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ORIGINAL CONTRIBUTION

Coffee consumption and risk of hypertension: a dose–response meta-analysis of prospective studies

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Abstract

Purpose Recently, a large prospective study provided additional information concerning the debated possible association between habitual coffee consumption and risk of hypertension (HPT). Therefore, we updated the state of knowledge on this issue by carrying out a comprehensive new systematic review of the literature and a meta-analysis of the available relevant studies.

Methods We performed a systematic search for prospective studies on general population, published without language restrictions (1966–August 2017). A random-effects dose–response meta-analysis was conducted to combine study specific relative risks (RRs) and 95% confidence intervals. Potential non-linear relation was investigated using restricted cubic splines.

Results Four studies (196,256 participants, 41,184 diagnosis of HPT) met the inclusion criteria. Coffee intake was assessed by dietary questionnaire. Dose–response meta-analysis showed a non-linear relationship between coffee consumption and risk of HPT (p for non-linearity < 0.001). Whereas the habitual drinking of one or two cups of coffee per day, compared with non-drinking, was not associated with risk of HPT, a significantly protective effect of coffee consumption was found starting from the consumption of three cups of coffee per day (RR = 0.97, 95% CI = 0.94 to 0.99), and was confirmed for greater consumption.

Conclusions The results of this analysis indicate that habitual moderate coffee intake is not associated with higher risk of HPT in the general population and that in fact a non-linear inverse dose–response relationship occurs between coffee consumption and risk of HPT.

Keywords Coffee · Hypertension · Blood pressure · Dose–response meta-analysis

Introduction

Coffee is a widely consumed beverage worldwide, with more than 150 million of (60 kg) bags consumed in the only 2016 [1]. Consumption is particularly high in high-income countries [2], and pro-capita consumption is highest in Europe [3]. Because of its popularity and widespread diffusion, over the last decades several studies were performed analyzing its possible influence on cardiovascular disease (CVD) risk and recent literature reviews suggested an unpredicted protective effect of habitual coffee consumption toward the occurrence of CVD events [4–7]. Hypertension (HPT) is a leading preventable cause of death worldwide with approximately 1.39 billion adults worldwide being hypertensive, with a prevalence of 28% in high-income countries [8–10], and a predicted worldwide increase by at least 30% by 2025 [11]. Given the role of high blood pressure (BP), it is conceivable that at least part of the protection afforded by coffee consumption toward CVD prevention is mediated through a positive effect on BP.

Experimental evidence suggests that there are many possible biological pathways through which a variety of bioactive substances in coffee having diuretic and natriuretic activity or antioxidant effects could exert a beneficial

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role on BP (12–14). However, the available clinical evidence is inconsistent and in some respect contradictory. While in randomized controlled trials, short-term coffee consumption was associated with a rise in BP [15, 16], long-term prospective observational studies did not indicate an increased risk of HPT [17, 18] in habitual coffee drinkers. Two recent meta-analyses on the relationship between habitual coffee consumption and risk of HPT showed discrepant results [19, 20]. In as much as one of them found an increased risk of HPT with low-moderate consumption of coffee with a J-shape relationship in dose–response analysis [19], whereas the other showed no association at all [20]. Limitations of these studies were the heterogeneous populations included in the analysis [21] and the inclusion of studies reporting inappropriate expressions of the outcome [22] and/or unevenly mixing the individual outcomes.

Following the publication of these two meta-analyses, an additional large prospective study has been published that reported on the relationship between habitual coffee intake and risk of HPT in a cohort of 30,000 post-menopausal women [17].

Therefore, considering (1) the large worldwide consumption of coffee, (2) the huge prevalence of HPT and its predicted increase, (3) the experimental evidence of the beneficial effect of coffee on BP, (4) the important limitations of previous meta-analyses, and (5) the new report available from a large sample of general population [17], we decided to perform a new systematic review and a dose–response meta-analysis of the prospective studies that explored the relationship between habitual coffee consumption and risk of HPT in the general population. To this end, we used more stringent inclusion criteria and tried to overcome the limitations inherent in the cited previous meta-analyses [19, 20].

Materials and methods

Data sources and searches

This meta-analysis was planned, conducted and reported according to the PRISMA statement [23] (Online Resource-Table S1). We performed a systematic search of the available publications using MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) (from 1966) and the Cochrane Library (http://onlinelibrary.wiley.com/cochranelibrary/search/), through August 2017. The search strategy without restrictions was conducted using the key terms (words in the title or abstract of the manuscript) "coffee" OR "caffeine" AND "hypertension" OR "blood pressure". Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

Study selection

To be included in the meta-analysis a published study had to meet the following criteria: (1) original article, (2) prospective design, (3) adult population, (4) assessment of coffee cups consumption per day as baseline exposure, (5) diagnosis of HPT as outcome, (6) indication of the number of participants exposed and the rate or number of events in different categories of coffee cups intake per day, (7) assessment of relative risk (RR) or hazard ratio (HR) for three or more quantitative categories of coffee cups intake, (8) follow-up of at least 2 years (mean or median).

Data extraction and quality assessment

Two reviewers (LD and ELF) independently assessed study eligibility and extracted the data. Discrepancies about inclusion of studies and interpretation of data were resolved in conference, and consensus was reached after discussion. The following characteristics of the identified studies and respective populations were recorded: publication reference, total number of participants, number of participants that developed HPT, gender, country, age, follow-up, outcome assessment method, coffee intake assessment method.

The quality of the studies included in the meta-analysis was evaluated by the Newcastle-Ottawa Scale [24]. LD end ELF developed the evaluation criteria. A greater score was considered to be an indicator of better quality on a scale of 9 (Online Resource-Table S2). Funding sources for the various studies, if any, are reported in Online Resource-Table S3.

Statistical analysis

A random-effect dose–response meta-analysis was performed [25, 26], which takes into account the correlation between the RR estimates across categories of coffee consumption. The median coffee consumption for each specific category was assigned to each corresponding RR estimate. If the median consumption was not reported by the authors, the midpoint between the upper and lower boundary was used. If the lowest category was open-ended, its lower boundary was set to zero. If the upper boundary of the highest category was left unspecified, we assumed the category to be of the same amplitude as the preceding one. The possibility of non-linear relationship was explored by modeling coffee consumption using restricted cubic splines with three knots at fixed percentiles (25, 50, and 75%) of coffee distribution. Departure from linearity was assessed by testing the null hypothesis that the coefficient of the second spline was equal to zero [27].

Statistical heterogeneity across studies was assessed using the Q and I^2 statistics [28]. Funnel plots were constructed and visually assessed for the presence of publication bias, and the Egger's test was used to test for funnel plot asymmetry [29]. In the case of significant funnel plot asymmetry, suggesting a number of possibly "missing" publications, the pooled RR estimate was recalculated based on the estimated number of "missing" studies and their effect sizes and SEs, a method known as "trim and fill" [30]. Meta-regression analysis was used to identify associations between risk of HPT and relevant study's or patients' characteristics as possible sources of heterogeneity.

For the dose–response analysis, it was necessary to account for the different amounts of beverage contained in 1 cup of coffee according to the different authors (~ 100 mL for Hu and coworkers [31], ~ 177 mL for Rhee and colleagues [17], and ~ 200 mL for the other American studies [18, 32]). Then, the results were leveled to ~ 200 mL for 1-cup of coffee.

All statistical analyses were performed using the Stata Corp. software (version 11.2) and the MIX software (version 1.7).

Results

Of a total of 2547 publications retrieved (Fig. 1), eight studies were potentially relevant and reviewed in full-text [17, 18, 21, 22, 31–34]. However, four of these studies were not included in the analysis, because two of them reported an inaccurate expression of risk [22, 33], one considered participants who were already hypertensive at baseline [21], and one reported not comparable results [34]. One of the four included studies reported the results of two cohorts of women, hence we considered these cohorts separately [18]. Therefore, overall 4 studies (5 cohorts) met the inclusion criteria and were eventually used for the meta-analysis [17, 18, 31, 32]. A total of 196,256 total participants from 2 countries (4 cohorts from the USA and 1 from Finland) were included in the meta-analysis were included in the meta-analysis. Detailed figures on population size, number of HPT cases, and general characteristics of the studies included in the meta-analysis are given in Table 1. Two studies recruited three large cohorts of young, middle-aged and post-menopausal women [17, 18], one was made of a small cohort of young men [32] and one included a large cohort of both male and female individuals [31]. Coffee intake was assessed in two studies by a dietary survey [18, 32]: in one of them there was a specific question on the number of coffee cups

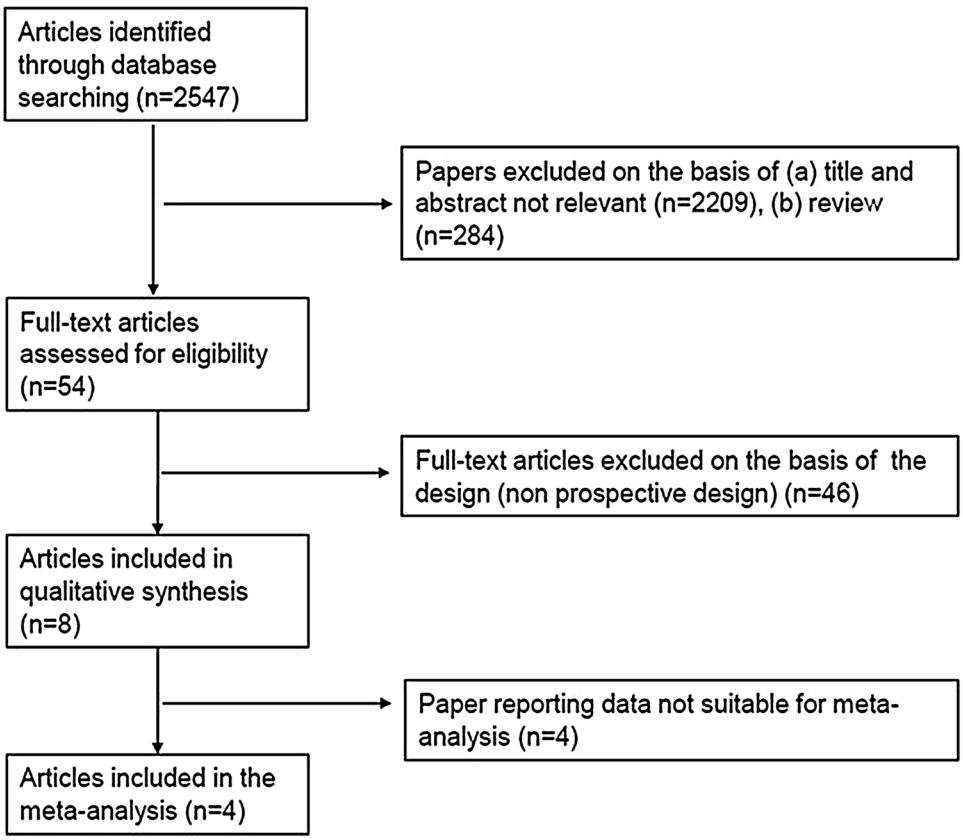

Fig. 1 Stepwise procedure for selection of the studies. Flowchart indicating the results of the systematic review with inclusions and exclusions

Table 1 Characteristics of the prospective studies included in the meta-analysis

First author, year (ref)	Country	Gender	Participants (*n*)	No. of cases	Age (years) [range]	Follow-up (years)	Outcome (s)	Outcome assessment	Coffee intake assessment	Quality assessment	Factors controlled for in multivariate analysis
Klag, 2002 [32]	USA	Men	1017	281	26 [–]	33	Diagnosis of hypertension	Self-reported, confirmed by internist	Questionnaire	8	Age, BMI, family history of hypertension, physical activity, smoking, alcohol intake
Winkelmayer, 2005 [18]	USA	Women	(I) 53,175 (II) 87,369	19,364 13,468	55.4 [30–55] 36.0 [25–42]	12	Diagnosis of hypertension	Self-reported	FFQ	7	Age, BMI, alcohol intake, family history of hypertension, physical activity, smoking (plus oral contraceptive use in II)
Hu, 2007 [31]	Finland	Men and Women	24,710	2505*	43.5 [25–64]	13.2	Start of antihypertensive treatment	Direct assessment	Self-administered questionnaire	8	Age, gender, BMI, baseline systolic blood pressure, education, physical activity, smoking, alcohol intake, high cholesterol, history of diabetes, intake of tea, fruit, vegetables, sausage, and bread, and study year
Rhee, 2016 [17]	USA	Women	29,985	5566	62.5 [50–79]	3	Diagnosis of hypertension	Direct assessment	Self-administered FFQ	7	Age, baseline blood pressure, BMI, physical activity ,hormone replacement therapy, alcohol intake, smoking, total caloric intake, and intake of sodium, magnesium, calcium, potassium, and phosphorus

*n of patients that started antihypertensive treatment; FFQ: food frequency questionnaire

consumed every day and the information on caffeinated coffee was considered for the analysis [32], while in the other investigation a validated structured food frequency questionnaires on intake of foods and beverages was used, including a section on common beverages with or without caffeine [18]. In two other studies, coffee intake was assessed by a validated self-administered questionnaire [17, 31], including a question on the number of coffee cups consumed daily, but only one included the information on caffeinated or decaffeinated coffee [17].

The follow-up period ranged between 3 and 33 years. The overall number of participants who became hypertensive during the follow-up period in the four studies was 41,184. The endpoint was assessed by direct BP measurement [17] or by direct records of antihypertensive therapy initiation [31]. In another study self-reported information on the outcome was confirmed by an internist [32], while only one study considered self-reported information [18]. In all five cohorts, the multivariate model included the adjustment for age, BMI, smoking, physical activity, and alcohol intake, while only two studies also adjusted for baseline blood pressure [17, 31], and one for sodium and potassium intake [17]. All the studies had high quality scores (Table 1, Online Resource-Table S2).

Meta-analysis

The analysis of departure from linearity indicated indeed a non-linear association between coffee consumption and risk of HPT (p for non-linearity < 0.001). Compared with no coffee consumption, one or two cups of coffee per day were not significantly associated with risk of HPT (1 cup: RR = 1.00, 95% CI = 0.99 to 1.01; 2 cups: RR = 0.99, 95% CI = 0.97 to 1.02) (Fig. 2). On the other hand, a significant protective effect of coffee consumption was found for higher levels of reported coffee intake in the range of 3–7 cups per day compared with no coffee consumption (Fig. 2).

The assessment of individual studies showed a trend toward a favorable association between coffee intake and risk of HPT in three cohorts [17, 18], with significantly lower risk in two of them [18]. By contrast, a not significant adverse association was observed in the other two cohorts [31, 32].

There was low-moderate not statistically significant heterogeneity across the studies ($Q = 5.98$, $p = 0.20$, $I^2 = 33\%$). The funnel plot for the effect of coffee intake on risk of HPT was symmetrical on visual inspection, suggesting no significant publication bias, whereas the Egger's test did detect a possible publication bias (Egger's test, $p = 0.02$). Nevertheless, the "trim and fill" method, that identified 2 possibly missing studies, did not show a net change of HPT risk upon adding these two studies (pooled RR from 0.984 to 0.982).

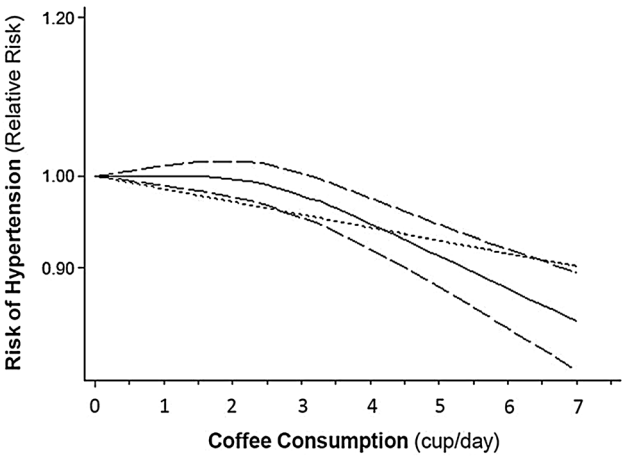

Fig. 2 Coffee consumption and Risk of Hypertension. Pooled dose–response association between coffee consumption and risk of hypertension. Coffee consumption was modeled with restricted cubic splines in a multivariate random-effects dose–response model (solid line). Dashed lines represent the 95% confidence intervals for the spline model. The dotted line represents the linear trend. The vertical axis is on a log scale. 1 cup of coffee ~ 200 mL. Risk of hypertension for 1 cup per day: RR = 1.00, 95% CI = 0.99 to 1.01; 2 cups per day: RR = 0.99, 95% CI = 0.97 to 1.02; 3–4 cups per day: RR = 0.97, 95% CI = 0.94 to 0.99; > 4–5 cups per day: RR = 0.94, 95% CI = 0.91 to 0.97; > 5–6 cups per day: RR = 0.90, 95% CI = 0.86 to 0.0.93; > 6–7 cups per day: RR = 0.86, 95% CI = 0.82 to 0.91 compared with no coffee consumption

Meta-regression analysis did not find any significant source of heterogeneity with respect to the cohorts' characteristics, i.e., age, length of follow-up, year of publication ($p > 0.05$).

Discussion

Main study results

The results of this meta-analysis of the available prospective studies involving general population samples indicate that habitual coffee consumption is not associated with increased risk of HPT. In fact, a non-linear dose–response association was detected between coffee consumption and the rate of incident HPT with evidence of a statistically significant protective effect starting with the intake of 3 cups of coffee per day.

Strengths and limitations

The results are strengthened by the large number of participants (~ 200,000) in a wide age range, by the extended length of follow-up, by the low heterogeneity among studies, and by the feature of low risk of bias in all the studies included.

Limitations are given in the first place by the observational nature of the studies dealt with by this meta-analysis which impairs any conclusion about a possible cause-effect relationship; in the second place, by the geographical limitation of the available studies to the American continent and Finland, countries in which the type, composition, preparation, and amount of the coffee beverage consumed is markedly different from the one consumed in other parts of the world. This notwithstanding, previous evidence showed no substantial difference in using adjusted or unadjusted measures of coffee with regard to the study outcome [35]. In addition our results were leveled to ~ 200 mL per cup of coffee.

The self-reported coffee consumption could be a limitation. However, the recall of coffee intake was valid and reproducible [36, 37]. Likewise, a potential limitation may be the heterogeneity in the outcome assessment, since in three studies there was a direct assessment and in one self-reported information [18], that anyhow was found to be highly reliable [38].

Furthermore, differences in HPT diagnosis could be a source of heterogeneity, because for instance one study considered the prescription of antihypertensive treatment as the only diagnostic index of HPT [31], thus underestimating the diagnosis. However, the observational design and the process of meta-analysis, with the calculation of a pooled estimate of the effect in a large number of participants, are functional to overcome at least in part this problem.

Of note, although all the included studies adjusted for several relevant confounding factors (including age, body mass index, smoking, physical activity, alcohol consumption), residual confounding by other potential factors (e.g., sodium and potassium intake) is not possible to rule out.

Finally, further limitations are given by the relatively small number of studies and cohorts available, by the residual possibility of publication bias and by the difficulty to draw definite conclusions with regard to the interaction with age,gender and race given the peculiar composition of the study cohorts available.

Other meta-analyses have previously evaluated the relationship between coffee consumption and HPT risk [19, 20]. Zhang and collaborators found an inverse "J-shape" relationship, with increased risk up to 3 cups per day and a not significant slight decrease for greater consumption [19]. However, the results of this study had an important limitation in the inclusion of a small Italian study of previously diagnosed hypertensive participants [21] and another European study reporting an inaccurate expression of risk [22]. The other meta-analysis by Steffen and coworkers, showing no association between coffee consumption and HPT risk [20], was faulted by pooling in the analysis the risks associated with any amount of coffee consumption from all studies. In addition, also this meta-analysis included a cohort of patients previously diagnosed as hypertensive [21].

Our results are also in agreement with a recent study on a large Asian population, in which a higher coffee intake was associated with significant lower risk of HPT [34]. However, in this study the consumption of one cup of coffee per day was considered as reference category, hence the risk of HPT for this prevalent category of consumption in respect to lower intake was not assessed.

Possible mechanisms of the effect of coffee consumption on risk of hypertension

Although, as stated above, our results do not allow to draw a conclusion about cause-effect relationships, it is reasonable to speculate on the possible mechanisms of the putative protective effect of habitual coffee consumption against the development of HPT. Coffee is a complex beverage containing thousands of bioactive elements in addition to caffeine, its major compound [39]. Although some evidence showed that caffeine has an acute BP raising effect [15, 16], in particular in hypertensive individuals [15, 40], a number of long-term prospective observational studies [17, 18] and experimental investigations did not support an increased risk of HPT in habitual coffee drinkers [12, 41, 42]. In keeping with these findings, it was shown that the production of BP counter-regulatory hormones upon habitual coffee intake may induce tolerance to the BP raising effect of caffeine [41]. In addition, caffeine has diuretic and natriuretic activity [12, 42] that is mediated by blockade of the adenosine A1 receptor [43–46]. Other ingredients of coffee have favorable effects on BP. In particular, minerals, such as potassium and magnesium, and antioxidant compounds [14, 39] can contribute to the beneficial effect on BP. A particularly favorable effect has been attributed to chlorogenic acid (a major polyphenol in coffee), which exhibits anti-inflammatory activity by inhibiting the production of such mediators as TNF-α and IL-6 [39]. In particular, chlorogenic acid inhibits the generation of intracellular superoxide anion [47] and the activity of angiotensin-converting enzyme [48, 49] through reduced generation of NAD(P)H-dependent superoxide [13, 50]. Among the chlorogenic acid metabolites, ferulic acid may have a favorable effect on BP by increasing nitric oxide bioavailability and enhancing acetylcholine-induced endothelial-dependent vasodilation [51, 52].Coffee also contains high amounts of soluble fiber and polyphenols [53], that may have beneficial effects on BP [54].

In addition, the beneficial effect of coffee consumption on BP may be mediated by its inverse relationship with serum uric acid concentration [55–57], that is a predictor of cardiovascular risk [58]. A plausible mechanism involved is the improvement in insulin sensitivity induced by non-caffeine compounds of coffee, including potassium, magnesium and chlorogenic acid [59, 60]. In particular, polyphenols ameliorate acute insulin secretion and reduce postprandial glycemic

responses and fasting hyperglycemia by the activation of insulin receptors, the modulation of glucose release from the liver and of glucose uptake in insulin-sensitive tissues [61], and the inhibition of intestinal glucose uptake [62]. In addition, coffee appears to contain substances which inhibit xanthine oxidase and thus the conversion of xanthine to uric acid [55]. A beneficial effect of coffee on glucose metabolism is also exerted by trigonelline [63, 64], a phytoestrogen, in particular by the interaction with dipeptidylpeptidase-4 which enhances the concentration of active GLP-1 [65]. On the other hand, trigonelline may be also impact BP by reducing the plasma angiotensin-converting-enzyme (ACE) [65, 66].

Noteworthy, the effects of coffee on BP and glucose metabolism seem common to those of cocoa. The common compounds such as minerals (K, Mg), soluble fiber and polyphenols, and the source of caffeine in cocoa [67], may explain these similar effects [68, 69].

Also the inverse association between coffee intake and body weight could contribute to its favorable effect on BP. This relationship was found both in observational studies [70, 71] and in experimental studies on rodents [72, 73], in which a decrease in adipose-pad weight [72, 73] and on the number of adipocytes [73] were also found.

Finally, also roasting may help explain the antihypertensive effect of coffee. Indeed, the roasting of coffee beans induces the synthesis of hydroxyhydroquinone that inhibits the effect of chlorogenic acid [74, 75]. Likewise, in addition to the type of coffee, also the dietary fiber content of coffee depends on the degree of roasting and grinding, and on the brewing procedure [76].

Genetic factors could affect the relationship between coffee intake and HPT, since caffeine is metabolized by the liver cytochrome P450-1A2 (CYP1A2) enzyme [77]. Various factors may interact with this activity, such as cigarette smoking [77–79], an inducer of CYP1A2 [80]. Indeed, CYP1A2 variants were associated with HPT in non-smokers, while not in smokers. Moreover, higher CYP1A2 activity seems linearly associated with lower BP in non-smokers who reported higher caffeine consumption and in those who quit smoking [77]. In our meta-analysis, no studies investigated the role of genes in the association between coffee and HPT risk, but all the studies accounted for the effect of smoking.

Conclusions

The results of our study show that habitual coffee consumption is not associated with increased risk of HPT and that actually regular coffee intake was associated with apparent protection against the development of HPT through a non-linear relationship. These results are in keeping with the evidence of a statistical inverse association between regular coffee consumption and risk of cardiovascular disease [6, 7].

Given the importance of HPT as a major cause of CVD [8, 11] and popularity of coffee consumption around the world [1–3, 81, 82], the relationship between these two factors assumes considerable relevance.

Although a cause-effect relationship between coffee consumption and risk of HPT cannot be stated based on the evidence available, our results indicate that there is currently no reason for the adult general population to refrain from coffee consumption for the prevention of HPT and CVD. Further studies are warranted to try and determine a cause-effect relationship, to discriminate the role of caffeine and of other component of the various coffee beverages, to assess the effect of different types of coffee consumed in different parts of the world, and to overcome the lacking or very limited evidence with respect to the interactions with gender, age and ethnicity. In particular, intervention studies based on careful assessment of coffee intake should evaluate the mechanisms of its antihypertensive effect, namely its interaction with renal sodium handling and endothelial function, taking into account the interaction between coffee consumption and lifestyle factors (e.g., diet, physical activity, smoking, etc.), cardiovascular risk factors and polymorphisms in genes involved in the metabolism of coffee.

Author contributions LD conceived the study aims and design, contributed to the systematic review and to the data extraction, performed the analysis, interpreted the results, and drafted the manuscript. ELF contributed to the systematic review and to the data extraction, contributed to interpretation of results, and drafted the manuscript. LS contributed to the preparation of revised version of the manuscript. FG contributed to the systematic review and to interpretation of results, and drafted the manuscript. PS contributed to the systematic review, interpretation of results and drafted the manuscript.

Compliance with ethical standards

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