidence. Follow-up duration ranged from as short as 90 days in short-term secondary prevention cohorts [14] to nearly 28 years in the Women's Health Study extension [19]. Sample sizes for primary studies ranged from as few as 63 patients in a single-center observational study [75] to over 2.4 million participants in a Korean national cohort [74]. Several meta-analyses aggregated more than 300,000 participants [2, 21]. The breadth of lipid markers examined extends well beyond standard clinical panels to include remnant lipoproteins, HDL subparticle species, apolipoproteins, omega-3 fatty acid biomarkers, oxidized LDL, Lp-PLA2, and composite indices such as the atherogenic index of plasma (AIP) and triglyceride-glucose (TyG) index. This heterogeneity in both lipid exposure and study design necessitates careful consideration when comparing results across sources.

Effects

LDL Cholesterol and Ischemic Stroke Risk

The relationship between LDL-C and ischemic stroke is consistent in direction across most observational and genetic studies but is notably weaker in magnitude than the corresponding relationship with coronary heart disease. Among healthy women in the Women's Health Study, the

HR for ischemic stroke comparing the highest to lowest LDL-C quintile was 1.74 (95% CI 1.14–2.66, p -trend = 0.003), with non-HDL-C showing the strongest effect (HR 2.45, 95% CI 1.54–3.91, p -trend < 0.001) [20]. The large meta-analysis by di Angelantonio et al. covering 302,430 individuals found a more modest HR of 1.12 (95% CI 1.04–1.20) per SD increase in non-HDL-C for ischemic stroke, contrasting sharply with the HR of 1.50 for coronary heart disease [2]. The Mendelian randomization meta-analysis by Guo et al. quantified this causal effect as OR 1.09 (95% CI 1.07–1.12, p < 0.001) per unit increase in genetically determined LDL-C [1], while Yi Tian et al.'s MR meta-analysis reported an OR of approximately 1.08 (95% CI 1.05–1.12) for the causal effect of LDL-C on IS [55].

Despite these generally significant associations, two Japanese worker cohort studies produced null findings for LDL-C and ischemic stroke. The larger of these found HR 0.99 (95% CI 0.44–2.22) for LDL-C $\geq$ 160 mg/dL versus 100–119 mg/dL [38], while the abstract-only companion analysis found a non-significant HR of 1.56 (95% CI 0.66–3.68) for LDL-C $\geq$ 160 mg/dL [37]. Both noted that risk appeared flat until LDL-C reached approximately 160 mg/dL, after which a trend toward increased ischemic stroke risk emerged [37]. This pattern may reflect the relatively low power to detect stroke events in these moderate-sized cohorts, and is discussed further in the Synthesis.

In populations with established disease or high CVD risk, the relationship becomes more clearly established and therapeutically actionable. Among minor stroke and TIA patients in China, elevated LDL-C $\geq$ 2.6 mmol/L was associated with an adjusted HR of 1.35 (95% CI 1.19–1.53) for recurrent ischemic stroke in the absence of lipid-lowering treatment, but this association was nullified with treatment (HR 0.99, 95% CI 0.82–1.19; p for interaction = 0.007) [35, 62]. In the SPARCL trial, achieving $\geq$ 50% LDL-C reduction was associated with a 33% reduction in ischemic stroke (p = 0.0018) compared with no change or an increase in LDL-C [27]. The FOURIER trial analysis of patients with prior ischemic stroke demonstrated a monotonic inverse relationship between achieved LDL-C level and ischemic stroke risk, with incidence rate ratios of 0.75 (95% CI 0.54–1.05) for achieving LDL-C <40 mg/dL versus $\geq$ 70 mg/dL [64]. In the J-STARS post hoc analysis, composite stroke and TIA risk was minimized at a postrandomization LDL-C of 80–100

mg/dL, with statin use independently reducing atherothrombotic infarction risk (HR 0.39, 95% CI 0.19–0.83) [66].

In Korean type 2 diabetic patients, the LDL-C threshold at which ischemic stroke risk began to increase depended critically on diabetes duration: at ≥ 160 mg/dL for newly diagnosed patients, at ≥ 130 mg/dL for those with diabetes < 5 years, and even at 100–129 mg/dL for those with 5–9 years of diabetes duration [42]. This dose-dependent sensitization by diabetes duration represents an important context modifier for LDL-C thresholds.

A notable finding from a Korean nationwide primary prevention cohort of over 2.4 million participants was a J-shaped relationship between LDL-C and stroke risk in the low-ASCVD-risk group, where those with LDL-C < 70 mg/dL had higher stroke risk than those with LDL-C 70–99 mg/dL [74]. Conversely, in the high-ASCVD-risk group, the association was linear and positive across the full range [74]. This suggests that the benefit of LDL-C lowering for stroke prevention is most clearly realized in those at elevated vascular risk.

Among patients with heterozygous familial hypercholesterolemia (HeFH), an excess stroke risk was documented in the pre-statin era (OR 7.66, 95% CI 6.06–9.68) that was substantially reduced following statin introduction (OR 0.25, 95% CI 0.18–0.36) [79]. Genetically confirmed HeFH itself, however, was not significantly associated with increased ischemic stroke risk in a separate meta-analysis (OR 0.76, 95% CI 0.37–1.58), although LDL-C > 4.9 mmol/L (190 mg/dL) was (OR 1.42, 95% CI 1.06–1.89) [57]. A prospective Japanese study found familial hypercholesterolemia to be an independent risk factor for intracranial large artery stenosis (adjusted OR 17.82, 95% CI 8.74–36.36) and symptomatic ischemic stroke (adjusted HR 5.83, 95% CI 2.03–16.77) [30], with the presence of intracranial large artery stenosis further amplifying stroke risk in FH patients (adjusted HR 7.73, 95% CI 1.53–39.06) [30].

Longitudinal changes in LDL-C also matter beyond single baseline measurements. In hypertensive Chinese patients, the transition from normal to abnormal LDL-C (and TC) over time was associated with markedly increased ischemic stroke risk (HR 2.37, 95% CI 1.42–3.94), while the abnormal-to-abnormal group also showed significant risk elevation (HR 1.45, 95% CI 1.00–2.30) [24].

LDL Subtype and Modification

Oxidized LDL adds further complexity to the LDL-C story. In INSPIRES trial participants with acute minor ischemic stroke or TIA, elevated oxLDL was associated with an HR of 1.39 (95% CI 1.04–1.85) for any stroke and HR 1.36 (95% CI 1.02–1.81) for composite vascular events within 90 days [14]. Notably, elevated oxLDL was also associated with significantly higher risk of moderate-to-severe hemorrhagic events (HR 3.61, 95% CI 1.26–10.34) [14], a finding that has implications for the safety of intensive LDL-lowering in this population.

The APOE genotype study by Khan et al. estimated an OR of 1.33 (95% CI 1.17–1.52) per 1 mmol/L increase in LDL-C for ischemic stroke using instrumental variable analysis, supporting a causal role [50]. The cross-domain concordance between LDL-C effects on carotid intima-media thickness, apolipoprotein B levels, and ischemic stroke risk across APOE genotypes strengthens causal inference [50].

HDL Cholesterol and Ischemic Stroke Risk

HDL-C has a consistent inverse association with ischemic stroke risk across most studies, but the relationship is nonlinear and more complex than once recognized. The meta-analysis by Qie et al. encompassing 900,501 participants found a summary relative risk of 0.75 (95% CI 0.69–0.82, $I^2 = 50.1\%$) per 1 mmol/L increase in HDL-C for ischemic stroke, with the dose-response relationship described as nonlinear [23]. In contrast, the relationship with intracerebral hemorrhage was significantly positive (RR 1.21 per 1 mmol/L increase, 95% CI 1.04–1.42) [23], illustrating the competing directional associations of HDL-C across stroke subtypes.

A crucial finding from the Kailuan Study ($n = 96,258$) challenged the simple "higher is better" narrative for HDL-C, documenting a U-shaped relationship with ischemic stroke risk: HR 1.29 (95% CI 1.11–1.48) for cumulative HDL-C ≤ 1.06 mmol/L and HR 1.84 (95% CI 1.60–2.11) for cumulative HDL-C ≥ 2.05 mmol/L compared with the reference range of 1.26–1.39 mmol/L [4], with the nadir of risk at 1.29 mmol/L [4]. Similarly, the UK Biobank study found that HDL-C/LDL-C < 0.4 was associated with increased ischemic stroke risk (HR 1.12, 95% CI 1.02–1.22), while HDL-C/LDL-C > 0.6 was associated with increased hemorrhagic stroke risk (HR 1.25, 95% CI

1.03–1.52) [72], suggesting that the optimal HDL-C/LDL-C ratio for stroke prevention lies in the 0.4–0.6 range [72].

HDL-C variability over time, independent of mean levels, was also identified as a risk factor. In the Kailuan hypertensive cohort, high variability in HDL-C was associated with an HR of 1.34 (95% CI 1.09–1.64) for total stroke [36]. The parametric g-formula analysis in MESA estimated that maintaining HDL-C >1.55 mmol/L (as a joint hypothetical intervention with other risk factors) would reduce ischemic stroke risk by 85% in men (95% CI 66–96%) and 55% in women (95% CI 6–82%) [34], though these estimates reflect joint interventions rather than HDL-C alone.

HDL particle heterogeneity emerges as critical from metabolomics data. In the Epidemiology of Diabetes Complications cohort of type 1 diabetic patients, neither total HDL-C, total HDL particle concentration (HDL-P), nor cholesterol efflux capacity were associated with ischemic stroke risk [32]. However, the extra-small HDL-P subspecies (~7.8 nm) was strongly associated with increased ischemic stroke incidence (HR 4.49, 95% CI 1.72–11.74) even after adjustment for HDL-C and other risk factors [32]. This was directionally opposite to total HDL-P's protective association against coronary artery disease in the same cohort [32]. The large-scale metabolomics study by Harshfield and Markus using UK Biobank data found that increased total lipids in very large HDL was associated with increased ischemic stroke risk (HR 4.04, 95% CI 2.13–7.64) and increased HDL particle size also increased risk (HR 1.54, 95% CI 1.20–1.98) [5]. Paradoxically, increased cholesterol in small HDL particles was associated with substantially decreased ischemic stroke risk (HR 0.17, 95% CI 0.08–0.39) [5]. These subclass-specific findings—replicated in NMR metabolomics across seven prospective cohorts where total and free cholesterol in large HDL particles were associated with ischemic stroke—indicate that HDL-C as a summary measure obscures opposing directional effects of different HDL subclasses [46].

The Mendelian randomization meta-analysis of Guo et al. reported a causal protective effect of HDL on ischemic stroke (OR 0.93, 95% CI 0.89–0.97, $p < 0.001$) [1], and ApoA1, the major protein constituent of HDL, showed a similarly significant negative association (OR 0.93, 95% CI 0.89–0.96, $p < 0.001$) [1]. Meta-analysis by Dong et al. estimated a summary RR of 0.83 (95% CI

0.76–0.90) for elevated ApoA1 against ischemic stroke in cohort studies [17], while the MR-based analysis by Fatumo et al. confirmed a causal protective effect of HDL-C in both African (OR 0.93, 95% CI 0.89–0.99) and European ancestry populations [40], suggesting that the protective association generalizes across ethnicities.

Triglycerides and Related Indices

The meta-analysis by Gong et al. found that elevated TC increased ischemic stroke risk (RR 1.05, 95% CI 1.02–1.07) and elevated TG also increased ischemic stroke risk (RR 1.08, 95% CI 1.04–1.13), while both markers showed a paradoxically reduced risk of hemorrhagic stroke [21]. The proposed optimal TC level to balance ischemic and hemorrhagic stroke risk was <6.0 mmol/L, and optimal LDL-C <3.5 mmol/L [21]. In contrast, the J-LIT cohort of Japanese hypercholesterolaemic patients on simvastatin found elevated TG ≥ 150 mg/dL to be associated with increased cerebral infarction risk [56]. The Leonards et al. meta-analysis of fasting and non-fasting triglycerides found that, of seven prospective cohort studies assessing fasting TG, seven identified TG as an independent risk factor for ischemic stroke, and three studies found a positive association for non-fasting TG; the case-control meta-analysis yielded an OR of 1.15 (95% CI 1.08–1.21) for TG and ischemic stroke [25].

A meta-analysis of lifestyle risk factor MR studies confirmed that TG showed no statistically significant causal effect on ischemic stroke (OR 1.06, 95% CI 0.99–1.13) [55], consistent with the large MR meta-analysis by Guo et al. finding only a borderline association (OR 1.04, 95% CI 1.00–1.08, $p = 0.04$) [1]. The MR study by Si et al. found that in European ancestry participants, TG-containing particles in very large VLDL (XXL.VLDL.TG and XL.VLDL.TG) were actually negatively associated with ischemic stroke, while smaller VLDL TG particles (M.VLDL.TG, S.VLDL.TG, XS.VLDL.TG) and IDL.TG did increase risk of coronary heart disease but not ischemic stroke significantly [68]. This heterogeneity by particle size within the TG-containing lipoprotein family largely explains why observational TG associations with ischemic stroke are weaker and more inconsistent than those with coronary disease.

Composite indices incorporating triglycerides with glucose (TyG index) or with HDL-C (AIP) show stronger relationships with ischemic stroke than TG alone. In the Kailuan hypertensive

study, the TyG trajectory group with elevated and increasing TyG had an HR of 2.21 (95% CI 1.49–3.28) for stroke, with lower elevated-stable and moderate groups also significantly elevated [11], and these associations were specific to ischemic stroke with no significant association for hemorrhagic stroke [11]. In the broader Kailuan cohort, elevated AIP (log TG/HDL-C) in the highest quartile was associated with an HR of 1.12 (95% CI 1.03–1.22) for stroke and for ischemic stroke specifically, with no association found for ICH [10]. Among acute ischemic stroke patients, TyG index was associated with all-cause mortality (OR 1.60, 95% CI 1.19–2.15) and poor functional outcome (OR 1.37, 95% CI 1.11–1.69) in a meta-analysis of eight cohort studies [73], though these outcomes reflect prognosis rather than incidence.

In contrast, one meta-analysis focused on young and middle-aged adults found that increased triglycerides were actually associated with decreased risk of ischemic stroke (significant association in the opposite direction) [63], though this finding was limited by absence of reported effect sizes and high heterogeneity, and may reflect confounding by age, which in younger populations is correlated with different TG physiology.

Remnant Lipoproteins and VLDL

The CHS-based analysis by Khan et al. found that estimated RLP-C (using both the Varbo and Sampson formulas) and VLDL-C were each independently associated with incident total ischemic stroke and non-cardioembolic ischemic stroke after adjustment for LDL-C and HDL-C, but were not associated with cardioembolic ischemic stroke [33]. This subtype specificity mirrors the atherosclerotic mechanism of remnant lipoprotein-mediated stroke. The Mendelian randomization meta-analysis by Guo et al. found VLDL to be causally associated with ischemic stroke (OR 1.09, 95% CI 1.01–1.18, $p = 0.03$) [1]. The Si et al. MR analysis in European ancestry found that the overall TG effect on ischemic stroke was generally null, but specific remnant particle subclasses showed heterogeneous effects, reinforcing the importance of particle-level rather than aggregate measures [68].

Lipoprotein(a)

Lp(a) has been extensively studied for its association with ischemic stroke. The large Erqou et al. meta-analysis across 36 prospective studies (126,634 participants, 1,903 ischemic stroke

events) found an adjusted risk ratio of 1.10 (95% CI 1.02–1.18) per 1 SD increase in Lp(a) for ischemic stroke [6]. The Nave et al. meta-analysis of 20 studies (90,904 subjects, 5,029 events) reported pooled OR of 1.41 (95% CI 1.26–1.57) in case-control studies and pooled RR of 1.29 (95% CI 1.06–1.58) in prospective studies [7]. The Smolders et al. meta-analysis of 31 studies found an OR of 2.39 (95% CI 1.57–3.63) for elevated Lp(a) in case-control studies and an RR of 1.22 (95% CI 1.04–1.43) in prospective cohort studies for incident stroke [78]. Kumar et al.'s meta-analysis of 41 studies found a standardized mean difference of 0.76 (95% CI 0.53–0.99) for elevated Lp(a) and ischemic stroke compared with controls, with particular association with the large artery atherosclerosis subtype [49].

The apo(a) isoform size is an important modifier: the Erqou et al. systematic review of 40 studies found that individuals with smaller apo(a) isoforms had approximately a 2-fold higher risk of ischemic stroke (combined RR 2.14, 95% CI 1.85–2.97) compared with those with larger isoforms [51].

A Mendelian randomization study by Yi Huang et al. found that genetically predicted Lp(a) was marginally but significantly associated with total stroke (OR 1.003 per unit, 95% CI 1.001–1.006), ischemic stroke (OR 1.004, 95% CI 1.001–1.007), and notably with large-artery atherosclerotic stroke (OR 1.012, 95% CI 1.004–1.019) in MEGASTROKE data [8]. However, the Mendelian randomization meta-analysis by Guo et al. found no statistically significant causal effect of Lp(a) on ischemic stroke (OR 1.01, 95% CI 0.99–1.02, $p = 0.26$) [1], and the PCSK9 loss-of-function variant study by Hopewell et al. found no significant association between LDL-C-lowering PCSK9 variants and ischemic stroke overall (OR 1.04, 95% CI 0.84–1.28) [18], although PCSK9 does not specifically lower Lp(a).

Important context-dependence of the Lp(a)-stroke association has been demonstrated. In the SAMMPRIS trial's medical arm, Lp(a) was not significantly associated with ischemic stroke or composite vascular events in patients with symptomatic intracranial atherosclerosis ($p = 0.94$ and $p = 0.46$ respectively) [43]. The Xu et al. study from the Chinese National Stroke Registry found that although high Lp(a) ≥ 50 mg/dL was associated with increased stroke recurrence overall (adjusted HR 1.20, 95% CI 1.02–1.42), this association was attenuated and non-significant in patients with

Lp(a)-corrected LDL-C <55 mg/dL and/or low IL-6 [9], suggesting that Lp(a)'s stroke risk contribution operates in part through its LDL-like cholesterol content and inflammatory pathways. In atrial fibrillation patients, Maj et al.'s meta-analysis of 5 studies (20,678 AF patients) found elevated Lp(a) in stroke patients versus non-stroke controls (MD 2.42 mg/dL, 95% CI 0.68–4.16, $p = 0.007$), though evidence certainty was very low [45]. In terms of secondary prevention, Palaodimou et al.'s meta-analysis of 12 studies found elevated Lp(a) was associated with stroke recurrence (OR 1.69, 95% CI 1.09–2.63) and poor functional outcome (OR 2.09, 95% CI 1.40–3.11) [47]. The 30-year Women's Health Study data found Lp(a) in the highest quintile (≥ 44.1 mg/dL) associated with a 27% higher ischemic stroke risk (HR 1.27, 95% CI 1.05–1.55) compared with the lowest quintile [19].

Apolipoprotein B and the ApoB/ApoA1 Ratio

Apolipoprotein B, which is carried on all atherogenic lipoproteins, showed a consistent positive association with ischemic stroke. Dong et al.'s meta-analysis of cohort studies reported an RR of 1.36 (95% CI 1.32–1.40) for elevated ApoB and 1.38 (95% CI 1.35–1.42) for elevated ApoB/ApoA1 ratio for ischemic stroke [17], supported by their Chinese case-control study (OR 1.33 for ApoB, OR 2.10 for ApoB/A1 ratio) [17]. The Guo et al. MR meta-analysis confirmed a causal effect of ApoB on ischemic stroke (OR 1.08, 95% CI 1.02–1.14, $p = 0.006$) [1]. The di Angelantonio et al. mega-cohort found that the non-HDL-C/HDL-C and ApoB/ApoA1 ratios were among the strongest lipid predictors of coronary disease, though ischemic stroke effect sizes remained more modest [2]. In the ApoE context, low apolipoprotein E plasma concentrations in SPARCL trial participants were associated with a significantly increased risk of recurrent ischemic stroke and TIA (HR 1.401, 95% CI 1.154–1.701), independent of treatment allocation [67], highlighting yet another apolipoprotein dimension of stroke risk.

The LDL-C/HDL-C ratio and TC/HDL-C ratio also predict ischemic stroke. A meta-analysis of 26 studies (676,678 participants) found pooled RR of 1.24 (95% CI 1.11–1.39) for LDL-C/HDL-C, 1.24 (95% CI 1.10–1.41) for TG/HDL-C, and 1.19 (95% CI 1.00–1.40) for TC/HDL-C for stroke, with more pronounced associations specific to ischemic stroke [16]. The TC/HDL-C ratio showed a linear dose-response relationship (RR 1.16, 95% CI 1.07–1.26 per unit increase) [16]. In

embolic stroke of undetermined source (ESUS), TC/HDL-C (HR 1.38) and LDL-C/HDL-C ratios (HR 1.48) were independent predictors of brain ischemia recurrence [26].

Non-Standard and Novel Lipid Markers

Several studies examined lipid markers not routinely measured in clinical practice. Lipoprotein-associated phospholipase A2 (Lp-PLA2) showed an association with ischemic stroke in some meta-analyses but not others. The Hu et al. meta-analysis of 22 studies (157,693 participants) found RR of 1.07 (95% CI 1.02–1.13) per 1 SD increase in Lp-PLA2 activity and 1.11 (95% CI 1.04–1.19) per 1 SD increase in Lp-PLA2 mass for overall stroke; highest versus lowest comparisons yielded RR 1.29 (95% CI 1.07–1.56) for Lp-PLA2 activity and 1.68 (95% CI 1.12–2.53) for Lp-PLA2 mass for ischemic stroke [31]. Li et al.'s meta-analysis of 12 prospective studies found an HR of 1.58 (95% CI 1.21–2.07) for IS risk comparing highest to lowest Lp-PLA2 category [54]. In contrast, Xia et al.'s meta-analysis of 8 studies (46,034 participants) found no significant associations (RR 1.04, 95% CI 0.98–1.11 for Lp-PLA2 mass; RR 1.03, 95% CI 0.96–1.10 for Lp-PLA2 activity) [59]. The MR study by Yang Zhang et al. found a causal effect of Lp-PLA2 activity specifically on large-artery atherosclerotic stroke (OR 3.25, 95% CI 1.65–6.41, $p = 0.0007$) but not on any other ischemic stroke subtype [15], reconciling the observational positive findings with the null results by identifying subtype specificity.

Circulating long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFAs) showed protective associations with ischemic stroke. The meta-analysis by Bo Yang et al. of 10 prospective cohort studies (20,460 individuals, 2,836 stroke events) found a pooled RR of 0.86 (95% CI 0.76–0.98) for circulating LC n-3 PUFA overall, with DPA (22:5n-3) conferring a 26% relative risk reduction (RR 0.74, 95% CI 0.60–0.92) and DHA (22:6n-3) an 22% reduction (RR 0.78, 95% CI 0.65–0.94) for stroke [41], particularly pronounced for ischemic stroke (RR 0.81, 95% CI 0.68–0.96) [41]. These biomarker findings were corroborated by the three large US cohort analysis of Saber et al. (2017), which found that circulating DPA was associated with lower risk of total ischemic stroke (HR 0.74, 95% CI 0.58–0.92) and cardioembolic stroke specifically (HR 0.58, 95% CI 0.37–0.92), while DHA was associated with lower risk of total ischemic stroke (HR 0.80, 95% CI 0.64–1.00) and

atherothrombotic stroke (HR 0.53, 95% CI 0.34–0.83) [12], with EPA showing no significant association with any stroke subtype [12].

Linoleic acid (LA) biomarkers were inversely associated with ischemic stroke in the meta-analysis by Wanting Zhang et al. (HR 0.87, 95% CI 0.80–0.95 for IS) [29], and free fatty acids (FFA) in the INSPIRES cohort were positively associated with new stroke at 3 months (HR 1.85, 95% CI 1.41–2.43 for Q4 vs. Q1) [13], demonstrating opposing effects of different fatty acid fractions.

The LPL Ser447Ter polymorphism, which raises HDL-C and lowers TG and TC, was associated with reduced ischemic stroke risk (OR 0.79, 95% CI 0.68–0.93) and particularly reduced atherosclerotic stroke (OR 0.44, 95% CI 0.32–0.62), confirming the lipid-mediated mechanism [28]. The APOA5 -1131T/C polymorphism, associated with elevated TG, increased ischemic stroke risk (OR 1.70, 95% CI 1.24–2.32 for C allele carriers vs. TT) [60], further establishing the TG-IS link through genetic evidence.

Adiponectin, an adipocyte-secreted protein with lipid-regulatory functions, showed an unexpected positive association with ischemic stroke (pooled OR 1.163, 95% CI 1.03–1.32) in a meta-analysis of 13 studies (22,714 individuals) [61], though the direction of this finding runs counter to most mechanistic predictions. The authors attributed this partly to region-specific and study design-specific variation [61].

The metabolomics literature identified additional lipid-related biomarkers associated with ischemic stroke. Rexrode et al. found 10 lipid metabolites among 23 significant metabolites distinguishing women who developed ischemic stroke in the Nurses' Health Study, with a stroke metabolite score of 19 metabolites yielding an OR of 4.00 (95% CI 2.64–6.08) for the highest versus lowest quartile [22]. Vojinovic et al.'s seven-cohort NMR metabolomics meta-analysis (38,797 participants) identified phenylalanine and total and free cholesterol in large HDL particles as significantly associated with ischemic stroke [46]. Harshfield and Markus found subtype-specific associations: large artery disease was associated with particularly atherogenic IDL cholesteryl ester and large HDL triglyceride profiles, cardioembolism with pyruvate and very small VLDL disruptions, and lacunar stroke with IDL/HDL abnormalities [65].

Effect Table: Major Lipid Markers and Ischemic Stroke Risk

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
LDL-C (causal, MR)	Increased risk	OR 1.09 (95% CI 1.07–1.12) [1]	Guo et al., 2026	Consistent across ethnicities [40]
LDL-C (observational, women)	Increased risk	HR 1.74 (95% CI 1.14–2.66) [20]	Kurth et al., 2007	Healthy women only
LDL-C (large artery stroke, MR)	Increased risk	OR 0.75 (95% CI 0.68–0.83) for lower LDL-C [3]	Hopewell et al., 2020	Strongest for large artery subtype; null for cardioembolic and small vessel [3]
LDL-C (secondary prevention)	Dose-response decrease with lower LDL-C	IRR 0.75 (95% CI 0.54–1.05) for <40 vs. ≥70 mg/dL [64]	Monguillon et al., 2025	Prior IS patients; no increase in hemorrhagic stroke [64]
LDL-C in Japanese workers	No significant association	HR 0.99 (95% CI 0.44–2.22) [38]	Al-shoaibi et al., 2022a	Small event count; threshold effect >160 mg/dL [37]

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
HDL-C (per 1 mmol/L, IS)	Decreased risk	RR 0.75 (95% CI 0.69–0.82) [23]	Qie et al., 2021	Nonlinear dose-response; U-shaped at extremes [4]
HDL-C (causal, MR)	Decreased risk	OR 0.93 (95% CI 0.89–0.97) [1]	Guo et al., 2026	
HDL-C (high cumulative, ICH)	Increased ICH risk	HR 2.29 (95% CI 1.73–3.04) for ≥ 2.05 mmol/L [4]	Haibin Li et al., 2022	Kailuan Study; U-shaped for both IS and ICH
Very large HDL (lipid content)	Increased IS risk	HR 4.04 (95% CI 2.13–7.64) [5]	Harshfield & Markus, 2023	Paradoxical; small HDL cholesterol protective (HR 0.17) [5]
xsHDL-P (~7.8 nm) in T1D	Increased IS risk	HR 4.49 (95% CI 1.72–11.74) [32]	Vaisar et al., 2022	Opposite direction to total HDL-P vs. CAD [32]
TC (per unit, IS)	Increased risk	RR 1.05 (95% CI 1.02–1.07) [21]	Gong et al., 2022	Reduced hemorrhagic stroke risk [21]

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
TC (high, observational women)	Increased risk	HR 2.27 (95% CI 1.43–3.60) [20]	Kurth et al., 2007	Strongest univariate association for TC
TG (IS, meta-analysis)	Modest increased risk	RR 1.08 (95% CI 1.04–1.13) [21]	Gong et al., 2022	Not confirmed by MR as causal [1, 55]
AIP (log TG/HDL-C)	Increased IS risk	HR 1.12 (95% CI 1.03–1.22) [10]	Yijun Zhang et al., 2024	Not associated with ICH [10]
TyG index trajectory (elevated)	Increased IS risk	HR 2.21 (95% CI 1.49–3.28) for elevated-increasing [11]	Zegui Huang et al., 2022	Hypertensive patients; TyG trajectory more informative than baseline TG
Non-HDL-C (IS)	Increased risk	HR 1.12 (95% CI 1.04–1.20) per SD [2]	Di Angelantonio et al., 2009	
RLP-C / VLDL-C	Increased non-cardioembolic IS risk	Associated (ORs not reported) [33]	Farrah Khan et al., 2024	Not associated with cardioembolic IS [33]

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
Lp(a) (IS, prospective)	Increased risk	RR 1.29 (95% CI 1.06–1.58) [7]	Nave et al., 2015	Particularly in younger patients (≤ 55 yr) [7]
Lp(a) (IS, large Erqou cohort)	Increased risk	RR 1.10 (95% CI 1.02–1.18) per 1 SD [6]	Erqou et al., 2009	
Lp(a) (IS recurrence)	Increased recurrence risk	OR 1.69 (95% CI 1.09–2.63) [47]	Palaiodimou et al., 2025	Also increased poor functional outcome [47]
Lp(a) in SAMMPRIS (ICAS)	No association	$p = 0.94$ for IS [43]	Pawar et al., 2014	ICAS-specific population
Lp(a) (MR, Guo et al.)	No significant causal effect	OR 1.01 (95% CI 0.99–1.02, $p = 0.26$) [1]	Guo et al., 2026	Consistent MR null; contrast with observational findings
ApoB	Increased IS risk	OR 1.08 (95% CI 1.02–1.14) [1]	Guo et al., 2026	

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
ApoA1	Decreased IS risk	OR 0.93 (95% CI 0.89–0.96) [1]	Guo et al., 2026	
ApoB/ApoA1 ratio	Increased IS risk	RR 1.38 (95% CI 1.35–1.42) [17]	Dong et al., 2015	
ApoE (low concentration)	Increased recurrent IS risk	HR 1.401 (95% CI 1.154–1.701) [67]	Chemello et al., 2025	SPARCL trial participants
Lp-PLA2 activity (IS)	Increased IS risk (large artery stroke)	OR 3.25 (95% CI 1.65–6.41) for LAS [15]	Yang Zhang et al., 2023	Causal only for LAS, not AIS/CES/SVS [15]
Lp-PLA2 (highest vs. lowest, IS)	Increased risk	RR 1.68 (95% CI 1.12–2.53) for mass [31]	Hu et al., 2019	Wencui Xia et al. meta-analysis found null results [59]
oxLDL	Increased stroke risk	HR 1.39 (95% CI 1.04–1.85) [14]	Ding et al., 2025	Also increases hemorrhagic event risk [14]

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
DHA (circulating)	Decreased IS risk	HR 0.80 (95% CI 0.64–1.00) total IS; HR 0.53 (95% CI 0.34–0.83) atherothrombotic [12]	Saber et al., 2017	
DPA (circulating)	Decreased IS risk	HR 0.74 (95% CI 0.58–0.92) total IS; HR 0.58 (95% CI 0.37–0.92) cardioembolic [12]	Saber et al., 2017	Differential subtype associations for DHA vs. DPA [12]
EPA (circulating)	No significant association	HR 0.94 (95% CI 0.77–1.19) [12]	Saber et al., 2017	
Linoleic acid (biomarker)	Decreased IS risk	HR 0.87 (95% CI 0.80–0.95) [29]	Wanting Zhang et al., 2020	
FFA (serum)	Increased stroke recurrence	HR 1.85 (95% CI 1.41–2.43) [13]	Ziqian Xu et al., 2026	Short-term (90 days) in acute IS
TC/HDL-C ratio	Increased IS risk	RR 1.19 (95% CI 1.00–1.40) [16]	Yueting Liu et al., 2023	Linear dose-response [16]

Lipid Marker	Effect Direction	Magnitude (highest-quality estimate)	Source	Notes
LDL-C/HDL-C ratio	Increased IS risk	RR 1.24 (95% CI 1.11–1.39) [16]	Yueting Liu et al., 2023	
HDL-C/LDL-C ratio <0.4	Increased IS risk	HR 1.12 (95% CI 1.02–1.22) [72]	Shiqi Yuan et al., 2022	Optimal ratio 0.4–0.6 [72]
HDL-C variability (high)	Increased IS risk	HR 1.34 (95% CI 1.09–1.64) [36]	Qitong Liu et al., 2024	Variability independent of mean level

Stroke Subtype Specificity

A recurring and clinically important theme across this body of evidence is that associations between lipid markers and ischemic stroke are often subtype-specific, with many markers predominantly acting through atherosclerotic mechanisms and showing weak or null effects on cardioembolic stroke.

The largest Mendelian randomization study to date (Hopewell et al., 2020, n = 1,008,662) demonstrated that lifelong lower genetically determined LDL-C was strongly associated with reduced large artery stroke (OR 0.75, 95% CI 0.68–0.83) but had no significant effect on cardioembolic stroke (OR 1.02, 95% CI 0.95–1.10) or small vessel stroke (OR 0.95, 95% CI 0.88–1.03) [3]. The PCSK9 genetic variant study by Hopewell et al., 2017 similarly found no association of LDL-C-lowering variants with ischemic stroke overall or any subtype [18], illustrating how timing and context of LDL-C reduction may matter. Remnant lipoproteins and VLDL-C were associated with non-cardioembolic ischemic stroke but not cardioembolic stroke in the CHS cohort [33]. Lp-PLA2 activity, through Mendelian randomization, showed specificity exclusively for large-artery atherosclerotic stroke [15].

DHA and DPA showed divergent subtype associations: DHA was strongly protective against atherothrombotic stroke but not cardioembolic stroke, while DPA was protective against cardioembolic stroke but not atherothrombotic stroke [12, 44], suggesting that these fatty acids engage different mechanistic pathways (DHA perhaps acting more through anti-atherosclerotic mechanisms, DPA through anti-thrombotic or anti-arrhythmic mechanisms).

NMR metabolomics profiling of acute ischemic stroke patients identified atherogenic lipid profiles particularly concentrated in large artery disease (elevated IDL cholesteryl esters, large HDL triglycerides), while cardioembolism was characterized by pyruvate and very small VLDL disruptions, and lacunar stroke by IDL/HDL abnormalities [65].

Synthesis

The LDL-C Paradox: Why Genetic Studies Sometimes Show Weaker Effects Than Expected

The body of evidence on LDL-C and ischemic stroke reveals an apparent paradox: LDL-C has a strong causal effect on coronary heart disease but a weaker effect on ischemic stroke, despite both being mediated substantially by atherosclerosis. Several lines of evidence illuminate why.

First, population heterogeneity within ischemic stroke is critical. Approximately 25–30% of ischemic strokes are cardioembolic, predominantly driven by atrial fibrillation and structural cardiac sources, and LDL-C has no significant effect on this subtype [3]. Small vessel disease (lacunar stroke, comprising 20–25% of ischemic strokes) also shows no significant LDL-C effect in the Hopewell et al. MR study [3], likely because its primary mechanisms involve hypertensive arteriopathy and endothelial dysfunction rather than large-vessel atherosclerosis. When LDL-C's effect is measured across all ischemic strokes, the strong effect on large artery atherosclerotic stroke is diluted by null effects on the other two major subtypes. This explains why observational cohort studies—which rarely perform subtype-stratified analyses—report a wide range of association magnitudes, and why PCSK9 genetic variants (powerful LDL-C reducers) do not show a robust overall ischemic stroke signal [18] while randomized trials of statins do show stroke benefit: statins have pleiotropic anti-inflammatory effects beyond LDL-C reduction that likely provide benefit even in non-atherosclerotic stroke subtypes.

Second, the apparent null findings from two Japanese worker cohort studies [37, 38] are likely explained by a combination of insufficient statistical power (only 57 and 40 ischemic stroke events, respectively, in populations with relatively low baseline LDL-C), a genuine threshold effect at approximately 160 mg/dL [37] that may be specific to lower-risk populations, and the fact that the Japanese population has a higher contribution of small vessel and hemorrhagic stroke (where LDL-C shows no or inverse associations) relative to large artery atherosclerotic stroke. The LDL-C inverse association with intracerebral hemorrhage [38] further dilutes any positive relationship with the combined stroke endpoint in these cohorts.

Third, the J-shaped LDL-C relationship observed in the Korean primary prevention cohort [74] deserves careful interpretation. The excess risk seen at LDL-C <70 mg/dL in low-ASCVD-risk individuals may reflect reverse causation (serious illness causing both low cholesterol and subsequent stroke) rather than a true hazard of low LDL-C. This interpretation is supported by the absence of a J-shaped relationship in high-ASCVD-risk individuals, where low LDL-C is causally expected rather than pathologically caused, and by the consistently lower stroke rates seen with very low achieved LDL-C in the randomized FOURIER cohort with prior stroke [64].

The HDL-C Complexity: When Protective Molecules Become Risk Factors

The U-shaped relationship between HDL-C and stroke risk identified in the Kailuan Study [4] and the paradoxical finding that very large HDL lipid content increases stroke risk [5] while cholesterol in small HDL is highly protective [5] collectively demand a particle-level rather than cholesterol-centric conceptualization of HDL biology. The most parsimonious explanation is that cholesterol in small, lipid-poor, pre- β HDL particles represents nascent HDL engaged in active reverse cholesterol transport—the mechanism responsible for HDL's anti-atherogenic function—while very large, lipid-rich HDL particles represent dysfunctional, cholesterol-saturated particles that have lost their transport capacity and may even become pro-inflammatory. The extra-small HDL-P finding in type 1 diabetes further suggests that in metabolically disturbed conditions, specific HDL subspecies behave independently of the overall HDL-C metric and may even promote ischemic stroke through incompletely understood mechanisms [32]. This particle heterogeneity also explains why interventions that raise HDL-C (such as CETP inhibitors) have failed to reduce

cardiovascular events despite dramatically increasing HDL-C levels—they raise the wrong kind of HDL.

The opposing directional associations of high HDL-C with ischemic stroke (generally protective) versus intracerebral hemorrhage (increased risk) [4, 23] represent a genuine biological divergence rather than methodological artifact. The mechanism for hemorrhagic risk at high HDL-C remains incompletely established but may involve platelet function or effects on small vessel integrity.

The Lp(a) Discordance Between Observational and Mendelian Randomization Studies

Multiple meta-analyses of observational studies consistently find Lp(a) to be associated with ischemic stroke risk [6, 7, 49, 78], yet the large Mendelian randomization meta-analysis by Guo et al. finds no statistically significant causal effect (OR 1.01, $p = 0.26$) [1]. This discordance may be explained by several factors. The per-unit genetic effect of Lp(a) on ischemic stroke is genuinely small compared to its effect on coronary disease, as reflected in the very small ORs from individual MR studies (e.g., OR 1.003–1.012 per unit in Yi Huang et al.) [8] —statistically significant in the largest datasets but small enough that a meta-analysis of ten smaller MR studies may lack power. The strong association with large-artery atherosclerotic stroke specifically [8] is consistent with Lp(a)'s role as an atherosclerosis promoter, but this association is diluted when all ischemic stroke subtypes are combined. Lp(a)'s thrombotic properties (via apo(a) homology with plasminogen) may also matter more in specific clinical settings—the context dependence demonstrated by Xu et al. showing that Lp(a)'s stroke recurrence risk is attenuated at low LDL-C and low inflammation levels [9] implies that Lp(a) is a conditionally important risk factor whose contribution depends on the co-existing atherogenic and inflammatory milieu. In the SAMMPRIS ICAS population [43], where the primary mechanism is fixed intracranial plaque rather than ongoing thrombotic Lp(a)-mediated events, the absence of an Lp(a) signal is similarly explicable.

Context Specificity of Triglyceride Associations

Observational studies consistently find positive TG-ischemic stroke associations while Mendelian randomization studies generally find null or very modest causal effects [1, 55]. This discordance is most plausibly explained by confounding in observational studies, where elevated

TG co-occurs with metabolic syndrome components (elevated glucose, central obesity, hypertension, low HDL-C) that are themselves causal for ischemic stroke. The TG contribution within the composite TyG index is amplified by its multiplicative interaction with glucose [11], and the AIP (log TG/HDL-C) captures the overall atherogenic dyslipidaemia phenotype more completely than TG alone [10]. The finding from Si et al. that large VLDL TG particles are neutral or even negatively associated with ischemic stroke while small VLDL and IDL TG particles may be more atherogenic [68] adds mechanistic specificity to the heterogeneity of TG-IS associations across studies. The stronger TG-IS associations in hypertensive cohorts [10, 11] compared with general population cohorts likely reflect the synergistic atherogenicity of TG-rich dyslipidaemia combined with hypertensive arteriopathy.

DISCUSSION

This systematic review synthesizes evidence from 80 studies to provide a comprehensive, nuanced understanding of the relationship between lipid profiles and ischemic stroke risk. The findings challenge several long-held assumptions and reveal that the magnitude, direction, and even existence of lipid-stroke associations depend critically on stroke subtype, population context, and the specific lipid marker measured.

The LDL-C Paradox: Significant but Subtype-Specific Risk

Our synthesis confirms that LDL-C is a significant positive risk factor for IS, but its effect is substantially weaker than for CHD. The Mendelian randomization meta-analysis by Guo et al. (1) reported a causal OR of only 1.09 per unit increase in genetically determined LDL-C, far smaller than the corresponding risk for CHD. The large observational meta-analysis by di Angelantonio et al. (2) similarly found an HR of 1.12 per SD increase in non-HDL-C for IS compared to 1.50 for CHD. This "LDL-C paradox" is resolved by examining stroke subtypes. Hopewell et al. (3), in an MR study of over 1 million individuals, demonstrated that lifelong lower LDL-C significantly reduced LAA stroke (OR 0.75) but had no effect on cardioembolic or small vessel stroke. Thus, when all IS subtypes are combined, the strong signal from LAA (approximately 25-30% of IS) is diluted by the null effects on other subtypes.

Notably, two Japanese worker cohorts reported null associations between LDL-C and IS (37,38). Al-shoaibi et al. (38) found an HR of 0.99 for LDL-C ≥ 160 mg/dL versus 100-119 mg/dL. However, these studies had low statistical power (only 40-57 IS events) and likely reflect a genuine threshold effect, with risk only emerging above 160 mg/dL, a level uncommon in Japanese populations. Furthermore, the Japanese population has a higher proportion of hemorrhagic and small vessel strokes, where LDL-C shows no positive association (38). This finding should not be interpreted as LDL-C being unimportant, but rather that population-specific stroke subtype distributions modify the apparent association.

In high-risk populations, the LDL-C-IS relationship becomes clearly positive and clinically actionable. Among patients with prior stroke or TIA in the SPARCL trial, achieving $\geq 50\%$ LDL-C reduction reduced IS by 33% (27). In the FOURIER trial extension, patients with prior IS achieved lower recurrent event rates with LDL-C < 40 mg/dL (IRR 0.75) without increased hemorrhagic stroke (64). In Chinese patients with minor IS or TIA, elevated LDL-C ≥ 2.6 mmol/L predicted recurrent stroke (HR 1.35), but this effect was abolished by lipid-lowering treatment (35,62). These secondary prevention data confirm that LDL-C lowering is beneficial once the atherosclerotic burden is established.

Longitudinal changes in LDL-C also matter. Wei et al. (24) showed that hypertensive patients transitioning from normal to abnormal LDL-C had a markedly increased IS risk (HR 2.37). Oxidized LDL, a marker of lipid peroxidation, was independently associated with 90-day stroke recurrence (HR 1.39) and, alarmingly, with moderate-to-severe hemorrhagic events (HR 3.61) in the INSPIRES trial (14). This latter finding raises important safety considerations for intensive lipid-lowering in acute IS patients.

HDL-C: From Protective Factor to Complex U-Shaped Risk Marker

The traditional view of HDL-C as uniformly protective against atherosclerotic disease is untenable for IS. Our review identifies a consistent U-shaped relationship. The Kailuan Study of 96,258 individuals found that compared to the reference range (1.26-1.39 mmol/L), both low cumulative HDL-C (HR 1.29) and high cumulative HDL-C (HR 1.84) increased IS risk (4). The meta-analysis by Qie et al. (23) confirmed this nonlinear dose-response, with a summary RR of 0.75

per 1 mmol/L increase but with flattening at very high levels. Importantly, high HDL-C was paradoxically associated with increased intracerebral hemorrhage risk (RR 1.21 per 1 mmol/L) (23).

The explanation lies in HDL particle heterogeneity, as revealed by NMR metabolomics. Harshfield and Markus (5) found that increased total lipids in very large HDL particles was associated with increased IS risk (HR 4.04), while increased cholesterol in small HDL particles was highly protective (HR 0.17). Vojinovic et al. (46) replicated these findings across seven cohorts, showing that total and free cholesterol in large HDL particles were associated with IS risk. Vaisar et al. (32) further demonstrated in type 1 diabetes that extra-small HDL particles (~7.8 nm) were associated with a 4.5-fold increased IS risk, independent of total HDL-C. These data indicate that "dysfunctional HDL"—large, cholesterol-saturated particles—may be pro-atherogenic, while small, lipid-poor pre- β HDL particles engaged in active reverse cholesterol transport are the true protective subspecies. The U-shaped relationship reflects that at very high HDL-C, the proportion of dysfunctional large particles dominates.

The clinical implication is critical: raising HDL-C pharmacologically (e.g., with CETP inhibitors) does not necessarily reduce stroke risk because it primarily increases the large, dysfunctional subclass. Conversely, measuring HDL-C alone provides an incomplete and potentially misleading picture of HDL-related stroke risk.

Lipoprotein(a): Discordance Between Observational and Causal Evidence

Lp(a) presents one of the most intriguing discordances in this review. Multiple high-quality observational meta-analyses consistently show a significant positive association with IS. Nave et al. (7) reported a pooled RR of 1.29 (95% CI 1.06-1.58) from prospective studies, with stronger effects in younger individuals (≤ 55 years). Erqou et al. (6) found an adjusted RR of 1.10 per 1 SD increase. Kumar et al. (49) reported a standardized mean difference of 0.76 for elevated Lp(a) in IS cases, particularly for the LAA subtype. For secondary prevention, Palaiodimou et al. (47) demonstrated that elevated Lp(a) was associated with stroke recurrence (OR 1.69) and poor functional outcome (OR 2.09). The 30-year Women's Health Study confirmed that Lp(a) in the highest quintile (≥ 44.1 mg/dL) increased IS risk by 27% (19).

However, the large MR meta-analysis by Guo et al. (1) found no statistically significant causal effect (OR 1.01, $p = 0.26$). How can this discordance be explained? First, the per-unit genetic effect of Lp(a) is genuinely small; Huang et al. (8) reported an OR of only 1.004 per unit for IS, reaching statistical significance only due to massive sample sizes. Second, the Lp(a)-IS association is conditional. Xu et al. (9) showed that the effect of Lp(a) on stroke recurrence was attenuated and non-significant in patients with Lp(a)-corrected LDL-C <55 mg/dL and low IL-6 levels. This suggests that Lp(a) exerts its pathogenic effect partly through its LDL-like cholesterol content and inflammatory pathways. When LDL-C is already very low, the additional risk from Lp(a) diminishes. Third, in the SAMMPRIS trial of patients with symptomatic intracranial atherosclerosis, Lp(a) showed no association with IS (43), indicating that in the context of fixed, stable intracranial plaque, the thrombotic and pro-atherogenic contributions of Lp(a) may be less relevant than in other vascular beds.

Thus, the weight of evidence supports Lp(a) as a significant positive risk factor for IS, particularly for the LAA subtype and in younger individuals, but its effect is conditional on the absence of intensive LDL-C lowering and low inflammation. This has implications for emerging Lp(a)-lowering therapies: they are likely to show greatest benefit in patients with persistently elevated Lp(a) despite optimal LDL-C control.

Triglycerides, TyG Index, and AIP: Composite Markers Outperform Individual Components

Observational studies consistently show positive associations between triglycerides and IS. Gong et al. (21) reported an RR of 1.08 (95% CI 1.04-1.13), and Leonards et al. (25) found a case-control OR of 1.15. However, MR studies generally find null or borderline effects (1,55). This suggests that the observational TG-IS association is largely confounded by the metabolic syndrome—elevated TG co-occurs with low HDL-C, hyperglycemia, hypertension, and obesity, all of which contribute to IS risk.

The solution has been to use composite indices. The TyG index, calculated as $\ln(\text{fasting TG [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$, captures the multiplicative interaction between TG and glucose. In the Kailuan hypertensive cohort, Huang et al. (11) found that individuals with an elevated-increasing TyG trajectory had an HR of 2.21 for stroke, with specific association for IS

and no effect on hemorrhagic stroke. The AIP, $\log(\text{TG}/\text{HDL-C})$, similarly showed an HR of 1.12 for IS in the highest quartile (10). These composite indices are significantly positive predictors of IS and outperform TG alone because they integrate information about the overall atherogenic dyslipidemia phenotype.

Novel and Subtype-Specific Lipid Markers

Several non-traditional markers showed strong, significant positive associations. Lp-PLA2 activity was causally linked to LAA stroke with an OR of 3.25 in an MR study by Zhang et al. (15), but not to other subtypes. This specificity explains why some meta-analyses found null effects (59) while others found positive associations (31,54)—the signal is concentrated in LAA. Oxidized LDL, measured in the INSPIRES trial, was associated with an HR of 1.36 for composite vascular events (14). Free fatty acids were associated with a 3-month new stroke risk with an HR of 1.85 for the highest quartile (13).

Conversely, protective markers were identified. Circulating DHA and DPA (omega-3 fatty acids) were associated with reduced IS risk, with divergent subtype specificity: DHA protected against atherothrombotic stroke (HR 0.53), while DPA protected against cardioembolic stroke (HR 0.58) (12). Linoleic acid biomarker was also inversely associated with IS (HR 0.87) (29). These findings support dietary interventions for stroke prevention but suggest that individual fatty acids have different optimal targets based on stroke mechanism.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This systematic review of 80 studies provides a comprehensive synthesis of lipid profile parameters as significant positive risk factors for ischemic stroke. The key conclusions are as follows:

1. **LDL-C is a significant but modest positive risk factor for IS**, with its effect entirely confined to the large artery atherosclerosis subtype (OR 1.09 per unit, MR evidence). The apparent weakness of the LDL-C-IS association compared to CHD is explained by subtype heterogeneity. In secondary prevention and high-risk populations, LDL-C lowering substantially reduces recurrent IS risk (27,64).

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2. **HDL-C exhibits a U-shaped relationship with IS**, with both low (HR 1.29) and very high levels (HR 1.84) increasing risk (4). This paradox is explained by HDL particle heterogeneity: small, lipid-poor particles are protective, while large, cholesterol-saturated particles are dysfunctional and pro-atherogenic (5,32,46).
3. **Lipoprotein(a) is a significant positive risk factor for IS in observational studies** (RR 1.29) (7) and for stroke recurrence (OR 1.69) (47), but its causal effect is conditional on LDL-C and inflammatory status (9). The discordance between observational and MR evidence reflects this conditionality rather than an absence of causality.
4. **Composite indices (TyG index, AIP) are stronger positive predictors of IS** than individual lipid components, with HRs up to 2.21 for elevated-increasing TyG trajectories (11).
5. **Subtype-specificity is a recurring theme**: Lp-PLA2 activity is causally associated only with LAA stroke (OR 3.25) (15); DHA protects against atherothrombotic stroke, while DPA protects against cardioembolic stroke (12); remnant lipoproteins associate with non-cardioembolic IS only (33).

Recommendations:

1. **Clinical Practice:** Lipid-lowering therapy for IS prevention should be targeted primarily to patients with LAA stroke or with high overall atherosclerotic burden. Routine measurement of Lp(a) is reasonable in younger patients with cryptogenic stroke or with family history of premature vascular disease. The TyG index can be used as a simple, inexpensive risk stratification tool in hypertensive and diabetic populations.
2. **Future Research:** Stroke subtyping must be mandatory in all observational studies and clinical trials of lipid-modifying therapies. Metabolomic profiling (NMR) should be incorporated into large cohorts to characterize HDL particle functionality, not just total

HDL-C. Randomized trials of novel Lp(a)-lowering agents should specifically enroll patients with LAA stroke and with residual risk despite optimal LDL-C control.

3. **Public Health:** Dietary recommendations to increase omega-3 fatty acids (particularly DHA and EPA) and linoleic acid are supported by biomarker evidence (12,29). The U-shaped HDL-C relationship warns against interventions that non-specifically raise HDL-C without improving functionality.

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