Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality


CRD summary
The authors concluded that under a wide range of circumstances there were continuous, independent and modest associations of Lp(a) concentration with the risk of coronary heart disease and stroke that appeared exclusive to vascular outcomes. This was a well-conducted review. The authors conclusions reflected the evidence presented and are likely to be reliable.

Authors' objectives
To assess the relationship of Lp(a) (lipoprotein (a)) concentration with the risk of major vascular and non-vascular outcomes.

Searching
MEDLINE and EMBASE were searched between January 1970 and March 2009. No language restrictions were used. Search terms were reported. References of retrieved articles and of previous reviews were searched and authors contacted in order to identify additional studies.

Study selection
Eligible studies were prospective cohort studies or analyses of nested case-control or case-cohort subsets that had baseline information on age, sex, Lp(a) and risk factors for cardiovascular disease. Studies used quantitative Lp(a) assay methods and recorded cause-specific mortality and/or major vascular morbidity using accepted criteria. Participants had no previous history of cardiovascular disease (myocardial infarction, angina or stroke) at baseline and had accrued more than one year of follow up. Primary outcomes of interest were non-fatal coronary heart disease (CHD), non-fatal stroke and cause-specific mortality (or at least fatal coronary heart disease and fatal stroke).

Studies originated from North America, Western Europe, Greece, Turkey, Australia and New Zealand. Forty seven per cent of participants were European and 50 per cent were North American. Participants' mean age at study entry was 57 years (standard deviation eight years). Forty eight per cent of participants were women and 52 per cent men.

A range of sources was used to identify participants. The method of patient preparation prior to blood sampling and storage of samples, and methods to assay samples, varied across the studies.

The authors stated neither how relevant studies were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Individual patient data were obtained and checked for internal consistency, which was confirmed by the collaborators.

Data extraction
Investigators of included trials were asked to provide individual patient data at baseline and subsequent follow ups in order to calculate hazard ratios and 95% confidence intervals (CI) for cohort studies and odds ratios and 95% CI for case controls.

Methods of synthesis
Hazard ratios and odds ratios were assumed to approximate the same relative risk and were described by the authors collectively as risk ratios. Risk ratios were pooled in both fixed-effects and random-effects models. Heterogeneity was assessed using the I^2 test. Sources of heterogeneity (such as racial group, study design and laboratory method) were investigated using subgroup analysis and meta-regression. Within-person variation and potential confounders were adjusted using conditional expectations of long-term average Lp(a) levels.
Results of the review
Thirty six studies were included in the meta-analysis (126,634 individuals): 26 were prospective cohorts (112,108 individuals) and 10 were nested case-control studies (14,526 individuals).

Coronary heart disease (30 studies, 106,645 individuals, 8,362 cases): There was a statistically significant association per 3.5 fold increase in Lp(a) and the risk for coronary heart disease adjusted for age and sex (risk ratio was 1.16; 95% CI: 1.11 to 1.22) and also for the risk of coronary heart disease adjusted for age, sex, systolic blood pressure, smoking status, history of diabetes, body mass index and total cholesterol (risk ratio was 1.13; 95% CI: 1.09 to 1.18). There was evidence of moderate heterogeneity ($I^2$=49%). Results of extensive subgroup analyses were reported.

Ischaemic stroke (13 studies, 69,539 individuals, 1,684 cases): There was a statistically significant association per 3.5 fold increase in Lp(a) and the risk of ischaemic stroke adjusted for age and sex (risk ratio was 1.11; 95% CI: 1.02 to 1.20) and also the risk of ischaemic stroke adjusted for age, sex, systolic blood pressure, smoking status, history of diabetes, body mass index and total cholesterol (risk ratio was 1.10; 95% CI: 1.02 to 1.18). There was evidence of moderate heterogeneity ($I^2$=30%).

There was no statistically significant association per 3.5 fold increase in Lp(a) and the risk of cancer deaths, non vascular deaths other than cancer and all non vascular deaths including cancer.

Authors' conclusions
Under a wide range of circumstances there were continuous, independent and modest associations of Lp(a) concentration with the risk of coronary heart disease and stroke that appeared exclusive to vascular outcomes.

CRD commentary
The review addressed a clear research question and was supported by detailed inclusion criteria. The search strategy was adequate and without language or publication restrictions, which reduced the risk of language or publication bias. Checking of individual patient data was satisfactory. Synthesis methods were appropriate. This was a well-conducted review. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed in non-white racial groups, particularly in black and South Asian populations, which have different Lp(a) concentrations. Further studies were also needed to explore sources of heterogeneity and joint effects with other lipid markers, and to assess the proposed synergy in the promotion of vascular disease through oxidative damage.

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