Published in final edited form as:
J Nutr. 2006 December ; 136(12): 3039–3045.

Dietary Flavonoids and Flavonoid-Rich Foods Are Not Associated with Risk of Type 2 Diabetes in Postmenopausal Women

Jennifer A. Nettleton[2], **Lisa J. Harnack**[2], **Carolyn G. Scrafford**[3], **Pamela J. Mink**[3], **Leila M. Barraj**[3], and **David R. Jacobs Jr.**[2,4,*]

[2]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

[3]Exponent, Inc., Washington, DC

[4]Department of Nutrition, University of Oslo, Oslo, Norway

Abstract

Flavonoids have anti-inflammatory and antioxidative effects and thus may protect against diabetes. Therefore, we hypothesized that consumption of flavonoids and specific food and beverage sources of flavonoids would be associated with reduced risk of incident diabetes. At baseline (1986), diet (by food frequency questionnaire) and health information were collected from 35,816 postmenopausal women free of diabetes. Self-reported incident diabetes was ascertained 5 times during the study (1987, 1989, 1992, 1997, and 2004). Cox proportional hazards regression was used to calculate hazard ratios for incident diabetes according to categories of total flavonoids and anthocyanidins, flavones, flavanones, flavonols, flavan-3-ol monomers, isoflavones, and proanthocyanidins. Hazard ratios according to intake categories of flavonoid-rich foods and beverages were also calculated (apples, pears, berries, broccoli, bran, citrus, tea, and red wine). Flavonoid consumption was not associated with diabetes risk after multivariable adjustment. Although other flavonoid-rich foods and beverages were not associated, red wine was inversely associated with diabetes. Women who reported drinking red wine ≥1 time/wk had a 16% reduced risk of diabetes than those drinking wine <1 time/wk [HR (95% CI): 0.84 (0.71, 0.99)], with parallel findings for white wine, beer, and liquor. In conclusion, these data do not support a diabetes-protective effect of flavonoids. The suggestive evidence of a protective effect of regular red wine consumption is shared with an inverse association between alcohol drinks in general and diabetes risk and may reflect the effects of nonflavonoid constituents that are common to all alcohol drinks.

Introduction

Type 2 diabetes may be caused by chronic inflammation leading to impaired β-cell function (1–4) and insulin resistance (5,6). Flavonoids are biologically active, polyphenolic contituents of plant foods and are found in various fruits, vegetables, legumes, and in beverages such as tea and wine. Flavonoids are composed of several subclasses that have the ability to scavenge free radicals and chelate metals (7). Given the hypothesized relation between diabetes and inflammation (8–10) and the potential for flavonoids to protect the body against free radicals and other pro-oxidative compounds (11,12), it is biologically

*To whom correspondence should be addressed. jacobs@epi.umn.edu..

plausible that consumption of flavonoids or flavonoid-rich foods may reduce the risk of diabetes.

Several studies, although not all, have shown a reduced risk of cardiovascular disease in association with flavonoid intake (7); however, only 2 studies have evaluated the association between intake of various flavonoids and incident diabetes (13,14). Whereas the earlier of the 2 studies found suggestive, but nonsignificant relations between incident diabetes and the flavonols quercitin and myricetin (13), the more recent study found no association between diabetes and flavones, flavonols, or total flavonoid intake (14). Both studies reported significant inverse associations between the risk of diabetes and apple intake (a source of the flavonol, quercitin) in both populations. However, adjustment for quercitin in the study by Song et al. (14) did not attenuate the relative risk of diabetes attributed to apple consumption, suggesting that other compounds contained in apples or other factors associated with apple consumption may be important in mediating the observed relation between apple intake and diabetes risk.

The analyses presented here describe the association between flavonoid consumption and self-reported incident type 2 diabetes in the Iowa Women's Health Study. Our primary hypothesis was that consumption of each specific flavonoid subclass would be associated inversely with risk of self-reported incident diabetes. Our secondary hypothesis was that consumption of important food sources of flavonoids defined a priori would also be related inversely to incident diabetes.

Methods

Subjects

The Iowa Women's Health Study is a prospective cohort study initiated in January 1986. Women 55–69 y of age, with valid 1985 Iowa drivers' licenses (n = 99,826), were sent a questionnaire in which they were asked questions about their education, diet, physical activity level, smoking habits, reproductive history, medication use, history of disease, height, weight, and waist and hip circumferences (15). Of the 41,836 women who completed the baseline questionnaire (41.9% of those randomly selected), 35,816 were included in the current analysis (85.6% of the original cohort). Women were excluded from analyses if they were not postmenopausal at baseline (n = 569), reported energy intake <600, >5000 kcal/d,[5] or left >30 items on the food frequency questionnaire blank (n = 3,096), or reported a history of diabetes or medication for diabetes at baseline (n = 2752) (numbers not mutually exclusive). The study was approved by the University of Minnesota Institutional Review Board.

Incident type 2 diabetes

In 1987 (91% response rate), 1989 (90%), 1992 (83%), 1997 (79%), and 2004 (69%) women from the baseline cohort were mailed questionnaires designed to assess their current health status. Self-reported incident cases of diabetes were determined from participant responses to the following question: “(since previous contact) were you diagnosed for the first time by a doctor as having sugar diabetes?” Over the 5 follow-up surveys, 3395 women reported having diabetes (1987, n = 363; 1989, n 342; 1992, n = 474; 1997 n = 750; and 2004, n = 1466).

[5] 1 kcal = 4.184 kJ.

Diet assessment

The participants' usual diet was assessed at baseline with a 127-item semiquantitative FFQ (16,17). Women were asked the frequency with which they consumed various foods during the previous year (portion sizes given in parentheses). Frequency categories ranged from never or less than once per month to 6 or more times per day. The questionnaire included 15 questions addressing fruit intake, 29 addressing vegetable intake, and questions each for chocolate, bran added to foods, tea, red wine, white wine, beer, and liquor. Certain flavonoid-rich foods (e.g., berries, onions) were not queried specifically, although participants were given the opportunity to report foods consumed at least weekly that were not included in the questionnaire. Nutrient composition values for foods on the FFQ were obtained from the Harvard University Food Composition Database (18).

Flavonoid intake

Flavonoid levels of individual foods assessed in the FFQ were derived from 3 flavonoid databases developed by the USDA Nutrient Data Laboratory (NDL) (19–21), providing data for the following flavonoid classes: anthocyanidins, flavones, flavanones, flavonols, flavan-3-ols (monomers), isoflavones, plus proanthocyanidins (condensed tannins or flavan-3-ols polymers). The flavonoid content of each participant's diet was calculated by multiplying the reported consumption frequency by the flavonoid content of each food as assessed by responses to the FFQ. Questions containing multiple flavonoid-containing foods (e.g., fresh apples or pears; raisins or grapes) were assigned a value weighted according to the mean per capita consumption of each food in 1986 (22). In the absence of such data, the Continuing Survey of Food Intake by Individuals was used (23).

Statistical analysis

For those women not reporting diagnosis of diabetes, person-time-at-risk was calculated from baseline to the date of the last completed follow-up survey, date of death, or end of the study period. For those reporting a diagnosis of diabetes, person-time-at-risk was calculated from the sum of the known disease-free period and half of the period during which the diagnosis was made. Mortality status was updated annually through linkage with the State Health Registry of Iowa. The National Death Index was used for nonrespondents and those no longer living in Iowa.

Participant characteristics and nutrient intakes were calculated according to flavonoid intake quintiles (Proc GLM, SAS Institute, version 9.1). Cox proportional hazards regression was used to determine the hazard ratio for type 2 diabetes according to baseline flavonoid intake (SAS Proc TPHREG), using the lowest intake category as the referent. Due to skewed distribution and low intake in the majority of women, anthocyanidin intake was modeled as a 3-level variable according to predefined categories: 0 mg/d, >0–0.042 mg/d, and >0.042 mg/d; all others were analyzed in quintiles. Tests for trend across categories were performed by assigning each category its median flavonoid intake value and treating the variable as a continuous term. We also calculated hazard ratios according to intake of specific foods and food groups high in flavonoids and shown in previous studies to be related to diabetes (13,14) or shown in this cohort to be related to cardiovascular disease (24) (P. J. Mink, unpublished data): fresh apples and pears, berries (strawberries, blueberries, and other reported berries), broccoli, bran added to foods, citrus fruits, juices (grapefruit, grapefruit juice, oranges, and orange juice), tea, and red wine. Hazard ratios for incident diabetes were calculated according to consumption frequency categories, which varied depending on the spread of the data (<1 time/wk vs. ≥1/wk for each of berries, broccoli, bran, tea, and red wine; <1 time/wk, 1–2 times/wk, and >2 times/wk for apples; <5 times/wk, 5–8 times/wk, and >8 times/wk for citrus fruits and juices). We adjusted all risk analyses for the following confounders: age (y), energy (kcal/d), education level (less than, equal to, or greater than a

high school degree), physical activity (low, medium, high), BMI (kg/m^2), waist:hip ratio, smoking status (current, former, or never), pack years (0, 1–19, 20–39, 40+ y), regular use of multivitamin supplements (yes/no), current use of hormone therapy (yes/no). Tests for interaction with flavonoid intake for risk of diabetes were performed by adding a cross-product term to the multivariable model. The following modifying variables were considered: BMI, waist:hip ratio, smoking status, family history of diabetes, and physical activity.

Results

Age, education, physical activity level, supplement use, and hormone therapy were positively associated with flavonoid intake ($P \leq 0.002$, Table 1). In contrast, smoking prevalence, BMI, and waist:hip ratio were inversely associated with intake ($P < 0.001$). Neither family history of diabetes ($P = 0.26$) nor self-reported hypertension ($P = 0.20$) differed across flavonoid quintiles.

Total energy, carbohydrate (% of energy), fiber, vitamin A, vitamin C, vitamin E, β-carotene, iron, magnesium, and servings of whole grain and total fruit and vegetables increased across quintiles of total flavonoid intake, whereas the percentage of energy from total and all types of dietary fat decreased across quintiles of flavonoid intake ($P < 0.001$, Table 2). Percent of energy from protein was not associated with total flavonoid intake ($P = 0.71$).

Neither total flavonoid intake nor intake (Table 3) of the subclasses (data not shown) was inversely associated with incident diabetes after multivariable adjustment. All results were similar after excluding participants reporting a history of heart disease or heart attack at baseline (data not shown). Family history of diabetes, smoking status, BMI, waist:hip ratio, or physical activity level did not modify associations between flavonoid intake and risk of diabetes after full model adjustment ($P \geq 0.35$). As expected, given the predicted direction of attenuation, adjustment for potential nutrient and food confounders also did not importantly alter these results [fiber (25), whole grains (25), magnesium (25), iron (26), polyunsaturated fat (27), vegetable fat (27), vitamin E, β-carotene, vitamin C, vitamin A; data not shown].

We tested the proportional hazards regression assumption by stratifying the analysis by year of follow-up. We generally observed uniform hazard ratios independent of duration of follow-up (date of reported incident diabetes: 1987, 1989, 1992, 1997, and 2004), suggesting the proportional hazards assumption of uniform risk over time was met. The 2004 survey yielded almost half of the incident diabetes cases after 18 y of follow-up, but exclusion of those data did not reveal important differences from the results of the 2004 data analysis.

Intake of each apples, berries, broccoli, bran, citrus fruits or juices, and tea was not associated with incident diabetes after multivariable adjustment (data not shown). In contrast, multivariable analysis for red wine showed that women who reported drinking red wine at least once per week had a 16% reduced risk of developing diabetes compared with women who did not drink red wine or who drank infrequently (<1 time/wk) [HR (95% CI): 0.84 (0.71, 0.99); Table 4]. Modeling red wine consumption in categories of abstainers vs. drinkers produced similar results. To determine whether the association was independent of flavonoid content, we further adjusted the analysis for each of the flavonoid subclasses present in high levels in wine: total flavonoid, anthocyanidins, flavan-3-ol monomers, proanthocyanidins, and total proantocyanidins. None of these adjustments markedly changed the hazard ratio associated with wine drinking. Adjustment for potential confounding food and nutrient variables that may cluster with a healthy lifestyle also did not attenuate the

relation observed between red wine intake and risk of diabetes (fiber, whole grains, iron, magnesium, vitamin E, vitamin A, vitamin C, β-carotene, vegetable fat, and polyunsaturated fat). To evaluate whether these results were unique to red wine vs. true of all alcoholic beverages, we adjusted the above analyses for total alcohol intake [sum of red wine (10.8 g alcohol), white wine (10.8 g alcohol), beer (13.2 g alcohol), and liquor (15.1 g alcohol)], and found the association attenuated [HR (95% CI): 0.94 (0.83, 1.05)]. When the same analyses were repeated separately for each of the other alcoholic beverages, results mirrored those of red wine (Table 4). Similarly, analysis of total alcohol intake in relation to diabetes risk (categorized as 0 g/d, 1–14 g/d, ≥15 g/d) were analogous [HR (95% CI): 0.83 (0.77, 0.90) for 1–14 g/d; 0.66 (0.55, 0.79) for ≥15 g/d]. These data were robust to adjustment for specific alcoholic beverage types (data not shown).

Despite low numbers in the upper categories of intake, we also ran multivariable-adjusted analyses to assess the potential for increased risk of diabetes with higher levels of consumption. We found risk of diabetes across categories of intake (>1–7 drinks/wk, 8–14 drinks/wk, 15–21 drinks/wk, > 21 drinks/wk) to progressively decrease compared with women who drank <1 drink/wk (P trend < 0.001, data not shown). Furthermore, exclusion of women who consumed >21 drinks/wk (n = 400) did not materially impact results (Table 4).

Discussion

In this study of predominantly white, postmenopausal women, we did not observe evidence of an independent association of flavonoid consumption with incident diabetes. Overall, our results are in contrast to those of Knekt et al. (13), who reported that intakes of the flavonols quercetin and myricetin were inversely associated with risk of type 2 diabetes in Finnish men and women aged ≥40 y, but are consistent with the results of Song et al. (14), who found no association between risk of diabetes and total flavonoids nor individual flavonols and flavones in U.S. women aged ≥45 y. Both the Knekt and Song studies reported suggestive inverse associations between apple consumption and risk of type 2 diabetes, whereas we observed no such inverse associations with diabetes risk and specific foods high in flavonoids (including apples among others). Methodological differences among the 3 studies (13,14) may have contributed to the inconsistent findings.

In all 3 studies (13,14), most women reported their perimenopausal or early postmenopausal diets, which may have been poor reflections of lifetime dietary exposures of likely importance to disease risk (28–31). Accuracy of the dietary data may have varied among studies because of the use of FFQs in ours and Song's (14) studies vs. the more comprehensive dietary history method in the Finnish study (13). Specific sources of flavonoids (e.g., onions or berries) may have been missed or measured less accurately in studies [like ours and Song's (14)] that relied on data from FFQs, potentially biasing estimates toward the null. Furthermore, because all 3 studies were conducted in culturally and geographically unique regions, differences among populations in dietary patterns or flavonoid content of identical foods may have influenced results. Lastly, differences in the comprehensiveness of flavonoid databases used in each study complicate comparison.

Although we found no evidence of an inverse association between flavonoids and risk of type 2 diabetes, we did find an inverse association between diabetes and red wine consumption. The Iowa Women's Health Study has previously reported an inverse association between total alcohol intake and diabetes risk with fewer years of follow-up (26), and other studies conducted in women also support the diabetes-protective associations of wine or alcohol (32–36). Various mechanisms have been proposed to explain observations suggesting a protective effect of wine for diabetes (37–40). These reported

effects are thought to be related to the flavonoid (41), resveratrol (42), or ethanol (43) component of red wine. Our finding that the reduced risk of diabetes associated with red wine consumption was independent of flavonoid intake but not of total alcohol intake, suggests that nonflavonoid constituents are responsible. Alternatively, it may be that the food and beverage matrix is needed to confer the protective effects of certain food or beverage constituents (44,45). Similarly, our lack of significant association between risk of diabetes and intake of flavonoids or flavonoid-rich foods may be in part due to a need for synergy among foods. Many have reported inverse associations between diabetes risk and dietary patterns, which for the most part, include flavonoid-rich fruits and vegetables (46–49). The small effects of flavonoids may be undetectable with the type of reductive approach utilized in the current investigation.

We acknowledge some limitations to our analysis. First, these results may be biased by the overall low intake of flavonoids and flavonoid-rich foods, and it is possible that biological effect thresholds were not reached at the level of intake observed in our cohort. Second, these results may be influenced by an inadequate determination of incident diabetes. Although self-reported diabetes has been shown in studies of health professionals to be highly valid (50), the validity of self-report in population-based studies like ours is less sound (51). Third, whereas long-term follow-up can be advantageous in terms of accruing outcomes, the advantage can be lost with regard to dietary exposures measured only at baseline, potentially increasing exposure misclassification over time and attenuating risk estimates. Although we found no evidence to support this when we stratified analyses by follow-up year, it may be that cases were too few in early follow-ups to detect meaningful associations. Furthermore, we may have missed subjects with diabetes who died before periodic follow-ups; although this is less of an issue with a more slowly developing disease like diabetes, important comorbidities can result rapidly in death. Lastly, even though we observed significant inverse associations between risk of diabetes and consumption of alcoholic beverages (including red wine), these findings should be interpreted cautiously, given the number of comparisons made and the relatively crude categorization of consumption. Healthy diet and lifestyle characteristics often cluster with drinking and are difficult to fully account for in observational investigations, which may be particularly problematic in our study where drinking prevalence (any alcoholic beverage) was relatively low (41.4%). Moreover, given that only 4.1% of our cohort (and 0.7% of cases) consumed >2 alcoholic beverages per week, our analyses using multiple intake categories cannot fully evaluate the possibility of increased risk of diabetes at higher intake levels (32,33,52,53).

In conclusion, despite the substantial size of our cohort and the use of a comprehensive flavonoid database, we did not find flavonoid intake to be associated with a reduced risk of diabetes in postmenopausal women. These findings may be due to a true absence of a protective effect of these compounds with regard to type 2 diabetes, or alternatively, the result of improper timing and quality of dietary assessment, insufficient diabetes assessment, or failure to adequately account for the collective contribution of other dietary constituents. Lastly, our findings provide evidence that regular consumers of alcoholic beverages like red wine have a significantly reduced risk of developing diabetes compared with those who do not, or irregularly, consume alcohol. Diet represents a complex myriad of exposures that are likely to have both beneficial and harmful effects with regard to diabetes risk. Although we found no evidence of the protective effect of only one food constituent, flavonoids, in relation to diabetes risk, ours is one of few studies that have evaluated this association. The conflicting results among current studies suggests that further research in this area is warranted, perhaps with greater focus on potential synergies among foods, lifestyle, and other environmental or genetic factors.

Acknowledgments

The authors thank Dr. Aaron R. Folsom for providing the Iowa Women's Health Study data and Ching Ping Hong, MS, for statistical consultation and assistance in data preparation prior to analysis.

The Iowa Women's Health Study was supported by grant R01 CA39742 from the National Cancer Institute. Funding for this particular work was provided by training grant T32 HL07779 from the National Heart, Lung, and Blood Institute (J.A.N.). Additional grants were provided by the International Life Sciences Institute (ILSI) to the University of Minnesota (D.R.J. and L.J.H.) and to Exponent (P.J.M., C.G.S., and L.M.B.) to facilitate assignment of flavonoid values and data analysis. None of the sponsors were involved in writing this article.

Literature Cited

1. Bast A, Wolf G, Oberbaumer I, Walther R. Oxidative and nitrosative stress induces peroxiredoxins in pancreatic beta cells. Diabetologia 2002;45:867–76. [PubMed: 12107731]
2. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 2004;24:816–23. [PubMed: 14976002]
3. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? Diabetes 2003;52:1–8. [PubMed: 12502486]
4. Oberley LW. Free radicals and diabetes. Free Radic Biol Med 1988;5:113–24. [PubMed: 3075947]
5. Ceriello A. Oxidative stress and glycemic regulation. Metabolism 2000;49:27–9. [PubMed: 10693917]
6. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72. [PubMed: 12379575]
7. Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr 2005;81:317S–25S. [PubMed: 15640497]
8. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003;52:1799–805. [PubMed: 12829649]
9. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813–23. [PubMed: 14988310]
10. Ziegler D. Type 2 diabetes as an inflammatory cardiovascular disorder. Curr Mol Med 2005;5:309–22. [PubMed: 15892650]
11. Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 1996;20:933–56. [PubMed: 8743980]
12. Kandaswami C, Middleton E Jr. Free radical scavenging and antioxidant activity of plant flavonoids. Adv Exp Med Biol 1994;366:351–76. [PubMed: 7771265]
13. Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, Heliovaara M, Reunanen A, Hakulinen T, Aromaa A. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002;76:560–8. [PubMed: 12198000]
14. Song Y, Manson JE, Buring JE, Sesso HD, Liu S. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. J Am Coll Nutr 2005;24:376–84. [PubMed: 16192263]
15. Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. Am J Epidemiol 1998;148:1187–94. [PubMed: 9867265]
16. Munger RG, Folsom AR, Kushi LH, Kaye SA, Sellers TA. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am J Epidemiol 1992;136:192–200. [PubMed: 1415141]

17. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99. [PubMed: 3337073]
18. Willett, WC. Nutritional epidemiology. 2nd ed.. Oxford University Press; New York: 1998.
19. USDA database for the flavonoid content of selected foods. 2003 [cited November 22, 2004]. Available from: http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html
20. USDA database for the proanthocyanidin content of selected foods. 2004 [cited September 7, 2004]. Available from: http://www.nal.usda. gov/fnic/foodcomp/Data/PA/PA.html
21. USDA-Iowa State University database on the isoflavone content of foods. 1999 [cited September 7, 2004]. Available from: http://www.nal. usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html
22. USDA food consumption (per capita) data system: food availability. 2005 [cited May 10, 2005]. Available from: http://www.ers.usda.gov/data/foodconsumption/FoodAvailIndex.html
23. U.S. Department of Agriculture (USDA). CSFII data set and documentation: the 1994–96, 1998 continuing surveys of food intakes by individuals. Food Surveys Research Group. Beltsville Human Nutrition Research Center. Agricultural Research Service; Apr. 2000
24. Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. Am J Epidemiol 1999;149:943–9. [PubMed: 10342803]
25. Meyer KA, Kushi LH, Jacobs DR Jr. Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 2000;71:921–30. [PubMed: 10731498]
26. Lee DH, Folsom AR, Jacobs DR Jr. Dietary iron intake and Type 2 diabetes incidence in postmenopausal women: the Iowa Women's Health Study. Diabetologia 2004;47:185–94. [PubMed: 14712349]
27. Meyer KA, Kushi LH, Jacobs DR Jr. Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 2001;24:1528–35. [PubMed: 11522694]
28. Klein-Platat C, Drai J, Oujaa M, Schlienger JL, Simon C. Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. Am J Clin Nutr 2005;82:1178–84. [PubMed: 16332649]
29. Berenson GS, Srinivasan SR, Nicklas TA. Atherosclerosis: a nutritional disease of childhood. Am J Cardiol 1998;82:22T–9T. [PubMed: 9671003]
30. Pereira MA, Kartashov AI, Ebbeling CB, Van Horn L, Slattery ML, Jacobs DR Jr. Ludwig DS. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. Lancet 2005;365:36–42. [PubMed: 15639678]
31. Kaitosaari T, Ronnemaa T, Viikari J, Raitakari O, Arffman M, Marniemi J, Kallio K, Pahkala K, Jokinen E, Simell O. Low-saturated fat dietary counseling starting in infancy improves insulin sensitivity in 9-year-old healthy children: the special Turku coronary risk factor intervention project for children (STRIP) study. Diabetes Care 2006;29:781–5. [PubMed: 16567815]
32. Beulens JW, Stolk RP, van der Schouw YT, Grobbee DE, Hendriks HF, Bots ML. Alcohol consumption and risk of type 2 diabetes among older women. Diabetes Care 2005;28:2933–8. [PubMed: 16306557]
33. Wannamethee SG, Camargo CA Jr. Manson JE, Willett WC, Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med 2003;163:1329–36. [PubMed: 12796069]
34. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, Speizer FE. A prospective study of moderate alcohol drinking and risk of diabetes in women. Am J Epidemiol 1988;128:549–58. [PubMed: 3414660]
35. Monterrosa AE, Haffner SM, Stern MP, Hazuda HP. Sex difference in lifestyle factors predictive of diabetes in Mexican-Americans. Diabetes Care 1995;18:448–56. [PubMed: 7497852]
36. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790–7. [PubMed: 11556298]
37. Ceriello A, Bortolotti N, Motz E, Lizzio S, Catone B, Assaloni R, Tonutti L, Taboga C. Red wine protects diabetic patients from meal-induced oxidative stress and thrombosis activation: a pleasant

approach to the prevention of cardiovascular disease in diabetes. Eur J Clin Invest 2001;31:322–8. [PubMed: 11298779]

38. Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. Diabetes Care 1994;17:115–9. [PubMed: 7907975]
39. Leikert JF, Rathel TR, Wohlfart P, Cheynier V, Vollmar AM, Dirsch VM. Red wine polyphenols enhance endothelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. Circulation 2002;106:1614–7. [PubMed: 12270851]
40. Napoli R, Cozzolino D, Guardasole V, Angelini V, Zarra E, Matarazzo M, Cittadini A, Sacca L, Torella R. Red wine consumption improves insulin resistance but not endothelial function in type 2 diabetic patients. Metabolism 2005;54:306–13. [PubMed: 15736107]
41. Teissedre PL, Frankel EN, Waterhouse AL, Peleg H, German JB. Inhibition of in vitro human LDL oxidation by phenolic antioxidants from grapes and wines. J Sci Food Agric 1996;70:55–61.
42. Su HC, Hung LM, Chen JK. Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. Am J Physiol Endocrinol Metab. 2006
43. McMonagle J, Felig P. Effects of ethanol ingestion on glucose tolerance and insulin secretion in normal and diabetic subjects. Metabolism 1975;24:625–32. [PubMed: 1128232]
44. Anderson JW. Whole grains and coronary heart disease: the whole kernel of truth. Am J Clin Nutr 2004;80:1459–60. [PubMed: 15585755]
45. Jacobs DR Jr. Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy. Am J Clin Nutr 2003;78:508S–13S. [PubMed: 12936941]
46. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med 2004;164:2235–40. [PubMed: 15534160]
47. Gittelsohn J, Wolever TM, Harris SB, Harris-Giraldo R, Hanley AJ, Zinman B. Specific patterns of food consumption and preparation are associated with diabetes and obesity in a Native Canadian community. J Nutr 1998;128:541–7. [PubMed: 9482761]
48. Montonen J, Knekt P, Harkanen T, Jarvinen R, Heliovaara M, Aromaa A, Reunanen A. Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol 2005;161:219–27. [PubMed: 15671254]
49. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med 2002;136:201–9. [PubMed: 11827496]
50. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–8. [PubMed: 1681160]
51. Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB. Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. J Clin Epidemiol 1991;44:329–34. [PubMed: 1999691]
52. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. Diabetes Care 2003;26:2785–90. [PubMed: 14514580]
53. Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K. Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka health survey. Diabetes Care 1999;22:1432–7. [PubMed: 10480505]

TABLE 1

Select demographic and lifestyle characteristics according to quintiles of total flavonoid intake in 35,816 postmenopausal women in the Iowa Women's Health Study[1]

	Quintile of total flavonoid intake					
	1	2	3	4	5	*P* for trend[2]
n	7163	7163	7164	7163	7163	
Median intake, *mg/d*	90.4	167.0	238.5	342.5	680.4	
Intake range, *mg/d*	0.63–132.9	132.9–201.4	201.5–281.4	281.4–425.6	425.6–3524	
Incident diabetes, *cases/person-y*	686/88,908	674/92,793	732/93,646	653/94,255	650/94,033	
Age, *y*	61.2 ± 0.05	61.4 ± 0.05	61.6 ± 0.05	61.9 ± 0.05	61.9 ± 0.05	<0.001
>High school education, %	32.7	38.5	40.8	43.6	45.7	<0.001
BMI, kg/m^2	26.8 ± 0.06	26.8 ± 0.06	26.9 ± 0.06	26.8 ± 0.06	26.6 ± 0.06	0.001
Waist:hip ratio	0.84 ± 0.001	0.83 ± 0.001	0.83 ± 0.001	0.83 ± 0.001	0.83 ± 0.001	<0.001
Physical activity,[3] % *high level*	17.1	20.9	26.1	29.1	32.2	<0.001
Smoking, *% current*	22.5	16.7	13.2	10.8	10.6	<0.001
Multivitamin use, %	28.3	30.7	33.3	35.3	37.4	<0.001
Hormone therapy, *% ever users*	37.8	38.9	39.5	38.2	40.6	0.002
Family history of diabetes,[4] %	21.7	23.2	22.3	22.5	22.8	0.26
Self-reported hypertension, %	34.3	35.1	35.5	35.2	33.7	0.20

[1] Values for continuous variables are means ± SEM, and for categorical variables, percentages. Person-y represents person time at risk (y).

[2] Tests for a trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[3] Women who participated in vigorous activity ≥2 times/wk and those who reported moderate activity >4 times/wk were categorized as having a "high" level of physical activity.

[4] Family history of type 2 diabetes was assessed during the third follow-up in 1997 and thereafter. Person-y associated with this variable for total flavonoid intake quintiles 1–5 are as follows: Q1 = 21,218; Q2 = 22,819; Q3 = 22,089; Q4 = 22,419; Q5 = 23,221.

J Nutr. Author manuscript; available in PMC 2011 February 5.

TABLE 2

Energy-adjusted nutrient intakes according to quintiles of total flavonoid intake in 35,816 postmenopausal women in the Iowa Women's Health Study[1]

	Quintile of total flavonoid intake					
	1	**2**	**3**	**4**	**5**	***P* for trend[2]**
n	7163	7163	7164	7163	7163	
Energy,[3] *kcal/d*	1468 ± 7	1684 ± 7	1824 ± 7	1960 ± 7	2071 ± 7	<0.001
Carbohydrate, *% energy*	44.7 ± 0.09	47.6 ± 0.09	49.3 ± 0.09	50.7 ± 0.09	52.0 ± 0.09	<0.001
Protein, *% energy*	17.9 ± 0.04	18.0 ± 0.04	18.0 ± 0.04	18.1 ± 0.04	17.9 ± 0.04	0.71
Total fat, *% energy*	36.8 ± 0.07	34.9 ± 0.06	33.7 ± 0.06	32.6 ± 0.06	31.7 ± 0.07	<0.001
Saturated fat, *% energy*	13.1 ± 0.03	12.3 ± 0.03	11.8 ± 0.03	11.3 ± 0.03	10.9 ± 0.03	<0.001
Polyunsaturated fat, *% energy*	6.2 ± 0.02	6.1 ± 0.02	6.0 ± 0.02	5.9 ± 0.02	5.9 ± 0.02	<0.001
Monounsaturated fat, *% energy*	14.2 ± 0.03	13.3 ± 0.03	12.8 ± 0.03	12.3 ± 0.03	11.9 ± 0.03	<0.001
Vegetable fat, *% energy*	14.7 ± 0.06	14.3 ± 0.06	14.0 ± 0.06	13.7 ± 0.06	13.6 6 ±.06	<0.001
Vitamin A, *μmol/d*	120.2 ± 1.2	136.6 ± 1.2	149.7 ± 1.2	168.6 ± 1.2	180.6 ± 4.1	<0.001
Vitamin C, *μmol/d*	12,196 ± 204	14,990 ± 199	16,750 ± 199	19,130 ± 199	21,230 ± 204	<0.001
Vitamin E, *μmol/d*	757.4 ± 27.9	9,10.7 ± 27.9	1,004 ± 27.9	1,174 ± 27.9	1,323 ± 27.9	0.001
β-Carotene, *μmol/d*	66.6 ± 0.8	80.4 ± 0.8	90.4 ± 0.8	103.9 ± 0.8	113.9 ± 0.8	<0.001
Magnesium, *μmol/d*	111.0 ± 0.4	118.4 ± 0.4	123.1 ± 0.4	129.0 ± 0.4	138.1 ± 0.4	<0.001
Iron, *μmol/d*	3,150 ± 32	3,276 ± 50	3,508 ± 32	3,670 ± 32	3,705 ± 32	<0.001
Dietary fiber, *g/d*	15.6 ± 0.07	17.9 ± 0.07	19.7 ± 0.07	21.4 ± 0.07	23.6 ± 0.07	<0.001
Whole grain intake, *servings/d*	1.3 ± 0.01	1.5 ± 0.01	1.6 ± 0.01	1.7 ± 0.01	2.1 ± 0.01	<0.001
Fruits and vegetables, *servings/d*	4.4 ± 0.03	5.5 ± 0.03	6.3 ± 0.03	7.2 ± 0.03	7.9 ± 0.03	<0.001

[1] Values are means ± SEM. With the exception of energy intake, all nutrient/food values are adjusted for total energy intake (kcal/d).

[2] Tests for trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term.

[3] 1 kcal = 4.184 kJ.

TABLE 3

Hazard ratios for type 2 diabetes according to quintiles of total flavonoid intake in 35,816 postmenopausal women in the Iowa Women's Health Study[1]

	Quintile of flavonoid intake, *mg/d*					
Total flavonoids	**1**	**2**	**3**	**4**	**5**	***P* for trend**
Median intake	90.4	167.0	238.5	342.5	680.4	
Intake range	0.63–132.9	132.9–201.4	201.5–81.4	281.4–425.6	425.7–3524	
Cases of diabetes/total person-y	688/88,842	681/92,978	715/94,147	665/93,794	646/93,873	
Age + energy[2]	1.00	0.90 (0.81, 1.00)	0.90 (0.81, 1.01)	0.83 (0.74, 0.92)	0.79 (0.70, 0.88)	<0.001
+ Multivariable[3]	1.00	0.96 (0.86, 1.08)	1.01 (0.90, 1.12)	0.98 (0.87, 1.10)	0.97 (0.86, 1.10)	0.73

[1] Values represent hazard ratios using quintile 1 as the referent. Tests for a trend across intake categories were performed by assigning each quintile its median intake value and treating the variable as a linear term. Person-y represents person time at risk (y).

[2] Adjusted for age (y) and energy (kcal/d; 1 kcal = 4.184 kJ).

[3] Adjusted for above variables and education level (<high school, = high school, >high school), BMI, waist:hip ratio, activity level (low, medium, high), smoking status (current, past, nonsmoker), pack y (0, 1–19, 20–39, 40+), multivitamin use (current vs. never/past), and hormone therapy (ever vs. never).

TABLE 4

Hazard ratios for type 2 diabetes according to alcoholic beverage consumption in 35,816 postmenopausal women in the Iowa Women's Health Study stratified by beverage type[1]

	<1 time/wk	≥1 time/wk
Red wine consumption, *118-mL glass*		
Cases/total person-y	3235/430,159	160/33,475
Age + energy[2]	1.00	0.62 (0.53, 0.73)
Multivariable[3]	1.00	0.84 (0.71, 0.99)
Multivariable + total proanthocyanidins[4]	1.00	0.84 (0.71, 0.99)
Multivariable + total alcohol[5]	1.00	0.94 (0.80, 1.11)
A. Multivariable + foods/nutrients[6]	1.00	0.84 (0.71, 0.99)
B. Multivariable + foods/nutrients[6]	1.00	0.84(0.71, 0.99)
White wine consumption, *118-mL glass*		
Cases/total person-y	3195/419,047	200/44,587
Age + energy[2]	1.00	0.57 (0.50, 0.66)
Multivariable[3]	1.00	0.84 (0.72, 0.97)
Multivariable + total alcohol[5]	1.00	0.94(0.81, 1.10)
A. Multivariable + foods/nutrients[6]	1.00	0.84 (0.72, 0.97)
B. Multivariable + foods/nutrients[6]	1.00	0.84 (0.72, 0.98)
Beer consumption, *1 glass, can, or bottle*		
Cases/total person-y	3142/417,175	253/46,459
Age + energy[2]	1.00	0.72 (0.64, 0.82)
Multivariable[3]	1.00	0.78 (0.69, 0.90)
Multivariable + total alcohol[5]	1.00	0.92(0.79, 1.06)
A. Multivariable + foods/nutrients[6]	1.00	0.77 (0.67, 0.88)
B. Multivariable + foods/nutrients[6]	1.00	0.79(0.69, 0.91)
Liquor consumption, *1 shot or 1 drink*		
Cases/total person-y	3044/389,305	351/74,329
Age + energy[2]	1.00	0.60 (0.54, 0.67)
Multivariable[3]	1.00	0.72(0.64, 0.81)
Multivariable + total alcohol[5]	1.00	1.08(1.00, 1.17)
A. Multivariable + foods/nutrients[6]	1.00	0.71 (0.63, 0.80)
B. Multivariable + foods/nutrients[6]	1.00	0.71 (0.63, 0.79)

B. excludes women who reported consuming more than 21 drinks/wk (n = 400).

[1] Values are hazard ratios (95% CI) for diabetes compared with referent category (<1 time/wk) for red wine [118-mL glass (10.8 g alcohol)]; white wine [118-mL glass (10.8 g alcohol)]; beer [1 glass, can, or bottle (13.2 g alcohol)]; liquor [1 shot (~42 mL) or 1 drink (15.1 g alcohol)]. Person-y represents person time at risk (y).

[2] Adjusted for age (y) and energy (kcal/d; 1 kcal = 4.184 kJ).

[3] Adjusted for age, energy, and education level (<high school, = high school, >high school), BMI, waist:hip ratio, activity level (low, medium, high), smoking status current, past, nonsmoker), pack y (0, 1–19, 20–39, 40+), multivitamin use (current vs. never/past), and hormone therapy (ever vs. never).

[4] Adjusted for variables listed in note 3 and total proanthocyanidins (proanthocyanidins + flavan-3-ols, mg/d). Results were similar when adjusted for total flavonoids, anthocyanidins, flavan-3-ol (monomers), or proanthocyanidins (excluding monomers); therefore, for simplicity, only data adjusted for total proanthocyanidins (anthocyanidins + flavan-3-ols) are presented.

[5] Adjusted for variables listed in note 3 and total alcohol (g/d).

[6] Adjusted for variables listed in note 3 and total fiber, whole grain consumption, iron, magnesium, vitamin E, vitamin A, vitamin C, β-carotene, vegetable fat, and polyun-saturated fat all as continuous variables). A. Includes all women (n = 35,816);