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META-ANALYSIS

Fruit and vegetable consumption and risk of type 2 diabetes mellitus: A dose-response meta-analysis of prospective cohort studies

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Abstract *Background and aims:* We conducted a dose-response meta-analysis to summarize the evidence from prospective cohort studies regarding the association of fruit and vegetable consumption with risk of type 2 diabetes mellitus (T2DM).
Methods and results: Pertinent studies were identified by searching Embase and PubMed through June 2014. Study-specific results were pooled using a random-effect model. The dose-response relationship was assessed by the restricted cubic spline model and the multivariate random-effect meta-regression. We standardized all data using a standard portion size of 106 g. The Relative Risk (95% confidence interval) [RR (95% CI)] of T2DM was 0.99 (0.98–1.00) for every 1 serving/day increment in fruit and vegetable (FV) ($P = 0.18$), 0.98 (0.95–1.01) for vegetable ($P = 0.12$), and 0.99 (0.97–1.00) for fruit ($P = 0.05$). The RR (95%CI) of T2DM was 0.99 (0.97–1.01), 0.98 (0.96–1.01), 0.97 (0.93–1.01), 0.96 (0.92–1.01), 0.96 (0.91–1.01) and 0.96 (0.91–1.01) for 1, 2, 3, 4, 5 and 6 servings/day of FV ($P_{\text{for non-linearity}} = 0.44$). The T2DM risk was 0.96 (0.95–0.99), 0.94 (0.90–0.98), 0.94 (0.89–0.98), 0.96 (0.91–1.01), 0.98 (0.92–1.05) and 1.00 (0.93–1.08) for 1, 2, 3, 4, 5 and 6 servings/day of vegetable ($P_{\text{for non-linearity}} < 0.01$). The T2DM risk was 0.95 (0.93–0.97), 0.91 (0.89–0.94), 0.88 (0.85–0.92), 0.92 (0.88–0.96) and 0.96 (0.92–1.01) for 0.5, 1, 2, 3 and 4 servings/day of fruit ($P_{\text{for non-linearity}} < 0.01$).
Conclusions: Two-three servings/day of vegetable and 2 servings/day of fruit conferred a lower risk of T2DM than other levels of vegetable and fruit consumption, respectively.

Introduction

Worldwide, the cases of diabetes have increased from nearly 150 million in 1980 to almost 350 million in 2008 [1] and to 382 million in 2013 [2], and this number is expected to rise to 592 million by 2035 [2]. In China, it is estimated that 92.4 million adults are afflicted with diabetes and 148.2 million adults with prediabetes, and a large and highly variable proportion of cases are undiagnosed [3]. According to the reports of World Health Organization, 3.4 million people died from consequences of high fasting blood glucose in 2004, and diabetes will be the 7th leading cause of death in 2030, and type 2 diabetes mellitus (T2DM) comprises 90% of people with diabetes around the world (http://www.who.int/mediacentre/factsheets/fs312/en/, accessed June 22, 2014). Increasing fruit and vegetable (FV) consumption could improve the overall diet profile by increasing intakes of the micronutrients, polyphenols and fiber, and FV also has a high

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water content and a low energy content [4]. In addition, FV consumption confers beneficial effects on markers of inflammation and oxidative stress [5]. Although a previous meta-analysis [6] found no significant benefit of FV consumption on T2DM risk, results from subsequent prospective cohort studies [7–13] are inconsistent, and the potential threshold effect of FV consumption on T2DM risk is also unknown. Considering the popularity of FV consumption as well as increasing prevalence and burden of T2DM [14–17], even small health effect of FV consumption on T2DM risk could have considerable public health consequences, thus we conducted a dose-response meta-analysis to quantitatively assess the effect of FV consumption on T2DM risk.

Methods

Literature search and selection

We performed a literature search with PubMed (1950-June, 2014) and Embase (1974-June, 2014) databases, using the search term (((*fruit**) *OR vegetable**)) *AND* ((*diabetes*) *OR type 2 diabetes*) without limitations. The reference lists of retrieved articles were also scrutinized. For inclusion, studies had to fulfill the following criteria: a prospective cohort design; the exposure of interest was FV; the outcome of interest was T2DM; the number of cases and participants or person-years and a risk estimate [eg, hazard ratio, relative risk (RR) or odds ratio) with its 95% confidence interval (95% CI) for 3 or more quantitative categories of FV consumption were provided. We reported all results with RR, and hazard ratio and odds ratio [11] were assumed to be equivalent or accurate estimates of RR as did in previous meta-analysis [18,19]. With regards to multiple publications and for the purpose of this dose-response meta-analysis, the one providing the above-mentioned data for dose-response analysis was included. For multiple publications that both provided the data for dose-response analysis, the one with FV, fruit and vegetable (instead of specific types) as the exposure of interest and the most number of participants was included.

Data extraction

The following data were extracted from each study: first author's name, publication year, study location, follow-up duration, sex, age, sample size, number of cases, methods for measurement of FV consumption, number of cases and participants (person-years) and RR (95% CI) for each level of FV consumption, adjusted covariates. We extracted the RR that reflected the greatest degree of adjustment for confounding variables. For each study, the median level of FV consumption for each category was assigned to each corresponding RR estimate. If upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. We standardized all data into servings per day, using a standard portion size of 106 g [6].

Statistical analysis

The study-specific RR (95% CI) for every 1 serving/day of fruit and vegetable was first estimated using the generalized least squares trend estimation [20], and then the inverse variance weighted mean of the logarithm of the above-mentioned RR with 95% CI was calculated.

Heterogeneity was assessed with I2, and I2 values of 25, 50 and 75% represent low, moderate and high heterogeneity [21], respectively. Lower values of I2 mean the study-specific trends of T2DM risk are more similar among the included studies. Meta-regression and subgroup analysis were conducted to explore potential sources of heterogeneity and perform comparisons between groups, and *P* values from meta-regression were calculated with a permutation test of 1000 to control the spurious findings [22]. Sensitivity analysis was performed with one study removed at a time to evaluate the influence of individual studies on the overall risk estimate. Publication bias was evaluated using Egger test [23] and Begg test [24] at the $P < 0.10$ level of significance, and the trim and fill method [25] was used to incorporate the theoretical missing studies when publication bias was indicated. Study quality was assessed using the 9-star NewcastleeOttawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed 3/12/2014).

For assessing a potential non-linear relationship, a 2-stage random-effects dose-response meta-analysis [26] was performed taking into account the between-study heterogeneity. First, a restricted cubic spline model, with 3 knots at the 25th, 50th, and 75th percentiles of FV consumption, was estimated taking into account the correlation within each set of published RRs [20]. Then, we combined the 2 regression coefficients (3 knots minus 1) within each study by the restricted maximum likelihood method in a multivariate random-effects meta-analysis [27]. A *P* value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0, and a non-linear relationship is indicated when *P* value for non-linearity ($P_{\text{for non-linearity}}$) $\leq$0.05. The lowest value (the reference group) was set to 0 in all analysis. The pooled risk of T2DM for each serving/day of fruit and vegetable was derived using a procedure to tabulate and plot results [28]. One study [11] reported the association by sex, thus we combined these 2 estimates with a fixed-effect in the main analyses and combined each estimate with other respective estimates in sex-specific random-effects analyses. Stata 12.0 was used and $P \leq 0.05$ was considered statistically significant (except for the publication bias test). This meta-analysis was conducted following the MOOSE criteria [29].

Results

Literature search and study characteristics

The flow chart is shown in Supplementary Fig. 1. 2 prospective studies were excluded because of missing data for a dose-response analysis [10,30]. 7 articles [8,11,13,31–34]