RESEARCH ARTICLE

Coffee, tea, caffeine and risk of depression: A systematic review and dose–response meta-analysis of observational studies

Giuseppe Grosso[1], Agnieszka Micek[2], Sabrina Castellano[3], Andzrej Pajak[2] and Fabio Galvano[3]

[1] Integrated Cancer Registry of Catania-Messina-Siracusa-Enna, Catania, Italy
[2] Department of Epidemiology and Population Studies, Jagiellonian University Medical College, Krakow, Poland
[3] Department of Biomedical and Biotechnological Sciences, Section of Pharmacology and Biochemistry, University of Catania, Catania, Italy

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Scope: The aim of the study was to systematically review and analyze results from observational studies on coffee, caffeine, and tea consumption and association or risk of depression.
Methods and results: Embase and PubMed databases were searched from inception to June 2015 for observational studies reporting the odds ratios or relative risks (RRs) and 95% confidence intervals (CI) of depression by coffee/tea/caffeine consumption. Random effects models, subgroup analyses, and dose–response analyses were performed. Twelve studies with 23 datasets were included in the meta-analysis, accounting for a total of 346 913 individuals and 8146 cases of depression. Compared to individuals with lower coffee consumption, those with higher intakes had pooled RR of depression of 0.76 (95% CI: 0.64, 0.91). Dose–response effect suggests a nonlinear J-shaped relation between coffee consumption and risk of depression with a peak of protective effect for 400 mL/day. A borderline nonsignificant association between tea consumption and risk of depression was found (RR 0.70, 95% CI: 0.48, 1.01), while significant results were found only for analysis of prospective studies regarding caffeine consumption (RR = 0.84, 95% CI: 0.75, 0.93).
Conclusion: This study suggests a protective effect of coffee and, partially, of tea and caffeine on risk of depression.

Keywords:
Caffeine / Coffee / Depression / Meta-analysis / Tea

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1 Introduction

Depression is a leading cause of disability worldwide [1]. Its prevalence varies largely by country, ranging from 3% of adult population in Japan to 17% in the United States [1]. Overall, incidence of depressive disorders is progressively increasing, ranking among the leading conditions contributing to the global burden of disease [2]. Recent epidemiological evidence suggests that dietary factors may play an important role in the development of depression. A number of investigations support the hypothesis that certain dietary patterns (i.e., plant-based or Mediterranean) may decrease risk of depression due to richness in antioxidant and anti-inflammatory compounds [3–5]. Pooled analyses of randomized controlled trials suggested that n-3 PUFAs might be among the main candidates to exert a protective effect against depression [6]. Nevertheless, the impact of other important food sources of antioxidants or compounds directly acting at central nervous system level is largely unexplored.

Coffee and tea are the most consumed beverages worldwide after water. Drinking pattern, amount of intake, and type of beverage vary with a great extent according to cultural and geographical background. Coffee has been reported to be highly consumed in Central-Northern European countries and the United States, while tea is mainly consumed in Eastern Europe and Asian countries [7]. Due to their impact on various populations, it is not surprising that coffee and tea are

Correspondence: Giuseppe Grosso
E-mail: giuseppe.grosso@studium.unict.it

Abbreviations: **HR**, hazard ratio; **OR**, odds ratio; **RR**, relative risk

the main sources of a number of compounds demonstrating potential beneficial effects against depression. Among the most important, polyphenols such as chlorogenic acid and catechins shown antioxidant and anti-inflammatory actions, while caffeine has been suggested to modulate dopaminergic transmission and facilitate the release of serotonin [8]. However, up to date information from population studies on the association between these beverages and depressive disorders are sparse and inconsistent. Coffee and tea consumption has been considered mostly as dichotomous variable (daily intake yes/no) with poor or limited data on quantity and pattern of intake [9, 10]. Findings from studies performed in clinical settings on patients with psychiatric disorders suffer of similar limitations, accounting for contrasting results [11, 12]. However, a recent analysis reported a strong inverse association between coffee consumption and suicide, which is highly associated with depression [13]. Moreover, a meta-analysis recently published during the preparation of the present study demonstrated an association between tea consumption and depression, despite it included low-quality studies lacking of dose of exposure [14]. Overall, it would be of interest to evaluate whether coffee and tea drinking is associated with depressive status in nonpsychiatric patients. Therefore, we performed a meta-analysis of observational studies to compare the risk of depression in high versus low coffee and tea drinkers, also in relation to caffeine intake, and to evaluate whether a dose–response association existed.

2 Subjects and methods

2.1 Search strategy

We performed a systematic search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Embase (http://www.embase.com/) databases of all English language studies published up to June 2015. The search terms used for the study selection were "coffee," "tea," and "caffeine" combined with "depression," "depressive disorder," or "depressive symptom." Inclusion criteria were as follows: (i) had a cross-sectional, case-control, or prospective design, (ii) evaluated association between consumption of coffee/tea/caffeine and depression, (iii) did not included patients with psychiatric or neurological diseases, (iv) assessed and reported hazard ratios (HRs) or odds ratios (ORs) and the corresponding 95% confidence interval (CI) for depression, and (v) reported dose of coffee/tea/caffeine consumption. Reference lists of included manuscripts were also examined for any additional study not previously identified. If more than one article reported duplicated data, only the most comprehensive and most updated study was included in the meta-analysis. The selection process was independently performed by two authors (G.G. and S.C.) and retrieved articles examined.

2.2 Data extraction

Data were abstracted from identified study by using a standardized extraction form. The following information was collected: (i) first author name; (ii) year of publication; (iii) country; (iv) number of participants; (v) sex of participants; (vi) age range of the study population at baseline; (vii) ascertainment of cases/depression scale used; (viii) distributions of cases/person-years, HRs/ORs, and 95% CIs for all categories of exposure; (ix) covariates used in adjustments. This process was independently performed by two authors (G.G. and A.M.) and discrepancies were discussed and resolved by consensus.

The quality of each study was assessed according to the Newcastle-Ottawa Quality Assessment Scale [15], which consists of three variables of quality as follows: selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (9 representing the highest quality). Studies scoring 7–9 points, 3–6 points, and 0–3 points were identified as high, moderate, and low quality, respectively.

2.3 Statistical analysis

In this meta-analysis, ORs and HRs were deemed equivalent to relative risks (RRs) [16]. ORs/HRs with 95% CI for all categories of exposure were extracted for the analysis and random effects models were used to calculate pooled RR with 95% CIs for highest versus lowest category of exposure. The risk estimate from the most fully adjusted models in the analysis of the pooled RR was used. Heterogeneity was assessed by using the Q test and I^2 statistic. The level of significance for the Q test was defined as $p < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values $\leq$25%, $\leq$50%, $\leq$75%, and $>$75% indicated no, small, moderate, and significant heterogeneity, respectively. A sensitivity analysis by exclusion of one study at a time was performed to assess the stability of results and potential sources of heterogeneity. Subgroup analyses were also performed to check for potential source of heterogeneity according to geographical area, sample size, year of publication, study quality, type of exposure ascertainment method, and length of follow-up. Publication bias was evaluated by a visual investigation of funnel plots for potential asymmetry.

A dose–response analysis was performed by using the method reported by Greenland and Orsini to calculate study-specific slopes (generalized least squares) on the basis of results across categories of coffee/caffeine intake [17, 18]. We extracted data on the amount of coffee/tea/caffeine intake, distributions of cases and person-years (when available), and ORs/HRs with 95% CIs for $\geq$3 exposure categories. The median or mean intake of coffee/caffeine in each category was assigned to the corresponding OR/HR with the 95% CI for

each study. When coffee/caffeine consumption was reported by ranges of intake, the midpoint of the range was used. When the highest category was open ended, we assumed the width of the category to be the same as the adjacent category. When the lowest category was open ended, we set the lower boundary to zero. Furthermore, dose–response analysis was modeled by using restricted cubic splines with three knots at fixed percentiles (25%, 50%, and 75%) of the distribution [19]. The description of methodology is presented elsewhere [19]. Briefly, in the first stage a restricted cubic spline model with two spline transformations (three knots minus one) was fitted taking into account the correlation within each set of retrieved RRs. In the second stage, we combined the two regression coefficients and the variance/covariance matrices that had been estimated within each study, using the multivariate extension of the method of moments in a multivariate random-effects meta-analysis. All analyses were performed with R version 3.0.3 software (Development Core Team).

3 Results

3.1 Study characteristics

The process of identification and study selection is summarized in Fig. 1. Among the initial 123 articles screened on the basis of title, 31 articles were screened by reading the full texts. Thirteen studies were excluded after a full-text examination because reported insufficient statistics ($n = 6$) were conducted on psychiatric patients ($n = 2$), did not reported coffee/tea dose of consumption ($n = 6$), considered coffee among the adjustments ($n = 2$), and did not studied depression as outcome ($n = 6$). This inclusion strategy resulted in the final selection of 12 studies and 23 datasets eligible to be included in the analysis [20–31], accounting for a total of 346 913 individuals and 8146 cases of depression.

Table 1 shows the information extracted from all included studies. The results of quality assessment yielded a score of 7 or above for 9 of 12 studies. Among them, two studies considered coffee consumption as the main variable of interest [25, 28], three considered tea [29–31], three considered caffeine [20, 21, 27], and four considered more than one source of exposure [22–24,26]. Seven studies had a cross-sectional design [20,21,25,26,28,29,31], four were prospective [22–24, 30], and one study reported both cross-sectional and prospective evaluation [27]. The studies have been conducted in Finland [22], Japan [25, 26, 29], United States [13, 20, 24], China [30], Singapore [30], United Kingdom [21], Korea [28], and France [27]. Most of the studies defined cases of depression using validated depression severity scales assessed by questionnaire, while two studies [20, 27] used personal interviews. Caffeine intake was estimated mainly from consumption of coffee and tea, as soft drinks containing caffeine were rarely consumed among elderly samples.

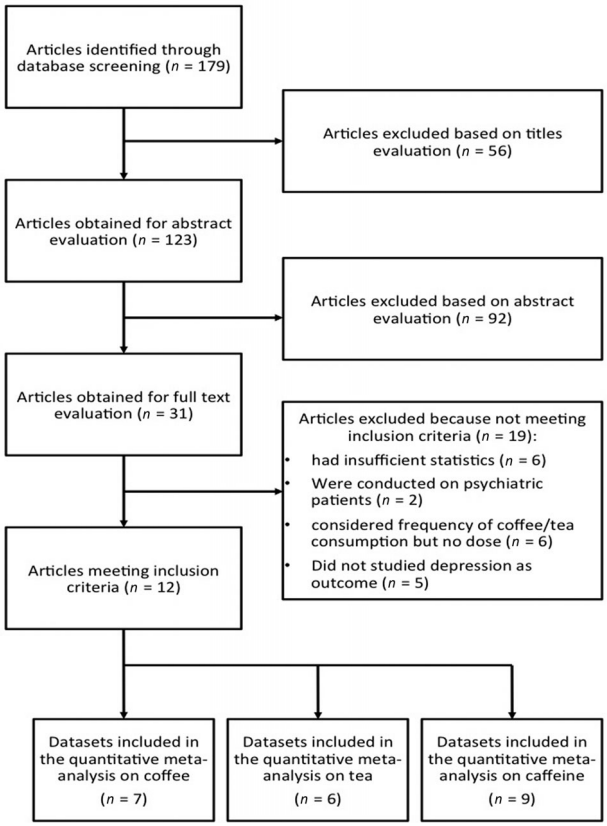

Figure 1. Flowchart indicating the results of the systematic review of relevant studies exploring association between coffee/caffeine intake and risk of depression.

3.2 Association of coffee consumption and depression

Six articles [22–26, 28] including 327 697 individuals and 5253 cases of depression were considered for the analysis of the extreme categories of coffee consumption and depression. RRs with 95% CIs of depression for the highest versus the lowest (reference) coffee consumption category was calculated for seven datasets and resulted in a 24% decreased risk of depression (RR = 0.76, 95% CI: 0.64, 0.91; Fig. 2). However, small heterogeneity was found among prospective and cross-sectional studies (Fig. 2). Among prospective, all studies reported decreased risk of depression for higher intake of coffee, while the main contributor for heterogeneity was the study of Ruusunen et al. [22] due to large 95% CI (the study accounted for only 49 cases of depression of 2183 individuals). Among cross-sectional investigations, the study of Omagari et al. [25] reported a much lower risk estimate than the others and very large CIs due to small sample and low number of cases (89 individuals and 15 depressed patients). Visual inspection of the funnel plot suggested asymmetry toward the study of Omagari et al. [25] (Supporting Information Fig. 1). Possible reasons may be study size, study quality, and lack of adjustments for any confounders. After exclusion of

Table 1. Characteristics of studies and participants included in the meta-analysis of the association between coffee consumption, caffeine intake, and risk of depression

Author, year	Study design	Setting	Population	No. of cases	Outcome assessment	Exposure	Exposure category	RR (95% CI) for the highest versus lowest category	Adjustments	Study quality
Kendler, 2006 [20]	Cross-sectional	United States	3706	NA	DSM-III-R criteria (personal interview)	Caffeine (from caffeinated beverages)	>650 mg/day	1.79 (1.47, 217)	Age, gender	6
Smith, 2009 [21]	Cross-sectional	United Kingdom	3223	NA	HADS	Caffeine (from caffeinated beverages)	>250 mg/day	0.12 (0.1, 0.2)	NA	6
Niu, 2009 [31]	Cross-sectional	Japan	1058	484	Geriatric Depression Scale (GDS)	Tea	>4 cups/day	0.56 (0.39, 0.81)	Age; gender; BMI; hypertension; diabetes; history of cardiovascular diseases, cancer, or arthritis; high C-reactive protein; history of smoking and drinking habits; physical activity; cognitive status; impaired instrumental activities of daily living; self-reported body pain; educational level; living alone; marital status; serum albumin concentration, total energy intake, intakes per 2000 kcal of energy intake as protein and folate, black or oolong tea consumption, coffee consumption, lack of perceived social support and visiting friends	
Ruusunen, 2010 [22]	Prospective	Finland	2232	49	CES-D	Coffee	>813 mL/day	0.25 (0.07, 0.91)	Age, examination year, socioeconomic status, smoking, alcohol consumption, maximal oxygen uptake, BMI, daily intake of folate and PUFA, and Human Population Laboratory Depression Scale scores	8
Ruusunen, 2010 [22]	Prospective	Finland	2232	49	CES-D	Caffeine (from coffee and tea)	>781 mg/day	0.85 (0.34, 2.15)	Age, examination year, socioeconomic status, smoking, alcohol consumption, maximal oxygen uptake, BMI, daily intake of folate and PUFA, and Human Population Laboratory Depression Scale scores	
Chen, 2010 [29]	Cross-sectional	China	1399	363	CES-D	Tea	>100 g/month	0.39 (0.19, 0.84)	Age at cancer diagnosis, duration, income, marital status, exercise, comorbidity, menopausal symptoms, metastasis, radiotherapy, and quality of life	

Table 1. Continued

Author, year	Study design	Setting	Population	No. of cases	Outcome assessment	Exposure	Exposure category	RR (95% CI) for the highest versus lowest category	Adjustments	Study quality
Lucas, 2011 [23]	Prospective	United States	50 739	2607	Self-reported physician-diagnosed depression and antidepressant use	Coffee	>4 cups/day	0.80 (0.64, 0.99)	Age; interval; total energy intake; current menopausal hormones; smoking status; BMI; physical activity; marital status; not involved in a church, volunteer, or community group; retired; diabetes mellitus; cancer; hypertension; myocardial infarction or angina; and Mental Health Index score	8
Lucas, 2011 [23]	Prospective	United States	50 739	2607	Self-reported physician-diagnosed depression and antidepressant use	Caffeine (from coffee, tea, caffeinated soft drinks, chocolate)	>550 mg/day	0.80 (0.68, 0.95)	Age; interval; total energy intake; current menopausal hormones; smoking status; BMI; physical activity; marital status; not involved in a church, volunteer, or community group; retired; diabetes mellitus; cancer; hypertension; myocardial infarction or angina; and Mental Health Index score	8
Feng, 2012 [30]	Prospective	Singapore	1615	73	GDS	Tea	>6 cups/day	0.30 (0.11, 0.85)	Age, education, housing time, marital status, physical exercise, social and productive activities, Mini-Mental State Examination, GDS score at baseline.	
Pham, 2013 [26]	Cross-sectional	Japan	537	157	CES-D	Coffee	>2 cups/day	0.61 (0.38, 0.98)	Age, gender, workplace, history of cancer, CVD, diabetes mellitus or chronic hepatitis, marital status, living status, overtime work, job position, occupational physical activity, non-occupational physical activity, current smoking, alcohol drinking, BMI, PUFA intake, red meat, vegetable and fruit, green tea, serum CRP, serum folate.	8
Pham, 2013 [26]	Cross-sectional	Japan	537	157	CES-D	Caffeine (from green tea and coffee)	>291 mg/day	0.57 (0.30, 1.05)	Age, gender, workplace, history of cancer, CVD, diabetes mellitus or chronic hepatitis, marital status, living status, overtime work, job position, occupational physical activity, non-occupational physical activity, current smoking, alcohol drinking, BMI, PUFA intake, red meat, vegetable and fruit, green tea, serum CRP, serum folate	8

Table 1. Continued

Author, year	Study design	Setting	Population	No. of cases	Outcome assessment	Exposure	Exposure category	RR (95% CI) for the highest versus lowest category	Adjustments	Study quality
Pham, 2013 [26]	Cross-sectional	Japan	537	157	CES-D	Tea	>4 cups/day	0.54 (0.29, 1.00)	Age, gender, workplace, history of cancer, CVD, diabetes mellitus or chronic hepatitis, marital status, living status, overtime work, job position, occupational physical activity, nonoccupational physical activity, current smoking, alcohol drinking, BMI, PUFA intake, red meat, vegetable and fruit, green tea, serum CRP, serum folate	8
Guo, 2014 [24]	Prospective	United States	263 923	2000	Self-reported physician-diagnosed depression	Coffee	>4 cups/day	0.91 (0.84, 0.98)	Age, gender, race, education, marital status, smoking, alcoholic beverage intake, physical activity, BMI, and energy intake	8
Guo, 2014 [24]	Prospective	United States	263 923	2000	Self-reported physician-diagnosed depression	Tea	>4 cups/day	1.14 (0.98, 1.31)	Age, gender, race, education, marital status, smoking, alcoholic beverage intake, physical activity, BMI, and energy intake	
Omagari [25]	Cross-sectional	Japan	89	15	HADS	Coffee	>3 cups/day	0.082 (0.009, 0.711)	None	6
Park, 2014 [28]	Cross-sectional	Korea	10 177	425	Self-reported physician-diagnosed depression	Coffee	>3 cups/day	0.41 (0.24, 0.70)	Age, gender, BMI, smoking status, alcohol consumption, physical activity, educational level, marital status, history of ischemic heart diseases and stroke, perceived stress level, consumption of green tea, soft drink, vegetable, fruit, blue-backed fish, bean and red meat	8
Ritchie, 2015 [27]	Cross-sectional	France	8215	1973	CES-D or DSM-IV criteria (personal interview)	Caffeine (coffee and tea)	>3 cups/day	M 0.94 (0.76, 1.18) F 0.92 (0.80, 1.06)	Age, gender, education, cardiovascular pathologies, respiratory pathologies, hypertension, BMI, HDL cholesterol, triglycerides, mobility, diabetes	8
Ritchie, 2015 [27]	Prospective	France	5785	NA	CES-D or DSM-IV criteria (personal interview)	Caffeine (coffee and tea)	>3 cups/day	M 0.85 (0.66, 1.08) F0.86 (0.74, 1.01)	Age, gender, education, cardiovascular pathologies, respiratory pathologies, hypertension, BMI, HDL cholesterol, triglycerides, mobility, diabetes	8

CES-D, Center for Epidemiological Studies-Depression scale; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HADS, Hospital Anxiety and Depression Scale; RR, risk ratio.

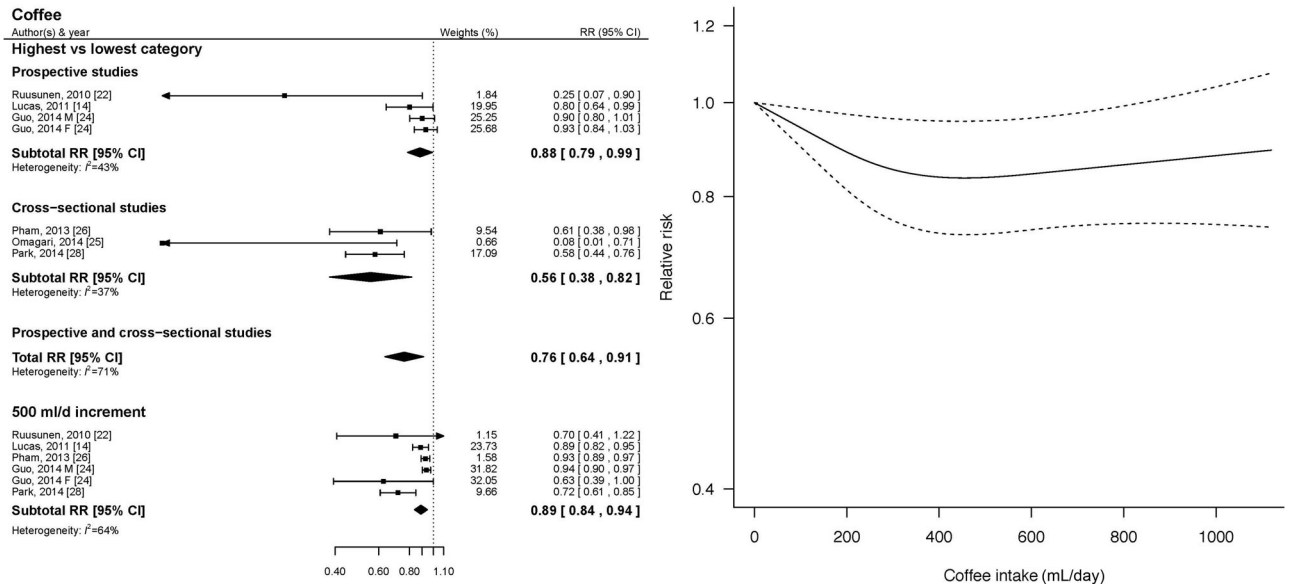

Figure 2. Forest plot of summary relative risks (RRs) of depression for higher versus low level of coffee consumption and dose–response analysis.

studies one at a time, absence of the study of either Ruusunen et al. [22] or Omagari et al. [25] did not change overall risk estimates, but leaded to significant reduction of heterogeneity ($I^2 = 0\%$) and confirmed a significant reduced risk of depression among prospective studies (RR = 0.90, 95% CI: 0.84, 0.97). Subgroup analyses were conducted to test the stability of results (Table 2). Overall, higher coffee consumption had a protective effect against depression in all subgroups except when analyses were not adjusted for dietary variables or social isolation (Supporting Information Table 1).

A dose–response analysis was performed pooling together five studies including six datasets. The cumulative RR of depression for an increase of 500 mL/day of coffee intake resulted in 0.89 (95% CI: 0.84, 0.94; Fig. 2), despite with moderate evidence of heterogeneity ($I^2 = 64.39\%$) and asymmetry at funnel plot toward the study of Pham et al. [26] due to large intervention effect (Supporting Information Fig. 1). Sensitivity analysis revealed that heterogeneity was due to the study of Ruusunen et al. [22], which exclusion dropped heterogeneity but maintained unchanged risk estimates. Visual examination of the dose–response effect (Fig. 2) suggests a non-linear J-shaped relation between coffee consumption and risk of depression with a peak of protective effect for 400 mL/day, which was stable toward slight increase for higher intakes (Table 2). In the subgroup analyses, the associations between coffee consumption and risk of depression were similar to the previous analyses, but further lack of significance was found for grouped analysis of cross-sectional studies, those conducted in countries with low prevalence of depression, and not controlled for physical activity status (Supporting Information Table 1).

3.3 Association of tea consumption and depression

A total of five studies [24, 26, 29–31] including 268 532 individuals and 3077 cases of depression were considered for

Table 2. Dose–response analyses for various category of exposure and risk of depression

	Dose					
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
	0 mL/day	200 mL/day	400 mL/day	600 mL/day	800 mL/day	1000 mL/day
Coffee	1.00	0.89 (0.81, 0.97)	0.84 (0.73, 0.96)	0.84 (0.74, 0.96)	0.86 (0.75, 0.99)	0.88 (0.75, 1.04)
Tea	1.00	0.98 (0.89, 1.07)	0.97 (0.87, 1.08)	0.98 (0.86, 1.11)	0.99 (0.79, 1.25)	1.01 (0.71, 1.43)
Model 1[a)]	1.00	0.91 (0.78, 1.05)	0.84 (0.67, 1.06)	0.79 (0.62, 1.02)	0.76 (0.58, 1.00)	0.72 (0.53, 0.99)
Model 2[b)]	1.00	0.83 (0.74, 0.93)	0.72 (0.57, 0.91)	0.66 (0.46, 0.94)	0.61 (0.37, 1.01)	0.56 (0.29, 1.09)
	0 mg/day	150 mg/day	300 mg/day	450 mg/day	600 mg/day	750 mg/day
Caffeine	1.00	0.63 (0.29, 1.35)	0.45 (0.12, 1.66)	0.54 (0.22, 1.33)	0.76 (0.57, 1.02)	1.08 (0.58, 2.01)

a) Model 1 included RRs for "caffeinated hot tea" and "decaffeinated hot tea" from the study of Guo et al. [24].
b) Model 2 included RR for only "caffeinated hot tea" from the study of Guo et al. [24].

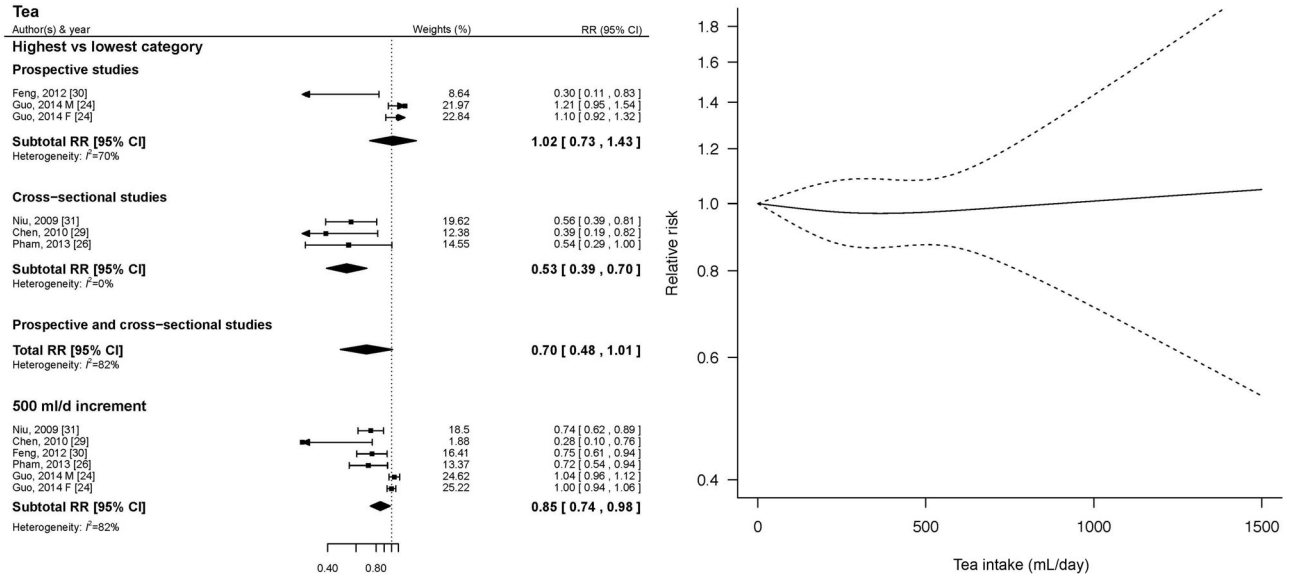

Figure 3. Forest plot of summary relative risks (RRs) of depression for higher versus low level of tea consumption and dose–response analysis.

the analysis of the extreme categories of tea consumption and depression. Pooled analysis of both cross-sectional and prospective studies showed a borderline nonsignificant association between tea consumption and risk of depression (RR 0.70, 95% CI: 0.48, 1.01; Fig. 3), with significant heterogeneity and suspect of publication bias at funnel plot (Supporting Information Fig. 2). In fact, both forest and funnel plot demonstrated heterogeneity due to the results of the study of Guo et al. [24], which reported nonsignificant increased risk of depression. The study had the largest sample size accounting for the highest weight in our models. Sensitivity and subgroup analyses confirmed that exclusion of this study resulted in a significant reduced risk of depression by tea consumption (RR 0.50, 95% CI: 0.38, 0.66) with no evidence of heterogeneity (Supporting Information Table 2).

A dose–response analysis per 500 mL/day increase of tea consumption suggested significant reduced risk of depression associated with tea consumption (RR 0.85, 95% CI: 0.74, 0.98; Fig. 3), yet with evidence of heterogeneity and conclusions of subgroup analyses due to the aforementioned study of Guo et al. [24] (Supporting Information Table 2). Visual inspection of dose–response effect (Fig. 3) revealed no significant correlation between tea and risk of depression (Table 2). However, the study of Guo et al. [24] showed also a subgroup analysis by caffeinated or decaffeinated beverages, resulting in a significant decreased risk of depression for the second and the third highest category of caffeinated tea consumption versus the lowest (reference). Therefore, two additional models including risk estimates from (i) caffeinated and decaffeinated tea and (ii) caffeinated tea only showed a potential reduced risk of depression for increased intake of tea (Supporting Information Table 2 and Supporting Information Fig. 3).

3.4 Association of caffeine consumption and depression

A total of six studies [20–23, 26, 27] including 78 829 individuals and 5211 cases of depression were considered for the analysis of the extreme categories of caffeine consumption and depression. RRs with 95% CIs of depression for the highest versus the lowest (reference) caffeine consumption category was calculated for nine datasets and resulted in nonsignificant risk estimates (RR = 0.67, 95% CI: 0.40, 1.13; Fig. 4). However, significant heterogeneity was found due to great differences observed among cross-sectional studies. In fact, pooled analysis of prospective studies resulted in significant lower risk of depression for high versus low caffeine intake (RR 0.84, 95% CI: 0.75, 0.93) with no evidence of heterogeneity, whereas results from pooled analysis of cross-sectional studies suffered by high heterogeneity due to extreme results from the studies of Kendler et al. [20] (reporting increased risk of depression for high coffee consumption). Reasons for such different results may be addressed by analyzing the study content. In fact, despite fitting the inclusion criteria for this meta-analysis, the research of Kendler et al. [20] aimed to assess "caffeine use, toxicity and dependence" and was conducted by asking the respondent to define "a time in your life when you drank caffeine the most." With such design, the authors assessed "heavy" caffeine intake (>625 mg/day) intended as potentially associated with a pathological trait. Due to the cross-sectional design, it is more likely that in this study caffeine intake was a consequence of depression rather than a potential cause. Visual inspection of the funnel plot indicated small asymmetry due to slight heterogeneity rather than publication bias (Supporting Information Fig. 4).

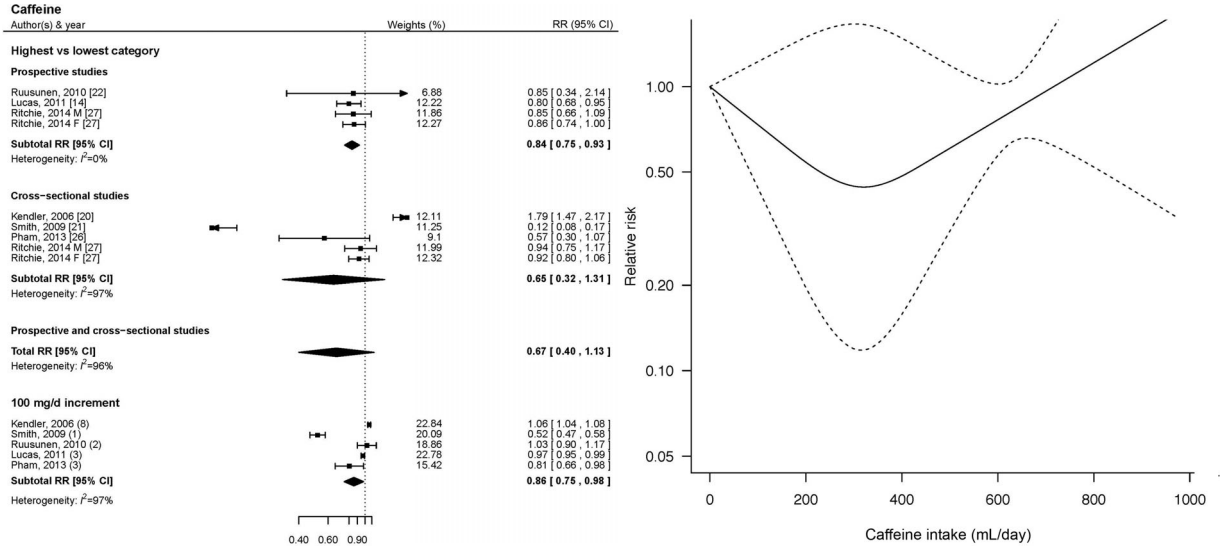

Figure 4. Forest plot of summary relative risks (RRs) of depression for higher versus low level of caffeine consumption and dose–response analysis.

Subgroup analyses were conducted to test the stability of results (Supporting Information Table 3). Grouping by study quality, excluding the studies with moderate score, leaded to significant reduction of heterogeneity ($I^2 = 0\%$) and confirmed decreased risk of depression to 13% (RR = 0.87, 95% CI: 0.79, 0.96). Overall, all other analyses were affected by significant heterogeneity due to the extreme RRs of the studies of Kendler et al. [20] and Smith [21].

The dose–response analysis for increase of 100 mg/day of caffeine resulted in significant reduced risk of depression (RR 0.86, 95% CI: 0.75, 0.98; Fig. 4), but suffered of similar limitations in terms of heterogeneity (Table 2). Sensitivity analysis revealed that heterogeneity persisted even though each study was excluded one at the time. Also visual inspection of the dose–response for caffeine intake and risk depression showed that caffeine was associated with nonsignificant decreased risk of depression only up to 300 mg/day (about 3–4 cups/day of coffee; Fig. 4). In the subgroup analyses, all analyses were affected by high heterogeneity and leaded to significant results only when considering prospective studies (Supporting Information Table 3).

4 Discussion

In this meta-analysis, we found that consumption of coffee was associated with lower risk of depression. The dose–response analysis identified a J-shaped association between coffee consumption and the risk of depression, with a decreased risk for consumption of up to about 600 mL/day. Also the analysis conducted on tea consumption and depression strongly suggested that an association may exist, but evidence was depending on datasets used in sensitivity analysis. Notably, when the analysis was conducted on caffeine, findings were similar after exclusion of studies with lower quality. However, results were not entirely overlapping, suggesting that other compounds over caffeine may contribute to the potentially protective effect of coffee against depression. Up to date, this is the first pooled analysis suggesting the potential association between coffee, tea, and caffeine consumption and depression.

Results from prospective studies on both coffee consumption and caffeine intake and risk of depression resulted in more firm findings than those with a cross-sectional design. The latter provided significant evidence of heterogeneity due to one study reporting inconsistent association between coffee and depression [20]. As discussed above, cross-sectional studies may suffer of reversal causation, as it is not possible to identify whether the variable of interest determines the outcome or the opposite. Thus, results from prospective studies are more reliable from a methodological point of view. Among other potential source of heterogeneity, other dietary components and lifestyle factors (such as physical activity, alcohol consumption, and social integration) may be potential confounders influencing the relationship between coffee consumption and depression. Overall, the analysis of association between coffee consumption and depression showed similar results in all subgroups except for studies not controlled for dietary factors and social isolation, suggesting that potential differences according background characteristics may exist. However, studies with better design (prospective) and quality were concordant that increased coffee and caffeine consumption were associated with lower risk of depression.

Regarding the association between tea consumption and depression, the analysis was puzzling due to the controversial results of the study of Guo et al. [24]. In fact, the models built with risk estimates of depression by gender from this study resulted in evident contrasting results, while when the

analysis included RR by caffeinated or decaffeinated beverages, and, in a sensitivity analysis, restricted to only caffeinated tea, pooled RR resulted significant for consumption of up to 1000 and 600 mL/day, respectively. These findings suggest that caffeine may play a role in the prevention of depression.

Recent epidemiological studies have shown several positive effects of coffee and tea consumption on health, including prevention of cardiovascular risk factors and metabolic disorders [32, 33]. However, it has been suggested that benefits provided by coffee consumption are not necessarily driven by caffeine content [34]. The mechanisms underlying the favorable association between coffee and tea consumption and depression are largely unknown, but some biological explanations have been hypothesized. As previously mentioned, a possible protective effect of coffee and tea may be mediated by their caffeine content. In fact, caffeine could stimulate the central nervous system and enhance dopaminergic neurotransmission. Our results only partially support this hypothesis, as caffeine has been demonstrated to decrease the risk of depression but the pooled analysis suffered of heterogeneity. Notably, studies responsible of heterogeneity reporting an association between caffeine intake and increased risk of depression may have suffered of reverse causation. However, it is reasonable that other mechanisms beyond the possible positive effects of coffee and tea on depression require further attention. In addition to caffeine, coffee and tea contain a number of compounds that may play a role in preventing depression. For instance, coffee compounds such as trigonelline, *N*-methylpyridinium, chlorogenic acid, catechol, pyrogallol, and 5-hydroxytryptamides have been demonstrated to increase calcium signaling and dopamine release [35]. Increased dopamine release may counteract the depressed status, as depression is associated with alteration of the dopamine system. Moreover, as depression has been also correlated with a low-grade inflammation, certain phenolic compounds contained in coffee, such as chlorogenic and caffeic acids, may exert beneficial effects through their antioxidant and anti-inflammatory activity [8]. Equally, also certain flavonoids derived from catechins, such as epigallocatechin gallate contained in tea, has been reported to exert powerful antioxidant effects and potential antidepressant-like effects probably through increasing brain-derived neurotrophic factor level, neuronal survival and plasticity, and inhibition of monoamine oxidase toward serotonin [36].

This study has several strengths. We considered three variables of interest, such as coffee, tea, and caffeine, and we investigated the dose–response relationship with risk of depression for all of them. Moreover, we included a number of subgroup analyses to test for potential confounding factors for risk of depression as well as a number of sensitivity analyses to test stability of results. However, findings have to be considered in light of some limitations. First, the number of datasets was sufficient to perform a meta-analysis, but the amount of studies was relatively low to draft substantial conclusions. Second, we found significant heterogeneity when comparing certain studies and asymmetry of funnel plots, which may weaken results. However, asymmetry of funnel plots was not necessarily indicating publication bias, rather it could depend on very small studies showing larger intervention effect because they were conducted and analyzed with less methodological rigor than others. Third, the nature of studies included in this meta-analysis was observational, thus no causal relationship can be assessed and residual confounders (i.e., quality of life, family and social support, etc.), despite partially taken into consideration in the analysis, may still remain. Forth, methods of assessment for coffee/caffeine consumption and ascertainment of depression differed across studies, adding further heterogeneity to the pooled analysis. For instance, studies included lack of information about length of consumption of caffeinated beverages or caffeine and of specific coffee type/preparation methods, which may have a confounding effect on the outcome. Moreover, in some studies the determination of a depressive disorder was based on personal interviews and this may present a reporting bias, especially in light of the large sample size for the studies that included self-reported depression. Finally, the search was limited to Embase/PubMed databases and articles published in other databases may be missing.

In conclusion, results from this meta-analysis showed that coffee consumption act as an independent protective factor for depression and similar effects may be shared by tea. We hypothesized that part of this effect can be attributed to caffeine, but the protective action of caffeine against depression was not entirely explaining the relationship found with coffee and tea consumption. Due to significant heterogeneity across studies, additional investigations with proper design and without the limitations recognized in this study are needed to confirm such hypotheses. Specifically, considering the known determinants of the outcome explored, it is fundamental to better assess the role of socioeconomic status and social support/isolation as potential confounding factors. Moreover, it would be the optimal harmonization of the tools used to assess the depressive status using instrument more properly validated for the population-based studies. Finally, further effort should be made to explore the role of characteristics related with the habit of coffee consumption (i.e., length of consumption, type of coffee, etc.) as well as the effects of individual compounds (i.e., caffeine and polyphenols) in preventing depression.

G.G. designed the study and wrote the paper; G.G. and S.C. searched the references; G.G. and A.M. extracted and analyzed the data; A.P. and F.G. provided critical revision and significant improvement of the manuscript.

The authors have declared no conflict of interest.

5 References

[1] Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A. et al., Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med.* 2011, *9*, 90.

[2] Mathers, C. D., Loncar, D., Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006, *3*, e442.

[3] Lai, J. S., Hiles, S., Bisquera, A., Hure, A. J. et al., A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am. J. Clin. Nutr.* 2014, *99*, 181–197.

[4] Rahe, C., Unrath, M., Berger, K., Dietary patterns and the risk of depression in adults: a systematic review of observational studies. *Eur. J. Nutr.* 2014, *53*, 997–1013.

[5] Murakami, K., Sasaki, S., Dietary intake and depressive symptoms: a systematic review of observational studies. *Mol. Nutr. Food Res.* 2010, *54*, 471–488.

[6] Grosso, G., Pajak, A., Marventano, S., Castellano, S. et al., Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PloS One* 2014, *9*, e96905.

[7] Grosso, G., Stepaniak, U., Topor-Madry, R., Szafraniec, K. et al., Estimated dietary intake and major food sources of polyphenols in the Polish arm of the HAPIEE study. *Nutrition* 2014, *30*, 1398–1403.

[8] Godos, J., Pluchinotta, F. R., Marventano, S., Buscemi, S. et al., Coffee components and cardiovascular risk: beneficial and detrimental effects. *Int. J. Food Sci. Nutr.* 2014, *65*, 925–936.

[9] Hintikka, J., Tolmunen, T., Honkalampi, K., Haatainen, K. et al., Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. *Eur. J. Epidemiol.* 2005, *20*, 359–363.

[10] Xu, Q., Anderson, D., Courtney, M., A longitudinal study of the relationship between lifestyle and mental health among midlife and older women in Australia: findings from the Healthy Aging of Women Study. *Health Care Women Int.* 2010, *31*, 1082–1096.

[11] Gilliland, K., Andress, D., Ad lib caffeine consumption, symptoms of caffeinism, and academic performance. *Am. J. Psychiatry* 1981, *138*, 512–514.

[12] Greden, J. F., Fontaine, P., Lubetsky, M., Chamberlin, K., Anxiety and depression associated with caffeinism among psychiatric inpatients. *Am. J. Psychiatry* 1978, *135*, 963–966.

[13] Lucas, M., O'Reilly, E. J., Pan, A., Mirzaei, F. et al., Coffee, caffeine, and risk of completed suicide: results from three prospective cohorts of American adults. *World J. Biol. Psychiatry* 2014, *15*, 377–386.

[14] Dong, X., Yang, C., Cao, S., Gan, Y. et al., Tea consumption and the risk of depression: a meta-analysis of observational studies. *Aust. N Z J. Psychiatry* 2015, *49*, 334–345.

[15] Wells, G. A. S. B., O'Connell, D., Peterson, J., Welch V. et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, Ottawa: Ottawa Health Research Institute 1999.

[16] Greenland, S., Quantitative methods in the review of epidemiologic literature. *Epidemiol. Rev.* 1987, *9*, 1–30.

[17] Greenland, S., Longnecker, M. P., Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am. J. Epidemiol.* 1992, *135*, 1301–1309.

[18] Orsini, N., Belloco, R., Greenland, S, Generalized least squares for trend estimation of summarized dose-response data. *Stata J.* 2006, *6*, 40–57.

[19] Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D., Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am. J. Epidemiol.* 2012, *175*, 66–73.

[20] Kendler, K. S., Myers, J., O Gardner, G., Caffeine intake, toxicity and dependence and lifetime risk for psychiatric and substance use disorders: an epidemiologic and co-twin control analysis. *Psychol. Med.* 2006, *36*, 1717–1725.

[21] Smith, A. P., Caffeine, cognitive failures and health in a non-working community sample. *Hum. Psychopharmacol.* 2009, *24*, 29–34.

[22] Ruusunen, A., Lehto, S. M., Tolmunen, T., Mursu, J. et al., Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Public Health Nutr.* 2010, *13*, 1215–1220.

[23] Lucas, M., Mirzaei, F., Pan, A., Okereke, O. I. et al., Coffee, caffeine, and risk of depression among women. *Arch. Intern. Med.* 2011, *171*, 1571–1578.

[24] Guo, X., Park, Y., Freedman, N. D., Sinha, R. et al., Sweetened beverages, coffee, and tea and depression risk among older US adults. *PloS One* 2014, *9*, e94715.

[25] Omagari, K., Sakaki, M., Tsujimoto, Y., Shiogama, Y. et al., Coffee consumption is inversely associated with depressive status in Japanese patients with type 2 diabetes. *J. Clin. Biochem. Nutr.* 2014, *55*, 135–142.

[26] Pham, N. M., Nanri, A., Kurotani, K., Kuwahara, K. et al., Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. *Public Health Nutr.* 2014, *17*, 625–633.

[27] Ritchie, K., Ancelin, M. L., Amieva, H., Rouaud, O. et al., The association between caffeine and cognitive decline: examining alternative causal hypotheses. *Int. Psychoger.* 2014, *26*, 581–590.

[28] Park, R. J., Moon, J. D., Coffee and depression in Korea: the fifth Korean National Health and Nutrition Examination Survey. *Eur. J. Clin. Nutr.* 2015, *69*, 501–504.

[29] Chen, X., Lu, W., Zheng, Y., Gu, K. et al., Exercise, tea consumption, and depression among breast cancer survivors. *J. Clin. Oncol.* 2010, *28*, 991–998.

[30] Feng, L., Li, J., Kua, E. H., Lee, T. S. et al., Association between tea consumption and depressive symptoms in older Chinese adults. *J. Am. Geriatr. Soc.* 2012, *60*, 2358–2360.

[31] Niu, K., Hozawa, A., Kuriyama, S., Ebihara, S. et al., Green tea consumption is associated with depressive symptoms in the elderly. *Am. J. Clin. Nutr.* 2009, *90*, 1615–1622.

[32] Grosso, G., Stepaniak, U., Micek, A., Topor-Madry, R. et al., Association of daily coffee and tea consumption and metabolic syndrome: results from the Polish arm of the HAPIEE study. *Eur. J. Nutr.* 2014, *54*, 1129–1137.

[33] Grosso, G., Stepaniak, U., Polak, M., Micek, A. et al., Coffee consumption and risk of hypertension in the Polish arm of the HAPIEE cohort study. *Eur. J. Clin. Nutr.* 2015, doi: 10.1038/ejcn.2015.119.

[34] Grosso, G., Marventano, S., Galvano, F., Pajak, A., Mistretta, A., Factors associated with metabolic syndrome in a Mediterranean population: role of caffeinated beverages. *J. Epidemiol.* 2014, *24*, 327–333.

[35] Walker, J., Rohm, B., Lang, R., Pariza, M. W. et al., Identification of coffee components that stimulate dopamine release from pheochromocytoma cells (PC-12). *Food Chem. Toxicol.* 2012, *50*, 390–398.

[36] Trebaticka, J., Durackova, Z., Psychiatric disorders and polyphenols: Can they be helpful in therapy? *Oxid. Med. Cell. Longev.* 2015, *2015*, 248529.

