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BMJ

BMJ 2013;347:f5001 doi: 10.1136/bmj.f5001 (Published 28 September 2013)

RESEARCH

Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies

Isao Muraki *research fellow*[1], Fumiaki Imamura *investigator scientist*[2], JoAnn E Manson *professor of medicine*[3 4 5], Frank B Hu *professor of nutrition and epidemiology*[1 3 5], Walter C Willett *professor of epidemiology and nutrition*[1 3 5], Rob M van Dam *associate professor*[1 6], Qi Sun *assistant professor*[1 5]

[1]Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA; [2]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [4]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [6]Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore

Abstract

Objective To determine whether individual fruits are differentially associated with risk of type 2 diabetes.

Design Prospective longitudinal cohort study.

Setting Health professionals in the United States.

Participants 66 105 women from the Nurses' Health Study (1984-2008), 85 104 women from the Nurses' Health Study II (1991-2009), and 36 173 men from the Health Professionals Follow-up Study (1986-2008) who were free of major chronic diseases at baseline in these studies.

Main outcome measure Incident cases of type 2 diabetes, identified through self report and confirmed by supplementary questionnaires.

Results During 3 464 641 person years of follow-up, 12 198 participants developed type 2 diabetes. After adjustment for personal, lifestyle, and dietary risk factors of diabetes, the pooled hazard ratio of type 2 diabetes for every three servings/week of total whole fruit consumption was 0.98 (95% confidence interval 0.96 to 0.99). With mutual adjustment of individual fruits, the pooled hazard ratios of type 2 diabetes for every three servings/week were 0.74 (0.66 to 0.83) for blueberries, 0.88 (0.83 to 0.93) for grapes and raisins, 0.89 (0.79 to 1.01) for prunes, 0.93 (0.90 to 0.96) for apples and pears, 0.95 (0.91 to 0.98) for bananas, 0.95 (0.91 to 0.99) for grapefruit, 0.97 (0.92 to 1.02) for peaches, plums, and apricots, 0.99 (0.95 to 1.03) for oranges, 1.03 (0.96 to 1.10) for strawberries, and 1.10 (1.02 to 1.18) for cantaloupe. The pooled hazard ratio for the same increment in fruit juice consumption was 1.08 (1.05 to 1.11). The associations with risk of type 2 diabetes differed significantly among individual fruits (P<0.001 in all cohorts).

Conclusion Our findings suggest the presence of heterogeneity in the associations between individual fruit consumption and risk of type 2 diabetes. Greater consumption of specific whole fruits, particularly blueberries, grapes, and apples, is significantly associated with a lower risk of type 2 diabetes, whereas greater consumption of fruit juice is associated with a higher risk.

Introduction

Fruits are rich in fibre, antioxidants, and phytochemicals that may have beneficial health effects. Increasing fruit consumption has been recommended for the primary prevention of many chronic diseases, including type 2 diabetes,[1] although epidemiologic studies have generated somewhat mixed results regarding the link with risk of type 2 diabetes.[2-10] The inconsistency among these studies may be explained by differences in types of fruits consumed in different study populations as well as difference in participants' characteristics, study design, and assessment methods, although a meta-analysis did not show that the associations differed by sex, study design, or location.[10] Furthermore, in a recent study, the greater variety, but not quantity, of fruits consumed was associated with a lower risk of type 2 diabetes.[4] This finding suggested that individual fruits might not be equally associated with risk of type 2 diabetes in that fruits have highly variable contents of fibre, antioxidants, other nutrients, and phytochemicals that jointly may influence the risk.[11 12] Additionally, the glycemic index, which represents the quality of carbohydrate, or glycemic load, which represents the quality and quantity of carbohydrate and their interaction, vary substantially for individual fruits.[13]

Correspondence to: Q Sun qisun@hsph.harvard.edu

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Supplementary tables 1-5

We examined the associations of individual fruit consumption in relation to risk of type 2 diabetes using data from three prospective cohort studies in US adults. Moreover, we estimated substitution effects of individual fruits for fruit juice in relation to risk of type 2 diabetes. Secondarily, we examined the associations of fruit groups based on their glycemic index and glycemic load values with risk of type 2 diabetes.

Methods

Study population

We used data from the Nurses' Health Study (established in 1976; n=121 700), the Nurses' Health Study II (established in 1989; n=116 671), and the Health Professionals Follow-up Study (established in 1986; n=51 529). These cohort studies are discussed in detail elsewhere.[14-16] Every two years since baseline, follow-up questionnaires have been mailed to the participants to collect and update information on lifestyle practices and occurrence of chronic diseases. In all three cohorts the follow-up rates are approximately 90%.

We excluded participants who reported a diagnosis of diabetes (including types 1 and 2 and gestational diabetes), cardiovascular disease, or cancer at baseline (n=10 134 for the Nurses' Health Study, 6155 for the Nurses' Health Study II, and 6707 for the Health Professionals Follow-up Study), those who had missing data for individual fruits and fruit juice or an unusual level of total energy intake (<500 or >3500 kcal/day for the Nurses' Health Study and the Nurses' Health Study II and <800 or >4200 kcal/day for the Health Professionals Follow-up Study) (n=4765 for the Nurses' Health Study, 5647 for the Nurses' Health Study II, and 5750 for the Health Professionals Follow-up Study), those whose diagnosis date of type 2 diabetes was unclear (n=200 for Health Professionals Follow-up Study), and those who completed only the baseline questionnaire (n=719 for the Nurses' Health Study, 699 for the Nurses' Health Study II, and 1103 for the Health Professionals Follow-up Study). After excluding these participants, 66 105 women in the Nurses' Health Study, 85 104 women in the Nurses' Health Study II, and 36 173 men in the Health Professionals Follow-up Study were available for the analysis.

Assessment of fruit consumption

In 1984 a 118 item food frequency questionnaire was sent to the participants of the Nurses' Health Study to assess their habitual diet in the past year. In 1986 and every four years thereafter, a similar but expanded questionnaire was sent to the participants to update their dietary information. The expanded questionnaire was also administered every four years to assess diet among the participants in the Health Professionals Follow-up Study since 1986 and those in the Nurses' Health Study II since 1991. In all food frequency questionnaires we asked the participants how often, on average, they consumed each food in a standard portion size. Participants could choose from nine possible responses, ranging from "never, or less than once per month" to "six or more times per day." We consistently asked about 10 individual fruits since baseline: grapes or raisins; peaches, plums, or apricots; prunes; bananas; cantaloupe; apples or pears; oranges; grapefruit; strawberries; and blueberries. We calculated total whole fruit consumption by summing the consumption levels of the 10 individual fruits and watermelon, which we inquired about sporadically during follow-up. Fruit juice included apple, orange, grapefruit, and other juices. The food frequency questionnaires were validated against diet records among 173 participants in the Nurses' Health Study in 1980 and 127 participants in the Health Professionals Follow-up Study in 1986.[17-19] Corrected correlation coefficients between food frequency questionnaire and diet record assessments of individual fruit consumption were 0.80 for apples, 0.79 for bananas, and 0.74 for oranges in women,[17] and 0.67 for total whole fruits, 0.76 for fruit juice, 0.95 for bananas, 0.84 for grapefruit, 0.76 for oranges, 0.70 for apples and pears, 0.59 for raisins and grapes, and 0.38 for strawberries in men.[18 19] For some individual fruits, the corrected correlation coefficients were not available owing to large within person variability in the comparison methods.

Assessment of covariates

In the follow-up questionnaires administered every two years, we inquired and updated information on anthropometric and lifestyle factors for chronic diseases, including body height and weight, cigarette smoking, physical activity, multivitamin use, and family history of diabetes. Among participants in the Nurses' Health Study and Nurses' Health Study II, we ascertained menopausal status, post-menopausal hormone use, and oral contraceptive use (Nurses' Health Study II only). Estimates of total physical activity levels were calculated by multiplying the energy expenditure in metabolic equivalent tasks (METs) measured in hours per week of each activity by hours spent on the activity and summing the values of all activities. Each MET hour is the caloric need per kilogram of body weight per hour of an activity, divided by the caloric need per kilogram of weight per hour at rest. Based on the food frequency questionnaire, we derived a score of the alternate healthy eating index, an indicator of adherence to healthy eating behavior, described in detail elsewhere.[20] In brief, the alternate healthy eating index score summarizes the consumption of 11 foods or nutrients (including consumption of vegetables, fruits, whole grains, sugar sweetened beverages and fruit juice, nuts and legumes, red and processed meat, *trans* fat, long chain n-3 fat, polyunsaturated fat, sodium, and alcohol). Each component was scored on a scale of 0 to 10. In the current analysis, we excluded fruits and fruit juice when calculating the alternate healthy eating index score.

Assessment of diabetes and death

In all three cohorts, to inquire about symptoms, diagnostic tests, and diabetes drug use we mailed a supplementary questionnaire to participants who reported physician diagnosed diabetes in the follow-up questionnaires. A type 2 diabetes diagnosis was confirmed if participants met at least one of the following National Diabetes Data Group criteria[21]: one or more classic symptoms (excessive thirst, polyuria, weight loss, and hunger) plus raised blood glucose levels (fasting levels ≥140 mg/dL (7.8 mmol/L), random blood levels ≥200 mg/dL (11.1 mmol/L), and/or two hour blood glucose levels ≥200 mg/dL during oral glucose tolerance testing), raised blood glucose levels on two different occasions in the absence of symptoms, or treatment with antidiabetic drugs (insulin or oral antidiabetic agent). The diagnostic criteria changed in June 1998 and a fasting blood glucose level of 126 mg/dL (7.0 mmol/L) instead of 140 mg/dL was considered the threshold for the diagnosis of diabetes.[22] The validity of the supplementary questionnaire for the diagnosis of diabetes has been examined in validation studies.[23 24] Of 62 self reported cases of type 2 diabetes randomly selected in the Nurses' Health Study, 61 (98%) were confirmed after an endocrinologist reviewed the medical records without the information from the supplementary questionnaire[23]; and in the Health Professionals Follow-up Study, 57 of 59 self reported cases of type 2 diabetes (97%) were confirmed by a review of medical records.[24]

Deaths were identified by reports from next of kin or postal authorities, or by searching the national death index. At least 98% of deaths were identified among the participants.[25]

Statistical analysis

We calculated each participant's person years from the return date of the baseline food frequency questionnaire to the date of the type 2 diabetes diagnosis, date of death, last return of a valid follow-up questionnaire, or end of follow-up (2008 for the Nurses' Health Study and Health Professionals Follow-up Study, or 2009 for the Nurses' Health Study II), whichever came first. To represent long term dietary intake and minimize within person variation, we calculated and used the cumulative average of dietary intake based on valid assessments from baseline to the end of follow-up.[26] To minimize the effects of chronic diseases diagnosed during follow-up on subsequent diet, we stopped updating dietary information after self reported diagnosis of hypertension, hypercholesterolemia, gestational diabetes, cardiovascular disease, or cancer, since these chronic diseases may lead to changes of fruit consumption levels in the cohorts.[27] To reduce the effect of potential outliers and to pool the results from the three cohorts, we used the same cut-off points to categorize consumption levels in these studies. The highest two consumption levels were combined for prunes, cantaloupe, and blueberries owing to the small number of participants with high consumption levels of these fruits.

To minimize missing covariates, we replaced missing data on body mass index and physical activity with the last valid values. For missing data on body mass index and physical activity at baseline, we created a dummy variable when making categories for these two continuous covariates. Similarly, we also used missing indicator variables to include participants with missing categorical variables, including cigarette smoking, oral contraceptive use (Nurses' Health Study II only), menopausal status, and post-menopausal hormone use. The overall percentages of missing data for body mass index and physical activity were, respectively, 6.8% and 9.5% in the Nurses' Health Study, 6.7% and 8.5% in the Nurses' Health Study II, and 12.8% and 14.0% in the Health Professionals Follow-up Study. The overall percentages of missing values during follow-up ranged from 0.6% (for cigarette smoking) to 5.1% (for menopausal status and post-menopausal hormone use) in the Nurses' Health Study, from 0.3% (for cigarette smoking) to 4.7% (for menopausal status and post-menopausal hormone use) in the Nurses' Health Study II, and from 0.1% (for physical activity) to 12.2% (for cigarette smoking) in the Health Professionals Follow-up Study.

Using Cox proportional hazard regression, we estimated the hazard ratios and 95% confidence intervals of type 2 diabetes for fruit consumption. We tested the proportional hazard assumption by including interaction terms between individual fruit consumption and duration of follow-up, and the assumption was unlikely violated (P>0.05 for all tests). We examined linear trend by modelling the median values for fruit consumption categories as a continuous variable. Using a fixed effects model, we pooled multivariable adjusted hazard ratios from three cohorts, and we used the Cochrane Q statistic and the I^2 statistic to examine the heterogeneity of associations among the cohorts.

To examine whether the associations with risk of type 2 diabetes were heterogeneous among individual fruits, we fitted two fully adjusted models: one with total fruit consumption and the other with total fruit consumption plus consumption of individual fruits excluding oranges (which had the most similar association as the total fruit consumption) to avoid over-fitting. Then we used the likelihood ratio test to examine whether the model including individual fruits had better fit than that including total fruit consumption only.

We also estimated potential effects of substituting specific fruit consumption for fruit juice consumption by examining the median values for consumption categories of individual fruits and fruit juice in the same multivariate model; the hazard ratios and 95% confidence intervals for substitution effects were calculated based on the differences in point estimates, and the variance and covariance for the regression coefficients of specific fruits and fruit juice.[28] To examine the robustness of our findings, we also conducted four sensitivity analyses: evaluating the influence of adjustment for major dietary variables including polyunsaturated to saturated fat ratio, and intakes of trans fat, red meat, fish, whole grains, sugar sweetened beverages, coffee, and nuts (all in fifths) instead of the modified alternate healthy eating index score; adjusting for baseline body mass index instead of updated body mass index to estimate the impact of potential over-adjustment; using baseline consumption levels as an exposure instead of cumulative average of intake levels; and stopping updating diet after diagnosis of gestational diabetes, cardiovascular disease, or cancer only when calculating the cumulative averages.

We further examined whether the associations of individual fruit consumption with risk of type 2 diabetes depended on the glycemic index/glycemic load values of fruits. We calculated the glycemic load values per serving for individual fruits based on the glycemic index values from the international glycemic index database[13] and the amount of carbohydrate in fruits from the USDA nutritional database[11] (see supplementary table 1). We categorized individual fruits into three groups based on their glycemic load values per serving: prunes, bananas, grapes, raisins, apples, and pears for high glycemic load fruits (glycemic load 8.1-19.2); cantaloupe, blueberries, and oranges for moderate glycemic load fruits (5.7-8.0); and peaches, plums, apricots, strawberries, and grapefruit for low glycemic load fruits (1.3-5.6). In terms of the categorization of fruits by the glycemic index values, high glycemic index fruits included cantaloupe, bananas, grapes, raisins (glycemic index 60-70); moderate glycemic index fruits included prunes, blueberries, and grapefruit (47-59); and low glycemic index fruits included apples, pears, oranges, peaches, plums, apricots, and strawberries (34-46). Moreover, to estimate the degree to which the observed associations were explained by flavonoid intake, in a secondary analysis we further adjusted for intake of flavonoid subtypes (flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins).

The analysis was stratified jointly by age and calendar year and adjusted for body mass index (kg/m^2; <23, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9, 35.0-36.9, 37.0-38.9, 39.0-40.9, 41.0-42.9, 43.0-44.9, ≥45.0, or missing), ethnicity (white, African-American, Hispanic, or Asian), physical activity (MET hours/week; <3, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0, or missing), cigarette smoking (never, former, currently smoke 1-14 cigarettes/day, currently smoke 15-24 cigarettes/day, or currently smoke ≥25 cigarettes/day, or missing), multivitamin use (yes or no), family history of diabetes (yes or no), menopausal status and post-menopausal hormone use (premenopause, post-menopause (never, former, or current hormone use), or missing) (for women), oral contraceptive use (yes, no, or missing) (Nurses' Health Study II only), total energy intake (kcal/day), fruit juice consumption (fifths), and the modified alternate healthy eating index score (fifths).[20] When examining the association for total whole fruit, we included total fruit consumption in the multivariate model without further adjusting for individual fruits. Likewise, when examining the

associations for individual fruits or fruit groups based on their glycemic index/glycemic load values, we included consumption levels of all other individual fruits or fruit groups instead of total fruit consumption in the final model.

Statistical analyses were performed with SAS 9.2. All P values were two sided, and statistical significance was defined as P<0.05.

Results

During 3 464 641 person years of follow-up, 12 198 participants developed type 2 diabetes (Nurses' Health Study: 6358 cases/1 394 127 person years; Nurses' Health Study II: 3153 cases/1 416 111 person years; Health Professionals Follow-up Study: 2687 cases/654 403 person years). The rate of loss to follow-up was low and similar between extreme comparison groups of total fruit consumption levels: the average rate of loss to follow-up for each two year follow-up cycle was 0.8% for <4 servings/week and 0.7% for ≥3 servings/day of total fruit consumption in the Nurses' Health Study. These values were 0.1% and 0.1% in the Nurses' Health Study II and 1.0% and 1.1% in the Health Professionals Follow-up Study, respectively.

In all three cohorts, total whole fruit consumption was positively correlated with age, physical activity, multivitamin use, total energy intake, fruit juice consumption, and the modified alternate health eating index score, and was inversely associated with body mass index and current smoking (table 1⇓). Whole fruit consumption was associated with an increased probability of using post-menopausal hormones in the Nurses' Health Study and with a reduced probability of using oral contraceptives in the Nurses' Health Study II. Individual fruits were correlated with each other weakly to moderately; the highest Spearman correlation coefficients were 0.44 between apples and oranges in the Nurses' Health Study, 0.47 between strawberries and peaches in the Nurses' Health Study II, and 0.48 between strawberries and blueberries in the Health Professionals Follow-up Study (see supplementary table 2). The Spearman correlation coefficients for total whole fruits in relation to the modified alternate healthy eating index score were 0.22 for the Nurses' Health Study, 0.29 for the Nurses' Health Study II, and 0.28 for the Health Professionals Follow-up Study; those for individual fruits ranged from 0.09 (for bananas) to 0.23 (for apples and pears) in the Nurses' Health Study, from 0.13 (for bananas) to 0.24 (for apples and pears) in the Nurses' Health Study II, and from 0.09 (for peaches, plums, and apricots) to 0.24 (for apples and pears) in the Health Professionals Follow-up Study.

Total whole fruit consumption was weakly associated with a lower risk of type 2 diabetes: the hazard ratio (95% confidence interval) of type 2 diabetes for every three servings/week of whole fruit consumption was 0.98 (0.96 to 0.99) (table 2⇓). In the age adjusted model, each individual fruit consumption was inversely associated with risk of type 2 diabetes in all cohorts (all P<0.001) (see supplementary table 3). Adjustment for personal factors, lifestyle, fruit juice consumption, and the modified alternate health eating index score attenuated these associations. The inverse association for cantaloupe consumption was no longer statistically significant after multivariable adjustments of the aforementioned covariates. Further adjustment for other individual fruit consumption changed the associations to various degrees (table 3⇓). The inverse associations for grapes and blueberries were attenuated, albeit remaining statistically significant. In contrast, associations for strawberries were attenuated toward the null, and cantaloupe consumption was associated with an increased risk of type 2 diabetes after adjustment for other individual fruits. For every three servings/week, the pooled hazard ratios (95% confidence intervals) of risk for type 2 diabetes was 0.74 (0.66 to 0.83) for blueberries, 0.88 (0.83 to 0.93) for grapes and raisins, 0.93 (0.90 to 0.96) for apples and pears, 0.95 (0.91 to 0.98) for bananas, and 0.95 (0.91 to 0.99) for grapefruit. In contrast, the pooled hazard ratio (95% confidence interval) of risk for type 2 diabetes for the same increment in cantaloupe consumption was 1.10 (1.02 to 1.18). A test for heterogeneity among three cohorts was significant for the associations of bananas and strawberries (P for heterogeneity <0.001 for bananas and 0.01 for strawberries). In the Nurses' Health Study II and Health Professionals Follow-up Study, banana consumption was associated with a lower risk of type 2 diabetes, whereas in the Nurses' Health Study a non-significant positive association was found. The association for strawberry consumption was significantly positive in the Health Professionals Follow-up Study but was non-significant and inverse in the Nurses' Health Study. Further adjustment for intake levels of flavonoid subtypes (flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins) in the final model did not appreciably attenuate the associations for individual fruits (see supplementary table 4).

The goodness of fit of model was significantly improved by adding consumption of individual fruits to the model with total whole fruit consumption and other covariates (P<0.001 for likelihood ratio test in each cohort), indicating that heterogeneity in the associations with risk of type 2 diabetes among individual fruits was significant.

In the sensitivity analyses, the associations for individual fruits did not change appreciably with adjustment for major dietary factors instead of the modified alternate healthy eating index score, or using baseline consumption levels of individual fruits instead of cumulative average of intake levels (see supplementary table 5). When we adjusted for baseline body mass index instead of updated body mass index or stopped updating diet after diagnosis of gestational diabetes, cardiovascular disease, or cancer when calculating the cumulative average of dietary intake, the inverse associations became weaker, although the associations for blueberries, grapes and raisins, and apples and pears remained statistically significant.

In the secondary analysis examining the associations between fruit consumption and risk of type 2 diabetes by glycemic index/glycemic load values of fruits, greater consumption of high glycemic load fruits was associated with a lower risk of type 2 diabetes, but not moderate and low glycemic load fruits (table 4⇓). In contrast, greater consumption of moderate glycemic index fruits, but not high and low glycemic index fruits, was inversely associated with risk of type 2 diabetes. Fruit juice consumption was associated with an increased risk of type 2 diabetes. The associations for low glycemic load fruits were heterogeneous among cohorts (P for heterogeneity =0.04): a significant, inverse association was found in the Nurses' Health Study, but not in the other two cohorts.

Replacing each three servings/week of fruit juice consumption with the same amount of total or individual whole fruits, the risk of type 2 diabetes in the pooled analysis was 7% (95% confidence interval 4% to 9%) lower for total whole fruits, 33% (24% to 40%) lower for blueberries, 19% (14% to 24%) lower for grapes and raisins, 14% (11% to 18%) lower for apples and pears, 13% (9% to 16%) lower for bananas, and 12% (8% to 17%) lower for grapefruit after adjustment for personal factors, lifestyle, and the modified alternate health eating index score (figure⇓). Additionally, we found that replacing fruit juice with oranges, peaches, plums, and apricots was also associated with

a lower risk of type 2 diabetes: 18% (8% to 28%) lower for prunes, 11% (5% to 16%) lower for peaches, plums, and apricots, and 8% (4% to 12%) lower for oranges.

Discussion

In three prospective cohorts of US men and women, we found that the associations with risk of type 2 diabetes differed significantly among individual fruits: greater consumption of blueberries, grapes, apples, bananas, and grapefruit were significantly associated with a reduced risk of type 2 diabetes. Most of these associations were quite consistent among three cohorts. Additionally, differences in the glycemic index/glycemic load values of fruits did not account for the association of specific fruits with risk of type 2 diabetes. Moreover, greater fruit juice consumption was associated with an increased risk, and substitution of whole fruits for fruit juice was associated with a lower risk, except for strawberries and cantaloupe.

Results in relation to other studies

In eight previous prospective studies, the association between total fruit consumption and risk of type 2 diabetes was examined,[2-9] and the results were mixed. Similar to previous analyses in the Nurses' Health Study[3] and the Finnish Mobile Clinic Health Examination Survey study,[2] the current findings supported an inverse association between total fruit consumption and risk of type 2 diabetes, but not in other studies.[4-9] In contrast to total fruit consumption, evidence on consumption of individual fruits or fruit groups with risk of type 2 diabetes is limited and incomplete. In four prospective studies, consumption of citrus fruit was not associated with a lower risk of type 2 diabetes.[5-8] Apple consumption was inversely associated with risk in the Women's Health Study[29] and in the Finnish study,[30] but not in the Iowa Women's Health Study.[31] In addition, greater consumption of berries was associated with a lower risk in the Finnish study,[2] but not in the Iowa Women's Health Study.[31] In our previous analyses that focused on anthocyanin rich fruits, intakes of blueberries, strawberries, and apples were associated with a lower risk of type 2 diabetes.[32] Consistently, in a clinical trial, increased consumption of berries improved glycemic control among people with diabetes.[33] Our current investigation extended the evidence in this regard and found novel, inverse associations for grapes, bananas, and grapefruit.

The different associations of individual fruits with diabetes risk may be due to the heterogeneous composition of these foods. Firstly, blueberries, apples, and red or black grapes contain high levels of anthocyanins.[12] In mice with diabetes, bilberry extract rich in anthocyanins can activate adenosine monophosphate-activated protein kinase, enhance glucose uptake and utilization in white adipose tissue and skeletal muscle, and reduce glucose production in the liver.[34] Our previous analyses also showed that levels of anthocyanin intake were inversely associated with risk of type 2 diabetes.[32] In the current study, further adjustment for anthocyanins did not substantially change the associations for individual fruits, suggesting that the inverse associations of individual fruits are likely due to other constituents of these foods. Both red and white grapes contain high levels of resveratrol in skin.[35] In mice, a high fat diet with 0.04% resveratrol increased insulin sensitivity at 24 months compared with the same diet without resveratrol.[36] However, randomized controlled trials examining the effects of supplementation of resveratrol on glucose metabolism have generated inconsistent results.[37-39] Prunes, peaches, plums, apricots, and apples contain chlorogenic acid,[40-43] which may potentially mediate the beneficial effects of coffee consumption on diabetes risk.[44] In rats, chlorogenic acid reduces glucose dependent insulinotropic peptide secretion by slowing glucose absorption in the intestine.[45] Moreover, chlorogenic acid increases muscle glucose uptake in mice with diabetes.[46] Finally, grapefruits contain high amounts of naringin.[12] In rats, naringin inhibits dipeptidyl peptidase 4 similarly to sitagliptin, a dipeptidyl peptidase 4 inhibitor used for the treatment of diabetes.[47] Inhibition of dipeptidyl peptidase 4 increases glucagon-like peptide 1, which subsequently leads to improved glucose tolerance.[48] In contrast to these specific fruits mentioned above, cantaloupe was associated with an increased risk of type 2 diabetes in the current analysis. Melons have lower levels of phytochemicals than the aforementioned fruits.[12] None the less, little evidence exists regarding the effects of melons on glucose metabolism. Although other fruits may also be beneficial for glucose metabolism, significant associations between other specific fruits and risk of type 2 diabetes were not found in the current and previous investigations.[5-8]

The glycemic index/glycemic load values of fruits did not seem to be the factor that determined their association with type 2 diabetes in the current study, although in a clinical trial, increased consumption of low glycemic index fruits improved glycemic control among people with diabetes.[33] In recent meta-analyses, a higher dietary glycemic index/glycemic load was associated with a greater risk of type 2 diabetes.[49 50] In the Nurses' Health Study and Health Professionals Follow-up Study, the associations between dietary glycemic index and risk of type 2 diabetes were positive, although the associations for dietary glycemic load were not significant.[51-53] None the less, the contribution of total fruit consumption to dietary glycemic load was rather small (about 10%) in these populations. Of individual fruits, the top three contributors to dietary glycemic load were bananas (3-4%), apples (2%), and grapes (1%). In contrast, the relatively high glycemic load values of fruit juices[13] along with reduced levels of beneficial nutrients through juicing processes[11 12] (for example, the glycemic load values per serving are 6.2 for raw oranges and 13.4 for orange juice, and fibre levels per serving are 3.1 g and 0.5 g, respectively) may explain the positive associations between fruit juice consumption and risk of type 2 diabetes. Moreover, the difference in the viscosity of foods is also an important factor affecting postprandial blood glucose dynamics. Fluids pass through the stomach to the intestine more rapidly than solids even if nutritional content is similar.[54] For example, fruit juices lead to more rapid and larger changes in serum levels of glucose and insulin than whole fruits.[55 56] Although these mechanisms may potentially explain the diverse associations for individual fruits, further research is apparently needed to confirm our findings on specific fruits in relation to type 2 diabetes and to further elucidate underlying mechanisms.

Strengths and limitations of this study

The present study has several limitations. Firstly, measurement errors were inevitable in the estimates of fruit consumption, especially for individual fruits with lower consumption levels.[17 18] Adjustment for energy intake and use of cumulatively averaged intake levels can reduce the magnitude of measurement errors to some extent.[26] Generally, random errors in exposure assessments attenuate true associations toward the null. Secondly, the possibility of false positive findings may exist because we examined the associations of multiple fruits in the current investigation without adjusting for multiple comparisons based on a priori hypotheses. Meanwhile, most associations were consistent across three cohorts, and the associations for

blueberries, grapes, and apples remained statistically significant even after applying the Bonferroni correction, a conservative method correcting for multiple comparisons. Thirdly, in our food frequency questionnaires, intakes of some individual fruits (apples and pears; peaches, plums, and apricots) were combined because these fruits have similar nutrient profiles. Therefore we could not determine whether the associations for these combined fruits can be ascribed to a specific individual fruit. Fourthly, we cannot exclude the possibility of recall bias in the assessments of diet based on the food frequency questionnaires. However, the prospective study design and exclusion of participants with chronic diseases at baseline should minimize such bias. Fifthly, although in the multivariable analysis we considered a multitude of lifestyle and dietary factors, including other individual fruits, residual or unmeasured confounding may still exist. Finally, our study populations primarily consist of health professionals with European ancestry. Thus our findings may not be generalized to other populations.

Conclusions

Our findings suggest that there is significant heterogeneity in the associations between individual fruits and risk of type 2 diabetes. Greater consumption of specific whole fruits, particularly blueberries, grapes, and apples, was significantly associated with a lower risk of type 2 diabetes, whereas greater fruit juice consumption was associated with a higher risk. The differences in the associations between individual fruits were not accounted for by variation in the glycemic index/glycemic load values of individual fruits. Overall, these results support recommendations on increasing consumption of a variety of whole fruits, especially blueberries, grapes, and apples, as a measure for diabetes prevention.

Contributors: RMvD, FBH, and WC obtained funding from the National Institutes of Health. IM, RMvD, and QS designed this study. RMvD, QS, JEM, FBH, and WCW were involved in data collection. IM, FI, QS, and RMvD provided statistical expertise. IM analysed the data and wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. IM and QS are the guarantors of this investigation.

Funding: This study was funded by research grants CA87969, CA176726, CA55075, CA50385, CA167552, DK58845, and DK082486 from the National Institutes of Health. Dr. Sun was supported by a career development award R00HL098459 from the National Heart, Lung, and Blood Institute. The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The authors are not affiliated with the funding institutions.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital, and the Harvard School of Public Health. The completion of the self administered questionnaire was considered to imply informed consent.

Data sharing: No additional data available.

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What is already known on this topic

Total fruit consumption is not consistently associated with a lower risk of type 2 diabetes

The possible heterogeneity among individual fruits regarding the associations with risk of type 2 diabetes has not been examined

What this study adds

The associations with risk of type 2 diabetes are different among individual fruits

Greater consumption of specific whole fruits, particularly blueberries, grapes, and apples, is significantly associated with a lower risk of type 2 diabetes, whereas increased consumption of fruit juices has the opposite association

In addition, the associations of individual fruits are not determined by their glycemic index or glycemic load values

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Accepted: 10 July 2013

Cite this as: *BMJ* 2013;347:f5001

Tables

Table 1| Baseline characteristics of women in Nurses' Health Study and Nurses' Health Study II and men in Health Professionals Follow-up Study. Values are means (standard deviations) or percentages unless stated otherwise

	Total whole fruit consumption				
Characteristics	**<4 servings/week**	**4-6 servings/week**	**1 serving/day**	**2 servings/day**	**≥3 servings/day**
Nurses' Health Study*:					
No of participants	6605	5748	12 170	20 706	20 876
Age (years)	48.0 (6.9)	48.2 (6.9)	49.2 (7.0)	50.1 (7.1)	51.3 (7.1)
Body mass index	24.7 (4.9)	24.9 (4.7)	24.9 (4.7)	24.9 (4.5)	24.8 (4.5)
Physical activity (MET hours/week)	9.8 (15.9)	11.9 (22.4)	12.3 (17.1)	13.9 (19.6)	17.4 (23.3)
Alcohol intake (g/day)	9.2 (14.8)	7.6 (12.2)	7.7 (12.3)	6.7 (10.4)	6.0 (9.6)
Current smoker (%)	44	33	28	21	16
White (%)	98	98	98	98	97
Family history of diabetes (%)	24	25	26	26	25
Multivitamin use (%)	28	31	34	38	42
Ever menopausal hormone use (%)	16	17	19	22	25
Total energy intake (kcal/day)	1467 (495)	1550 (495)	1605 (485)	1732 (483)	1986 (522)
Fruit juice consumption (serving/day)	0.08 (0.14)	0.19 (0.19)	0.44 (0.38)	0.70 (0.46)	1.25 (0.95)
Modified alternate healthy eating index score	44.3 (10.0)	46.3 (9.9)	47.4 (10.0)	49.1 (10.0)	51.4 (10.3)
Nurses' Health Study II†:					
No of participants	25 120	16 726	20 259	16 312	6687
Age (years)	35.9 (4.7)	36.0 (4.7)	36.1 (4.6)	36.3 (4.6)	36.4 (4.6)
Body mass index	24.6 (5.6)	24.6 (5.3)	24.5 (5.0)	24.5 (4.9)	24.3 (5.0)
Physical activity (MET hours/week)	15.8 (23.0)	18.7 (23.7)	21.3 (25.6)	25.7 (30.6)	33.2 (39.6)
Alcohol intake (g/day)	3.6 (7.3)	3.0 (5.8)	3.0 (5.5)	3.0 (5.4)	2.8 (5.4)
Current smoker (%)	18	12	9	8	7
White (%)	96	96	96	96	94
Family history of diabetes (%)	16	16	16	17	16
Multivitamin use (%)	37	42	46	50	52
Ever menopausal hormone use (%)	3	3	3	3	3
Current oral contraceptive use (%)	12	12	11	10	9
Total energy intake (kcal/day)	1559 (504)	1714 (502)	1820 (504)	1983 (516)	2215 (551)
Fruit juice consumption (serving/day)	0.45 (0.67)	0.61 (0.70)	0.70 (0.76)	0.82 (0.84)	1.02 (1.09)
Modified alternate health eating index score	45.3 (10.3)	48.0 (10.3)	50.1 (10.3)	52.4 (10.3)	54.8 (10.3)
Health Professionals Follow-up Study‡:					
No of participants	3230	2808	6250	10 682	13 203
Age (years)	49.9 (8.3)	50.4 (8.5)	51.2 (8.9)	52.5 (9.3)	53.7 (9.6)
Body mass index	25.1 (4.9)	25.2 (4.9)	25.0 (4.9)	24.9 (4.7)	24.8 (4.7)
Physical activity (MET hours/week)	14.3 (22.0)	15.8 (22.5)	18.2 (26.9)	21.1 (29.4)	26.2 (33.5)
Alcohol intake (g/day)	15.3 (19.7)	12.9 (17.1)	12.6 (16.4)	11.5 (14.8)	9.4 (13.3)
Current smoker (%)	21	15	12	8	5
White (%)	95	95	95	95	95
Family history of diabetes (%)	18	18	18	19	19
Multivitamin use (%)	34	36	38	42	46
Total energy intake (kcal/day)	1714 (559)	1812 (594)	1844 (568)	1964 (580)	2223 (624)
Fruit juice consumption (serving/day)	0.09 (0.10)	0.21 (0.18)	0.46 (0.36)	0.69 (0.43)	1.28 (1.09)
Modified alternate health eating index score	47.2 (10.9)	49.3 (10.9)	50.8 (10.8)	53.2 (10.7)	56.4 (10.7)

MET=metabolic equivalent of task.

Table 1 (continued)

	Total whole fruit consumption				
Characteristics	**<4 servings/week**	**4-6 servings/week**	**1 serving/day**	**2 servings/day**	**≥3 servings/day**

*Baseline was 1984.
†Baseline was 1991.
‡Baseline was1986.

Table 2| Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for total whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study

	Consumption levels						P values	
Variables	<4 servings/week	5-6 servings/week	1 serving/day	2 servings/day	≥3 servings/day	Linear trend*	For trend	For heterogeneity
Nurses' Health Study†:	478/94 121	523/105 022	1141/237 302	2068/459 062	2148/498 620			
Adjusted hazard ratio‡	1.00	0.93 (0.82 to 1.06)	0.86 (0.77 to 0.97)	0.81 (0.72 to 0.91)	0.82 (0.72 to 0.92)	0.97 (0.95 to 0.99)		
Nurses' Health Study II†:	995/358 762	620/287 918	718/368 180	598/295 904	222/105 347			
Adjusted hazard ratio‡	1.00	0.86 (0.77 to 0.95)	0.84 (0.76 to 0.94)	0.88 (0.78 to 0.98)	0.92 (0.78 to 1.08)	0.99 (0.96 to 1.02)		
Health Professionals Follow-up Study†:	219/48 762	236/47 865	482/107 372	799/199 357	951/251 047			
Adjusted hazard ratio‡	1.00	1.10 (0.91 to 1.33)	1.07 (0.90 to 1.27)	0.99 (0.83 to 1.17)	0.99 (0.82 to 1.19)	0.98 (0.95 to 1.01)		
Pooled results‡§	1.00	0.91 (0.85 to 0.99)	0.88 (0.82 to 0.95)	0.87 (0.81 to 0.94)	0.88 (0.81 to 0.96)	0.98 (0.96 to 0.99)	0.002	0.48

*Estimated based on every three servings/week increment.

†Cases/person years of observation.

‡Adjusted for age (years), ethnicity (white, African-American, Hispanic, or Asian), body mass index (<23, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9, 35.0-36.9, 37.0-38.9, 39.0-40.9, 41.0-42.9, 43.0-44.9, ≥45.0, or missing), smoking status (never, former, current (1–14, 15–24, or ≥25 cigarettes/day), or missing), multivitamin use (yes or no), physical activity (<3, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET (metabolic equivalent of task) hours/week, or missing), family history of diabetes (yes or no), menopausal status and post-menopausal hormone use (premenopause, post-menopause (never, former, or current hormone use), or missing, for women), oral contraceptive use (yes, no, or missing, for Nurses' Health Study II) total energy intake (kcal/day), fruit juice consumption (<1, 1, 2-4, 5-6, ≥7 servings/week) and the modified alternate healthy eating index score (fifths). Individual fruit consumption was mutually adjusted.

§Study estimates from three cohorts were pooled using a fixed effects model.

Table 3| **Pooled hazard ratios (95% confidence intervals) of type 2 diabetes for individual whole fruit consumption in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study**

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Grapes and raisins								
Nurses' Health Study†:	2307/406 031	2489/546 881	922/234 102	508/160 446	132/46 667			
Adjusted hazard ratio‡	1.00	0.91 (0.86 to 0.97)	0.88 (0.80 to 0.95)	0.80 (0.72 to 0.88)	0.77 (0.64 to 0.92)	0.84 (0.78 to 0.91)		
Nurses' Health Study II†:	1288/408 297	1175/575 319	396/225 712	241/167 194	53/39 589			
Adjusted hazard ratio‡	1.00	0.81 (0.74 to 0.88)	0.85 (0.75 to 0.96)	0.83 (0.72 to 0.97)	0.88 (0.66 to 1.16)	0.91 (0.81 to 1.02)		
Health Professionals Follow-up Study†:	984/207 158	937/225 458	366/94 345	292/89 649	108/37 793			
Adjusted hazard ratio‡	1.00	0.95 (0.87 to 1.05)	0.95 (0.84 to 1.08)	0.87 (0.76 to 1.01)	0.84 (0.69 to 1.04)	0.91 (0.82 to 0.99)		
Pooled results‡§	1.00	0.89 (0.85 to 0.93)	0.88 (0.83 to 0.94)	0.82 (0.77 to 0.89)	0.81 (0.72 to 0.92)	0.88 (0.83 to 0.93)	<0.001	0.42
Peaches, plums, and apricots								
Nurses' Health Study†:	1551/306 337	2215/487 935	1648/377 266	779/181 418	165/41 171			
Adjusted hazard ratio‡	1.00	0.99 (0.93 to 1.07)	1.00 (0.92 to 1.08)	1.04 (0.94 to 1.14)	0.92 (0.78 to 1.09)	1.00 (0.93 to 1.07)		
Nurses' Health Study II†:	847/323 168	1181/520 561	683/337 730	369/198 848	73/35 804			
Adjusted hazard ratio‡	1.00	1.07 (0.97 to 1.18)	1.03 (0.91 to 1.16)	0.99 (0.86 to 1.14)	1.01 (0.78 to 1.31)	0.97 (0.87 to 1.08)		
Health Professionals Follow-up Study†:	832/184 896	1077/264 314	483/119 655	251/70 773	44/14 766			
Adjusted hazard ratio‡	1.00	0.98 (0.88 to 1.08)	1.03 (0.90 to 1.18)	0.88 (0.75 to 1.04)	0.75 (0.55 to 1.04)	0.87 (0.77 to 0.99)		
Pooled results‡§	1.00	1.01 (0.96 to 1.06)	1.01 (0.95 to 1.07)	0.99 (0.92 to 1.06)	0.91 (0.80 to 1.04)	0.97 (0.92 to 1.02)	0.21	0.17
Prunes								
Nurses' Health Study†:	5108/1 056 374	957/241 136	150/47 746	143/48 871				
Adjusted hazard ratio‡	1.00	0.99 (0.92 to 1.07)	0.86 (0.73 to 1.02)	0.89 (0.75 to 1.06)		0.87 (0.74 to 1.03)		
Nurses' Health Study II†:	2746/1 160 917	296/188 256	57/34 465	54/32 473				
Adjusted hazard ratio‡	1.00	0.85 (0.75 to 0.96)	1.00 (0.77 to 1.31)	1.16 (0.88 to 1.53)		1.03 (0.79 to 1.34)		
Health Professionals Follow-up Study†:	1425/304 005	270/67 738	54/14 390	61/18 301				
Adjusted hazard ratio‡	1.00	0.92 (0.80 to 1.06)	0.83 (0.63 to 1.10)	0.86 (0.66 to 1.12)		0.82 (0.63 to 1.07)		
Pooled results‡§	1.00	0.95 (0.89 to 1.00)	0.89 (0.78 to 1.00)	0.94 (0.82 to 1.06)		0.89 (0.79 to 1.01)	0.07	0.47
Bananas								
Nurses' Health Study†:	555/127 955	1690/346 214	1 470/305 869	1 869/432 632	774/181 457			
Adjusted hazard ratio‡	1.00	1.08 (0.98 to 1.19)	1.05 (0.95 to 1.17)	1.04 (0.94 to 1.15)	1.08 (0.96 to 1.21)	1.01 (0.96 to 1.06)		
Nurses' Health Study II†:	363/132 406	956/362 359	731/318 389	827/440 879	276/162 077			
Adjusted hazard ratio‡	1.00	0.95 (0.84 to 1.07)	0.95 (0.83 to 1.08)	0.82 (0.72 to 0.94)	0.80 (0.67 to 0.94)	0.87 (0.81 to 0.94)		

Table 3 (continued)

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Health Professionals Follow-up Study†:	328/75 340	734/150 847	469/106 383	757/194 466	399/127 368			
Adjusted hazard ratio‡	1.00	1.09 (0.95 to 1.25)	1.01 (0.87 to 1.18)	0.93 (0.80 to 1.07)	0.86 (0.73 to 1.01)	0.89 (0.83 to 0.95)		
Pooled results‡§	1.00	1.04 (0.97 to 1.11)	1.01 (0.94 to 1.09)	0.95 (0.88 to 1.02)	0.95 (0.87 to 1.03)	0.95 (0.91 to 0.98)	0.002	<0.001
Cantaloupe								
Nurses' Health Study†:	1231/250 261	2292/516 604	2098/458 752	737/168 509				
Adjusted hazard ratio‡	1.00	1.00 (0.93 to 1.08)	1.06 (0.98 to 1.15)	1.07 (0.96 to 1.19)		1.08 (0.98 to 1.18)		
Nurses' Health Study II†:	890/345 001	1257/595 757	773/364 046	233/111 307				
Adjusted hazard ratio‡	1.00	0.99 (0.90 to 1.09)	1.05 (0.94 to 1.17)	1.11 (0.94 to 1.30)		1.12 (0.96 to 1.32)		
Health Professionals Follow-up Study†:	655/165 084	1230/292 381	562/137 179	240/59 759				
Adjusted hazard ratio‡	1.00	1.15 (1.03 to 1.27)	1.17 (1.03 to 1.34)	1.19 (1.01 to 1.40)		1.14 (0.98 to 1.34)		
Pooled results‡§	1.00	1.03 (0.98 to 1.08)	1.08 (1.02 to 1.14)	1.10 (1.02 to 1.19)		1.10 (1.02 to 1.18)	0.01	0.77
Apples and pears								
Nurses' Health Study†:	584/102 327	1375/275 896	1418/288 494	1861/437 158	1120/290 252			
Adjusted hazard ratio‡	1.00	0.94 (0.84 to 1.04)	0.94 (0.84 to 1.05)	0.85 (0.77 to 0.95)	0.82 (0.73 to 0.92)	0.91 (0.87 to 0.95)		
Nurses' Health Study II†:	334/98 142	835/322 737	688/303 354	881/463 781	415/228 096			
Adjusted hazard ratio‡	1.00	0.83 (0.72 to 0.95)	0.83 (0.72 to 0.96)	0.79 (0.68 to 0.91)	0.76 (0.64 to 0.90)	0.93 (0.86 to 0.99)		
Health Professionals Follow-up Study†:	251/50 846	631/144 067	527/123 440	786/203 567	492/132 482			
Adjusted hazard ratio‡	1.00	0.91 (0.78 to 1.06)	0.98 (0.83 to 1.16)	0.91 (0.77 to 1.07)	0.93 (0.78 to 1.11)	0.98 (0.92 to 1.06)		
Pooled results‡§	1.00	0.90 (0.83 to 0.96)	0.92 (0.85 to 0.99)	0.85 (0.78 to 0.92)	0.83 (0.76 to 0.90)	0.93 (0.90 to 0.96)	<0.001	0.19
Oranges								
Nurses' Health Study†:	1081/214 635	1772/384 598	1460/310 026	1459/351 173	586/133 695			
Adjusted hazard ratio‡	1.00	0.96 (0.89 to 1.04)	1.03 (0.94 to 1.13)	0.96 (0.87 to 1.05)	1.03 (0.92 to 1.15)	1.00 (0.95 to 1.06)		
Nurses' Health Study II†:	774/295 675	1132/514 849	640/308 088	489/244 557	118/52 943			
Adjusted hazard ratio‡	1.00	0.94 (0.85 to 1.04)	0.93 (0.82 to 1.05)	0.93 (0.81 to 1.07)	0.97 (0.78 to 1.21)	0.99 (0.89 to 1.09)		
Health Professionals Follow-up Study†:	491/102 463	738/176 033	523/129 393	640/169 083	295/77 431			
Adjusted hazard ratio‡	1.00	0.89 (0.79 to 1.01)	0.91 (0.79 to 1.04)	0.89 (0.78 to 1.03)	0.89 (0.76 to 1.05)	0.97 (0.90 to 1.05)		
Pooled results‡§	1.00	0.94 (0.89 to 1.00)	0.98 (0.91 to 1.04)	0.94 (0.87 to 1.00)	0.98 (0.90 to 1.07)	0.99 (0.95 to 1.03)	0.68	0.78
Grapefruit								
Nurses' Health Study†:	2225/411 039	1873/426 864	1177/269 719	813/212 965	270/73 539			

Table 3 (continued)

Variables	Consumption levels					Linear trend*	P value	
	<1 serving/month	1-3 servings/month	1 serving/week	2-4 servings/week	≥5 servings/week		For trend	For heterogeneity
Adjusted hazard ratio‡	1.00	0.91 (0.85 to 0.97)	0.95 (0.88 to 1.03)	0.88 (0.80 to 0.96)	0.86 (0.75 to 0.98)	0.92 (0.87 to 0.98)		
Nurses' Health Study II†:	1667/682 234	881/438 763	350/166 255	202/104 317	53/24 543			
Adjusted hazard ratio‡	1.00	1.00 (0.91 to 1.09)	1.06 (0.94 to 1.20)	0.97 (0.83 to 1.14)	0.91 (0.69 to 1.21)	0.97 (0.86 to 1.09)		
Health Professionals Follow-up Study†:	933/215 578	816/201 584	414/100 589	365/97 276	159/39 377			
Adjusted hazard ratio‡	1.00	1.03 (0.93 to 1.14)	1.09 (0.96 to 1.24)	0.93 (0.81 to 1.06)	1.08 (0.90 to 1.30)	0.99 (0.91 to 1.08)		
Pooled results‡§	1.00	0.96 (0.91 to 1.00)	1.00 (0.94 to 1.06)	0.91 (0.85 to 0.97)	0.93 (0.84 to 1.03)	0.95 (0.91 to 0.99)	0.02	0.42
Strawberries								
Nurses' Health Study†:	1255/227 188	2539/570 535	1920/429 463	555/145 069	89/21 870			
Adjusted hazard ratio‡	1.00	0.94 (0.87 to 1.01)	0.98 (0.90 to 1.07)	0.87 (0.77 to 0.98)	0.99 (0.79 to 1.25)	0.94 (0.85 to 1.03)		
Nurses' Health Study II†:	602/212 384	1257/566 425	836/414 673	393/190 675	65/31 954			
Adjusted hazard ratio‡	1.00	0.97 (0.87 to 1.08)	1.01 (0.89 to 1.15)	1.09 (0.93 to 1.27)	1.08 (0.81 to 1.43)	1.09 (0.97 to 1.22)		
Health Professionals Follow-up Study†:	895/194 981	1186/305 273	419/109 618	161/39 477	26/5054			
Adjusted hazard ratio‡	1.00	0.95 (0.85 to 1.05)	0.98 (0.85 to 1.13)	1.16 (0.95 to 1.42)	1.51 (1.00 to 2.28)	1.22 (1.03 to 1.43)		
Pooled results‡§	1.00	0.95 (0.90 to 1.00)	0.99 (0.93 to 1.05)	0.98 (0.90 to 1.07)	1.09 (0.92 to 1.28)	1.03 (0.96 to 1.10)	0.46	0.01
Blueberries								
Nurses' Health Study†:	3711/720 706	1798/448 560	693/176 252	156/48 609				
Adjusted hazard ratio‡	1.00	0.90 (0.85 to 0.96)	0.89 (0.82 to 0.98)	0.82 (0.69 to 0.98)		0.77 (0.66 to 0.91)		
Nurses' Health Study II†:	2021/761 856	757/435 865	280/153 746	95/64 644				
Adjusted hazard ratio‡	1.00	0.83 (0.76 to 0.91)	0.90 (0.79 to 1.04)	0.69 (0.55 to 0.87)		0.67 (0.54 to 0.83)		
Health Professionals Follow-up Study†:	1687/383 033	779/207 202	165/45 628	56/18 540				
Adjusted hazard ratio‡	1.00	0.94 (0.85 to 1.03)	0.96 (0.80 to 1.15)	0.74 (0.55 to 1.00)		0.75 (0.58 to 0.98)		
Pooled results‡§	1.00	0.89 (0.85 to 0.93)	0.91 (0.84 to 0.97)	0.77 (0.67 to 0.87)		0.74 (0.66 to 0.83)	<0.001	0.57

*Estimated based on every three servings/week increment.

†Cases/person years of observation.

‡Adjusted for age (years), ethnicity (white, African American, Hispanic, or Asian), body mass index (<23, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9, 35.0-36.9, 37.0-38.9, 39.0-40.9, 41.0-42.9, 43.0-44.9, ≥45.0, or missing), smoking status (never, former, current (1–14, 15–24, or ≥25 cigarettes/day), or missing), multivitamin use (yes or no), physical activity (<3, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET (metabolic equivalent of task) hours/week, or missing), family history of diabetes (yes or no), menopausal status and post-menopausal hormone use (premenopause, post-menopause (never, former, or current hormone use), or missing, for women), oral contraceptive use (yes, no, or missing, for Nurses' Health Study II) total energy intake (kcal/day), fruit juice consumption (<1, 1, 2-4, or 5-6 servings/week, or ≥1 serving/day) and the modified alternate healthy eating index score (fifths). Individual fruit consumption was mutually adjusted.

§Study estimates from three cohorts were pooled using a fixed effects model.

Table 4| Pooled hazard ratios (95% confidence intervals) of type 2 diabetes* for consumption of fruit juice and fruits grouped by their glycemic index/glycemic load in Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study

Variables	Consumption levels					Linear trend†	P value	
	<1 serving/week	1 serving/week	2-4 servings/week	5-6 servings/week	≥1 serving/day		For trend	For heterogeneity
Glycemic load‡:								
High	1.00	0.89 (0.81 to 0.98)	0.89 (0.82 to 0.96)	0.81 (0.74 to 0.88)	0.83 (0.76 to 0.91)	0.93 (0.91 to 0.96)	<0.001	0.13
Moderate	1.00	0.96 (0.90 to 1.03)	0.96 (0.90 to 1.02)	0.97 (0.90 to 1.05)	1.03 (0.94 to 1.13)	1.01 (0.98 to 1.04)	0.61	0.85
Low	1.00	0.94 (0.89 to 1.01)	0.96 (0.90 to 1.01)	0.92 (0.86 to 1.00)	0.93 (0.86 to 1.02)	0.98 (0.94 to 1.01)	0.14	0.04
Glycemic index§:								
High	1.00	0.99 (0.92 to 1.07)	0.94 (0.88 to 1.01)	0.92 (0.85 to 0.99)	0.99 (0.91 to 1.07)	0.98 (0.95 to 1.01)	0.21	0.20
Moderate	1.00	0.96 (0.91 to 1.01)	0.89 (0.84 to 0.94)	0.87 (0.80 to 0.94)	0.94 (0.85 to 1.05)	0.94 (0.90 to 0.97)	<0.001	0.97
Low	1.00	0.90 (0.82 to 1.00)	0.87 (0.80 to 0.94)	0.85 (0.78 to 0.93)	0.87 (0.80 to 0.95)	0.97 (0.94 to 1.00)	0.06	0.58
Fruit juice¶	1.00	1.03 (0.96 to 1.11)	1.05 (0.99 to 1.12)	1.08 (1.01 to 1.16)	1.21 (1.13 to 1.29)	1.08 (1.05 to 1.11)	<0.001	0.38

*Adjusted for age (years), ethnicity (white, African American, Hispanic, or Asian), body mass index (<23, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9, 35.0-36.9, 37.0-38.9, 39.0-40.9, 41.0-42.9, 43.0-44.9, ≥45.0, or missing), smoking status (never, former, current (1–14, 15–24, or ≥25 cigarettes/day), or missing), multivitamin use (yes or no), physical activity (<3, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET (metabolic equivalent of task) hours/week, or missing), family history of diabetes (yes or no), menopausal status and post-menopausal hormone use (premenopause, post-menopause (never, former, or current hormone use), or missing, for women), oral contraceptive use (yes, no, or missing, for Nurses' Health Study II) total energy intake (kcal/day), and modified alternate healthy eating index score (fifths). Results were pooled using a fixed effects model.

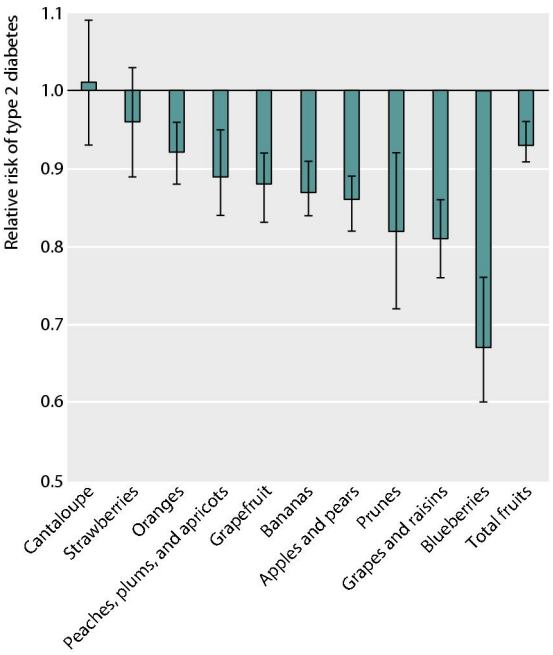
†Linear trend was modeled based on every three servings/week increment.

‡High glycemic load fruits included prunes, bananas, grapes, raisins, apples, and pears (glycemic load per serving 8.1-19.2), moderate glycemic load fruits included cantaloupe, oranges, and blueberries (5.7-8.0), and low glycemic load fruits included peaches, plums, apricots, grapefruit, and strawberries (1.3-5.6). Fruit juice consumption (<1, 1, 2-4, or 5-6 servings/week, or ≥1 serving/day) was further adjusted, and consumption of high, moderate, and low glycemic load fruits was mutually adjusted.

§High glycemic index fruits included cantaloupe, bananas, grapes, raisins (glycemic index 60-70), moderate glycemic index fruits included prunes, blueberries, and grapefruit (47-59), and low glycemic index fruits included apples, pears, oranges, peaches, plums, apricots, and strawberries (34-46). Fruit juice consumption (<1, 1, 2-4, or 5-6 servings/week, or ≥1 serving/day) was further adjusted, and consumption of high, moderate, and low glycemic index fruits was mutually adjusted.

¶Fruit juice included apple, orange, grapefruit, and other. Total whole fruit consumption (<4, or 4-6 servings/week, or 1, 2, or ≥3 servings/day) was further adjusted.

Figure



Pooled multivariate adjusted hazard ratios and 95% confidence intervals (error bars) of type 2 diabetes for substituting three servings/week of total or specific fruit for the same amount of fruit juice