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Original article

Polyphenol intake and cardiovascular risk factors in a population with type 2 diabetes: The TOSCA.IT study

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SUMMARY

Background: The role of polyphenol intake on cardiovascular risk factors is little explored, particularly in people with diabetes. **Aim:** To evaluate the association between the intake of total polyphenols and polyphenol classes with the major cardiovascular risk factors in a population with type 2 diabetes.

Abbreviations used: TOSCA.IT, Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial; BMI, body mass index; CRP, C-reactive protein; HbA1c, glycated hemoglobin; ACR, albumin to creatinine ratio; EPIC, European prospective investigation into cancer and nutrition; USDA, United States Department of Agriculture; FFQ, food frequency questionnaire; HPLC, high performance liquid chromatography; ANOVA, analysis of variance; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

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Keywords:

Dietary polyphenols
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Methods: Dietary habits were investigated in 2573 males and females participants of the TOSCA.IT study. The European Prospective Investigation on Cancer and Nutrition (EPIC) questionnaire was used to assess dietary habits. In all participants, among others, we assessed anthropometry, plasma lipids, blood pressure, C-reactive protein and HbA1c following a standard protocol. The USDA and Phenol-Explorer databases were used to estimate the polyphenol content of the habitual diet.

Results: Average intake of polyphenols was 683.3 ± 5.8 mg/day. Flavonoids and phenolic acids were the predominant classes (47.5% and 47.4%, respectively). After adjusting for potential confounders, people with the highest intake of energy-adjusted polyphenols (upper tertile) had a more favorable cardiovascular risk factors profile as compared to people with the lowest intake (lower tertile) (BMI was 30.7 vs 29.9 kg/m², HDL-cholesterol was 45.1 vs 46.9 mg/dl, LDL-cholesterol was 103.2 vs 102.1 mg/dl, triglycerides were 153.4 vs 148.0 mg/dl, systolic and diastolic blood pressure were respectively 135.3 vs 134.3 and 80.5 vs 79.6 mm/Hg, HbA1c was 7.70 vs 7.67%, and C-reactive Protein was 1.29 vs 1.25 mg/dl, $p < .001$ for all). The findings were very similar when the analysis was conducted separately for flavonoids or phenolic acids, the two main classes of polyphenols consumed in this population.

Conclusions: Polyphenol intake is associated with a more favorable cardiovascular risk factors profile, independent of major confounders. These findings support the consumption of foods and beverages rich in different classes of polyphenols particularly in people with diabetes.

Clinical trial: <http://www.clinicaltrials.gov>; Study ID number: NCT00700856.

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1. Introduction

In the last few years, the interest for polyphenols in the field of human nutrition has rapidly increased for their possible beneficial effects against the development of several chronic diseases – in particular cardiovascular diseases and diabetes [1–4] –, and in improving cardiovascular risk factors [5–9].

Polyphenols are natural bioactive compounds mainly found in plant-based foods, such as fruit, vegetables, legumes, cereals and cocoa, and plant-derived beverages, such as coffee, tea and wine. Based on the biochemical structure, five main classes of polyphenols with different properties and bioavailability have been identified: flavonoids (the group of polyphenols mostly studied), phenolic acids, stilbenes, lignans and others polyphenols [10].

To date, cross-sectional and prospective epidemiological studies have shown that the intake of total polyphenols and/or of specific foods rich in polyphenols, such as tea, coffee, and chocolate, are associated with a better cardiovascular risk factors profile (plasma lipids, glucose, blood pressure, platelet function, biomarkers of inflammation) [11,12] and, in some cases, with a decrease in cardiovascular diseases and diabetes incidence [13].

However, the majority of these studies have been performed in the general population and focused on the intake of flavonoids and their subclasses; indeed data on other types of polyphenols are scant, although they may be equally important, as suggested by some results from the PREDIMED study. In fact, this study showed that a high polyphenol intake, deriving especially from stilbenes and lignans, is associated with lower risk of overall mortality [14], whereas a high intake of total flavonoids (specifically flavanones and dihydroflavonols) and stilbenes is associated with a reduced risk of diabetes [15].

In addition to epidemiological studies, in vitro and animal data and some intervention studies in humans have confirmed and reinforced the evidence for beneficial effects on cardiovascular risk factors – mainly lipid and glucose metabolism – of different polyphenols and diets rich in polyphenols from different sources [16–21].

Considering the possible role of polyphenols in ameliorating several cardiovascular risk factors, it is relevant to evaluate the intake of polyphenols and the relation of the different classes of polyphenols with the cardiovascular risk factors profile in people with type 2 diabetes, a population characterized by a high cardiovascular risk.

Therefore, the aim of our study was to evaluate the association between total polyphenol intake and polyphenol classes with the

major cardiovascular risk factors (glucose control, lipid profile, blood pressure) and biomarkers of inflammation in a large population of people with type 2 diabetes. To the best of our knowledge, this is the first epidemiological observational study evaluating these aspects in type 2 diabetic patients.

2. Materials and methods

2.1. Study population

This cross-sectional study was conducted in 2573 people with type 2 diabetes, diagnosed according to ADA criteria [22], 1535 men and 1038 women, aged 50–75 years, enrolled in the TOSCA.IT study, a randomized clinical trial designed to compare the impact of glucose lowering drugs on cardiovascular events (<http://www.clinicaltrials.gov>, study ID number: NCT00700856). The study protocol has been already published [23]. The study participants were recruited in 60 centers distributed all over Italy. The study protocol was approved by the Ethics Review Committee of the Coordinating Center and of each participating center, and written informed consent was obtained from all participants before entering the study. For the purposes of the present analysis, baseline data – collected prior to randomization to study treatment – were used. Among the other parameters evaluated, body weight, height, waist and hip circumference, blood pressure, were measured according to standard procedures. Body Mass Index (BMI) was calculated as weight (kg)/height (m²). Blood samples were obtained in the morning after an overnight fast. All biochemical analyses were performed in a central laboratory. Total cholesterol, HDL-cholesterol, triglycerides and C-reactive protein (PCR) were measured by standard methods. LDL-cholesterol was calculated according to the Friedewald equation only for triglyceride values < 400 mg/dl. Glycated hemoglobin (HbA1c) was measured with High Liquid Performance Chromatography. At baseline, all participants were treated with metformin, as per study inclusions criteria. Data on the use of other medications were also collected.

2.2. Dietary assessment

Dietary habits were assessed with the Italian version of the European Prospective Investigation into Cancer and Nutrition (EPIC) questionnaire [24]. The questionnaire contains 248 items including the type of fat used as seasoning, or added after cooking. The person

filling in the questionnaire indicates the absolute frequency of consumption of each item (per day, week, month or year) and the quantity of the food consumed, selecting the image of a food portion showing a small, medium and large portion size, with additional quantifiers (e.g. “smaller than the small portion” or “between the small and medium portion” etc ...). The nutrient composition of the diet was calculated with a software containing the Italian Food Tables. Eighty-six incomplete questionnaires and questionnaires with implausible data (i.e. energy intake less than 800 or greater than 5000 Kcal/day) were excluded from the analyses.

2.3. Estimation of polyphenol intake

The intake of polyphenols and their classes was evaluated using the USDA database [25] in combination with the Phenol-Explorer® database [26] to enable the examination of the polyphenol content of as many foods as possible. Missing data from cereal products, such as pizza, polenta, biscuits, crisp toasts, crackers and breadsticks, were estimated based on refined wheat flour data from Phenol-Explorer® database. For processed foods such as canned foods and pre-packaged meals, the estimation was made according to the percentages of ingredients in the food products. Complex foods such as cakes and sauces were calculated as recipes; the individual ingredients were obtained from data available on the Internet. Different types of coffee, “espresso” and “decaffeinated”, were reported in the food frequency questionnaire. The polyphenol content of “espresso” coffee was estimated on the coffee brand frequently used in Italy; therefore, the mean polyphenol content in the Arabica and Robusta varieties from the Phenol-Explorer database was calculated and multiplied by 2 to avoid underestimation of polyphenol from coffee espresso, as suggested by Parras [27]. For “decaffeinated” coffee, the polyphenol content of “decaffeinated filtered coffee” from the Phenol-Explorer database was considered.

The polyphenol composition of tea was obtained from a mix of herbal teas considering the unspecified type of herbal tea in the food frequency questionnaire (FFQ).

Finally, individual polyphenol intake from each food was calculated by multiplying the content of each polyphenol by the daily consumption of each food. Mean intake of each polyphenol class (flavonoids, phenolic acids, stilbenes, lignans and other polyphenols) was determined. Total polyphenol intake was calculated as the sum of all individual polyphenol intakes from all the food sources reported by the FFQ.

The cut-off used for foods to be included in the polyphenol estimation was based on a previous study which referred to foods that contributed <1 mg/day to the overall polyphenol intake as minor contributors. Thus, foods containing less than 1 mg of polyphenols as consumed in a usual portion were excluded from the analysis.

2.4. Statistical analysis

Data from continuous variables are presented as mean \pm standard deviation. Percentages are used for categorical variables. Not normally distributed variables were logarithmically

transformed for statistical analyses and back-transformed to natural units for presentation in the text and tables.

Polyphenol intake is reported as mg of polyphenols per 1000 kcal to correct for total energy intake, which was higher in subjects with increased polyphenol consumption. Baseline characteristics and metabolic profile have been evaluated across tertiles of total polyphenol intake and of the two main polyphenol classes (flavonoids and phenolic acids). Differences between tertiles were tested by a one-factor analysis of variance (ANOVA) and Post-Hoc test for multiple comparisons (Bonferroni Test) for continuous variables, and by the chi-square test for categorical variables. The analysis was adjusted for gender, age, and all the variables which were significantly different between tertiles, i.e. BMI, waist and hip circumferences, smoke, alcohol intake, dietary lipids, saturated – SFA –, monounsaturated – MUFA –, and polyunsaturated – PUFA – fatty acids, added sugars and fiber intake.

All P-values reported were based on two-sided tests, the significance level was set at .05. IBM SPSS Statistic 20 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical analysis.

3. Results

The total polyphenol intake of our population was 683.3 ± 5.8 mg/day and, adjusting for energy intake, it was 378.7 ± 4.1 mg/1000 Kcal for men and 374.0 ± 4.9 mg/1000 Kcal for women, with no difference between genders. Flavonoids and phenolic acids represented the two main classes of polyphenol intake in our population, accounting for 95% of the total polyphenol intake (respectively 47.5% and 47.4%); the remaining 5.1% was represented by the others three classes (other polyphenols, stilbenes, and lignans, respectively 3.8%, .8%, and .5%) (Table 1).

Dividing the population according to tertiles of energy-adjusted polyphenol intake, significant differences in some demographic characteristics and in the nutrient composition of the diets were observed (Table 2). In fact, participants with a higher polyphenol intake were older, had lower BMI, waist and hip circumferences, were more likely to be smokers and consumed more alcoholic beverages (mostly wine and beer) ($p < .05$ for all). In addition, a higher intake of polyphenols was associated, at least to some extent, to better diet quality. In fact, a lower intake of saturated fatty acids and a higher intake of unsaturated fatty acids and fiber were associated with a higher consumption of polyphenols ($p < .001$ for all). The groups did not differ in terms of gender distribution and use of lipid and pressure lowering drugs.

Figure 1 shows the metabolic profile, blood pressure values and CRP according to the tertiles of energy-adjusted polyphenol intake. After adjusting for the potential confounders (gender, age, BMI, waist and hip circumferences, smoking, and all nutrients resulted different across the tertiles of energy-adjusted polyphenol intake), people in the higher tertile of energy-adjusted polyphenol intake (tertile 3) showed significantly higher HDL-cholesterol and lower LDL-cholesterol, triglycerides, systolic and diastolic blood pressure, HbA1c, and CRP compared to subjects in the lower tertiles (tertiles 1 and 2) ($p < .001$ for all, analysis of variance and post-hoc test for

Table 1

Percentage contribution of different classes to the total polyphenol intake and main food sources for each class.

	Contribution (%)	Main food sources in the cohort (% of total intake within each polyphenol class)
Flavonoids	47.5	Fruit (32.2%), Alcoholic beverages ^a (22.8%), Non-alcoholic beverages ^b (17.6%), Vegetables (15.1%), Legumes (7.5%)
Phenolic acids	47.4	Non-alcoholic beverages ^b (65.3%), Fruit (15.1%), Vegetables (10.9%), Alcoholic beverages ^a (4.4%), Cereal products (3.5%)
Stilbenes	.8	Alcoholic beverages ^a (97.1%)
Lignans	.5	Fruit (85.4%), Vegetables (6.4%), Fat and oils (6.3%)
Other Polyphenols	3.8	Fat and oils (52.2%), Cereal products (28.5%), Alcoholic beverages ^a (13.0%), Non-alcoholic beverages ^b (6.3%)

^a Alcoholic Beverages: wine and beer.

^b Non-alcoholic beverages: coffee and tea.

Table 2
Baseline characteristics and nutrient composition of the diet according to energy-adjusted tertiles of polyphenol intake.

	Tertile 1 (n 856)	Tertile 2 (n 860)	Tertile 3 (n 858)	P for Anova or χ^2
Total polyphenols (mg/1000 kcal)	228.5 ± 50.8 (51.8–297.7)	355.0 ± 32.8 (297.9–413.7)	546.4 ± 150.1 (413.7–1628.6)	
Gender				
Males (%)	59.4	58.4	61.2	.865
Females (%)	40.6	41.6	38.8	.912
Age (years)	61.9 ± 6.5°	61.9 ± 6.4°	62.5 ± 6.4	.041
BMI (kg/m ²)	30.7 ± 4.5°	30.3 ± 4.4°	29.9 ± 4.4	<.0001
Waist Circumference (cm)	105.5 ± 11.3	104.3 ± 11.6	103.6 ± 10.6	.002
Hip circumference (cm)	107.2 ± 10.7	106.4 ± 10.4	105.6 ± 9.5	.005
Smoking status (%)				
Non smoker	85.8	82.7	79.6	.009
Current smoker	14.2	17.3	20.4	.032
% on lipid lowering medications	56.7	61.3	68.1	.082
% on pressure lowering medications	93.2	92.9	91.2	.231
Proteins (% of TE)	18.3 ± 2.4	18.3 ± 2.4	18.1 ± 2.7	.368
Lipids (% of TE)	36.3 ± 5.9°	36.8 ± 5.6	36.9 ± 6.4	.014
SFA (% of TE)	12.4 ± 2.6°	12.3 ± 2.4°	11.8 ± 2.4	<.0001
MUFA (% of TE)	17.4 ± 3.5°	17.8 ± 3.4	18.3 ± 4.1	<.0001
PUFA (% of TE)	4.3 ± 1.1°	4.4 ± 1.0	4.6 ± 1.2	<.0001
Carbohydrates (% of TE)	45.4 ± 7.1	44.9 ± 6.9	45.1 ± 7.6	.353
Added sugars (% of TE)	2.1 ± 2.9°	2.4 ± 2.8	2.6 ± 3.7	.002
Fiber (g/1000 kcal)	9.4 ± 2.1°	10.7 ± 2.4°	12.1 ± 2.9	<.0001
Alcohol (g/day)	8.0 ± 13.9°	11.0 ± 14.4°	14.4 ± 18.5	<.0001

M ± SD.

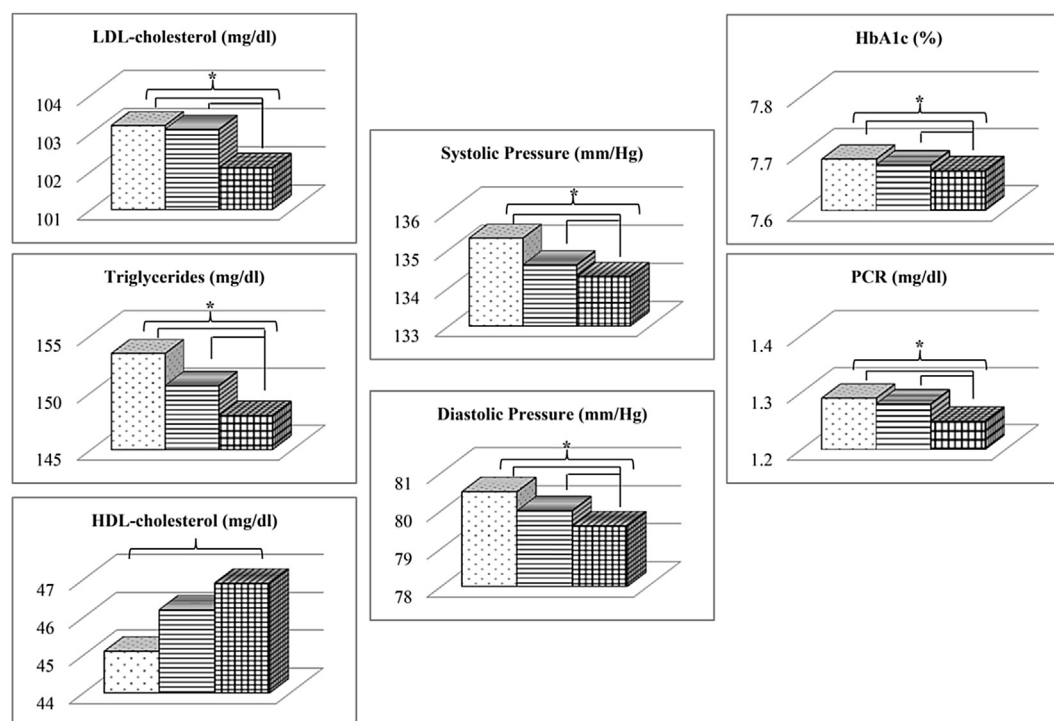
TE: Total Energy of the diet.

°p < .05 vs tertile 3, Post-Hoc Test for multiple comparisons (Bonferroni Test).

multiple comparisons). Moreover, a significant linear trend was observed ($p < .001$ for all).

The proportion of study participants on lipid lowering agents was equally distributed across the tertiles of polyphenol intake; however, a sensitivity analysis conducted with the exclusion of people on hypolipidemic drugs confirmed all the previous findings (Supplemental Table 1).

Flavonoids and phenolic acids were the two main contributors to the total polyphenol intake in our population; therefore, we analyzed the metabolic variables also according to tertiles of energy-adjusted intake of each of these two classes of polyphenols. The findings were the same as those found with total polyphenol intake (Tables 3 and 4), except for HbA1c, which was no longer significantly related to phenolic acid intake (Table 4).

* $p < .001$, Analysis of Variance and Post-Hoc Test for multiple comparisons (Bonferroni Test) between tertile 3 vs tertiles 1 and 2

Data adjusted for gender, age, BMI, waist and hip circumferences, smoke, alcohol intake, dietary lipids, SFA, MUFA, PUFA, added sugars and fiber

Fig. 1. Metabolic profile, blood pressure values and C-reactive protein according to tertiles of energy-adjusted polyphenol intake (■ tertile 1; ▨ tertile 2; ▩ tertile 3).

Table 3
Metabolic profile, blood pressure values and C-reactive protein according to energy adjusted tertiles of flavonoid intake.

	Tertile 1 (n 856)	Tertile 2 (n 860)	Tertile 3 (n 858)	P for Anova
Flavonoids (mg/1000 Kcal)	86.1 ± 23.9 (16.3–121.5)	156.2 ± 21.1 (121.6–193.9)	286.7 ± 118.8 (194.0–1181.3)	
LDL-cholesterol (mg/dl)	103.3 ± 3.8°	103.0 ± 3.9°	102.1 ± 3.9	2.2 × 10 ⁻⁸
Triglycerides (mg/dl)	152.9 ± 18.4°	150.7 ± 16.9°	148.3 ± 17.4	6.5 × 10 ⁻⁸
HDL-cholesterol (mg/dl)	45.2 ± 4.8°	46.2 ± 4.4°	47.0 ± 4.3	5.3 × 10 ⁻¹⁵
HbA1c (%)	7.69 ± .09°	7.69 ± .08°	7.67 ± .08	2.1 × 10 ⁻⁷
Systolic pressure (mm/Hg)	135.2 ± 3.4°	134.5 ± 3.4	134.6 ± 3.5	1.9 × 10 ⁻⁴
Diastolic pressure (mm/Hg)	80.5 ± 1.7°	80.0 ± 1.7°	79.7 ± 1.8	3.4 × 10 ⁻¹⁸
CRP (mg/dl)	1.29 ± .15°	1.28 ± .15°	1.25 ± .14	4.3 × 10 ⁻¹⁰

M ± SD.

°p < .05 vs tertile 3, Post-Hoc Test for multiple comparisons (Bonferroni Test).

Data adjusted for gender, age, BMI, waist and hip circumferences, smoke, alcohol intake, dietary lipids, SFA, MUFA, PUFA, added sugars and fiber.

Table 4
Metabolic profile, blood pressure values and C-reactive protein according to energy adjusted tertiles of phenolic acids intake.

	Tertile 1 (856)	Tertile 2 (860)	Tertile 3 (858)	P for Anova
Phenolic acids (mg/1000 Kcal)	96.8 ± 29.3 (18.6–137.5)	167.2 ± 18.2 (137.6–201.5)	281.5 ± 92.0 (201.6–1170.1)	
LDL-cholesterol (mg/dl)	103.0 ± 3.8°	102.9 ± 3.9	102.5 ± 4.1	5.1 × 10 ⁻⁴
Triglycerides (mg/dl)	152.0 ± 17.2°	150.9 ± 17.4°	148.9 ± 18.3	7.2 × 10 ⁻⁹
HDL-cholesterol (mg/dl)	45.8 ± 4.7°	46.1 ± 4.4°	46.7 ± 4.6	1.6 × 10 ⁻⁵
HbA1c (%)	7.69 ± .08	7.68 ± .08	7.68 ± .08	.217
Systolic pressure (mm/Hg)	135.5 ± 3.4°	134.8 ± 3.4°	134.0 ± 3.4	3.1 × 10 ⁻¹⁹
Diastolic pressure (mm/Hg)	80.4 ± 1.7°	80.1 ± 1.6°	79.5 ± 1.8	1.4 × 10 ⁻²⁹
CRP (mg/dl)	1.29 ± .15°	1.27 ± .15	1.26 ± .15	1.2 × 10 ⁻⁷

M ± SD.

°p < .05 vs tertile 3, Post-Hoc Test for multiple comparisons (Bonferroni Test).

Data adjusted for gender, age, BMI, waist and hip circumferences, smoke, alcohol intake, dietary lipids, SFA, MUFA, PUFA, added sugars and fiber.

4. Discussion

This is the first epidemiological observational study evaluating the association between polyphenol intake and major cardiovascular risk factors – glucose control, lipid profile, blood pressure – and a biomarker of subclinical inflammation (PCR) in people with type 2 diabetes.

The main and most relevant findings of this study were that a diet characterized by a higher intake of total polyphenols was associated with a better cardiovascular risk factors profile and a lower grade of subclinical inflammation. These findings were independent of other dietary components and potential confounders, such as gender, age, BMI, and smoking; moreover, the associations were evident also in a population at very high cardiovascular risk, who followed a more or less quite homogeneous diet not characterized by a high intake of polyphenols, and who were already on pharmacological treatment for their main cardiovascular risk factors. In addition to the associations with total polyphenol intake, also the consumption of flavonoids and phenolic acids – the two main classes of polyphenols consumed by our population – were significantly associated with a better cardiovascular profile, with the only exception of blood glucose control for phenolic acids. This difference could be explained either by a possible minor influence of phenolic acids on blood glucose metabolism, which should be better investigated in intervention studies, or, more likely, by confounders linked specifically to the intake of phenolic acids. As a matter of fact, the main contributor to phenolic acids intake is represented by non-alcoholic beverages and the added sugars generally utilized in these drinks could have counteracted or masked the relationship between phenolic acids and glucose control. Within this context, it is important to underline that in the same population a positive association was found between added sugars and HbA1c concentrations [28].

Inverse associations between polyphenols, in particular flavonoids, some foods rich in selected polyphenols (fruit and vegetables, coffee, tea, etc.) and cardiovascular risk factors and/or

cardiovascular events in the general population have been already reported [11–13]. Our study reinforces, in a different population, the data on flavonoids, extends the results to the other main class of polyphenols – i.e., the phenolic acids – and shows an inverse association also with markers of systemic subclinical inflammation.

Of course, the cross-sectional nature of our study does not allow us to infer a causal effect of polyphenols on the different outcomes. However, intervention studies in humans and in vitro and animal studies support this hypothesis. In fact, intervention trials with single foods/beverages rich in polyphenols (tea, chocolate and cocoa, coffee, wine, orange juice) or extracts of specific polyphenols indicate positive effects on cardiovascular risk factors (plasma lipids, glucose metabolism, blood pressure) and an improvement of the endothelial function [16,29,30]. Very recent data show that a diet naturally rich in polyphenols from different sources improves post-prandial lipid metabolism, oxidative stress, and glucose tolerance in metabolically high-risk patients, strongly supporting the possible causal effect of different polyphenols on multiple cardiovascular risk factors [18,19]. Moreover, there are also different plausible mechanisms possibly explaining the link between polyphenols and cardiovascular risk factors, which reinforce the possibility of a causal relation. The main one are slow-down in the digestion and absorption of lipids and glucose, increase in insulin secretion and/or decrease in insulin resistance, decrease in oxidative stress and subclinical inflammation, increase in nitric oxide bioavailability with subsequent vasodilation effect [5,9,31]. Data on the association between high polyphenol intake and lower BMI, waist and hip circumferences, are really interesting and in line with some evidences showing a possible effect of polyphenol in increasing energy expenditure [32]. However, they cannot explain the association between polyphenol and cardiovascular risk factors in our study because the above associations have been found after adjusting for BMI, waist and hip circumferences.

The differences in metabolic profile, blood pressure, and markers of inflammation among the different tertiles of polyphenols and their main classes are statistically significant but their magnitude is

modest and can hardly be considered of clinical interest, at least at the level of the individual patient; however, it could be relevant when translated at the population level. Moreover, considering the differences between tertiles of polyphenol intake in LDL-cholesterol, triglycerides, HDL-cholesterol and blood pressure, on the basis of prospective and intervention studies [33–37] it is possible to foresee an 11% reduction in the cardiovascular risk, which is certainly of clinical relevance taking also into account that this reduction is linked to only one component of the diet. Furthermore, from a practical point of view, the main sources of polyphenols in the diet of our population are represented by non-alcoholic beverages, such as tea and coffee (39.5%), fruit (23.0%), alcoholic beverages (13.9%), vegetables (12.4%), legumes (3.7%) which, except for alcoholic beverages, represent a good source of nutrients and other bioactive compounds able to positively influence cardiovascular risk factors.

Of course, our study has strengths and limitations.

The large size of the study sample, the selection of a cohort representative of the diabetic population seen in everyday clinical practice, the standardized collection of nutritional data, the centralized measurements of the biochemical variables, and the analysis of different classes of polyphenols, are the major strengths.

Among the limitations, the first one is represented by the cross-sectional design of the study, although, as reported previously, intervention and mechanistic studies support a possible causal relation. Other limitations may be linked to the estimation of polyphenol intake: variability or lack of information on polyphenol content in foods depending on ripeness at harvest time, environmental factors, processing and storage, and plant variety; lack of information about some foods in the FFQ, especially for wholegrain foods which could have, if anything, determined an underestimation of the intake of some polyphenols masking some differences.

In conclusion, the results of this study are relevant as they show, for the first time in people with type 2 diabetes, that a diet characterized by a higher intake of polyphenols is associated with a more favorable cardiovascular risk factor profile, and less subclinical inflammation. This is true even if the intake of polyphenols is not particularly high in our population compared to others. This should encourage the use of foods and beverages rich in different classes of polyphenols also in this category of patients as in the general population.

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Authors' contributions to the manuscript

OV, GR, AAR, MM, EB, SDP, CBG, AN, and SS designed research; SA, ACB, RB, EC, MC, MC, GC, SC, LC, FDA, EDA, GDC, LF, GG, SG, CG, RI, CI, AL, DL, LL, CM, SS, LT, RT, and CZ conducted research; LB, SG, and SS provided essential materials; MV, and SG analyzed data and performed statistical analysis; MV, AAR, and GR wrote paper; AAR, MV, and GR had primary responsibility for final content.

All authors read and approved the final manuscript.

Conflict of interest

All authors disclose any financial or personal relationships with the company or organization sponsoring the research at the time the research was done.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clnu.2016.11.002>.

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