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Meta-analyses

High cholesterol intake is associated with elevated risk of type 2 diabetes mellitus – A meta-analysis[1–4]

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SUMMARY

Background & aims: Some foods rich in cholesterol are associated with high risk of type 2 diabetes (T2D). To confirm the association between dietary cholesterol intake and T2D risk, we performed a meta-analysis of observational studies.
Methods: We searched for longitudinal studies that provided data on the relative risk (RR) for T2D in relation to the cholesterol intake level using MEDLINE (from 1950 for July 10, 2013) and EMBASE (from 1974 to July 10, 2013). The RR for the highest vs. lowest cholesterol intake category or for an increment of 100 mg/day in cholesterol consumption was pooled with an inverse-variance method.
Results: Five studies met the inclusion criteria. Compared with the lowest category, the highest category had a significantly higher association with T2D risk (RR [95% confidence interval (CI)], 1.25 [1.16–1.36]). The pooled RR for a 100-mg/day increment was also significant (RR [95% CI], 1.11 [1.06–1.15]).
Conclusion: Current meta-analysis suggested that high intake of cholesterol was positively associated with future T2D risk.

1. Introduction

Cholesterol is one of the most common nutrients; it is recommended that its intake is controlled in relation to the prevention of coronary heart disease (CHD).[1] Indeed, a well-known association exists between dietary cholesterol intake and elevated risk of CHD.[2]

Type 2 diabetes (T2D), as well as CHD, is a global epidemic. Interestingly, both T2D and CHD share insulin resistance as a precursor of disease.[3] Moreover, epidemiological studies have indicated that a high intake of processed meat,[4–7] red meat,[6] and eggs,[5] all of which are rich in cholesterol, is associated with a high risk of T2D. However, some studies did not find an association between cholesterol intake and risk of T2D.[8,9] In addition, the quantitative association between cholesterol and T2D (i.e. T2D risk per incremental increase in cholesterol intake) has not been determined.

The aim of this meta-analysis was to summarize findings in previous longitudinal studies evaluating the association between cholesterol intake and incidence of T2D, and to determine the quantitative association between dietary cholesterol and T2D.

2. Methods

2.1. Search strategies

An electronic literature search was conducted to identify longitudinal studies that investigated the associations between high cholesterol intake and the incidence of T2D using the search engine Embase.com, which incorporates MEDLINE (from 1950 for July 10, 2013) and EMBASE (from 1974 to July 10, 2013) so that these two databases could be searched simultaneously. Details of search terms are provided in Supplemental Table 1. We added a manual search using the reference lists of the relevant articles. This process was repeated until no additional articles could be identified. No language restriction was imposed. For inclusion, a study had to fulfill the following criteria: 1) use of a longitudinal design; 2) T2D as an independent outcome; and 3) relative risk (RR) for the highest

Abbreviations: CI, confidence interval; lnRR, natural logarithm of relative risk; RR, relative risk; T2D, type 2 diabetes.

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category or several categories as compared with lowest category of cholesterol intake. When multiple articles were published on one study,[10,11] the article giving most detailed data was selected.[10]

2.2. Data extraction and quality assessment

Two of the investigators (R.T. and S.K.) independently identified eligible studies, reviewed them, extracted all relevant data and assessed study quality. Discrepancies were resolved by a third investigator (H.S.). The data that was abstracted included the first author's name, year of publication, country of origin, study design, methods for ascertaining T2D, mean or range of follow-up duration, mean or range of participants' age, participants' sex, range of exposure, number of participants and T2D events, and adjusted variables. Study quality was assessed by the Newcastle–Ottawa Scale, which was modified to make it possible to apply to this meta-analysis (Supplemental Table 2). This scale was composed of 9 items, and we awarded each item one point if the study met the criteria for that individual item. If the total score was more than 6, we judged the study quality as high; otherwise it was judged as low. If one article reported two or more RRs, the fully-adjusted RRs were used after excluding the RR adjusted for some fat subtypes (e.g. saturated fatty acid or monounsaturated fatty acid) so that over adjustment due to the strong association between the two intakes of fat and cholesterol could be avoided. We considered that they were strongly correlated with dietary cholesterol intake.

2.3. Data synthesis and analysis

To qualitatively summarize the association of habitual high intake of cholesterol with the risk of T2D, the RR for the highest vs. lowest cholesterol intake category was selected (Qualitative analysis). We added a quantitative analysis to estimate the RR of T2D for an incremental increase of 100 mg/day in cholesterol consumption. For studies that analyzed the cholesterol intake level not on a continuum but as a categorical variable, we used the method for trend estimation (Stata GLST command)[12] to estimate RR in individual studies by regressing the lnRR for the difference in mean exposure between each risk group and the lowest intake group. This method enabled us to correct for covariance between risk estimates from the same study and to estimate the corrected linear trend using generalized least squares if data on the adjusted RR and the number of participants (or person-time) and cases for each category were provided.

In both the qualitative and quantitative analyses, the RR in each study was transformed into a natural logarithm (lnRR) and the lnRR was pooled using an inverse-variance method, where the random-effects model was adopted if between-study heterogeneity which was assessed by Q statistics and I-squared[13] was significant; otherwise the fixed effects model was adopted. Finally, the overall RR was calculated by exponentiation of the pooled RR. We also conducted sensitivity analyses, stratifying the included studies by key factors related to study quality or participant characteristics that we *a priori* identified based on the data extracted from the included studies. These were mean follow-up duration (<10 or ≥ 10 years), participants' sex, methods for identifying T2D (self-report or other), study quality score (<6 or ≥ 6), and adjustment for total energy intake. Meta-regression analyses were conducted to detect the study characteristics that significantly influenced the results.

Publication bias was primarily assessed by funnel plot, where the estimated RR in each study was plotted against its corresponding standard error, assuming that the plot is symmetrical in the absence of publication bias. Statistical assessments were secondarily added to ascertain publication bias, using two formal methods, Begg's rank correlation[14] and Egger's regression test.[15] Data were analyzed using STATA software version 11 (STATA Corporation, College Station, TX, USA). $P < 0.05$ was considered as statistically significant except for the test of publication bias, in which the level of significance was $P < 0.10$.[16]

3. Results

3.1. Study characteristics

Figure 1 shows details of the literature search. Our electronic literature search resulted in retrieval of 3968 citations. Of these, 3946 were excluded based on the title and abstract. This left 22 articles as well as 12 additional articles identified by the manual search for full-text review. After this review, of the 34 papers, 29 were excluded for the reasons shown in Fig. 1. Finally, we identified 5 studies[8–10,17,18] that included a total of 203,903 participants and 7589 incident cases.

Table 1 shows the characteristics of the included studies. All 5 studies were conducted in the U.S. One study included men only[8] and 3 women only.[10,17,18] One study included both sexes and reported separate results according to sex.[9] Mean follow-up duration ranged from 8.8 to 14 years. For assessing habitual dietary cholesterol intake, all studies used validated food frequency questionnaires. Incident T2D cases were identified by self-report in 4 studies.[8,10,17,18] Among these 4 studies, 2 followed up the information with supplementary questionnaires.[8,18] One study used measurements of blood glucose and medication inventory information to identify incident cases.[9]

All included studies adjusted the RR for the following 5 confounders: age, sex, body mass index, physical activity, alcohol intake, and smoking habit. All but one study[9] adjusted for total energy intake. Study quality was assessed using the Newcastle–Ottawa Scale; only 2 studies[9,17] fulfilled the criteria for a score ≥ 6 on the scale of 9.

3.2. Cholesterol intake and risk of T2D

Figure 2 shows pooled RRs for T2D for the highest category of cholesterol consumption as compared with the lowest category of cholesterol consumption. The method for categorization of cholesterol intake varied among studies. Except for one study,[8] the median cholesterol intake in the highest category of the included studies ranged from 273 to 501.2 mg/day and that in the lowest category ranged from 124.9 to 185 mg/day. The lowest category was consistent with the regimen recommended by the Third Report of

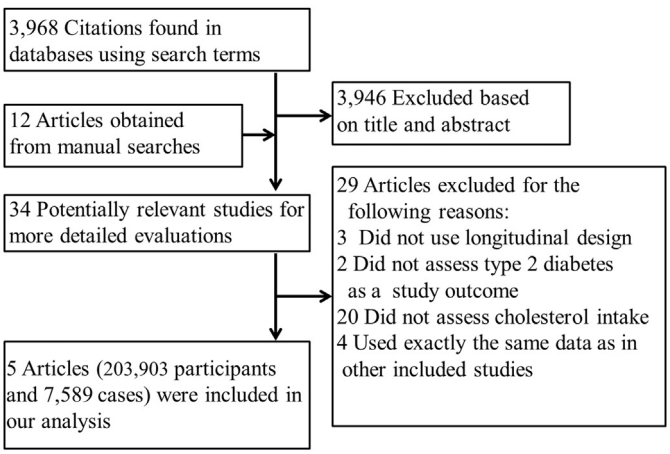

Fig. 1. Flow diagram of the systematic review.

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