# Polyphenol exposure and risk of type 2 diabetes: dose-response meta-analyses and systematic review of prospective cohort studies

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## ABSTRACT

**Background:** Type 2 diabetes is characterized by impaired glucose metabolism. Bioactive compounds in fruits and vegetables such as polyphenols have been suggested to influence glucose metabolism.

**Objective:** The aim of the current study was to systematically review the literature and conduct dose-response meta-analyses to summarize evidence of polyphenol exposure in association with incident type 2 diabetes.

**Design:** Prospective epidemiologic studies published before January 2018 were searched through 2 databases. Log-transformed multivariable adjusted hazard and odds ratios were combined in a random-effects model. Meta-analyses comparing extreme quantiles of polyphenol exposure were further explored with the use of linear and nonlinear dose-response meta-analyses.

**Results:** Eighteen studies investigated the association between polyphenols (51 different compounds in total) and type 2 diabetes. A comparison of extreme quantiles revealed inverse associations for intakes of polyphenols (HR: 0.56; 95% CI: 0.34, 0.93), flavonoids (HR: 0.88; 95% CI: 0.81, 0.96), flavonols (HR: 0.92; 95% CI: 0.85, 0.98), flavan-3-ols (HR: 0.89; 95% CI: 0.81, 0.99), catechins (HR: 0.86; 95% CI: 0.75, 0.97), anthocyanidins (HR: 0.86; 95% CI: 0.81, 0.91), isoflavones (HR: 0.92; 0.86, 0.97), daidzein (HR: 0.89; 95% CI: 0.83, 0.95), genistein (HR: 0.92; 95% CI: 0.86, 0.99), and stilbenes (HR: 0.44; 95% CI: 0.26, 0.72), and biomarkers of daidzein (HR: 0.81; 95% CI: 0.66, 0.99) and genistein (HR: 0.79; 95% CI: 0.62, 0.99). In the dose-response meta-analysis, nonlinear associations were observed for intakes of polyphenols, flavonoids, flavanones, anthocyanidins, anthocyanins, and biomarkers of genistein. A linear dose-response association was observed for phenolic acids.

**Conclusions:** This study adds to the evidence showing that diets rich in polyphenols, and particularly flavonoids, play a role in the prevention of type 2 diabetes. For most associations evidence for nonlinearity was found, suggesting a recommendable amount of intake associated with the lowest risk of type 2 diabetes. Therefore, future studies are warranted in which nonlinear associations are further explored. *Am J Clin Nutr* 2018;108:1–13.

**Keywords:** polyphenols, flavonoids, cohort, observational, epidemiology, dose-response meta-analysis, diabetes

## INTRODUCTION

The prevalence of type 2 diabetes is rising rapidly worldwide and has nearly doubled since 1980 (1). If left untreated, type 2 diabetes can lead to major micro- and macrovascular complications (1) and therefore poses a major challenge for health care systems. Prevention is partly related to modifiable lifestyle factors and might be achieved through the use of simple interventions such as regular physical activity, a healthy diet, refraining from smoking, maintaining a healthy weight, and monitoring of blood pressure and lipids (1). One important component of a healthy diet are plant-based foods, particularly those that are rich in phytochemicals such as polyphenols (2).

Polyphenols can be divided into four groups: flavonoids, phenolic acids, stilbenes, and lignans (2). Flavonoids comprise the largest group and are further subclassified into the following groups: flavonols (main food sources: onions, curly kale, leeks, broccoli, apples), flavanols including flavan-3-ols and proanthocyanidins (tea, grapes, cocoa), flavanones (citrus fruits), flavones (parsley, celery), anthocyanidins (berries, black grapes), isoflavones (soybeans), and dihydrochalcones (apples) (2). Phenolic acids are constituents of coffee, tea, and the outer part of fruits (2). Stilbenes are mainly present in wine and peanuts (2, 3), and lignans in linseed and cereals (2). In foods, polyphenols occur either as glycoside (conjugate), ester, or polymer, or in the free form (aglycone) (2). These chemical forms determine the molecular weight and in turn the bioavailability and bioactivity (2). Polyphenols have a range of effects on metabolism and play various roles in the occurrence of some diseases—properties that might to some extent be attributed to their chemical structure and form.

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Supplemental Tables 1 and 2 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviation used: FFQ, food-frequency questionnaire.

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Polyphenols influence glucose metabolism by inhibiting glucose absorption from the intestine, increasing insulin secretion from the pancreas, improving glucose uptake in muscle cells and adipocytes, and suppressing glucose release from the liver (4). These actions are critical in the occurrence, prevention, and management of type 2 diabetes. Previous epidemiologic evidence showed inverse associations between type 2 diabetes and intake of total flavonoids after pooling 6 cohort studies (5), and anthocyanidins after pooling 3 cohort studies (6). Our own meta-analysis of isoflavone biomarkers also found an inverse association (7). In epidemiology, dose-response is an important criteria for inferring causality, and as such dose-response relationships would further strengthen the evidence of the association between polyphenols and type 2 diabetes. Guo et al. (6) showed that increasing the daily intake of anthocyanins by 7.5 mg was associated with a 5% lower risk of type 2 diabetes. However, a comprehensive overview and dose-response meta-analysis of individual compounds and groups of polyphenols in relation to type 2 diabetes is still lacking. Therefore, the aim of the current study was to systematically review the literature for evidence of associations between polyphenol exposures and risk of type 2 diabetes in prospective cohort studies, and to conduct dose-response meta-analyses to fully characterize the functional relations of this association.

## METHODS

### Search

A systematic search was conducted in PubMed and Web of Science on 24 January 2018. The following search terms were used (both singular and plural): "biomarker," "plasma," "serum," "urine," "urinary," "excretion," "concentration," "level," "dietary", "intake," with "polyphenol," "flavonoid," "flavone," "flavanone," "flavonol," "proanthocyanidin," "anthocyanin," "isoflavone," "isoflavonoid," "apigenin," "luteolin," "hesperetin," "hesperedin," "naringenin," "kaempferol," "quercetin," "tamarixetin," "epicatechin," "coumestrol," "stilbene," "resveratrol," "lignans," "enterolactone," "enterodiol," "enterolignan," "pinoresinol," "lariciresinol," "secoisolariciresinol," "matairesinol," "phenolic acid," "phytoestrogen," with "impaired glucose tolerance," "impaired fasting glucose," "diabetes," "prediabetes," "type 2 diabetes mellitus," with "observational," "epidemiologic," "cohort," "longitudinal," "prospective," "nested case-control," not "animals" (MeSH terms were used in PubMed). MOOSE guidelines (8) were followed.

### Study selection

Two authors (J.R. and J.B.) independently screened the titles and abstracts of the publications. A third author acted as moderator to remove any discrepancies. Articles were retained for review if the following inclusion criteria were met: *1*) investigation of multivariable adjusted associations between any polyphenol exposure and risk of type 2 diabetes; *2*) use of a prospective study design; *3*) the study involved humans; and *4*) the study was published in a scientific journal (conference abstracts and comments were excluded). Articles were excluded if the risk of type 1 diabetes or gestational diabetes was investigated. Finally, reference lists of all included publications were screened. No constraints were put on the language of the articles.

### Data extraction and quality assessment

The following data were extracted from each article: first author, year of publication, country where the study was conducted, study design and name, characteristics of the participants, follow-up time, assessment method, polyphenolic compound, association measure, and confounding and matching variables. If an article considered more than one multivariable model, only data from the fully adjusted models were extracted. For the dose-response meta-analysis, the midpoint or median dose or concentration, number of cases and controls, and association measure for each exposure level were retrieved.

The quality of the included studies was assessed according to the Newcastle-Ottawa scale developed for nonrandomized studies (9). The scale appraised 3 aspects, including the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome. For exposure ascertainment, studies were awarded a star when they used biomarkers. The maximum number of "stars" awarded was 9.

### Statistical analysis

Meta-analyses comparing extreme quantiles of exposure were conducted when at least 2 studies with a common exposure were available. Heterogeneity was investigated because of differences in study design, population, and sex. For this purpose, the DerSimonian and Laird (10) random-effects model was used for pooling effect estimates, as it allows for both between- and within-study variation. Pooled estimates and 95% CIs were visualized with forest plots.

For all meta-analyses, risk estimates and 95% CIs were log transformed. Estimated standard errors were calculated from log 95% CIs by subtracting the lower bound of the CI from the upper bound and subsequently dividing by 2 times 1.96. Heterogeneity was analyzed based on the $I^2$ statistic (11). To identify sources of heterogeneity, subgroup analyses were performed according to geographic location and sex. Potential publication bias was investigated with the use of funnel plots and Egger's test (12).

Dose-response meta-analyses were conducted if data from $\geq$2 publications with $\geq$3 exposure levels were available for the following measures: *1*) the number of cases and controls; *2*) the intake or excretion (dose); and *3*) the risk estimate and 95% CI. Only studies reporting on the same chemical form of polyphenols (aglycones or glycosides) were pooled. When studies did not specify the number of cases or controls for each quantile, they were equally distributed across the quantiles [as in Schwingshackl et al. (13)]. If a range of intakes were given, the midpoint value was assigned to the exposure level. When ranges were open-ended, the midpoint value of the lowest category was set at 0.5 times the upper boundary of the lowest category, and the upper category was set at 1.5 times its lower boundary. For comparability across studies, intake of polyphenols expressed as mg per 1000 kcal was converted to a measure of intake per day. The intake was multiplied with the reported mean energy intake of the quantile. Nonlinearity of dose-response relationships was assessed according to the method of Greenland and Longnecker (14), and Crippa

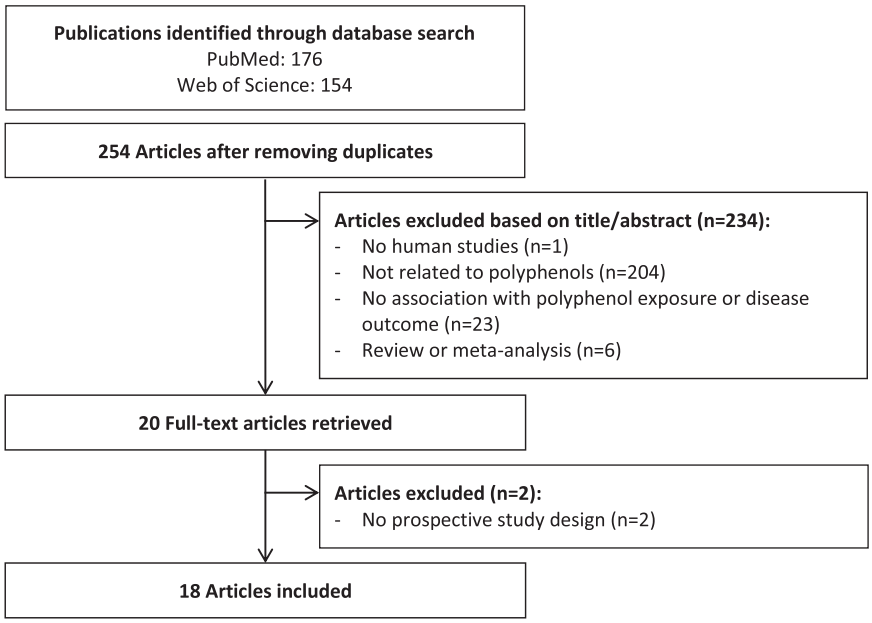


**FIGURE 1** Flowchart of study selection.

and Orsini (15). If the *P* value for nonlinearity was statistically significant, dose-response curves were modeled with the use of restricted cubic splines with 3 knots, one at each of the 10th, 50th, and 90th percentiles; otherwise, linear dose-response analyses were performed. The dose-response relationship was expressed based on the intake of polyphenol glycosides (16) or aglycones (17) in Europe. No dose was set for the studies that used biomarkers. *P* values $<0.05$ were considered statistically significant.

When studies reported results for individual compounds, the sum of these compounds was estimated to be the total intake of that flavonoid subclass. Subclasses (compounds) were flavonols [quercetin, kaempferol, myricetin (18–20)], flavones [luteolin, apigenin (20)], flavanones [naringenin, hesperetin (19)], and isoflavones [daidzein, genistein (21), daidzein, genistein, glycitein, equol (22)]. Effect estimates for the flavonoid subclasses were calculated by pooling the individual compounds per study. For the dose-response meta-analysis, the pooling was done for each exposure category. The "meta" (23) and "dosresmeta" (15) packages of R Software for Statistical Computing, version 3.3.2 (24) were used to conduct the meta-analyses, and "metabias" was used to assess publication bias.

## RESULTS

### Literature search and study characteristics

After duplicates were removed, 254 studies remained (**Figure 1**). Twenty full texts were read and in total 18 prospective studies (18–22, 25–37) were identified that investigated the association between any polyphenol exposure and risk of type 2 diabetes. Total polyphenols were investigated in 2 studies (30, 36). Forty-one different classes and compounds of flavonoids were investigated in 16 publications (18–22, 25–27, 30–37), 5 phenolic acids were investigated in 3 studies (30, 36, 37), stilbenes were investigated in 2 articles (30, 36), and 3 different classes and metabolites of lignans were investigated in 5 publications (28–30, 32, 36). In addition to the 4 common groups, 2 studies (30, 36) included the group "others" (**Supplemental Table 1**).

The characteristics and results of the included studies are presented in **Table 1**. To measure exposure, dietary assessment methods were used in 14 studies, including the use of a food-frequency questionnaire (FFQ) in 13 studies (18, 20–22, 25–27, 30–34, 36) and a diet history method in 1 study (19). Seven different food composition databases or publications were used. Two studies (30, 36) solely used Phenol-Explorer, 4 studies (25, 27, 31, 34) exclusively used the USDA database, 2 studies (32, 33) combined both databases, 3 studies (18–20) used data from Hertog et al. (38, 39) and 2 studies (18, 19) additionally used data on berries from Häkkinen et al. (40), 1 study (26) used the food composition tables of Singapore, 1 study (21) used values published by Kimira et al. (41), and 1 study (22) used a Korean database (42). Five studies used biomarkers of flavonoids, phenolic acids, and lignans; 4 studies used spot urine (28, 29, 35, 37) and 1 study used plasma (22).

Cases of type 2 diabetes were ascertained with the use of different criteria and methods. Twelve studies used self-administered questionnaires of which 6 studies (20, 28, 30, 34, 35, 37) ascertained cases of type 2 diabetes with the American Diabetes Association Criteria, 1 study used the National Diabetes Data Group criteria (31), 4 studies (21, 27, 29, 36) used self-reports, and 1 study (26) assessed type 2 diabetes during a telephone interview. Two studies (18, 19) used data from national disease registries, 2 studies (22, 25) measured fasting glucose and conducted a medical history interview, and the cohort studies (32, 33) included in the European Prospective Investigation into Cancer and Nutrition-InterAct (EPIC-InterAct) used a variety of methods to assess incidence of type 2 diabetes. Eleven studies used a prospective cohort (18–21, 25–27, 30, 31, 34, 36), 2 used a case-cohort (32, 33) and 5 a nested case-control study design (22, 28, 29, 35, 37). Fourteen different cohorts were included: 5 from Europe (18, 19, 30, 32, 33, 36), 6 from the USA (20, 25, 27, 28, 31, 34, 35, 37), and 3 from Asia (21, 22, 26, 29). The quality score

**TABLE 1**
Characteristics of prospective studies investigating polyphenol exposure and type 2 diabetes[1]

| Author (year), country, study design | Study | Cases/cohort, *n/n* (% women) | Mean age, y | Median follow-up time, y[2] | Outcome assessment | Exposure assessment | Exposure | Association (95% CI) for comparison of extreme quantiles | | Matching (M) and confounding (C) variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Ding (2016) (34), USA, ps | NHS | 4519/63,115 (100) | 63 | 24 | ADA Criteria | FFQ—USDA | ISO | HR Q5/Q1 | 0.97 (0.88, 1.07) | C: race, family history of diabetes, BMI, baseline disease status (hypertension, hypercholesterolemia), PA, AHEI score, energy intake, smoking, coffee consumption; in women: postmenopausal hormone use, menopausal status |
| | | | | | | | DAI | | 0.85 (0.76, 0.95) | |
| | | | | | | | GEN | | 0.80 (0.62, 1.02) | |
| | NHSII | 3920/79,061 (100) | 45 | 14 | | | ISO | HR Q5/Q1 | 0.92 (0.84, 1.02) | |
| | | | | | | | DAI | | 0.85 (0.76, 0.94) | |
| | | | | | | | GEN | | 0.81 (0.64, 1.04) | |
| | HPFS | 742/21,281 (0) | 66 | 8 (TP) | | | ISO | HR Q5/Q1 | 0.98 (0.89, 1.08) | |
| | | | | | | | DAI | | 0.87 (0.78, 0.97) | |
| | | | | | | | GEN | | 0.84 (0.65, 1.07) | |
| Ding (2015) (35), USA, ncc | NHS NHSII | 1111/2222 (100) | 53 | 4.6 (med) | ADA Criteria | Spot urine | ISO | OR Q3/Q1 | 0.80 (0.61, 1.05) | M: age at and month of urine collection, fasting status, first morning urine, race; NHS II additionally HRT, menopausal status, luteal day of menstrual cycle<br>C: hypertension and/or hypercholesterolemia at baseline, family history of diabetes, BMI, smoking, AHEI, energy intake, PA |
| | | | | | | | DAI | | 0.71 (0.55, 0.93) | |
| | | | | | | | GEN | | 0.74 (0.56, 0.97) | |
| | | | | | | | O-DMA | | 0.92 (0.70, 1.21) | |
| | | | | | | | DHD | | 0.80 (0.60, 1.06) | |
| | | | | | | | DHG | | 0.82 (0.62, 1.08) | |
| Grosso (2017) (36), POL, ps | HAPIEE | 456/5806 (53) | 57.4 | 4 | Self-reporting based on professional type 2 diabetes diagnosis or taking hypoglycemic medication in the last 2 wk | 148-item FFQ—PE | POLY | OR Q4/Q1 | 0.43 (0.30, 0.61) | C: BMI, physical activity, education, smoking, alcohol consumption, alcohol intake, menopausal status, dietary fiber and all main classes of flavonoids included in the table |
| | | | | | | | TF | | 0.44 (0.30, 0.63) | |
| | | | | | | | PA | | 0.60 (0.42, 0.84) | |
| | | | | | | | STIL | | 0.34 (0.24, 0.48) | |
| | | | | | | | LIG | | 1.18 (0.86, 0.61) | |
| | | | | | | | HBA | | 0.71 (0.51, 0.99) | |
| | | | | | | | HCA | | 0.61 (0.43, 0.86) | |
| | | | | | | | flavanols | | 0.54 (0.39, 0.76) | |
| | | | | | | | FLAVON | | 0.89 (0.63, 1.26) | |
| | | | | | | | FLAVAN | | 0.75 (0.54, 1.03) | |
| | | | | | | | FLAVO | | 0.47 (0.33, 0.68) | |
| | | | | | | | AC | | 0.68 (0.48, 0.98) | |
| | | | | | | | ISO | | 0.93 (0.65, 1.34) | |
| | | | | | | | DHC | | 1.12 (0.80, 1.57) | |
| | | | | | | | Others[3] | | 1.11 (0.81, 1.53) | |
| Jacques (2013) (25), USA, ps | FOS | 308/2915 (54.5) | 54 | mean 11.9 | Fasting plasma glucose ≥7.0 mmol/L or new use of hypoglycemic medication | sFFQ—USDA | TF[4] | log HR 2.5, fold increase in intake | 0.88 (0.76, 1.02) | C: sex, age, cardiovascular disease, current smoker, BMI, cumulative mean energy intake |
| | | | | | | | FLAVAN | | 0.97 (0.89, 1.07) | |
| | | | | | | | FLAVO | | 0.93 (0.77, 1.14) | |
| | | | | | | | FLAVON | | 0.74 (0.61, 0.90) | |
| | | | | | | | FLAVA-3 | | 0.89 (0.80, 1.00) | |
| | | | | | | | AC | | 0.98 (0.88, 1.10) | |
| | | | | | | | POLY-F[5] | | 0.90 (0.79, 1.02) | |

(*Continued*)

**TABLE 1**
(*Continued*)

| Author (year), country, study design | Study | Cases/cohort, *n/n* (% women) | Mean age, y | Median follow-up time, y[2] | Outcome assessment | Exposure assessment | Exposure | Association (95% CI) for comparison of extreme quantiles | | Matching (M) and confounding (C) variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Kataja-Tuomola (2011) (18), FIN, ps | ATBC | 660/25,505 (0) | 57.4 | 10.2 (med) | Drug reimbursement register | 276-item FFQ—Häkkinen et al. (40), Hertog et al. (38, 39) | KAE<br>MYR<br>QUE<br>LUT | RR Q5/Q1 | 1.03 (0.81, 1.33)<br>1.09 (0.86, 1.39)<br>1.06 (0.83, 1.35)<br>0.93 (0.72, 1.19) | C: age, supplementation, BMI, cigarettes smoked daily, smoking years, total cholesterol, HDL, blood pressure, leisure-time PA, daily intake of alcohol and energy |
| Knekt (2002) (19), FIN, ps | FMC | 526/9878 (51.5) | 49.2 | 28 | Register | Dietary history method—Häkkinen et al. (40), Hertog et al. (38, 39) | TF[6]<br>QUE<br>KAE<br>MYR<br>HES<br>NAR | RR Q4/Q1 | 0.98 (0.77, 1.24)<br>0.81 (0.64, 1.02)<br>0.92 (0.72, 1.18)<br>0.79 (0.62, 1.00)<br>0.96 (0.76, 1.22)<br>0.98 (0.78, 1.24) | C: age, sex |
| Ko (2015) (22), Korea, ncc | KoGES | 316/633 (100) | 40–69 | 7 (TP) | Serum glucose: fasting ≥7.0 mmol/L, after a 2-h OGTT ≥11.1 mmol/L or self-report of use of hypoglycemic medication | 103-item FFQ—Park et al. (41) Plasma | ISO (diet)<br>DAI<br>GEN<br>GLY<br>EQ | OR Q4/Q1 | 1.16 (0.72, 1.87)<br>0.91 (0.56, 1.48)<br>0.58 (0.35, 0.95)<br>1.28 (0.81, 2.02)<br>0.67 (0.43, 1.06) | M: age, sex, area of residence<br>C: age, area of residence, cigarette smoking, alcohol intake, BMI, SBP, FSG level at baseline |
| | | 377/758 (0) | | | | | ISO (diet)<br>DAI<br>GEN<br>GLY<br>EQ | | 1.11 (0.72, 1.73)<br>1.14 (0.72, 1.80)<br>1.15 (0.74, 1.81)<br>1.09 (0.70, 1.71)<br>1.30 (0.84, 2.01) | |
| Mueller (2012) (26), SGP, ps | SCHS | 2252/43,176 (57.6) | 55.2 | mean 5.7 | Self-report—validated | 165-item sFFQ Singapore FCD | ISO[7] | HR Q5/Q1 | 0.76 (0.58, 1.00) | C: age, sex, dialect, year of interview, soybean drink, educational level, smoking status, alcohol use, PA, baseline hypertensive, calcium, carbohydrate, polyunsaturated fatty acid, non-soy protein, total energy, BMI |
| Nanri (2010) (21), Japan, ps | JPHC | 634/25,872 (0) | 57.2 | 5 | Self-report—validated | 147-item FFQ—Kimira et al. (40) | DAI<br>GEN | OR Q5/Q1 | 1.01 (0.72, 1.40)<br>0.95 (0.77, 1.32) | C: age, study area, BMI, smoking habit, alcohol, family history of diabetes, leisure time PA, history of hypertension, coffee and green tea, magnesium, calcium, vegetable, fiber, fish, total energy intake |
| | | 480/33,919 (100) | | | | | DAI<br>GEN | | 0.92 (0.64, 1.32)<br>0.90 (0.63, 1.29) | |
| Nettleton (2006) (27), USA, ps | IWHS | 3395/35,816 (100) | 61.5 | 18 (TP) | Self-report | 127-item FFQ—USDA | TF | HR Q5/Q1 | 0.97 (0.86, 1.10) | C: age, energy, education level, BMI, waist:hip ratio, activity level, smoking status, pack year, multivitamin use, hormone therapy |

(*Continued*)

**TABLE 1**
(*Continued*)

| Author (year), country, study design | Study | Cases/cohort, *n/n* (% women) | Mean age, y | Median follow-up time, y[2] | Outcome assessment | Exposure assessment | Exposure | Association (95% CI) for comparison of extreme quantiles | | Matching (M) and confounding (C) variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Song (2005) (20), USA, ps | WHS | 1614/38,018 (100) | 53.8 | 8.8 | ADA Criteria | 131-item FFQ—Hertog et al. (37, 38) | TF[8] | RR Q5/Q1 | 0.92 (0.78, 1.09) | C: age, BMI, total energy intake, smoking, exercise, alcohol use, history of hypertension, history of high cholesterol, family history of diabetes, dietary intakes of fiber, total fat, magnesium, glycemic load |
| | | | | | | | QUE | | 0.97 (0.82, 1.15) | |
| | | | | | | | KAE | | 0.99 (0.84, 1.17) | |
| | | | | | | | MYR | | 0.98 (0.83, 1.16) | |
| | | | | | | | API | | 1.01 (0.85, 1.19) | |
| | | | | | | | LUT | | 1.04 (0.88, 1.23) | |
| Sun (2014) (28), USA, ncc | NHS | 452/904 (100) | 53–79 | 8–12 | ADA Criteria | Spot urine | ENL | OR Q4/Q1 | 0.78 (0.48, 1.25) | M: age at and month of urine collection, fasting status, first morning urine, race, menopausal status, HRT<br>C: BMI, smoking status, OC use, PA, alcohol, family history diabetes, history hypercholesterolemia or hypertension, AHEI score |
| | | | | | | | END | | 0.78 (0.48, 1.26) | |
| | NHSII | 655/1310 (100) | 32–52 | | | | ENL | | 0.47 (0.28, 0.80) | |
| | | | | | | | END | | 0.57 (0.34, 0.96) | |
| Sun (2015) (37), USA, ncc | NHS NHSII | 1111/2222 (100) | 25–55 | 4.6 (med) | ADA Criteria | Spot urine | QUE | OR Q3/Q1 | 0.83 (0.59, 1.17) | C: BMI, smoking, oral contraceptive use, HRT, PA, alcohol use, family history diabetes, history hypercholesterolemia or hypertension, AHEI |
| | | | | | | | ISOR | | 1.08 (0.76, 1.53) | |
| | | | | | | | NAR | | 0.87 (0.64, 1.20) | |
| | | | | | | | HES | | 0.68 (0.49, 0.96) | |
| | | | | | | | EC | | 0.92 (0.65, 1.31) | |
| | | | | | | | CAT | | 1.01 (0.73, 1.41) | |
| | | | | | | | CAF | | 0.73 (0.52, 1.02) | |
| | | | | | | | FER | | 1.12 (0.80, 1.58) | |
| Talaei (2016) (29), USA, ncc | SCHS | 564/1128 (58.3) | ≥20 | 4 | Self-report—validated | Spot urine | ISO | OR Q4/Q1 | 0.78 (0.54, 1.14) | M: age (3 y), date specimen collection (6 y), sex, dialect group; C: fasting duration, BMI, PA, education, smoking, alcohol, hypertension, energy intake, vegetable intake, fruits and related juices, SFAs, n–3 fatty acids |
| | | | | | | | DAI | | 0.75 (0.51, 1.10) | |
| | | | | | | | GEN | | 0.78 (0.53, 1.15) | |
| | | | | | | | GLY | | 0.85 (0.58, 1.24) | |
| | | | | | | | EQ | | 0.97 (0.67, 1.41) | |
| | | | | | | | LIG | | 0.93 (0.63, 1.38) | |
| Tressera-Rimbau (2016) (30), IT, ps | PREDIMED | 314/3430 (61.7) | 66.4 | 5.5 | ADA Criteria | 137-item sFFQ—PE | POLY | HR Q3/Q1 | 0.72 (0.52, 0.99) | C: age and stratified by sex, recruitment center, intervention group, smoking, BMI, PA, dyslipidemia, hypertension, education level, total energy intake, alcohol intake, adherence to the Mediterranean diet, fasting glucose concentrations at baseline |
| | | | | | | | TF | | 0.67 (0.48, 0.93) | |
| | | | | | | | PA | | 0.85 (0.62, 1.17) | |
| | | | | | | | STIL | | 0.78 (0.73, 0.88) | |
| | | | | | | | LIG | | 0.82 (0.58, 1.15) | |
| | | | | | | | Others[3] | | 0.97 (0.70, 1.36) | |
| | | | | | | | AC | | 0.88 (0.62, 1.24) | |
| | | | | | | | CAT | | 0.84 (0.60, 1.17) | |
| | | | | | | | DHC | | 1.15 (0.83, 1.61) | |
| | | | | | | | DHF | | 0.59 (0.40, 0.88) | |
| | | | | | | | PA | | 0.75 (0.54, 1.04) | |
| | | | | | | | FLAVAN | | 0.69 (0.49, 0.97) | |
| | | | | | | | FLAVO | | 0.98 (0.71, 1.35) | |
| | | | | | | | FLAVON | | 0.97 (0.68, 1.39) | |

(*Continued*)

**TABLE 1**
(*Continued*)

| Author (year), country, study design | Study | Cases/cohort, *n/n* (% women) | Mean age, y | Median follow-up time, y[2] | Outcome assessment | Exposure assessment | Exposure | Association (95% CI) for comparison of extreme quantiles | | Matching (M) and confounding (C) variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Wedick (2012) (31), USA, ps | NHS | 6878/70,539 (100) | 50.4 | 24 | National Diabetes Data Group criteria | 118- to 131-item FFQ—USDA | TF[9] | HR Q5/Q1 | 0.85 (0.79, 0.92) | C: age, BMI, smoking status, alcohol intake, multivitamin use, PA, family history of diabetes, postmenopausal status, hormone use (NHS and NHS II), oral contraceptive use (NHS II), ethnicity, total energy, polyunsaturated:saturated fat ratio, intakes of red meat, fish, whole grains, coffee, high-calorie sodas (including punch), trans fats |
| | | | | | | | FLAVON | | 0.84 (0.78, 0.91) | |
| | | | | | | | FLAVO | | 1.07 (0.99, 1.16) | |
| | | | | | | | FLAVAN | | 1.05 (0.97, 1.13) | |
| | | | | | | | FLAVA-3 | | 0.87 (0.81, 0.94) | |
| | | | | | | | AC | | 0.83 (0.77, 0.90) | |
| | NHSII | 3084/89,201 (100) | 36 | 16 | | | TF[9] | HR Q5/Q1 | 0.99 (0.89, 1.11) | |
| | | | | | | | FLAVON | | 0.99 (0.89, 1.10) | |
| | | | | | | | FLAVO | | 1.02 (0.91, 1.16) | |
| | | | | | | | FLAVAN | | 1.08 (0.97, 1.22) | |
| | | | | | | | FLAVA-3 | | 1.01 (0.91, 1.12) | |
| | | | | | | | AC | | 0.83 (0.73, 0.94) | |
| | HPFS | 2649/40,420 (0) | 52.9 | 20 (TP) | | | TF[9] | HR Q5/Q1 | 0.92 (0.81, 1.04) | |
| | | | | | | | FLAVON | | 0.88 (0.78, 1.00) | |
| | | | | | | | FLAVO | | 1.07 (0.94, 1.22) | |
| | | | | | | | FLAVAN | | 1.09 (0.96, 1.24) | |
| | | | | | | | FLAVA-3 | | 0.88 (0.78, 0.99) | |
| | | | | | | | AC | | 0.93 (0.81, 1.05) | |
| Zamora-Ros (2013) (32), DK/FR/GER/IT/NL/SP/SE/UK, caco | EPIC-InterAct | 11,559/26,088 (incl. 729 cases in subcohort) (62.2) | 52.4 | 11.7 | Self-report, record linkage, secondary care registers, medication register, hospital admissions, mortality data | 98-to 266-item country-specific FFQ or diet history—USDA, PE | TF | HR Q5/Q1 | 0.90 (0.77, 1.04) | C: age, sex, and total energy intake, educational level, PA, smoking status, BMI, intakes of alcohol, red meat, processed meat, sugar-sweetened soft drinks, coffee, fiber, vitamin C, magnesium |
| | | | | | | | Flavanols | | 0.82 (0.68, 0.99) | |
| | | | | | | | FLAVA-3 | | 0.73 (0.57, 0.93) | |
| | | | | | | | PA | | 0.91 (0.79, 1.05) | |
| | | | | | | | Theaflavin | HR Q4/Q1 | 0.83 (0.69, 1.01) | |
| | | | | | | | AC | HR Q5/Q1 | 0.94 (0.82, 1.08) | |
| | | | | | | | FLAVON | | 0.81 (0.69, 0.95) | |
| | | | | | | | FLAVAN | | 1.03 (0.79, 1.34) | |
| | | | | | | | FLAVO | | 0.89 (0.70, 1.14) | |
| | | | | | | | ISO | | 0.98 (0.77, 1.25) | |
| | | | | | | | LIG | | 0.88 (0.72, 1.07) | |

(*Continued*)

**TABLE 1**
(*Continued*)

| Author (year), country, study design | Study | Cases/cohort, *n/n* (% women) | Mean age, y | Median follow-up time, y[2] | Outcome assessment | Exposure assessment | Exposure | Association (95% CI) for comparison of extreme quantiles | | Matching (M) and confounding (C) variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Zamora-Ros (2014) (33), DK/FR/GER/IT/NL/SP/SE/UK, caco | EPIC-InterAct | 11,559/26,088 (incl. 729 cases in subcohort) (62.2) | 52.4 | 11.7 | Self-report, record linkage, secondary care registers, medication register, hospital admissions, mortality data | 98- to 266-item country-specific FFQ or diet history—USDA, PE | EGC-3G | HR Q5/Q1 | 0.64 (0.44, 0.92) | C: stratified by center and sex, total energy intake, educational level, smoking status, PA levels, BMI, intake of alcohol, red meat, processed meat, sugar-sweetened soft drink, coffee, fiber, vitamin C, magnesium |
| | | | | | | | EC-3G | | 0.80 (0.59, 1.08) | |
| | | | | | | | EGC | | 0.79 (0.61, 1.03) | |
| | | | | | | | EC | | 0.84 (0.69, 1.04) | |
| | | | | | | | CAT | | 0.86 (0.75, 0.99) | |
| | | | | | | | CAT-3G | HR Q4/Q1 | 0.80 (0.69, 0.93) | |
| | | | | | | | GC | HR Q5/Q1 | 0.84 (0.68, 1.05) | |
| | | | | | | | dimers | | 0.81 (0.71, 0.92) | |
| | | | | | | | trimers | | 0.91 (0.80, 1.04) | |
| | | | | | | | 4–6-mers | | 0.92 (0.80, 1.05) | |
| | | | | | | | 7–10-mers | | 0.93 (0.81, 1.07) | |
| | | | | | | | polymer | | 0.92 (0.80, 1.06) | |
| | | | | | | | QUE | | 0.91 (0.74, 1.11) | |
| | | | | | | | KAE | | 0.91 (0.78, 1.05) | |
| | | | | | | | MYR | | 0.77 (0.64, 0.93) | |
| | | | | | | | ISOR | | 0.97 (0.75, 1.25) | |

[1]AC, anthocyanins; ADA, American Diabetes Association; AHEI, alternative healthy eating index; API, apigenin; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention study; CAF, caffeic acid; caco, case-cohort; CAT, (+)-catechin; CAT-3G, (+)-catechin 3-gallate; DAI, daidzein; DHC, dihydrochalcones; DHD, dihydrodaidzein; DHF, dihydroflavonols; DHG, dihydrogenistein; DK, Denmark; EC, (–)-epicatechin; EC-3G, (–)-epicatechin 3-gallate; EGC, (–)-epigallocatechin; EGC-3G, (–)-epigallocatechin 3-gallate; END, enterodiol; ENL, enterolactone; EPIC-InterAct, European Prospective Investigation into Cancer and Nutrition; EQ, Equol; FCD, food composition database; FER, ferulic acid; FFQ, food-frequency questionnaire; FIN, Finland; FMC, Finnish Mobile Clinic Health Examination Survey; FLAVA-3, flavan-3-ols; FLAVAN, flavanones; FLAVO, flavones; FLAVON, flavonols; FOS, Framingham Offspring Study; FR, France; GC, (+)-gallocatechin; GEN, genistein; GER, Germany; GLY, glycitein; HAPIEE, Health, Alcohol, and Psychosocial factors in Eastern Europe study; HBA, hydroxybenzoic acid; HCA, hydroxycinnamic acid; HES, hesperetin; HPFS, Health Professionals Follow-up Study; HRT, hormone replacement therapy; incl., including; ISO, isoflavones; ISOR, isorhamnetin; IT, Italy; IWHS, Iowa Women's Health Study; JPHC, Japan Public Health Center-Based Prospective; KAE, kaempferol; KNHANES, Korean National Health and Nutrition Examination Survey; KoGES, Korean Genome and Epidemiology Study; LIG, lignans; med, median; MYR, myricetin; NAR, naringenin; ncc, nested case-control study; NHS (II), Nurses' Health Study (II); NL, the Netherlands; OC, oral contraceptives; OGTT, oral glucose tolerance test; PA, physical activity; PE, Phnol-Explorer; POLY, polyphenols; POLY-F, polymeric flavonoids; PREDIMED, PREvención con Dieta MEDiterránea; ps, prospective study; Q, quantile; QUE, quercetin; SCHS, Singapore Chinese Health Study; SE, Sweden; sFFQ, semiquantitative food frequency questionnaire; SGP, Singapore; SP, Spain; STIL, stilbenes; TF, total flavonoids; TP, total period; UK, United Kingdom; WHS, Women's Health Study.

[2]Median follow-up time: TP was calculated, when follow-up time was not reported, by subtracting the year of last follow-up from year of specimen collection.

[3]Others include: alkylmethoxyphenols, alkylphenols, curcuminoids, furanocoumarins, hydroxybenzaldehydes, hydroxybenzoketones, hydroxycinnamaldehydes, hydroxycoumarins, hydroxyphenylpropenes, methoxyphenols, naphthoquinones, phenolic terpenes, and tyrosols.

[4]Excluding isoflavones.

[5]Proanthocyanidins, theaflavins, thearubigins.

[6]Sum of flavonols, flavones, flavanones.

[7]Sum of daidzein, genistein, glycitein.

[8]Sum of flavonols and flavones.

[9]Sum of flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins.

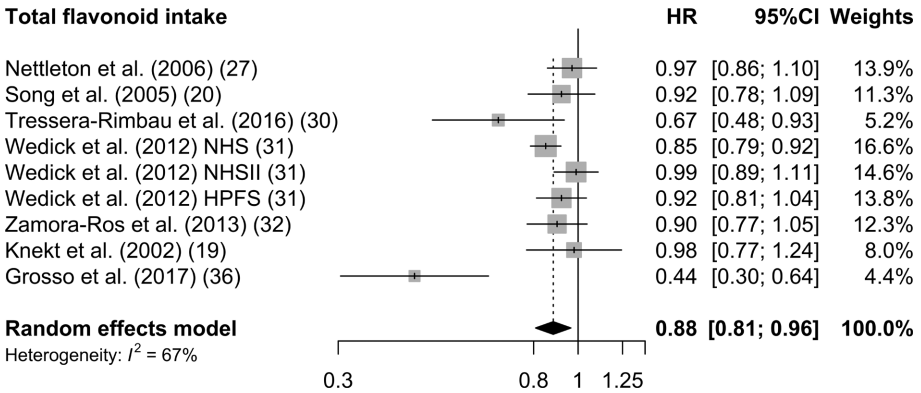


**FIGURE 2** Forest plot comparing extreme quantiles of the association between flavonoid intake and risk of type 2 diabetes.

ranged from 5 to 8 stars (**Supplemental Table 2**); thus the quality of the included studies was fair to good. All included studies adjusted the association for a wide range of confounding factors and all but 2 dietary assessment instruments used were validated; however, only in 5 studies was this specifically for polyphenol exposure (18, 19, 21, 26, 30).

### Meta-analyses

In total, 28 meta-analyses were conducted that compared the highest and lowest quantiles for 24 different polyphenol exposures. A comparison of extreme quantiles revealed a reduced risk of type 2 diabetes for intakes of total polyphenols (HR: 0.56; 95% CI: 0.34, 0.93), total flavonoids (HR: 0.88; 95% CI: 0.81, 0.96) (**Figure 2**), flavonols (HR: 0.92; 95% CI: 0.85, 0.98), flavan-3-ols (HR: 0.89; 95% CI: 0.81, 0.99), catechins (HR: 0.86; 95% CI: 0.75, 0.97), anthocyanidins (HR: 0.86; 95% CI: 0.81, 0.91), isoflavones (HR: 0.92; 95% CI: 0.86, 0.97), daidzein (HR: 0.89; 95% CI: 0.83, 0.95), genistein (HR: 0.92; 95% CI: 0.86, 0.99), and stilbenes (HR: 0.44; 95% CI: 0.26, 0.72) and biomarkers of daidzein (HR; 0.81;95% CI: 0.66, 0.99) and genistein (HR: 0.79; 95% CI: 0.62, 0.99) (**Table 2, Supplemental Figure 1**). For single compounds, statistically significant inverse associations were observed for dietary intake of catechin, daidzein, and genistein, and biomarkers of daidzein and genistein.

There was an indication of publication bias in the meta-analysis of flavones ($P = 0.05$) and flavanones ($P = 0.04$). Heterogeneity ranged from $I^2 = 0\%$ to 78.1%, and persisted after stratification by geographic location in European studies and decreased in studies conducted in the USA (data not shown). Both in US and European studies an inverse association was observed for total flavonoids (HR: 0.92; 95% CI: 0.86, 0.98; $I^2$: 37.4%; $n = 5$ and HR: 0.74; 95% CI: 0.55, 0.99; $I^2$: 81.1%; $n = 4$, respectively). A positive association was observed in US studies for flavones (HR: 1.05; 95% CI: 1.00, 1.11; $I^2$: 0%; $n = 4$) and flavanones (HR: 1.07; 95% CI: 1.01, 1.13; $I^2$: 0%; $n = 3$), but not in European studies. Stratification by sex showed only an inverse association for daidzein intake in women (HR: 0.89; 95% CI: 0.82, 0.95; $I^2$: 0%; $n = 2$, data not shown).

In addition to the comparison of extreme quantiles described above, dose-response meta-analyses were conducted. Nonlinear dose-response relationships were observed for intakes of total polyphenols ($P_{\text{nonlinearity}} = 0.017$, $n = 2$), total flavonoids (glycosides) ($P_{\text{nonlinearity}} = 0.0003$, $n = 2$), myricetin ($P_{\text{nonlinearity}} = 0.0003$, $n = 4$), flavanone ($P_{\text{nonlinearity}} = 0.006$, $n = 4$, aglycones and $P_{\text{nonlinearity}} = 0.017$, $n = 2$, glycosides), anthocyanidin ($P_{\text{nonlinearity}} = 0.0001$, $n = 4$, aglycone), anthocyanin ($P_{\text{nonlinearity}} = 0.029$, $n = 2$, glycosides), and biomarkers of genistein ($P_{\text{nonlinearity}} = 0.002$, $n = 2$) (**Figure 3**). These nonlinear dose-response relationships suggest a recommendable level of intake associated with a lower risk of type 2 diabetes. From Figure 3 it can be interpreted that an optimal intake of 1000 mg total polyphenols per day corresponds to the lowest risk of type 2 diabetes.

In the absence of nonlinearity, linear dose-response meta-analyses expressed as a daily dose were conducted. An increase in daily phenolic acid intake by 600 mg was associated with a 34% reduced risk of type 2 diabetes (HR: 0.76; 95% CI: 0.64, 0.89) (Table 2). Intakes of all other compounds and groups were not inversely associated with type 2 diabetes risk in the dose-response analysis. Heterogeneity ranged from 0% to 94.9%.

Separate dose-response meta-analyses were conducted for the subclass of isoflavones because intake in Asian countries is ~10 times higher than in Western countries (32). Only an inverse association was observed for a daily increase in daidzein intake of 0.2 mg in studies conducted in the USA (data not shown).

### Systematic literature review

Thirty-two polyphenol compounds were studied only once in 7 studies (25, 30, 32, 33, 35–37). Six studies (25, 30, 32, 33, 35, 37) investigated flavonoids. In line with the inverse association for flavonols in the meta-analysis, there is a 26% reduced risk for a 2.5-fold increase in flavonol intake (25). In contrast to the null association observed in the meta-analysis for dihydrochalcones, the Prevention with Mediterranean Diet (PREDIMED) shows an inverse association for dihydroflavonols (30). The inverse association for flavanols is consistent with the reduced risk of type 2 diabetes in EPIC-InterAct for higher intakes of epigallocatechin 3-gallate, catechin 3-gallate, and dimers, but not for higher intakes of theaflavin, epicatechin 3-gallate, epigallocatechin, epicatechin, gallocatechin, trimers, 4–6-mers, 7–10-mers, polymers, and isorhamnetin (32, 33). In our meta-analysis of dietary flavanones we did not observe an association, whereas urinary hesperetin was inversely associated with type 2 diabetes (37). The inverse associations observed for phenolic

**TABLE 2**
Meta-analyses comparing the highest and lowest quantile of exposure and dose-response meta-analyses for the association of polyphenol exposure with risk of type 2 diabetes[1]

| | High vs. low | | | | Dose-response | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Exposure[2] | No. of studies[3] | Cases/total sample size | Summary HR[4] | $I^2$, % | No. of studies[3] | Cases/total sample size | Dose, mg | Summary HR | $I^2$, % |
| Total polyphenols | 2 | 770/9236 | 0.56 (0.34, 0.93) | 77.5 | NA | | | | |
| Total flavonoids | 7 (9)[5] | 29,746/319,016 | 0.88 (0.81, 0.96) | 67.3 | 5 (7)[5,6] | 28,976/309,780 | 372 | 0.96 (0.92, 1.00) | 33.2 |
| | | | | | NA | | | | |
| Flavonols | 7 (9)[5] | 27,011/308,705 | 0.92 (0.85, 0.98) | 58 | 5 (7)[5,6] | 26,241/299,469 | 28 | 0.91 (0.83, 1.00) | 80.4 |
| | | | | | 2[7] | 770/9236 | 35 | 0.96 (0.86, 1.06) | 0 |
| Quercetin | 4 | 13,630/99,489 | 0.96 (0.85, 1.08) | 22.4 | 4 | 13,630/99,489 | 10 | 1.00 (0.94, 1.05) | 43.7 |
| Kaempferol | 4 | 13,630/99,489 | 0.95 (0.87, 1.05) | 0 | 4 | 13,630/99,489 | 4 | 0.98 (0.94, 1.01) | 0 |
| Myricetin | 4 | 13,630/99,489 | 0.90 (0.76, 1.05) | 58.6 | NA | | | | |
| Flavones | 5 (7)[5] | 25,825/273,322 | 0.97 (0.87, 1.08) | 71.1 | 3 (5)[5,6] | 25,055/264,086 | 4.6 | 1.05 (0.95, 1.16) | 48.3 |
| | | | | | 2[7] | 770/9236 | 5 | 0.90 (0.76, 1.07) | 94.0 |
| Luteolin | 2 | 2274/63,523 | 1.00 (0.87, 1.16) | 0 | 2 | 2274/63,523 | 0.1 | 1.02 (0.94, 1.10) | 0 |
| Flavanones | 5 (7)[5] | 24,737/245,182 | 1.01 (0.93, 1.10) | 46.1 | NA | | | | |
| Flavanols | 2 | 11,286/31,894 | 0.68 (0.45, 1.02) | 78.1 | | | | | |
| Flavan-3-ols | 2 (4)[5] | 23,441/226,068 | 0.89 (0.81, 0.99) | 64.6 | 2 (4)[5] | 23,441/226,068 | 79 | 0.97 (0.93, 1.00) | 61.4 |
| Catechin | 2 | 11,144/29,518 | 0.86 (0.75, 0.97) | 0 | | | | | |
| Proanthocyanidins | 2 | 11,144/29,518 | 0.88 (0.75, 1.02) | 11.2 | | | | | |
| Anthocyanidins | 4 (6)[5] | 24,211/235,304 | 0.86 (0.81, 0.91) | 13.5 | NA | | | | |
| Isoflavones | 6 (8)[8] | 24,469/299,667 | 0.92 (0.86, 0.97) | 0 | 5 (7)[6,8] | 24,013/293,861 | 0.63 | 1.00 (1.00, 1.00) | 21 |
| Isoflavone biomarkers | 3 | 2368/4741 | 0.90 (0.73, 1.10) | 41.9 | | | | | |
| Daidzein | 2 (4)[8] | 10,295/223,248 | 0.89 (0.83, 0.95) | 0 | 2 (4)[6,8] | 10,295/223,248 | 0.2 | 1.00 (1.00, 1.00) | 66.1 |
| Daidzein biomarkers | 3 | 2368/4741 | 0.81 (0.66, 0.99) | 13.5 | | | | | |
| Genistein | 2 (4)[8] | 10,295/223,248 | 0.92 (0.86, 0.99) | 0 | 2 (4)[6,8] | 10,295/223,248 | 0.25 | 1.00 (1.00, 1.00) | 18.5 |
| Genistein biomarkers | 3 | 2368/4741 | 0.79 (0.62, 0.99) | 31.6 | | | | | |
| Glycitein biomarkers | 2 | 1257/2519 | 1.03 (0.81, 1.31) | 0 | | | | | |
| Equol biomarkers | 2 | 1257/2519 | 0.95 (0.67, 1.35) | 53.5 | | | | | |
| Dihydrochalcones | 2 | 770/9236 | 1.14 (0.90, 1.44) | 0 | 2[7] | 770/9236 | 2 | 1.01 (0.98, 1.04) | 0 |
| Phenolic acids | 2 | 770/9236 | 0.72 (0.51, 1.01) | 52.6 | 2[7] | 770/9236 | 600 | 0.76 (0.64, 0.89) | 0 |
| Stilbenes | 2 | 770/9236 | 0.44 (0.26, 0.72) | 73 | 2[7] | 770/9236 | 2.7 | 0.14 (0.01, 1.51) | 94.9 |
| Lignans | 3 | 11,600/35,324 | 0.94 (0.77, 1.14) | 34.1 | 2[7] | 770/9236 | 3 | 1.27 (0.68, 2.42) | 52.5 |
| Lignan biomarkers | 2 (3)[9] | 1671/3342 | 0.72 (0.46, 1.14) | 65 | | | | | |
| Others[10] | 2 | 770/9236 | 1.04 (0.83, 1.31) | 0 | 2[7] | 770/9236 | 50 | 1.05 (0.89, 1.25) | 0 |

[1]HRs are presented with 95% CIs in parentheses. NA, not applicable—for these compounds a statistically significant nonlinear dose-response was observed.
[2]Exposures are dietary intake, unless otherwise indicated.
[3]Numbers in parentheses indicate the number of cohorts; this may exceed the "total number of studies" because some papers presented findings from more than one cohort.
[4]Random-effects models were used.
[5]Wedick et al. (2012) (31) included 3 cohorts (NHS, NHS II, HPFS).
[6]Aglycone values.
[7]Glycoside values (conjugates).
[8]Ding et al. (2016) (34) included 3 cohorts (NHS, NHS II, HPFS).
[9]Sun et al. (2014) (37) included 2 cohorts (NHS, NHS II).
[10]Others include: alkylmethoxyphenols, alkylphenols, curcuminoids, furanocoumarins, hydroxybenzaldehydes, hydroxybenzoketones, hydroxycinnamaldehydes, hydroxycoumarins, hydroxyphenylpropenes, methoxyphenols, naphthoquinones, phenolic terpenes, and tyrosols.

acids in the meta-analysis were also noted for hydroxybenzoic acid and hydroxycinnamic acid (36), but not for urinary caffeic and ferulic acid (37).

## DISCUSSION

To our knowledge, this is the first systematic review and dose-response meta-analysis to have comprehensively investigated the association between exposure to individual compounds and groups of polyphenols and subsequent risk of type 2 diabetes. A comparison of extreme quantiles revealed inverse associations for intake of total polyphenols, total flavonoids, flavonols, flavan-3-ols, catechins, anthocyanidins, isoflavones, daidzein, genistein, and stilbenes, and biomarkers of daidzein and genistein. Dose-response meta-analyses showed nonlinearity for dietary intake of polyphenols, flavonoids, flavanones, anthocyanidins, anthocyanins, and genistein. Linearity was only observed for a daily increment of phenolic acids.

The inverse association observed for total flavonoids underscores that a diet rich in plant foods could help in the prevention of type 2 diabetes. Consistent with our findings for intake of total flavonoids and flavonols are the inverse associations observed in

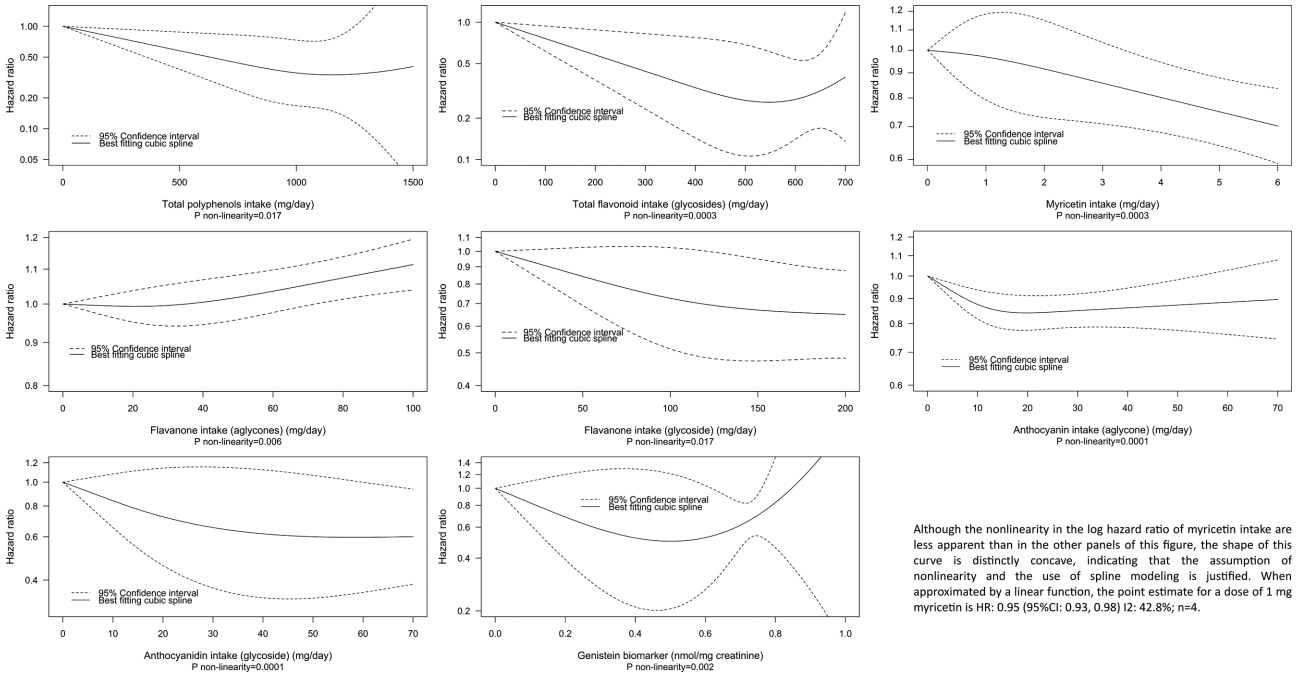


**FIGURE 3** Nonlinear dose-response curves for polyphenols.

previous meta-analyses for fruits (43, 44), vegetables (43), and cruciferous, green leafy, and yellow vegetables (44). Measurement error is likely to be the reason why no association was observed for flavones. Herbs are the main source of flavones and are usually not listed in FFQs. The null association for flavonones is in line with a meta-analysis of citrus fruits (45). The results for flavan-3-ols and catechins are in accordance with the reduced risks of type 2 diabetes in meta-analyses for drinking >3 cups of tea per day (46, 47) and chocolate (48). For green tea, which is richer in epigallocatechin-3-gallate than black tea, no association was observed (46). The strong inverse association observed for anthocyanidins is in line with the main source of these compounds, blueberries (44), in a previous meta-analysis. The reduced risk of type 2 diabetes observed for isoflavone intake was not observed for urinary concentrations of isoflavones. The FFQ used in two studies (21, 26) was validated against urinary and serum biomarkers and showed a good agreement for isoflavones (21, 49). Moreover, the inverse associations found for intake and dietary biomarkers of daidzein and genistein intake were consistent. Future studies should investigate the association with disease at both the intake and biomarker levels. Isoflavones, in contrast to the other classes of flavonoids, are mainly present in soy products and therefore intake is more likely to be accurately estimated from food composition tables. Furthermore, no associations were observed in the linear and nonlinear dose-response meta-analyses for isoflavones. This coincides with the nonsignificant trends across quantiles observed in most individual studies. Comparing extreme quantiles might therefore be suboptimal as not all data are considered in such analysis. The results for phenolic acids are consistent with the risk of type 2 diabetes being reduced by 8–33% by drinking 1–6 cups of coffee per day (50). The inverse association for stilbenes was also observed for wine consumption in a meta-analysis of prospective studies (51). No associations were observed for lignan intake and biomarkers. However, whole grains (43, 52) and dietary fiber (53) were inversely associated with type 2 diabetes.

Our results support the hypothesis that some polyphenols can potentially play beneficial roles in carbohydrate metabolism via several mechanisms. In vitro studies showed inhibitory effects of flavonoids and phenolic acids on $\alpha$-amylase and $\alpha$-glucosidase activities and intestinal glucose absorption by the glucose transporters SGLT1 and GLUT2 (4). Flavonoids protected $\beta$ cells from hyperglycemia in in vivo and cell culture studies (4). Polyphenols promoted the uptake of glucose in cell cultures by activating insulin-mediating pathways, e.g., the cAMP/protein kinase A and PI3K pathways (4). In the liver, polyphenol-rich foods prevented gluconeogenesis and stimulated glycogenesis (4).

The main strength of this study is the conduct of meta-analyses for 24 different polyphenol exposures including 9 individual compounds. Studying individual compounds greatly adds to the evidence because the distinct molecular structures between compounds of flavonoid subclasses are likely to exert a different effect on glucose metabolism due to variability in bioavailability and bioactivity (2). The dose-response meta-analysis considers data for all exposure categories. Furthermore, this enables the investigation of potential nonlinear relationships. Indeed, our results suggest that recommended intakes of some compounds are associated with minimizing the risk of type 2 diabetes. However, with the available studies and the limited number of data points, dose-response curves could not be fully explored. Studies that used both dietary assessment methods and biomarkers were included. However, data from either method were analyzed separately as misclassification due to a difference in metabolism, and excretion of polyphenols cannot be accounted for in food composition tables. Biomarkers are regarded as a more objective measure; they account for bioavailability and metabolism after ingestion of foods and are not prone to reporting bias (54). In addition, data for aglycones and glycosides were analysed separately.

Certain weaknesses of this study should be mentioned. Some dose-response curves should be interpreted with caution, as confidence intervals varied in width. In particular, the risk estimates at higher intakes are uncertain because few data were available. For 8 studies we assumed an equal distribution of cases or controls (19, 20, 26, 30–34) across the quantiles of polyphenols. Since the incidence was <10% it is reasonable to assume that the controls are evenly distributed.

The publication bias observed for flavones and flavanones was likely the result of a small study effect. Furthermore, nondifferential misclassification could have resulted from the assessment of polyphenol exposure at a single time point. An actual change in dietary behavior could have occurred during follow-up. Generally, polyphenolic compounds have relatively short half-lives and it is questionable whether a single biosample is a valid measure of long-term exposure. The majority of the included studies used an FFQ: this could have led to an underestimation of intake because the food list might have lacked important polyphenol-containing foods. Incomplete food composition databases might not cover the polyphenol content for all foods and compounds. Furthermore, the polyphenol content of fruit and vegetables fluctuates as a result of climate, soil, ripeness, processing, and storage (54). Although heterogeneity of the included studies was further investigated by subgroup analysis, several other factors exist that could not be further investigated but should be considered. First, between-study variation in polyphenol intake was observed. This is not solely due to a difference in dietary habits but can be partly attributed to food composition tables. Through continuous updates, these databases become more accurate and comparable with the passage of time. In general, intake was lower in older publications because older food databases included fewer subclasses. For example, for the calculation of total flavonoid intake, 2 studies (27, 32) included 7 subclasses of flavonoids, 2 studies (25, 31) included 5 subclasses, 1 study (19) included 3 subclasses, and 1 study (20) included 2 subclasses. The reported intakes of isoflavones are likely to be due to true differences in dietary habits between Asian and Western countries (32). Higher intakes of isoflavones were observed in the Japanese study by Nanri et al. (21), although they included only 2 compounds to calculate isoflavones in comparison with other studies that included 3 (26, 34, 55) to 6 (32) compounds. Regarding the outcome definition, all but one study (27) that used self-reported questionnaires to ascertain type 2 diabetes were validated. As follow-up ranged from 4 to 28 y, it cannot be ruled out that the induction period was too short in the studies with a short follow-up time.

In conclusion, there is evidence to suggest that a diet rich in polyphenols, particularly flavonoids, plays a role in the prevention of type 2 diabetes. Nonlinearity was observed for several subclasses and compounds, suggesting that recommendable intake level should minimize the risk of type 2 diabetes. Therefore, future studies are warranted in which nonlinear associations are further explored.

The authors' responsibilities were as follows—JR and UN: designed the study; JR and JB: conducted the literature search; JR: extracted and analyzed the data with support from KO and MS; JR: wrote the manuscript; and all authors: contributed to the interpretation of the data and to the discussion, and critically reviewed and edited the manuscript. None of the authors reported a conflict of interest.

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