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Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis

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ABSTRACT

Background: Raised total cholesterol is a strong risk factor for cardiovascular disease (CVD). It remains unknown whether sex differences exist in the relationship between total cholesterol and CVD outcomes.
Methods: PubMed was searched in December 2014 for cohort studies reporting on the relationship between total cholesterol and coronary heart disease (CHD) and total stroke, separately in men and women. Random effects meta-analyses with inverse variance weighting were used to obtain adjusted pooled sex-specific relative risks (RR) and women-to-men ratio of RRs (RRRs).
Results: Data from 97 cohorts, 1,022,276 individuals, and 20,176 CHD and 13,067 stroke cases were included. The pooled RR (95% confidence interval) for CHD associated with a 1-mmol/L increase in total cholesterol was 1.20 (1.16; 1.24) in women and 1.24 (1.20; 1.28) in men, resulting in a RRR of 0.96 (0.93; 0.99). Corresponding RRs for the risk of total stroke were 1.01 (0.98; 1.05) in women, and 1.03 (1.00; 1.05) in men, with a pooled RRR of 0.99 (0.93; 1.04). Pooled RRRs (95% CI) comparing individuals in the highest TC category to those in the lowest, such as the highest versus lowest third, were 0.87 (0.79; 0.96) for CHD and 0.86 (0.76; 0.97) for total stroke.
Conclusion: Raised total cholesterol is a strong risk factor for CHD, with evidence of a small, but significantly stronger, effect in men compared to women. Raised total cholesterol had little effect on the risk of total stroke in both sexes.

1. Introduction

Cardiovascular disease (CVD) is the world's leading cause of death, accounting for 17.5 million deaths (31% of all deaths) globally in 2012 [1]. Of these deaths, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke. Much of the burden of CVD can be prevented by adequate management and control of a set of modifiable risk factors, primarily high blood pressure, smoking, diabetes, excess weight, and raised total cholesterol.

A lack of sex-specific data has typically led to the assumption that the associations between these risk factors and CVD outcomes were equivalent in women and men. However, recent meta-analyses have reliably shown that there are clinically meaningful sex differences in the relationships between some risk factors and the risk of CHD and stroke, with stronger effects in women than in men for smoking and diabetes [2–5]. However, stronger excess relative risks in women are not inevitable: elevated levels of systolic blood pressure and body mass index were found to have equally deleterious effects on the risk of CHD and stroke in both sexes [6,7]. Whether a sex difference exists for the association between total cholesterol and CHD and stroke has never been

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systematically evaluated. Many studies on the association between total cholesterol and CVD outcomes did not specifically examine or report the possible sex differences in such relationships. Moreover, findings from previous studies that did report sex-specific effects have been inconsistent, with investigators reporting stronger, similar, or weaker effects of elevated total cholesterol on the risk of CHD or stroke in women as compared with men [8–17].

Evidence for any clinically meaningful sex differences in associations between total cholesterol and CVD outcomes would help to better understand the aetiology of CVD and would inform health care policy makers in tailoring specific interventions for the management and treatment of raised cholesterol in both men and women. Hence, we conducted a systematic review with meta-analyses summarising all available evidence to date of the sex-specific effects of total cholesterol on the risk of incident CHD and stroke.

2. Methods

2.1. Search strategy

PubMed MEDLINE (www.ncbi.nlm.nih.gov) was searched until December 2014 using a combination of the following text and MeSH terms: 'men', 'male', 'women', 'female', 'coronary artery disease', 'ischaemic heart disease', 'coronary heart disease', 'cardiovascular diseases', 'stroke', 'heart disease', 'cerebrovascular disease', 'cohort studies', 'prospective studies', 'cholesterol', 'lipids', 'dyslipidemia', 'hypercholesterolemia', and 'total cholesterol'. No limits were placed on the basis of language, country or publication date. The reference lists of all relevant original research and review articles were scanned to capture missed studies.

2.2. Study selection and data extraction

Observational cohort studies were included if they reported sex-specific relative risks (RRs), or equivalent, on the relationship between TC and CVD, CHD and/or stroke. Studies were excluded if the variability around the point estimate was not reported, if they had not been adjusted for at least age, or if the study was performed in a population selected on the basis of a prior CVD event or other underlying condition. Studies were only a small proportion of individuals had a known history of CVD were not excluded. In case of duplicate reports from the same study, the report involving the longest follow-up or the highest number of cases was included. Individual participant data (IPD) from four studies available to the authors were also used: the Asia Pacific Cohort Studies Collaboration (APCSC) [18], the Atherosclerosis Risk in Communities Study (ARIC) [19], the National Health and Nutrition Examination Survey III (NHANES) [20], and the Scottish Heart Health Extended Cohort Study (SHHEC) [21]. A predesigned data extraction form was used to collect relevant information on study size, baseline population, location of study, age at baseline, duration of follow-up, reported degree of adjustment, and study outcomes. Two independent investigators (YS and DM) conducted the screening of studies by title and abstract, and extracted the data. In case of disagreement, decision was reached through consensus or consultation with a third independent author (RRH). A modified version of the Newcastle-Ottawa Quality assessment scale was used to assess the methodological quality of all included studies (eTable 1) [22].

2.3. Statistical analyses

The primary endpoints were incident (fatal or non-fatal) CHD or stroke. The primary metrics were the pooled multiple-adjusted RRs and 95% confidence intervals (CI), and the women-to-men ratio of RRs (RRR) and 95% CIs per additional 1-mmol/L in total cholesterol. Studies presenting results in categories of total cholesterol were used to compare individuals in the highest total cholesterol group to those in the lowest total cholesterol group. Studies varied considerably in the thresholds used in the categorisation of total cholesterol (eTable 2). For each study, the extracted sex-specific RRs were log-transformed and their differences were computed. The differences were then pooled across studies using random effects meta-analysis weighted by the inverse of the variances of the log RRs, and then back-transformed to obtain the pooled women-to-men ratio of the RRR. The standard error of the log RRR was calculated as the square root of the sum of the variance of the two sex-specific log RRs for each of the studies. Fixed-effect meta-analyses were used as a sensitivity analyses. So to include the largest set of individuals and disease endpoints, studies that showed either age-adjusted or multiple-adjusted results were included in the primary analyses. In pooling the multiple-adjusted results, the set of multiple adjustments made were allowed to vary by study, but had to include at least one other risk factor in addition to age. The I^2 statistic was used to estimate the percentage of variability across studies due to between-study heterogeneity. The presence of publication bias for all primary analyses was graphically examined using funnel plots, plotting the natural log of the RRR against its standard error, and tested using Begg's test. Pre-defined subgroup analyses were conducted by study region (Asia or non-Asia), year of study baseline (pre or post 1985), duration of follow-up (<10, 10–19, ≥20), study outcome (fatal only or fatal and non-fatal combined), level of adjustment (age-adjusted or multivariable), and stroke subtype (ischemic or hemorrhagic). Random effects meta-regression analyses were used to test for differences between subgroups. All analyses were performed using Stata version 12.0. A p-value <0.05 was considered to denote significance.

3. Results

The systematic search identified 15,246 articles; of these, 313 qualified for full-text evaluation, and 29 studies published summary data on the association between total cholesterol and risk of CHD or stroke. The database was extended with data from APCSC, ARIC, NHANES III, and SHHEC (Fig. 1). Baseline characteristics of the included studies are described in Table 1. Baseline surveys were conducted between 1959 and 2008, and the duration of follow-up ranged from 2 to 35 years. Overall, data were available on 97 cohorts, 1,022,276 individuals, and 20,176 CHD and 13,067 stroke cases.

3.1. Sex-specific relationship between total cholesterol and CHD

Data from 68 cohorts (884,416 individuals, 14,837 CHD cases) provided information on the risk of CHD associated with a 1-mmol/L increase in total cholesterol, and 86 cohorts (891,322 individuals, 16,261 CHD cases) reported on the risk of CHD in categories of total cholesterol.

The pooled maximum-adjusted RR (95% CI) associated with a 1-mmol/L increase in total cholesterol was 1.20 (1.16; 1.24) in women, and 1.24 (1.20; 1.28) in men (Fig. 2). The corresponding women-to-men RRR was 0.96 (0.93; 0.99) (Fig. 3), with moderate indication for between-study heterogeneity (I^2 = 12.7%, p = 0.30), and no evidence for publication bias (p = 0.79) (eFigure 1). Comparing individuals in the highest category of total cholesterol to those in the lowest category of total cholesterol, the pooled maximum-adjusted RR (95% CI) for CHD was 1.55 (1.37; 1.76) in women, and 1.77 (1.58; 1.99) in men (eFigure 2). The corresponding women-to-men RRR was 0.87 (0.79; 0.96) (eFigure 3), with minimal heterogeneity between studies (I^2 = 5.7%; p = 0.38), and no evidence of publication