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Coffee consumption is associated with a lower risk of prostate cancer: a meta-analysis

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Abstract

Background Although in vitro and in vivo experiments have suggested that coffee may exert inhibitory effects on prostate carcinogenesis, epidemiological studies have reported inconsistent results on the association between coffee consumption and prostate cancer.

Methods We conducted a meta-analysis of cohort studies to assess the association between coffee consumption and prostate cancer risk. PubMed and Embase were searched for eligible studies up to Jan 2020. Study-specific risk estimates were combined using fixed or random effects models depending on whether significant heterogeneity was detected.

Results Fifteen prospective cohort studies, with 50,200 cases of prostate cancer and 949,752 total cohort members, were included in the meta-analysis. A statistically significant inverse association was detected between coffee consumption and prostate cancer risk. The pooled relative risk (RR) was 0.91 (95% CI: 0.84, 0.98; $I^{2=}$ 53.2%) for the highest coffee consumption compared with lowest consumption. The association exhibited a linear trend (P =0.006 for linear trend), and the pooled RR was 0.989 (95% CI: 0.982, 0.997) for an increase of 1 cup of coffee per day. The pooled RRs were 0.93 (95% CI: 0.87, 0.99), 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08) for localized, advanced and fatal prostate cancer, respectively. No publication bias was detected.

Conclusions Our findings provide more evidence that increased coffee consumption is associated with lower prostate cancer risk. It implies that men might be encouraged

to increase the coffee intake to lower their risk of prostate cancer.

Key words Coffee; Prostate cancer; Cohort studies; Meta-analysis; Dose-response relationship

Introduction

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, with an estimated 1,276,000 new cancer cases and 359,000 cancer deaths in 2018 [1]. Nearly three-quarters of the registered cases occur in developed countries [1]. Since 1970s, the incidence of prostate cancer has also increased rapidly in some Asia countries, such as China, Singapore and Japan, where the incidences have always been much lower than some Western countries [1, 2]. As such, primary prevention of prostate cancer is therefore a critical public health challenge worldwide.

Coffee is one of the most widely consumed beverages in the world. Since its popularity continues to increase worldwide, even small effects of coffee on individuals may exert a large effect on public health. Coffee is known to be a major source of dietary caffeine, cafestol and antioxidants in industrialized nations [3]. Its various constituents such as caffeine, caffeic acid and chlorogenic acid can potentially impact the development of cancer of various sites through multiple pathways, from carcinogenesis to cellular apoptosis [4, 5]. Inverse associations were observed between coffee consumption and the risk of cancer in sites such as the liver,

colorectum and breast [6]. However, previous studies of the association between coffee consumption and prostate cancer risk have produced inconsistent results. Although earlier prospective studies did not detect an association [7-15], more recent studies conducted in some Western countries including the United States, Sweden and the United Kingdom reported that coffee consumption was associated with a lower risk of localized [16, 17] and advanced prostate cancer [18-20]. In Japan, a country with increasing popularity of coffee, a cohort study also found a significant inverse association between coffee consumption and the risk of prostate cancer [21].

Previous meta-analysis of cohort studies up to 2015 reported a significant positive association for coffee consumption on total prostate cancer risk, with highly varied results in different subgroups [22, 23]. Since then, four cohort studies have explored the association, but still reported inconsistent results [24-27]. Thus, we conducted a meta-analysis with the most up-to-date evidence from prospective cohort studies to assess the association between coffee consumption and prostate cancer risk, and expected to direct future primary prevention strategy on prostate cancer.

Methods and Methods

Study Selection

This systematic review was reported using PRISMA guidelines [28]; the PRISMA checklist is provided as **Additional file 1**. A literature search up to Jan 2020 was performed using PubMed and Embase with the following key words: coffee and prostate and (cancer or carcinoma or neoplasm or tumor). The identified publications

were reviewed independently for their relevance to the research topic by two authors. We also manually searched the reference lists of relevant publications to identify additional studies. To be included in the meta-analysis, studies had to: (a) use an observational, prospective cohort design, (b) present information on coffee consumption as the exposure of interest, (c) report prostate cancer as the outcome of interest, and (d) provide relative risk (RR)/ hazard ratio (HR) estimates with confidence intervals (CIs) or standard errors. Instances in which data were insufficient or missing, we attempted to contact the authors of the articles to request the relevant data, and then two authors [15, 20] provided us with the relevant information about the person-years of follow-up for specific categories of coffee intake to facilitate the dose-response analyses.

We used the reported relative risk as the measure of the association between coffee consumption and the risk of prostate cancer. If multiple estimates were provided, priority was given to the multivariable adjusted risk estimates. If more than one study was conducted in the same population, we selected the most recent report.

Data Extraction and Study Quality Assessment

We abstracted the following data from each publication: the first author's name, the year of publication, the country in which the study was performed, the duration of follow-up, the size of the cohort, the number of prostate cancer cases, the assessment of coffee consumption, the primary study outcome, the categories of coffee consumption, the RRs and 95% CIs for all prostate cancer outcomes associated with coffee consumption and the covariates included for adjustment in multivariable

111 models.

112 The Newcastle-Ottawa Scale [29] was used to assess study quality. Study was
113 judged on 3 broad categories for cohort studies as follows: the selection of study
114 groups, comparability of groups, and ascertainment of either the exposure or outcome
115 of interest.

116 ***Statistical Analysis***

117 We pooled the RR estimates for the highest versus the lowest coffee consumption
118 category from each study. We used a fixed effect model to pool the study specific
119 estimates unless significant heterogeneity was observed, then the random effect model
120 proposed by DerSimonian and Laird was used [30]. Additionally, we conducted
121 analyses stratified by study location and prostate cancer stage. Based on definitions of
122 each original studies, the prostate cancer categories were classified as follows: (1)
123 localized prostate cancer which included localized or nonaggressive cancers, (2)
124 advanced prostate cancer which included advanced or aggressive cancers, (3) fatal
125 prostate cancer, a subset of advanced prostate cancer, which included fatal/lethal
126 cancers or prostate cancer specific deaths (**Additional file 2**). We also conducted
127 analyses stratified by whether the studies adjusted for potentially important
128 confounders including history of prostate-specific antigen (PSA) testing, a family
129 history of prostate cancer, total energy intake, smoking status, alcohol consumption,
130 physical activity, body mass index (BMI), or history of diabetes. Since PSA testing
131 was generally introduced after 1986 [31], studies with follow-up periods that ended
132 before 1986 were classified in the PSA-adjusted group. We also performed a

sensitivity analysis of the influence of individual studies on the summary estimate by repeating the meta-analysis excluding one study at a time.

We further examined the potential dose-response relationship between coffee consumption and the risk of prostate cancer. Twelve studies had sufficient information for the dose-response analyses. The pooled relative risk for an increase of 1 cups of coffee per day was estimated using a procedure described by Orsini and Greenland [32]. We examined a potential nonlinear relation between coffee consumption and prostate cancer risk by modeling coffee consumption using restricted cubic splines for nonlinear trends with 4 knots at fixed percentiles (5%, 35%, 65%, and 95%) of the distribution [33]. A P value for nonlinearity was computed by testing the null hypothesis that the coefficients of the second and third splines which represent the non-linear component are equal to zero.

Heterogeneity among studies was assessed with the Q and the I^2 statistic and results were defined as heterogeneous for a *P* value <0.10 or an I^2 >50% [34]. Small study effects such as publication bias were evaluated by Begg's and Egger's tests [35, 36]. Statistical analyses were conducted using Stata version 14.0 (StataCorp LP, College Station, Texas). Two-sided *P* values <0.05 were considered statistically significant. The analysis dataset was shown in **Additional file 3**.

Results

Literature Search

A total of 316 records were identified from the two databases, of which 291 records

were excluded after review of the titles and abstracts based on the pre-specified inclusion criteria. After reviewing the full text of the remaining 25 cohort studies, 10 studies were excluded as no useful risk estimates or 95% CIs were reported. Two studies were excluded as newer data was available. Thirteen studies were obtained from full-text screening. In addition, two studies were identified by checking the reference lists of retrieved articles Thus, we included 15 studies in the final analysis [9-11, 13-19, 21, 24-27]. (**Figure 1)**

Study Characteristics and Quality Assessment

Descriptive data for the studies included in our analysis are summarized in **Table 1**. The included studies were conducted in the North America (n=7), Europe (n=6), Japan (n=2). There were a total of 949,752 men in the 15 cohort studies, of whom 50,200 developed prostate cancer. To measure coffee consumption, 11 studies used food-frequency questionnaires and four used a self-administered dietary questionnaire. Most studies included adjustment for the most potential confounders, such as age, family history of prostate cancer, race, smoking, alcohol consumption, total energy intake, body mass index (BMI), and physical activity, et al. Study-specific quality scores are summarized in **Additional file 4**. The quality scores ranged from 6 to 9, and most studies were assessed as high quality studies.

Overall Analyses and Dose-Response Analyses

As shown in **Figure 2**, the overall analysis of 15 studies showed a 9% reduction in the risk of prostate cancer for high consumption of coffee (RR=0.91; 95% CI: 0.84, 0.98), with statistical significant heterogeneity (P=0.008, I^2=53.2%). In dose-response

analyses, we found evidence of a linear inverse association between coffee consumption and prostate cancer risk (P=0.006 for linear trend) (**Figure 3**). The pooled RR of prostate cancer was 0.989 (95% CI: 0.982, 0.997) for an increase of 1 cup of coffee per day. There was no evidence of a nonlinear relation between coffee consumption and risk of prostate cancer (P=0.193 for non-linearity). There was no indication of small study effects such as publication bias either from the results of Egger's test (P= 0.409) or Begg's test (P= 0.843) (**Additional file 5**).

Subgroup and Sensitivity Analyses

The effects of coffee consumption on prostate cancer risk in subgroup analyses are shown in **Table 2**. For localized prostate cancer, there was a 7% reduction in risk for high consumption of coffee (RR=0.93; 95% CI: 0.87, 0.99). The pooled RRs were 0.88 (95% CI: 0.71, 1.09) and 0.84 (95% CI: 0.66, 1.08) for advanced and fatal prostate cancer, respectively. When stratified by study location, the pooled RRs were 0.96 (95%CI: 0.90 , 1.03), 0.85 (95%CI: 0.74 , 0.98) and 0.85 (95%CI: 0.48 , 1.51) for studies conducted in North America (six in the United States and one in Canada) and European countries and Japan. When we stratified studies by adjustment for specific confounders, significant inverse associations were observed in all of the confounder adjusted subgroups.

In sensitivity analyses, we recalculated the pooled RRs by sequentially excluding one study. The study-specific RRs ranged from 0.89 (95% CI: 0.82, 0.97) to 0.93 (95% CI: 0.86, 1.00) after omissions of Hashibe et al. and Terdal et al., respectively.

Discussion

In this meta-analysis, increased coffee consumption was significantly associated with a reduced risk of prostate cancer in men. In the dose-response analysis, a nearly 1% reduction in risk of prostate cancer was observed for an increase of 1 cup of coffee per day. The combined estimate for prostate cancer was robust across sensitivity analyses and no publication bias was detected.

Previous meta-analysis detected a statistically significant positive association between coffee consumption and prostate cancer risk (RR=1.16; 95% CI: 1.01, 1.33) [22]. However, this observed effect was confined to the case-control studies (RR=1.21; 95% CI: 1.03, 1.43), and no significant association in the cohort studies (RR=1.06; 95% CI: 0.83, 1.35) when stratified by study design [22]. Considering the case-control design patients with prostate cancer might differentially recall their past coffee consumption habits compared to healthy controls which might generally lead to biased estimates. This potential recall bias could generate a spurious positive association between coffee consumption and prostate cancer risk. Additionally, selection bias which can occur in case-control studies may distort the association between coffee consumption and prostate cancer risk. In another meta-analysis of cohort studies with 539,577 participants and 34,105 cases, the pooled RR for the highest vs. lowest coffee intake was 0.90 (95% CI: 0.85-0.95) for total prostate cancer. In the current updated meta-analysis of 949,752 cohort members and 50,200 cases, the overall result was similar with the previous one, but for subgroups of localized, advanced and fatal prostate cancers, the strength of associations tended to be weaker

compared with the previous study.

An inverse association between coffee and risk of prostate cancer is biologically plausible. Coffee improves glucose metabolism, decreases concentrations of plasma insulin and insulin-like growth factors-1, has anti-inflammatory and antioxidant effects, and affects sex hormone levels, all of which may play roles in the initiation, development and progression of prostate cancer [3, 18, 20, 37]. Coffee is also a major source of chlorogenic acids; intake of quinides, the degradation products of chlorogenic acids, has been observed to increase insulin sensitivity and lower blood glucose levels [3]. Moreover, coffee intake has been shown to be associated with higher adiponectin plasma levels [38, 39], an endogenous insulin sensitizer [40]. Higher adiponectin plasma levels lead, in turn, to decreased concentrations of plasma insulin [40]. In two prospective studies, insulin levels were observed to be directly associated with prostate cancer specific mortality [41, 42].

Coffee is a major contributor of dietary antioxidants such as caffeic acid and chlorogenic acid [20]. A prospective cohort study from the United States found that dietary antioxidants from coffee, e.g. the caffeic acid, were inversely associated with risk of total, advanced and lethal prostate cancer [20]. Additional research has led to the conclusion that antioxidants protect cells from damage caused by oxidative stress and its associated pathological conditions including inflammation which is a precursor of neoplastic transformation in the prostate [43]. Additionally, preclinical studies have shown that dietary antioxidants may slow or prevent prostate cancer progression through oxidative stress reduction which is generally considered a key event in the

initiation, development and progression of prostate cancer [43].

Coffee drinking may be associated with increased sex hormone-binding globulin (SHBG) and total testosterone levels [44, 45]. A pooled analysis of 18 prospective studies found an inverse association between SHBG levels and prostate cancer incidence [37]. Of note, a nested case-control study found that caffeine and caffeinated coffee intakes were positively associated with plasma SHBG levels, but with no association between decaffeinated coffee and plasma SHBG levels which suggested that caffeine may be the key component of coffee responsible for determining plasma SHBG levels [45].

A strength of this meta-analysis was the prospective cohort design of the included studies, which should have eliminated the selection and recall bias that could be of concern from case-control studies. In addition, the large number of total cohort members and prostate cancer cases could provide sufficient statistical power to assess even a relatively small effect of coffee consumption on prostate cancer risk. Furthermore, we were able to conduct the dose-response analysis support the hypothesis of an inverse linear association between coffee consumption and risk of prostate cancer.

Our study also has some limitations. Because of the observational design, residual confounding may distort the association between coffee consumption and prostate cancer and we were not able to address problems with confounding inherent in the original studies. For example, the inverse association between coffee consumption and prostate cancer could be attributed to other factors related to coffee consumption,

such as family history of prostate cancer, physical exercise, or other healthy habits and dietary factors. However, most studies included in this meta-analysis adjusted for at least some of the major potential confounders. When we restricted the analysis to studies that adjusted for the potential confounders, the magnitude of the associations in the subgroups tended to be larger in comparison with the overall association. Another limitation is misclassification of coffee consumption, due to the self-reported nature of the exposure in the included studies. However, results from validation studies indicated that coffee consumption was assessed with relatively high validity. The correlations between coffee consumption assessed by questionnaire and diet records were 0.80 in US men [16], 0.71 in Swedish men [17], and 0.72 in Japanese men [21]. In cohort studies, even if misclassification occurred, it would most likely be non-differential and would bias results toward the null. Therefore, the association between coffee consumption and risk of prostate cancer may be even stronger. Finally, there was significant heterogeneity among studies results. There are several potential explanations for the observed between-study heterogeneity. First, the range of coffee consumption between the high and low category varied between studies. The risk estimates would be assumed to be higher in studies with broader ranges of coffee consumption. Second, the type of coffee and different brewing methods included in the coffee consumption groups differed. Third, the size of cohort and the length of follow-up varied from study to study. Because the strength of the association differed between studies, which resulted in statistical heterogeneity, the summary risk estimates should be interpreted with caution.

Conclusions

This meta-analysis demonstrated that an increased coffee consumption is associated with a reduced risk of prostate cancer. These findings add to and extend the evidence that increased coffee consumption may have protective effects on prostate cancer; thus, men should be encouraged to increase their coffee consumption to potentially decrease their risk of prostate cancer. Moreover, the underlying mechanisms and active compounds in coffee that are responsible for this association remain to be further elucidated.

List of abbreviations

BMI, body mass index;

CI, confidence interval;

FFQ, food frequency questionnaire

HR, hazard ratio;

IGF, insulin-like growth factors

PSA, prostate-specific antigen

RR, relative risk;

SHBG, sex hormone-binding globulin;

Declarations

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable

Availability of data and materials: The datasets supporting the conclusions of this article are included within the article and its additional files.

Competing Interests Statement: The authors declared no conflict of interest.

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Author Contributions Kefeng Wang obtained the funding, developed the research design, interpreted the results, and also had primary responsibility for the final content; Xiaonan Chen, Yiqiao Zhao, Zijia Tao analyzed the data and interpreted the results; Xiaonan Chen and Kefeng Wang drafted manuscript; all authors critically reviewed and approved the manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.** *CA Cancer J Clin* 2018, **68:**394-424.

2. Cullen J, Elsamanoudi S, Brassell SA, Chen Y, Colombo M, Srivastava A,

McLeod DG: **The burden of prostate cancer in Asian nations.** *J Carcinog* 2012, **11:**7.

3. Tunnicliffe JM, Shearer J: **Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators.** *Appl Physiol Nutr Metab* 2008, **33:**1290-1300.

4. Lee WJ, Zhu BT: **Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols.** *Carcinogenesis* 2006, **27:**269-277.

5. Bode AM, Dong Z: **The enigmatic effects of caffeine in cell cycle and cancer.** *Cancer Lett* 2007, **247:**26-39.

6. Yu X, Bao Z, Zou J, Dong J: **Coffee consumption and risk of cancers: a meta-analysis of cohort studies.** *BMC Cancer* 2011, **11:**96.

7. Jacobsen BK, Bjelke E, Kvale G, Heuch I: **Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study.** *J Natl Cancer Inst* 1986, **76:**823-831.

8. Nomura A, Heilbrun LK, Stemmermann GN: **Prospective study of coffee consumption and the risk of cancer.** *J Natl Cancer Inst* 1986, **76:**587-590.

9. Severson RK, Nomura AM, Grove JS, Stemmermann GN: **A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii.** *Cancer Res* 1989, **49:**1857-1860.

10. Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ: **Diet, tobacco use, and fatal prostate cancer: results**

from the Lutheran Brotherhood Cohort Study. *Cancer Res* 1990, **50:**6836-6840.

11. Le Marchand L, Kolonel LN, Wilkens LR, Myers BC, Hirohata T: **Animal fat consumption and prostate cancer: a prospective study in Hawaii.** *Epidemiology* 1994, **5:**276-282.

12. Stensvold I, Jacobsen BK: **Coffee and cancer: a prospective study of 43,000 Norwegian men and women.** *Cancer Causes Control* 1994, **5:**401-408.

13. Ellison LF: **Tea and other beverage consumption and prostate cancer risk: a Canadian retrospective cohort study.** *Eur J Cancer Prev* 2000, **9:**125-130.

14. Iso H, Kubota Y, Japan Collaborative Cohort Study for Evaluation of C: **Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC).** *Asian Pac J Cancer Prev* 2007, **8 Suppl:**35-80.

15. Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B: **Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study.** *Cancer Causes Control* 2010, **21:**1533-1544.

16. Bosire C, Stampfer MJ, Subar AF, Wilson KM, Park Y, Sinha R: **Coffee consumption and the risk of overall and fatal prostate cancer in the NIH-AARP Diet and Health Study.** *Cancer Causes Control* 2013, **24:**1527-1534.

17. Discacciati A, Orsini N, Andersson SO, Andren O, Johansson JE, Mantzoros CS, Wolk A: **Coffee consumption and risk of localized, advanced and fatal**

prostate cancer: a population-based prospective study. *Ann Oncol* 2013, **24:**1912-1918.

18. Wilson KM, Kasperzyk JL, Rider JR, Kenfield S, van Dam RM, Stampfer MJ, Giovannucci E, Mucci LA: **Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study.** *J Natl Cancer Inst* 2011, **103:**876-884.

19. Shafique K, McLoone P, Qureshi K, Leung H, Hart C, Morrison DS: **Coffee consumption and prostate cancer risk: further evidence for inverse relationship.** *Nutr J* 2012, **11:**42.

20. Russnes KM, Wilson KM, Epstein MM, Kasperzyk JL, Stampfer MJ, Kenfield SA, Smeland S, Blomhoff R, Giovannucci EL, Willett WC, Mucci LA: **Total antioxidant intake in relation to prostate cancer incidence in the Health Professionals Follow-Up Study.** *Int J Cancer* 2014, **134:**1156-1165.

21. Li Q, Kakizaki M, Sugawara Y, Tomata Y, Watanabe T, Nishino Y, Tsuji I: **Coffee consumption and the risk of prostate cancer: the Ohsaki Cohort Study.** *Br J Cancer* 2013, **108:**2381-2389.

22. Park CH, Myung SK, Kim TY, Seo HG, Jeon YJ, Kim Y, Korean Meta-Analysis Study G: **Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies.** *BJU Int* 2010, **106:**762-769.

23. Liu H, Hu GH, Wang XC, Huang TB, Xu L, Lai P, Guo ZF, Xu YF: **Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies.** *Nutr Cancer* 2015, **67:**392-400.

24. Tverdal A: **Boiled coffee consumption and the risk of prostate cancer: follow-up of 224,234 Norwegian men 20-69 years.** *Br J Cancer* 2015, **112:**576-579.

25. Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, La Vecchia C: **Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort.** *Br J Cancer* 2015, **113:**809-816.

26. Pounis G, Tabolacci C, Costanzo S, Cordella M, Bonaccio M, Rago L, D'Arcangelo D, Filippo Di Castelnuovo A, de Gaetano G, Donati MB, et al: **Reduction by coffee consumption of prostate cancer risk: Evidence from the Moli-sani cohort and cellular models.** *Int J Cancer* 2017, **141:**72-82.

27. Sen A, Papadimitriou N, Lagiou P, Perez-Cornago A, Travis RC, Key TJ, Murphy N, Gunter M, Freisling H, Tzoulaki I, et al: **Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition.** *Int J Cancer* 2019, **144:**240-250.

28. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *PLoS Med* 2009, **6:**e1000097.

29. Wells GA SB OCD, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed December 2019.

30. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials* 1986, **7:**177-188.

31. Welch HG, Albertsen PC: **Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005.** *J Natl Cancer Inst* 2009, **101:**1325-1329.

32. Greenland S, Longnecker MP: **Methods for trend estimation from summarized dose-response data, with applications to meta-analysis.** *Am J Epidemiol* 1992, **135:**1301-1309.

33. 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.

34. Higgins JP, Thompson SG: **Quantifying heterogeneity in a meta-analysis.** *Stat Med* 2002, **21:**1539-1558.

35. Begg CB, Mazumdar M: **Operating characteristics of a rank correlation test for publication bias.** *Biometrics* 1994, **50:**1088-1101.

36. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ* 1997, **315:**629-634.

37. Endogenous H, Prostate Cancer Collaborative G, Roddam AW, Allen NE, Appleby P, Key TJ: **Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies.** *J Natl Cancer Inst* 2008, **100:**170-183.

38. Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, Blackburn GL, Hu FB,

Mantzoros CS: **Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes: a prospective cohort study.** *Diabetes Care* 2008, **31:**504-507.

39. Imatoh T, Tanihara S, Miyazaki M, Momose Y, Uryu Y, Une H: **Coffee consumption but not green tea consumption is associated with adiponectin levels in Japanese males.** *Eur J Nutr* 2011, **50:**279-284.

40. Ziemke F, Mantzoros CS: **Adiponectin in insulin resistance: lessons from translational research.** *Am J Clin Nutr* 2010, **91:**258S-261S.

41. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, Gaziano JM, Pollak M, Stampfer MJ: **Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis.** *Lancet Oncol* 2008, **9:**1039-1047.

42. Hammarsten J, Hogstedt B: **Hyperinsulinaemia: a prospective risk factor for lethal clinical prostate cancer.** *Eur J Cancer* 2005, **41:**2887-2895.

43. Thapa D, Ghosh R: **Antioxidants for prostate cancer chemoprevention: challenges and opportunities.** *Biochem Pharmacol* 2012, **83:**1319-1330.

44. Svartberg J, Midtby M, Bonaa KH, Sundsfjord J, Joakimsen RM, Jorde R: **The associations of age, lifestyle factors and chronic disease with testosterone in men: the Tromso Study.** *Eur J Endocrinol* 2003, **149:**145-152.

45. Goto A, Song Y, Chen BH, Manson JE, Buring JE, Liu S: **Coffee and caffeine consumption in relation to sex hormone-binding globulin and risk of type**

463 **2 diabetes in postmenopausal women.** *Diabetes* 2011, **60:**269-275.

464

Table 1. Characteristics of cohort studies of coffee consumption and prostate cancer risk included in the meta-analysis

Study	Country	Study period	Size of cohort	No. of cases	Assessment of coffee consumption	Outcome	Adjustments
Sen et al. 2019	Europe	1990s-2015	142196	7036	Validated FFQ	Total, Localized, advanced prostate cancer	Stratified by center and age at recruitment in 5 years categories, and adjusted for smoking status, BMI, history of diabetes, alcohol intake, education, physical activity, energy intake, as well as calcium, fish, tea, fruit and vegetable intake.
Pounis et al 2017	Italy	2005-2010	6989	100	Validated FFQ	Total prostate cancer	Age, energy intake, smoking habits and BMI
Hashibe et al. 2015	USA	1992-2011	46771	3037	Validated diet history questonnaire	Total prostate cancer	Age, sex, race, and education.
Tverdal et al. 2015	Norway	1985-1999	224234	5740	Questionnaire	Total prostate cancer	Age, smoking, BMI, height, physical activity, total cholesterol, triglycerides, systolic blood pressure, year of examination and diabetes
Li et al. 2013	Japan	1995-2005	18,853	318	Validated FFQ	Total prostate cancer incidence	Age, education, BMI, time engaging in sports or exercise, marital status, time spent walking, smoking status, family history of cancer, job status, total energy intake, passive smoking, alcohol drinking, daily consumption of miso soup
Discacciati et al. 2013	Sweden	1998-2010	44,613	3801	Validated self-administered FFQ	Localized and advanced prostate cancer incidence Prostate cancer mortality	Age, tea, alcohol, BMI, diabetes, family history of prostate cancer, smoke, physical activity, education, total energy intake.
Bosire et al. 2013	USA	1995-2008	288,391	23335	Validated FFQ	Total prostate cancer incidence	Age, race, height, BMI, physical activity, smoking, history of diabetes, family history of prostate cancer, PSA testing, intakes of tomato sauce,

							alpha-linolenic acid, and total energy intake.
Shafique et al. 2012	UK	1970-2007	6017	318	Self-administered questionnaire	Total prostate cancer incidence	Age at screening, cholesterol, systolic blood pressure, BMI, alcohol intake, tea consumption, smoking status, social class.
Wilson et al. 2011	USA	1986-2006	47,911	5035	Validated FFQ	Total prostate cancer incidence	Age in months, calendar time, race, BMI at age 21, current BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer in father or brother, multivitamin use, intakes of processed meat, tomato sauce, calcium, alpha-linolenic acid, supplemental vitamin E, alcohol intake, energy intake, history of PSA testing.
Nilsson et al. 2010	Sweden	1985-2007	30,930	653	Semi-quantitative FFQ	Total prostate cancer incidence	Age, BMI, smoking, education, recreational physical activity.
Iso et al. 2007	Japan	1990-2003	43,500	161	Validated FFQ	Prostate cancer mortality	Age, area of study
Ellison et al. 2000	Canada	1970-1993	3400	145	FFQ	Total prostate cancer incidence	Age, wine consumption.
Le Marchand et al. 1994	USA	1975-1989	20,316	198	Self-administered life-style questionnaire	Total prostate cancer incidence	Age, ethnicity, income.
Hsing et al. 1990	USA	1966-1986	17,633	149	FFQ	Prostate cancer mortality	Age, tobacco use.
Severson et al. 1989	USA	1965-1986	7998	174	FFQ + 24-h diet recall interview	Total prostate cancer incidence	Age

FFQ, food frequency questionnaire; RR, relative risk; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen

Table 2. Summary estimates and corresponding 95% confidence intervals for coffee consumption and prostate cancer

	No. of studies	Summary RR	95% CI	I^2 (%)	*P* value [a]
High versus low consumption	15	0.91	(0.84 , 0.98)	53.2	0.008
Prostate cancer category [2]					
Localized	6	0.93	(0.87 , 0.99)	37.0	0.159
Advanced	8	0.88	(0.71 , 1.09)	52.7	0.039
Fatal	6	0.84	(0.66 , 1.08)	46.3	0.097
Study location					
North America	7	0.96	(0.90 , 1.03)	17.7	0.295
Europe	6	0.85	(0.74 , 0.98)	63.3	0.018
Japan	2	0.85	(0.48 , 1.51)	68.5	0.075
Study quality					
High	9	0.87	(0.79 , 0.98)	69.4	0.001
Low	6	1.06	(0.89 , 1.26)	0	0.917
Adjustment for confounders					
PSA testing [c]					
Yes	6	0.86	(0.77 , 0.96)	31.8	0.197
No	9	0.94	(0.84 , 1.06)	60.5	0.009
Family history of prostate cancer					
Yes	4	0.83	(0.72 , 0.96)	57.8	0.068
No	11	0.95	(0.85 , 1.05)	50.8	0.026
Total energy intake					
Yes	6	0.85	(0.76 , 0.96)	61.1	0.025
No	9	0.97	(0.85 , 1.09)	47.7	0.053
Smoking status					
Yes	10	0.86	(0.79 , 0.94)	52.0	0.027
No	5	1.03	(0.95 , 1.11)	0	0.805
Alcohol consumption					
Yes	6	0.87	(0.84 , 0.98)	49.2	0.008
No	9	0.93	(0.84 , 1.03)	57.2	0.017
Physical activity					
Yes	7	0.87	(0.79 , 0.95)	58.4	0.025
No	8	1.00	(0.90 , 1.12)	10.5	0.348
BMI					
Yes	9	0.86	(0.78 , 0.94)	56.9	0.017
No	6	1.03	(0.95 , 1.11)	0	0.897
Diabetes					
Yes	5	0.87	(0.84 , 0.98)	64.9	0.022
No	10	0.97	(0.86 , 1.10)	22.8	0.233

[a] *P*-value for heterogeneity within each subgroup.

RR, relative risk; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen.

Figure legends

Figure 1 Flow diagram of study selection in the meta-analysis.

Figure 2 Forest plot for the association between coffee consumption and prostate cancer risk.

Figure 3 Dose-response relationship of coffee consumption with prostate cancer risk.

Additional files

Additional file 1 PRISMA 2009 checklist.

Additional file 2 The definition of prostate cancer groups across the studies in the meta-analysis.

Additional file 3 Analysis Dataset of the meta-analysis.

Additional file 4 Quality of cohort studies included in the meta-analysis.

Additional file 5 Funnel plot of coffee consumption and prostate cancer risk**.**

Figures

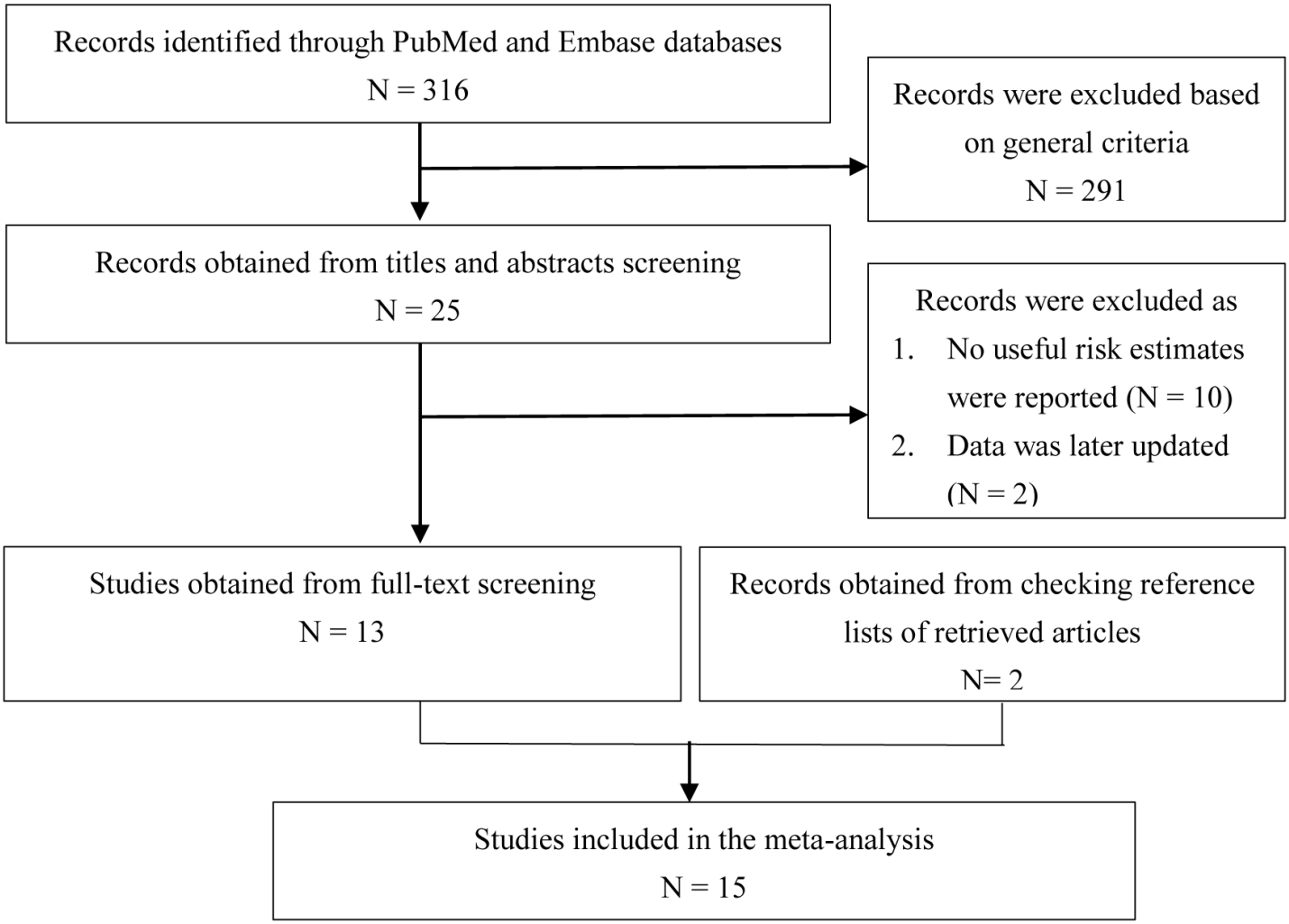

Figure 1

Flow diagram of study selection in the meta analysis.

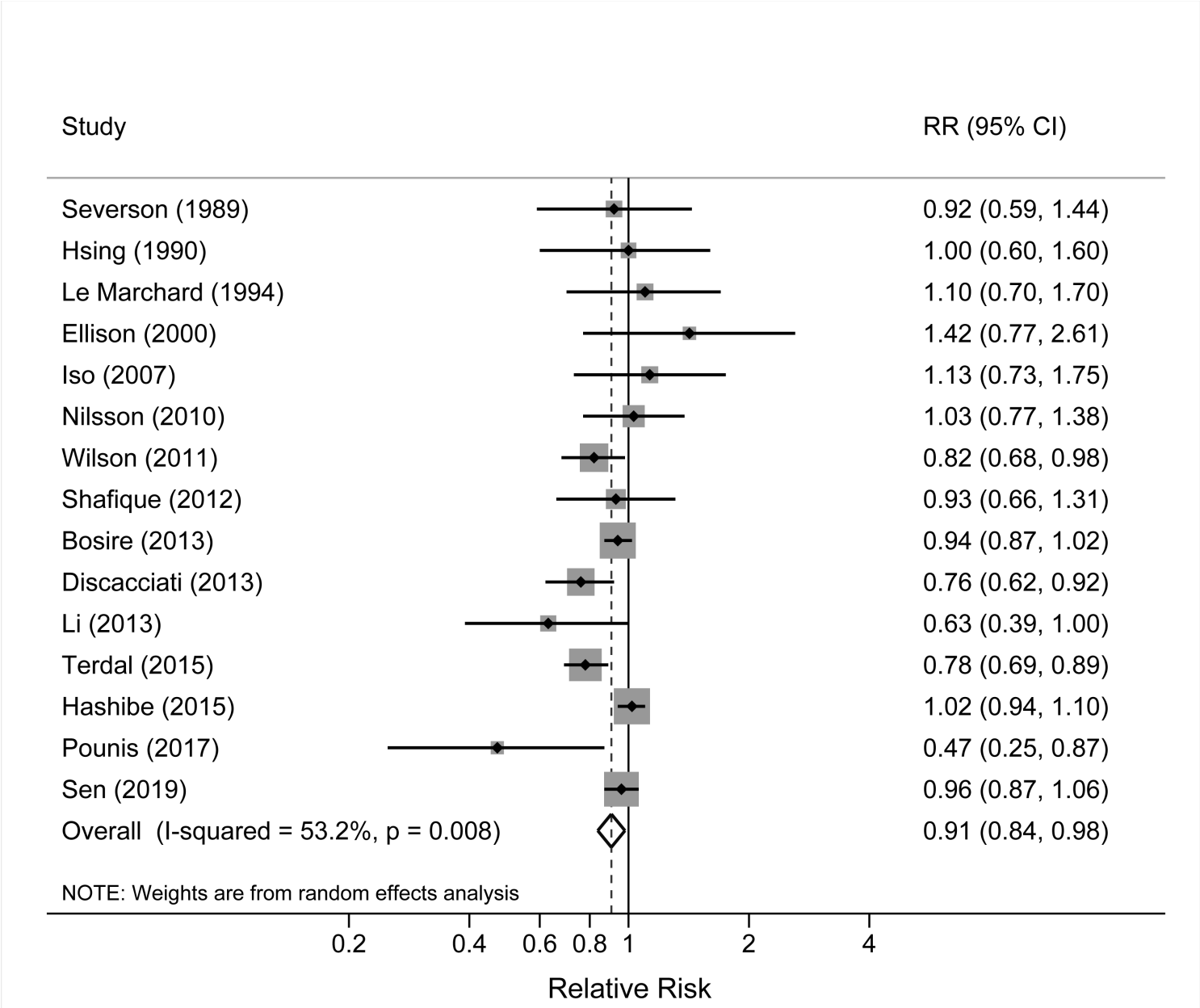

Figure 2

Forest plot for the association between coffee consumption and prostate cancer risk.

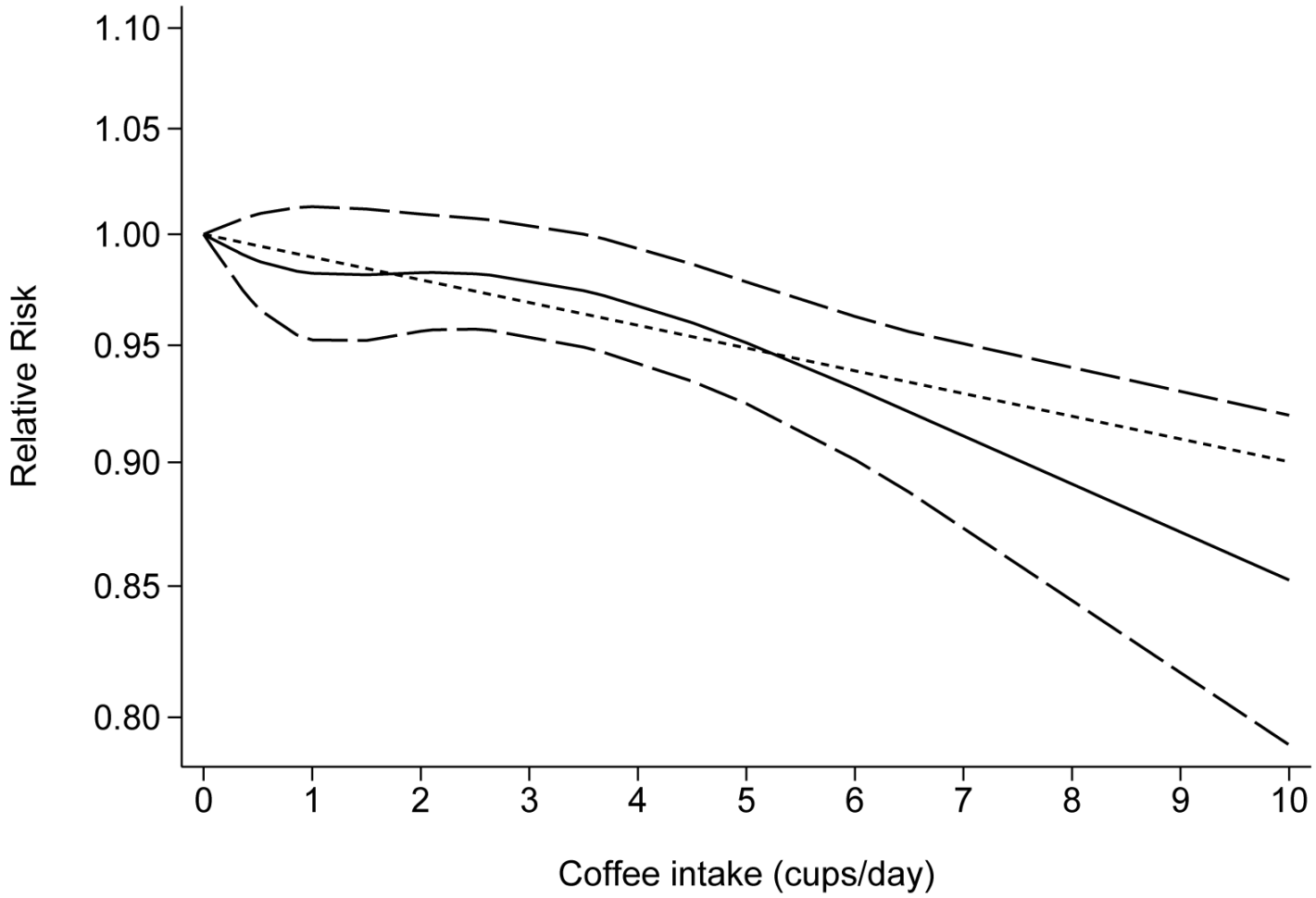

Figure 3

Dose response r elationship of coffee consumption with prostate cancer risk .

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile5Funnelplot.tif
- Additionalfile1PRISMAChecklist.doc
- Additionalfile2Definitions.doc
- Additionalfile3analysisdataset.xlsx
- Additionalfile4Studyqualityassessment.doc