

# INPLASY PROTOCOL

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**Review Stage at time of this  
submission:** Piloting of the  
study selection process.

**Conflicts of interest:**  
None declared.

## Association between extremely high-density lipoprotein cholesterol and adverse cardiovascular outcomes: A protocol for systematic review and meta-analysis

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**Review question / Objective:** The current research aimed to  
investigate the association between extremely high HDL-C  
and adverse cardiovascular outcomes in cohort studies using  
a systematic review and meta-analysis.

**Eligibility criteria:** Inclusion criteria Cohort studies will be  
included if the research (a) assess the association between  
extremely high HDL-C levels and risks of all-cause and  
cardiovascular death, stroke, MI, and heart failure; (b)  
containe relative risks (RR), hazard ratios (HR), or odds ratios  
(OR) of 95% confidence intervals (CI); (c) include estimates of  
at least three categories of HDL-C measurements in the  
analysis; (d) consider the normal levels of HDL-C as the  
reference range. Exclusion criteria The following research  
types including case-control studies, animal experiments,  
irrelevant outcomes, no extremely high levels of HDL-C,  
duplicate publications, reviews, meta-analyses, non-English  
language, abstracts, letters, case reports, and articles for  
which the full text will be not available were excluded.  
Besides, repetitive publications with an identical cohort,  
including HDL-C levels reported the most abundant data, or  
data with a larger number of outcomes or sample sizes will be  
excluded.

**INPLASY registration number:** This protocol was registered with  
the International Platform of Registered Systematic Review and  
Meta-Analysis Protocols (INPLASY) on 06 March 2023 and was  
last updated on 06 March 2023 (registration number  
INPLASY202330022).

### INTRODUCTION

**Review question / Objective:** The current  
research aimed to investigate the  
association between extremely high HDL-C

and adverse cardiovascular outcomes in  
cohort studies using a systematic review  
and meta-analysis.

**Condition being studied:** High-density lipoprotein cholesterol (HDL-C) has been identified as a risk factor for atherosclerotic cardiovascular disease (CVD), and numerous pieces of evidence have indicated the presence of a close association between HDL-C and adverse cardiovascular outcomes. Traditional cognition of HDL-C has argued that it is inversely correlated with CVD or mortality. Unfortunately, as the latest evidence accumulates gradually, more doubts are raised about its protective effect. Recent studies have shown that the dose-response relationship between HDL-C levels and cause-specific mortality is not a linear correlation any more as traditionally described. It is believed that an extremely high level of HDL-C not only fails in supporting the concept of protecting the heart but even paradoxically increases cardiovascular morbidity or mortality. Furthermore, heredity studies have indicated that high HDL-C levels do not reduce the risk of myocardial infarction (MI). However, there are also some published articles implying that the relationship between HDL-C and all-cause mortality, cardiovascular death, and stroke is not significant. It is therefore that there is uncertainty about the significance of HDL-C as a clinical indicator for assessing cardiovascular risk.

## METHODS

**Participant or population:** No limitation.

**Intervention:** Cohort studies were included if the research (a) assessed the association between extremely high HDL-C levels and risks of all-cause and cardiovascular death, stroke, MI, and heart failure; (b) contained relative risks (RR), hazard ratios (HR), or odds ratios (OR) of 95% confidence intervals (CI); (c) included estimates of at least three categories of HDL-C measurements in the analysis; (d) considered the normal levels of HDL-C as the reference range.

**Comparator:** Considered the normal levels of HDL-C as the reference range.

**Study designs to be included:** We will include cohort studies, prospective cohort, retrospective cohort, the following research types including case-control studies, animal experiments, irrelevant outcomes, no extremely high levels of HDL-C, duplicate publications, reviews, meta-analyses, non-English language, abstracts, letters, case reports, and articles for which the full text was not available were excluded.

**Eligibility criteria:** Inclusion criteria Cohort studies will be included if the research (a) assess the association between extremely high HDL-C levels and risks of all-cause and cardiovascular death, stroke, MI, and heart failure; (b) contain relative risks (RR), hazard ratios (HR), or odds ratios (OR) of 95% confidence intervals (CI); (c) include estimates of at least three categories of HDL-C measurements in the analysis; (d) consider the normal levels of HDL-C as the reference range. Exclusion criteria The following research types including case-control studies, animal experiments, irrelevant outcomes, no extremely high levels of HDL-C, duplicate publications, reviews, meta-analyses, non-English language, abstracts, letters, case reports, and articles for which the full text will be not available were excluded. Besides, repetitive publications with an identical cohort, including HDL-C levels reported the most abundant data, or data with a larger number of outcomes or sample sizes will be excluded.

**Information sources:** Embase, PubMed, Cochrane Library, and Web of Science.

**Main outcome(s):** All-cause and cardiovascular death, stroke, myocardial infarction, and heart failure.

**Quality assessment / Risk of bias analysis:** Two authors will screen potentially relevant articles and resolve all discrepancies through discussion. Both of the described authors will apply the Newcastle-Ottawa Scale to assess the quality of included studies based on the selection of study groups, the comparability of the groups, and the ascertainment of outcomes of

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interest . Each study will be awarded up to nine 9 stars, and those awarded >7 stars will be considered high quality.

**Strategy of data synthesis:** We will assume that the HR or OR for the risk of adverse cardiovascular outcomes is roughly the same as the RR, in the cohort study. Multivariate-adjusted RRs with 95%CI will be extracted and used for the current analysis. When heterogeneity ( $I^2$ ) < 50%, the combined RR and 95%CI will be estimated using a fixed-effects model; otherwise, a random-effects model is applied. The results will be stratified by sex and the data reported separately will be pooled using a fixed-effects model before inclusion in the meta-analysis. Cochran Q and  $I^2$  statistics will be applied to assess heterogeneity, and  $P < 0.05$  will be considered the Q statistics will be statistically significant.

**Subgroup analysis:** Subgroup analyses will be stratified by the sex of participants and experimental design.

**Sensitivity analysis:** Sensitivity analysis will be performed by excluding one study at a time and assessing whether the results will be strongly influenced by a single study. Additionally, potential publication bias will be assessed using Begg's and Egger's.

**Country(ies) involved:** China.

**Keywords:** High-density lipoprotein cholesterol, Meta-analysis, cohort studies, adverse cardiovascular outcomes.

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