Long-term interleukin-6 levels and subsequent risk of coronary heart disease
An abbreviated protocol for a systematic review

Background: There are conflicting data about whether there is an association between circulating levels of interleukin-6 (IL-6) and subsequent risk of coronary heart disease (CHD).

Objectives: Updated meta-analysis of prospective studies of IL-6 and CHD in general populations to support analyses in data from Reykjavik Study and British Regional Heart Study.

Study selection: Prospective studies: cohort, "nested" case-control or "nested" case-cohort studies.

Participants: Studies conducted in essentially general populations (ie, in which participants were no selected on the basis of previous disesase) and at least one year follow-up.

Exposure of interest: IL-6 measured in samples taken at baseline survey.

Outcome measures: CHD defined as nonfatal myocardial infarction or coronary death.

Search strategy: Search electronic databases, not limited to the English language, using MEDLINE, EMBASE and Science Citation Index; hand search relevant reference lists, papers and journals.

Search terms:

- MeSH search terms:
  - myocardial ischemia
  - Interleukin-6
- 'free' terms:
  - myocardial infarction, MI
  - coronary heart disease, CHD
  - Heart attack
  - Ischaemia, ischemia
  - IL6, IL-6, IL 6
  - interleukin 6, Interleukin6, interleukin-6

Data extraction: Data will be extracted on study design, geographic location, publication date, sample population, sampling methods (ie, complete, random, etc), sample source (plasma/serum), nature of sample (ie, fresh or frozen, storage temp), fasting status at time of blood sampling (duration of any fasting), blinding of lab worker to case/control status, assay type, source and standard, analysis methods and units, case definition, any matching criteria, sample size (of total cohort and numbers with IL-6 measurements), numbers of cases (total, fatal CHD, non-fatal MI), numbers of controls, mean age, sex, time of baseline survey, duration of follow-up, mean or median IL-6 values, adjustment of confounders and summary statistics.

Methods: 2 reviewers will independently conduct the search, select publications and extract data using the data abstraction form (attached). Any differences will be resolved by a third reviewer.

Interleukin-6 levels (and other continuous outcomes) will be presented as mean (standard deviation), log mean (log standard deviation) or median (interquartile range) in controls; dichotomous outcomes will be presented as n (%). Odds and hazard ratios are assumed to approximate the same measure of relative risk, and all effect measures will be converted to a common format for comparison (ie, odds or risk ratios per 2 standard deviation increase in IL-6). A random effects model will be used in the meta-analysis, and the summary measure will be a 2 standard deviation increase in IL-6, approximately comparable to top versus bottom third. Subsidiary analysis will include adjusting each estimate by a conservative RDR from the BRHS and Reykjavik Studies.

Heterogeneity will be assessed using standard χ^2 tests and the I^2 statistic. Subgroup analysis will be conducted to investigate the effects of different sampling populations and methods, duration of follow-up, source and type of IL-6 assay, blood storage temperature, geographical region, number of cases, sex, degree of adjustment of other cardiovascular risk factors, and whether individuals with CHD at baseline were excluded from analysis, on the results.

Initials

Data Abstraction Form

Prospective Studies of IL-6 plasma values and CHD

Study name:

First author, year

Location

Population framework

Population/Workforce/Other

Sampling method (circle appropriate answer)

Random/Complete/Other

Size of cohort

Total:
Blood taken from:

Exclusion criteria

If nested case-control, no. of controls

Age range in cohort

Time of baseline survey (may be a range)

% male in cohort

Mean duration of follow-up (yrs)

No. CHD cases

TOTAL_____

Fatal CHD_____
Confirmed non-fatal MI_____
Probable non-fatal MI_____

Case defn

Matching criteria (if applicable)

Fasting

Yes if Yes, mean duration_____
No
Not stated

Plasma

Serum

Lab worker blinding

Yes
No
Not stated

Assay source

Assay type

Standard

Nature of sample

Fresh (i.e. not deep frozen yet)
Frozen, if Frozen, storage temperature_____

Mean age cases (at baseline and/or event)

% male of cases

Confounder legend

+	age & sex
++	plus smoking
+++	plus classic risk factors
++++	plus CRP

Mean (SD) and/or log mean (log SD) plasma IL-6 values in controls

Summary statistics