



## Association of pepper intake with all-cause and specific cause mortality - A systematic review and meta-analysis



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### ABSTRACT

**Objective:** To conduct a comprehensive systematic review and meta-analysis to compare mortality and other clinical outcomes associated with chili pepper (CP) consumption versus no/rare consumption of CP.

**Methods:** A comprehensive search was performed using Ovid, Cochrane, Medline, EMBASE, and Scopus from inception till January 16, 2020. Observational studies and randomized controlled trials were included, while pediatric/animal studies, letters/case reports, reviews, abstracts, and book chapters were excluded. All-cause mortality was studied as the primary outcome. Cardiovascular mortality, cancer-related deaths and cerebrovascular accidents were studied as secondary outcomes.

**Results:** From 4729 studies, four studies met the inclusion criteria. Random effects pooled analysis showed that all-cause mortality among CP consumers was lower, compared to rare/non-consumers, with a hazard ratio (HR) of 0.87 [95% CI: 0.85–0.90;  $p < 0.0001$ ;  $I^2 = 1\%$ ]. HR for cardiovascular mortality was 0.83 [95% CI: 0.74–0.95;  $p = 0.005$ ,  $I^2 = 66\%$ ] and for cancer-related mortality as 0.92 [95% CI: 0.87–0.97;  $p = 0.001$ ;  $I^2 = 0\%$ ]. However, the HR for CVA was 0.78 [95% CI: 0.56–1.09;  $p = 0.26$ ;  $I^2 = 60\%$ ]. The mode and amount of CP consumption varied across the studies, and data were insufficient to design an optimal strategy guiding its intake.

**Conclusion:** Regular CP consumption was associated with significantly lower all-cause, cardiovascular, and cancer-related mortalities. However, based on current literature, it is difficult to derive a standardized approach to guide the optimal mode and amount of CP consumption. This warrants well-designed prospective studies to further investigate the potential health benefits of CP consumption.

### 1. Introduction

Diet and nutrition play an important role in population health due to its mortality and cardiovascular disease prevention benefits [1–3]. Plant-based and Mediterranean diets are recommended by the American College of Cardiology (ACC) and the American Heart Association (AHA) for the primary prevention of cardiovascular disease [4]. Diet modifications such as reduced intake of sodium, saturated fat, and refined carbohydrates, and limiting intake of added sugars and red meats have

shown to decrease the risk of mortality, compared to standard Western diets [5].

Foods such as fruits, vegetables, nuts, legumes, seafood and whole grains are known to decrease the risk of cardiovascular diseases [4–6]. Some of the beneficial effects are mediated through micronutrients, such as iron, iodine and vitamin D, influencing physiological function of major organ systems [7–9].

Since 7000 BCE, CP has been one of the most popular and regularly used culinary spice across the world [10]. It is known for its anti-

**Abbreviations:** ACC, American College of Cardiology; CP, chili pepper; CVA, cerebrovascular accidents; DM, diabetes mellitus; PICO, population, intervention, comparison, and outcomes.

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obesity, blood glucose regulation, anti-inflammatory, anti-oxidant and anti-cancer effects [11–13]. Previously published population based studies have reported that consumption of CP reduces all-cause mortality [14–17]. The benefit of chili pepper (CP) is attributed to the chemical compound, capsaicin, with potential cardio-protective, weight-reducing, and anti-tumorigenic effects [18]. However, the prior studies are non-randomized and there is a lack of medical equipoise on this topic, making it difficult to derive causal inference between CP consumption and mortality. Further, the mode and quantity of CP intake need further evaluation to develop a standardized approach to achieve optimal health benefits.

Hence, we designed this systematic review and meta-analysis to study the health impact of CP consumption on all-cause, cardiovascular, cancer-related mortality, and cerebrovascular accidents (CVAs).

## 2. Methods

### 2.1. Study design and population

This meta-analysis was designed to study the effect of CP consumption on all-cause, cardiovascular, cancer-related and cerebrovascular mortality using the population, intervention, comparison, and outcomes (PICO) framework [19] (PROSPERO registration number: CRD42021258687). Our population included: adults ( $\geq 18$  years); intervention group as those who regularly consumed CP and compared to those who rarely/never consumed CP. Regular (and rarely/never) consumers are defined as per documentation in these published studies. Outcomes included all-cause mortality as the primary, while cardiovascular mortality, cancer-related deaths and CVAs as secondary. Study level data was pooled from the selected articles for our analysis.

### 2.2. Literature search strategy

A comprehensive search strategy was performed on databases: MEDLINE, Ovid Embase, CINAHL Plus Full Text from EBSCO, Cochrane (Wiley) Central Register of Controlled Trials, and two platforms in Web of Science: Science Citation Index-Expanded and BIOSIS Citation Index. Studies in all languages were included from inception until January 16, 2020. The search strategy was constructed to retrieve published articles reporting the impact of CP intake on outcomes of our interest. Key words and truncation were used to capture plurals or alternative wording. Indexing terms were “exploded” to capture all possible concepts. The search terms and strategy are available in online supplemental (OS 1).

### 2.3. Data extraction and quality assessment

Two independent reviewers (MK and LZ) reviewed the identified studies according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. Any conflict or disagreement was resolved by discussion with another reviewer (BX). Data were extracted and tabulated from the primary manuscripts text, figures, and tables. Covidence application was used to manage the systematic review process and to maintain adherence to PRISMA guidelines [20]. Newcastle-Ottawa scale for cohort studies was used to evaluate the quality of the included studies.

### 2.4. Statistical analysis

Inverse variance method along with DerSimonian-Laird estimator (standard approach) and Sidik-Jonkman estimator with Hartung-Knapp adjustment (modified approach) for random effects model was applied. Calculations are made using both approaches to evaluate between-study variances. Hazard ratio along with 95% confidence interval was calculated as effect sizes to detect any differences in the outcomes of our interest between the intervention and control groups. P-value  $< 0.05$

is considered significant.  $I^2$  test was used to assess heterogeneity as low ( $< 25\%$ ), moderate (25–50%) and high ( $> 50\%$ ). For outcomes with  $I^2 > 50\%$  sensitivity analysis was conducted by re-calculating effect sizes after removing the study with highest overall heterogeneity contribution. Meta-regression and publication bias to evaluate for small study effect was planned. Statistical analysis including generation of figures was performed using software RStudio (Version 1.0.136 – © 2009–2016 RStudio, Inc.; packages - Meta, metaphor, metagen, dmetar and r meta).

## 3. Results

### 3.1. Literature search

7122 articles were identified after the initial database search, of which 2393 duplicates were removed. Initial screening for PICO framework included 4729 articles. Subsequently, 4701 articles were excluded due to not being pertinent to the intervention or outcome of our interest, or being non-observational, such as review articles, case reports, abstracts, letters to the editor, animal and pediatric studies. During full-text screening of 28 studies, we excluded 24 studies, mainly due to studies reporting outcomes not meeting our inclusion criteria. After PRISMA screening, only four studies met the criteria for quantitative meta-analysis (Fig. 1).

### 3.2. Study and participant characteristics

The included studies were found to be observational [14–17] and conducted in different continents: Iran [14], China [15], Italy [16] and United States (US) [17] (Table 1). It generated a pooled cohort of 570,762 participants between 18 and 79 years of age with diverse cultural and ethnical backgrounds. CP was consumed by 45.4% (259,184/570,762) study subjects, and the remaining 54.6% (311,578/570,762) rarely/never consumed it.

A description of the included studies, patient selection criteria and patient characteristics are shown in Tables 1, 2 and 3, respectively. In brief, Bonaccio et al. reported CP consumption impact on all-cause and cardiovascular, cancer-related and cerebrovascular mortalities in 22,811 Italian participants (2005 to 2010) using the EPIC (European Prospective Investigation Into Cancer) food frequency questionnaire (FFQ) [16]. Hashemian et al. reported the impact of chili and black pepper consumption on all-cause, cardiovascular and cancer-related mortalities in 38,383 prospectively enrolled Iranian participants (2004 until 2008) using a 116-item FFQ. This study reported outcomes of spice consumption (i.e. turmeric, pepper, cinnamon and saffron) of which data specific to pepper was extracted for our analysis [14]. Lv et al. reported the impact of CP consumption on mortality in 487,375 Chinese participants (2004 until 2008) using “how often do you eat spicy food” questionnaire [15]. A US based cohort from National Health and Nutrition Examination Survey (NHANES) evaluated 16,179 participants (1988 to 1994) using an 81-item FFQ. Dataset was linked with National Death Index to study the association of CP intake with all cause and specific cause mortality. Their results enhanced the generalizability of CP intake on population health, hence uniquely contributing to our study [17].

The types of CP consumed included hot red CP, black pepper, fresh CP, chili sauce or oil [14–17]. The frequency of CP intake was reported as at least once a week [15], up to 2 times per week to greater than 4 times per week [16], or as at least once per month [17]; however, the exact amounts and mode of CP consumed in these studies were not well defined. Outcome data were collected and confirmed from registries [15,16], death certificates [14] and national death index [17]. International classification of diseases (ICD) codes 9<sup>16</sup> and 10<sup>14,15,17</sup> were identified to collect cause-specific mortality (Table 1). These studies also reported the method of multivariable adjustment based on clinical, social and economic factors for their analysis (OS 2).

**Table 1**  
Characteristics of the studies included in the meta-analysis.

Last name of first author et al. (publication year)	Country	Years of patient enrollment	Type of study	Participants	Type of pepper	Intervention vs Control group (based on frequency of CP consumption)	Outcome Data Assessment	Ethnic Backgrounds	Food questionnaire (based on)	Follow-up (median in years)	Potential bias (adjustment)
Bonaccio et al. (2019)	Italy	2005 to 2010	Prospective cohort study; non-randomized	Men and women $\geq 35$ years of age	Chili pepper	CP consumers ( $n = 15,122$ ): up to 2 times/week to >4 times/week  Rare/Non-consumers ( $n = 7689$ )	Italian mortality registry. Other outcome data were collected from medical records using ICD-9 coding	Moli-Sani, a southern Mediterranean region in Italy	European Prospective Investigation into Cancer Food Frequency Questionnaire	8.2	Information/recall bias (confirmation of outcomes data with medical records). Possibility of residual and unobserved confounding At risk of selection bias
Hashemian et al. (2019)	Iran	2004 to 2008	Prospective cohort study; non-randomized	Individuals 40 to 75 years of age	Black or chili pepper	CP consumers ( $n = 31,071$ ): ever consumer of CP  Non-consumers ( $n = 13,327$ )	Death certificate and two internists evaluating the cause of death. Cause-specific mortality from the medical records using ICD-10 codes	Turkmen, non-Turkmen	116-item Food Frequency Questionnaire (FFQ)	11.1	Information/recall bias (extensive interviews)
Chopan et al. (2017)	USA	1988 to 1994	Prospective cohort study; non-randomized	Adults $\geq 18$ years including Mexican-American, other Hispanic, or non-Hispanic subjects	Hot red chili pepper	CP consumers ( $n = 4107$ ): once per month or more  Non-consumers ( $n = 12,071$ )	Matching with National Death Index. Cause specific mortality was collected from medical records using ICD-10 codes	Multi-culture (White, Black, Hispanics)	81-item Food Frequency Questionnaire	18.9	Residual confounding (inverse association between spicy food and mortality toward the null); At risk of selection bias
Lv et al. (2015)	China	2004 to 2008	Prospective cohort study; non-randomized	10 geographically diverse areas across China, aged 30–79 years	Various types: fresh chili pepper, dried chili pepper, chili sauce, chili oil	CP consumers ( $n = 208,884$ ): At least once a week  Rare/Non-consumers ( $n = 278,491$ )	Linkage with death registries and residential records. Cause-specific mortality was collected using ICD-10 codes	Chinese	Food Questionnaire: frequency of chili pepper intake (never or almost never, only occasionally, 1 or 2 days a week, 3 to 5 days a week, or 6 or 7 days a week)	7.2	Residual confounding (inverse association between spicy food and mortality toward the null); At risk of selection bias

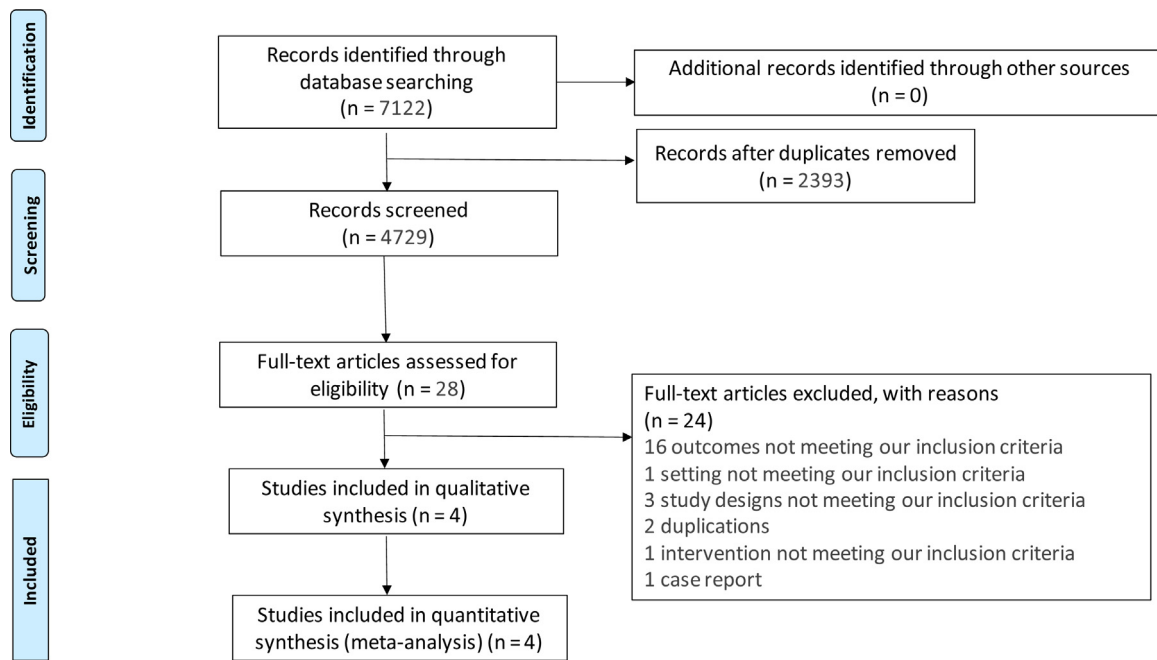


Fig. 1. PRISMA flow diagram for study selection.

**Table 2**  
Inclusion and exclusion criteria of the studies included in the meta-analysis.

Last name of first author et al. (publication year)	Inclusion Criteria	Exclusion Criteria
Bonaccio et al. (2019)	Subjects $\geq 35$ years of age randomly recruited from Molise, a southern Mediterranean region in Italy (data from the Moli-sani prospective cohort study)	Subjects with implausible energy intakes (<800 kcal/d in men and <500 kcal/d in women; >4000 kcal/d in men and >3500 kcal/d in women; 3.2% of cohort) Subjects with suboptimal medical/dietary questionnaires (1% and 3.9% of cohort, respectively) Subjects with missing information on main covariates, exposure, and cause-specific mortality (0.3%, 0.4% and 0.2% of cohort, respectively) 23 subjects (0.1%) were lost to follow-up
Hashemian et al. (2019)	Subjects aged 40 to 75 years of age from Golestan Province, Iran (Data from the Golestan prospective cohort study)	872 subjects with incomplete Food Frequency Questionnaire (FFQ) 599 subjects with implausible energy intakes (<300 kcal/d for women and 525 kcal/d for men; >3690 kcal/d for women and 4145 kcal/d for men) 3454 subjects with baseline self-reported history of heart disease, stroke, or cancer First two years of follow-up (722 subjects) were excluded to address proportional hazard consumption violation
Chopan et al. (2017)	Subjects $\geq 18$ years of age with complete data for the outcomes and the predictors (prospective cohort from the National Health and Nutritional Examination Survey (NHANES) III)	13,581 subjects <18 years of age 26 subjects with no mortality status 42 subjects with no hot red chili pepper consumption data 3371 subjects with missing data about $\geq 1$ confounders
Lv et al. (2015)	Subjects aged 30–79 years of age (data from the China Kadoorie Biobank prospective cohort study)	2577 subjects with cancer 15,472 subjects with existing heart disease 8884 subjects with existing stroke 3 subjects were lost to follow-up

### 3.3. Outcomes

Random effects pooled analysis with DerSimonian-Laird estimator approach showed that all-cause mortality among CP consumers was lower, compared to rare/non-consumers, with a hazard ratio (HR) of 0.87 [95% CI: 0.85–0.90;  $p < 0.0001$ ;  $I^2 = 1\%$ ] (Fig. 2a). HR for cardiovascular mortality was 0.83 [95% CI: 0.74–0.95;  $p = 0.005$ ,  $I^2 = 66\%$ ] and for cancer-related mortality as 0.92 [95% CI: 0.87–0.97;  $p = 0.001$ ;  $I^2 = 0\%$ ] (Fig. 3a & 4a respectively). However, the HR for CVA was 0.78 [95% CI: 0.56–1.09;  $p = 0.26$ ;  $I^2 = 60\%$ ] (Fig. 5a). Sidik-Jonkman estimator approach calculated HR of 0.87 [95% CI: 0.82–0.93;  $p = 0.006$ ;  $I^2 = 1\%$ ] for all-cause mortality, 0.84 [95% CI: 0.71–1.00;  $p = 0.046$ ;  $I^2 = 65\%$ ] for cardiovascular mortality, 0.92 [95% CI: 0.89–

0.95;  $p = 0.004$ ;  $I^2 = 0\%$ ] for cancer-related mortality and 0.80 [95% CI: 0.43–1.49;  $p = 0.26$ ;  $I^2 = 60\%$ ] for CVA related mortality (Fig. 2b, 3b, 4b and 5b respectively).

Sensitivity analysis for outcomes with  $I^2 > 50\%$  identified that the study by Hashemian et al. contributed towards higher heterogeneity for deaths due to cardiac causes, and the study by Bonaccio et al. contributed towards higher heterogeneity for deaths due to CVA (Fig. 6). After removing these studies, estimates for deaths due to cardiac causes, and for CVA were HR: 0.78 [95% CI: 0.75–0.81;  $p = 0.0013$ ;  $I^2 = 0\%$ ] (OS 3a), and HR: 0.87 [95% CI: 0.11–7.05,  $p = 0.55$ ;  $I^2 = 39\%$ ] (OS 3b), respectively. Due to the small number of studies (<10), meta-regression and assessment of publication bias could not be performed. Newcastle and Ottawa scale for non-randomized cohort studies showed these

**Table 3**Characteristics of the subjects in the studies included in the meta-analysis.% (n); Age (mean  $\pm$  standard deviation); BMI: body mass index; N/A: not available.

Last name of first author et al. (year of publication_	Subjects	Age	Male	Smokers	Cardiovascular Diseases	Cancer	Stroke	Diabetes Mellitus	Hypertension	BMI	Hyperlipidemia	Educational status	Alcoholism	Married
Bonaccio et al. (2019)	Total participants (n = 22,811)	55 $\pm$ 11	47.6 (10,871)	22.9 (5241)	5.2 (1179)	3.2 (737)	N/A	4.8 (1092)	27.3 (6222)	N/A	7.7 (1747)	13.2 (3001)	N/A	N/A
	Consumers - 66.3% (n = 15,122)	55 $\pm$ 11	54.3 (8210)	25.2 (3811)	5.3 (810)	2.9 (437)	N/A	5 (761)	27.3 (4131)	N/A	7.8 (1178)	14 (2117)	N/A	N/A
	Non-consumers - 33.7% (n = 7689)	55 $\pm$ 13	34.6 (266)	18.6 (1430)	4.8 (369)	3.9 (300)	N/A	4.3 (331)	27.2 (2091)	N/A	7.4 (569)	11.5 (884)	N/A	N/A
Hashemian et al. (2019)	Total participants (n = 38,383)*	51.9 $\pm$ 8.8	42.2 (16,185)	N/A	N/A	N/A	N/A	5.9 (2254)	17.2 (6603)	26.4 $\pm$ 5.3	N/A	69.3 (26,603)	N/A	88.9 (34,117)
	Consumers - 80.9% (n = 31,071)	51.3 $\pm$ 8.6	41.7 (12,949)	N/A	N/A	N/A	N/A	6 (1864)	16.7 (5194)	26.9 $\pm$ 5.4	N/A	66.3 (20,600)	N/A	89.4 (27,777)
	Non-consumers - 19.1% (n = 7312)	52.5 $\pm$ 9	44.3 (3236)	N/A	N/A	N/A	N/A	5.3 (390)	19.3 (1409)	25.8 $\pm$ 5.3	N/A	82.1 (6003)	N/A	86.7 (6340)
Chopan et al. (2017)	Total participants (n = 16,178)	45.1	46.8 (7577)	25.7 (4156)	N/A	N/A	N/A	11.7 (1888)	25.3(4088)	N/A	N/A	76.2 (12,334)	45.3 (7340)	59.7(9662)
	Consumers - 25.3% (4107)	41.9	58.1 (2386)	28 (1150)	N/A	N/A	N/A	10.4 (427)	19.9 (817)	N/A	N/A	64.6 (2653)	54.7 (2247)	64.8 (2661)
	Non-consumers - 74.6% (n = 12,071)	48.2	43 (5191)	24.9 (3006)	N/A	N/A	N/A	12.1 (1461)	27.1 (3271)	N/A	N/A	80.2 (9681)	42.2 (5094)	58 (7001)
Lv et al. (2015)	Total participants (n = 487,375)	51.4	40.9 (199,293)	26.7 (130,371)	N/A	N/A	N/A	5.4 (26,162)	33.7 (164,338)	23.6	N/A	49.2 (239,674)	15 (73,643)	90.8 (442,941)
	Consumers - 42.9% (n = 208,884)	49.9	42.3 (88,298)	31 (88,298)	N/A	N/A	N/A	4.2 (8837)	29.7 (62,061)	23.7	N/A	48.8 (101,965)	18 (37,684)	91.7 (191,492)
	Non-consumers - 57.1% (n = 278,491)	52.9	39.9 (278,491)	23.5 (65,482)	N/A	N/A	N/A	6.2 (17,325)	36.7 (102,277)	23.4	N/A	49.5 (137,709)	12.9 (35,959)	90.2 (251,449)

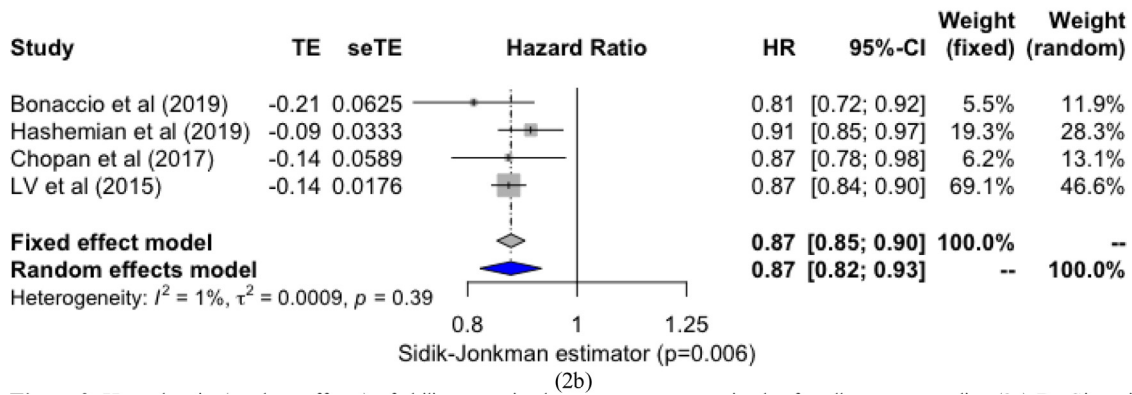
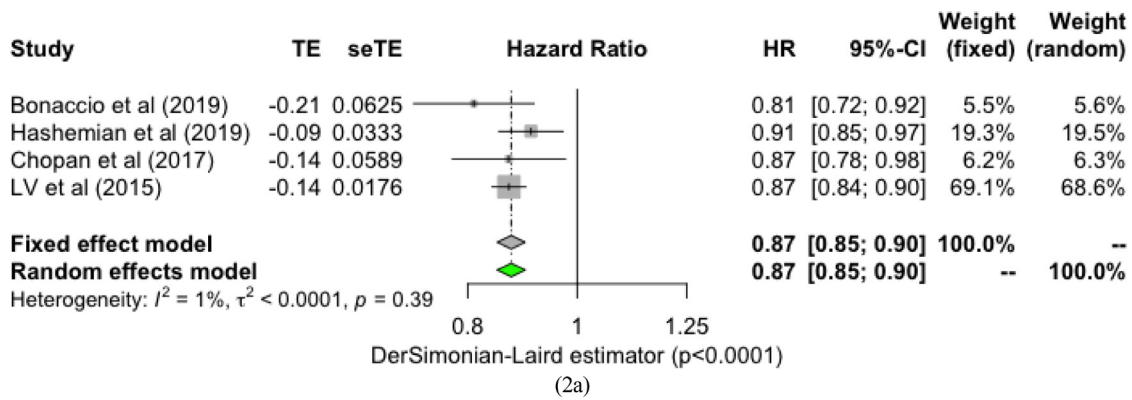


Fig. 2. Hazard ratio (random effects) of chili pepper intake versus no pepper intake for all cause mortality (2a) DerSimonian-Laird estimator HR: 0.87 [0.85; 0.90],  $p < 0.0001$ ;  $I^2 = 1\%$ ; (2b) Sidik-Jonkman estimator HR: 0.87 [0.82; 0.93],  $p = 0.006$ ;  $I^2 = 1\%$ .

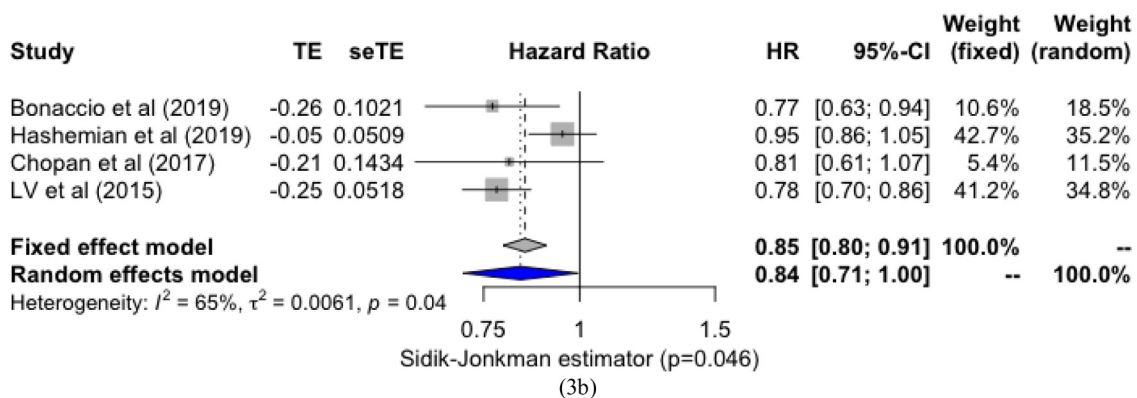
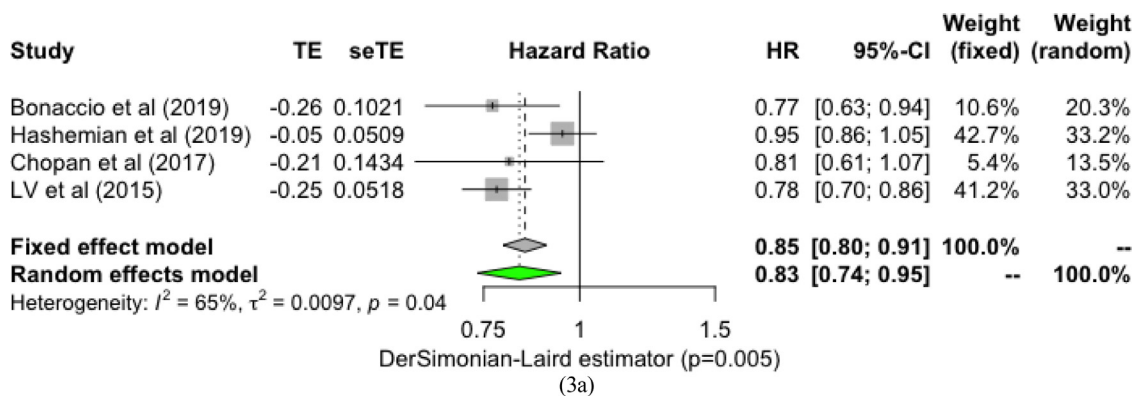


Fig. 3. Hazard ratio (random effects) of chili pepper intake versus no pepper intake for deaths due to cardiac causes (3a) DerSimonian-Laird estimator HR: 0.83 [0.74; 0.95],  $p = 0.005$ ;  $I^2 = 65\%$ ; (3b) Sidik-Jonkman estimator HR: 0.84 [0.71; 1.00],  $p = 0.046$ ;  $I^2 = 65\%$ .

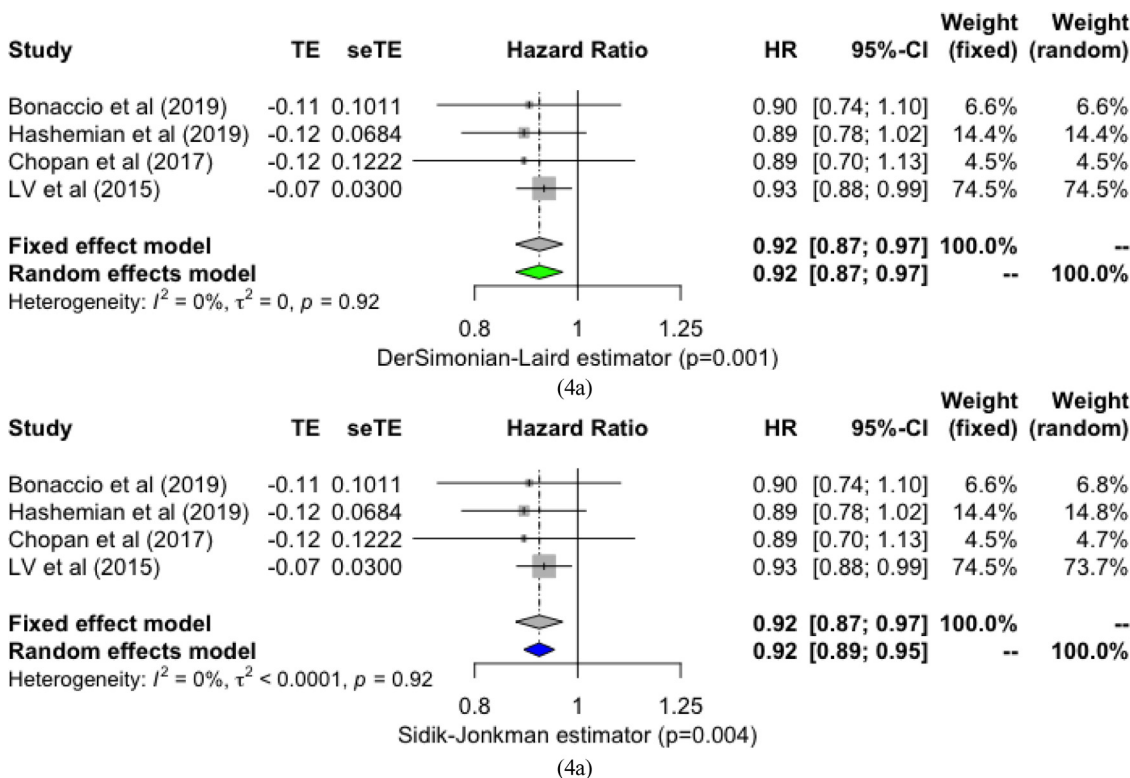


Fig. 4. Hazard ratio (random effects) of chili pepper intake versus no pepper intake for deaths due to cancer (4a) DerSimonian-Laird estimator HR: 0.92 [0.87; 0.97],  $p = 0.001$ ;  $I^2=0\%$ ; (4b) Sidik-Jonkman estimator HR: 0.92 [0.89; 0.95],  $p = 0.004$ ;  $I^2=0\%$ .

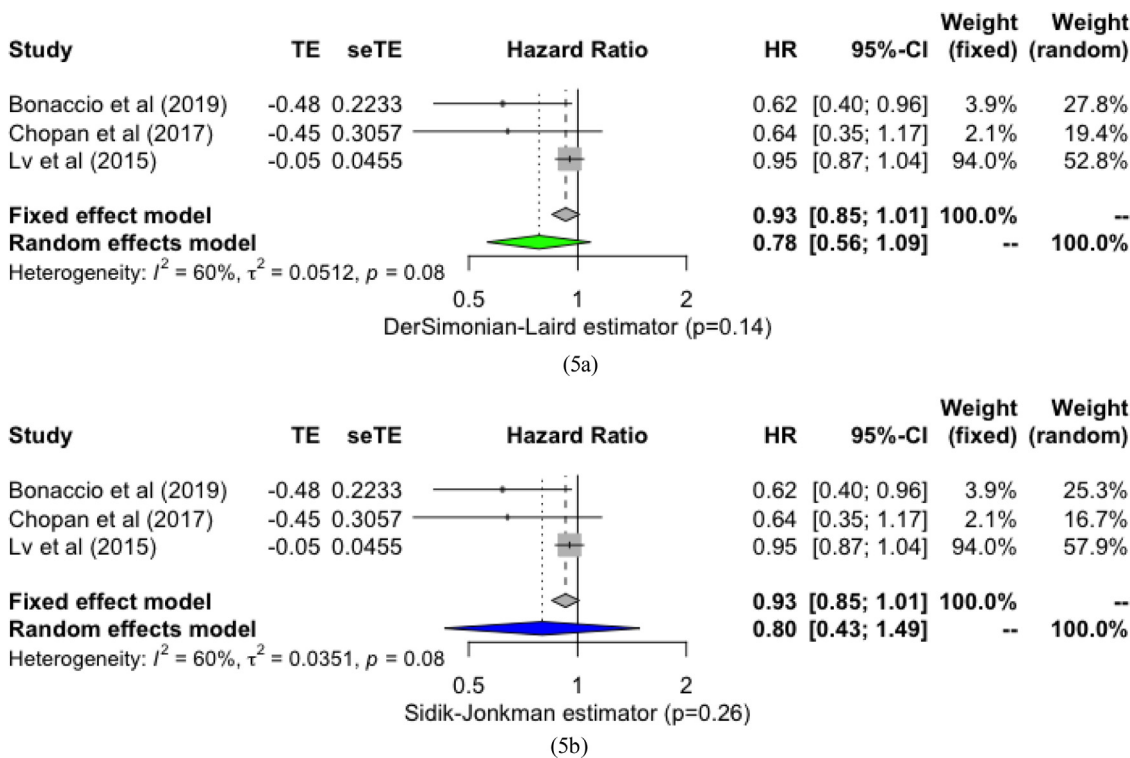


Fig. 5. Hazard ratio (random effects) of chili pepper intake versus no pepper intake for deaths due to cerebrovascular accidents (5a) DerSimonian-Laird estimator HR: 0.78 [0.56; 1.09],  $p = 0.14$ ;  $I^2=60\%$ ; (5b) Sidik-Jonkman estimator HR: 0.80 [0.43; 1.49],  $p = 0.26$ ;  $I^2=60\%$ .

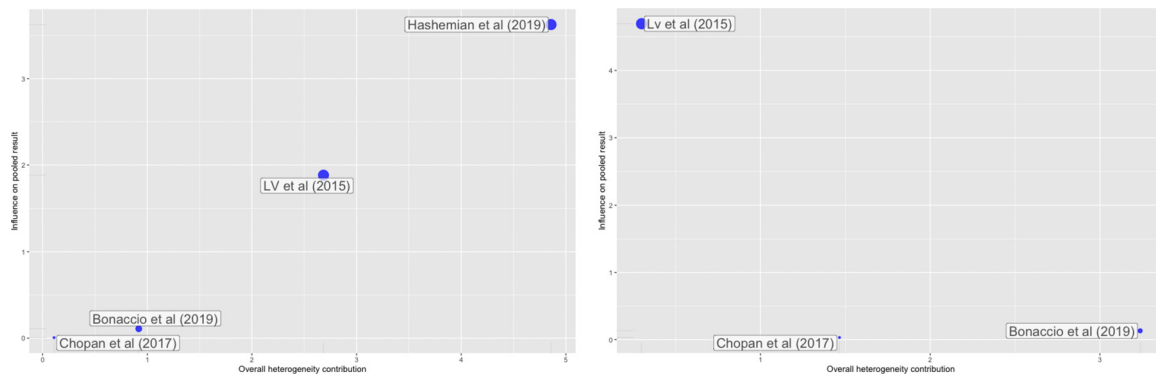


Fig. 6. Overall heterogeneity contribution of the included studies towards deaths due to (a) cardiovascular deaths (b) cerebrovascular accidents.

four studies provided evidence of high quality (OS 4). A study can be awarded a maximum of one star for each numbered item within the Selection (total 4) and Exposure (total 3) categories. A maximum of two stars can be given for Comparability. A score of 9 is the highest attainable. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis is described in detail at [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

#### 4. Discussion

This is the first comprehensive meta-analysis to evaluate the association between CP consumption and all-cause, cardiovascular and cancer related mortalities. We found a significant relative risk reduction in mortality among CP consumers, compared to rare/non-consumers. This intriguingly demonstrates the potential benefit of regular CP consumption on improving health outcomes. Though the magnitude and direction of findings generated after pooled meta-analysis suggest the benefits of CP consumption, there is significant heterogeneity and lack of standardization of CP intake, highlighting this as an important area for future research.

The studies included in this meta-analysis investigated similar clinically important outcomes. The study by Lv et al. demonstrated a 14% relative risk reduction in mortality in those who consumed CP 6–7 days per week as compared to less than once per week [15]. It additionally showed a significant decrease in the rate of respiratory diseases among frequent CP consumers [15]. Furthermore, the sub-group analysis among fresh CP consumers as compared to non-fresh CP suggested a significant mortality benefit related to ischemic heart disease (IHD), diabetes and cancer among those who consumed fresh CP [15]. The multivariate analysis of this study suggested female frequent CP consumers had a lower risk of death due to infections, but no statistically significant difference was found in cause related mortality by sex [15]. They analyzed all-cause mortality benefits by adjusting potential risk factors, such as age, smoking, alcohol status, BMI, and physical activity [15]. Hashemian et al. demonstrated the increased mortality benefits of pepper in women, as authors reported more consumption among women due to more involvement in cooking and meal preparation [14]. This study also supported all cause and cardiovascular mortality benefits among saffron and turmeric users [14]. However, no significant inverse correlation was found with mortality related to cancer due to the low number of deaths [14]. Additionally, no correlation was reported between all-cause mortality and cinnamon consumption [14]. The study by Chopan et al. was conducted in diverse patient populations including different races and ethnicities, and hence reported the generalizable mortality benefits of CP consumption [17]. Furthermore, Bonaccio et al. conducted the study in a large Mediterranean population suggested that capsaicin, present in CP, correlates with health benefits [16]. This is reflected by the observation that sweet pepper, which has a lower capsaicin content, was not associated with mortality benefits in terms of

cardiovascular disease [16]. This study also reported the health effect of CP consumption, independent of the quantity of CP consumed [16].

A possible mechanism for the mortality benefits of CP may be mediated through its alkaloids compounds capsaicinoids predominately capsaicin [21]. It is an active and powerful capsaicinoids which has been shown to facilitate weight reduction by activation of the transient receptor potential cation channel sub-family V member 1 (TRPV1) [18,21–23]. This can, in turn, lead to an increase in the intracellular calcium levels, activating the sympathetic nervous system and the release of catecholamines [18]. This promotes increased fat metabolism, thermogenesis, energy expenditure and improves blood glucose control [22,24], which would be expected to affect energy balance and decrease the risk of obesity and metabolic syndrome, thereby decreasing risk of cardiovascular events, stroke and mortality [18].

Yoshioka et al. reported in 30 participants that a high fat diet supplemented with capsaicin led to an increase in thermogenesis, and weight loss [25]. Another mechanism of action of capsaicin is activation of the hypothalamus, which suppresses appetite and increases satiety [22]. This is mediated by an increase in plasma glucagon like peptide (GLP-1) and a decrease in plasma ghrelin [26]. Furthermore, it has been reported that TRPV1 receptors are present in the sensory nerves near the epicardium and vascular endothelial cells in mice [27]. This has been suggested to be protective against myocardial injury, as there is up-regulation of the endogenous ligand (12-lipoxygenase-derived eicosanoids) of TRPV1 in mice [28].

It should be noted that there are conflicting data regarding the anti-platelet versus pro-aggregating properties of capsaicin. It has been reported in human subjects that capsaicin showed potent anti-platelet activity by inducing arachidonic acid and adenosine diphosphate (ADP) activity [29]. Another study on human participants, however, reported potential pro-aggregating property of capsaicin due to TRPV1 dependent serotonin release, and subsequently thrombin induced platelet activation [30]. This could potentially explain its variable impact on cardiovascular as opposed to cerebrovascular disease as found in our study.

Prior studies have reported that CP provides concentration dependent anti-microbial activity [31]. It disrupts bacterial cell membrane structural integrity via increasing the osmotic gradient, and inhibiting gene expression involved in bacterial cell growth [31]. However, it is not well studied if this effect of CP is associated with trimethylamine N-oxide (TMAO), a metabolite of gut microbial metabolism generated from choline, betaine and carnitine, known to promote atherosclerosis and cardiovascular disease [32–36]. Future well-designed studies could elucidate the underlying bio-chemical mechanisms that mediate its clinical effects.

CP constitutes an important ingredient in Mediterranean cuisines [16], a dietary pattern associated with a decreased risk of death and other co-morbidities [37,38]. After conducting weighted analysis, CP consumption was associated with significant relative reduction in all-cause, cardiovascular and cancer-related deaths. There is a need for



a standardized approach for optimal intake, including the frequency, mode and amount of CP consumption intake, as evidenced by the current significant variations related to geographical regions, cultural habits, dietary behavior, and amounts of CP intake [39–42].

#### 4.1. Study limitations

This meta-analysis included only four studies, which is attributed to the paucity of literature on this topic. Second, these studies originated from different countries, with varying cultural practices, modes and frequencies of CP consumption, which could limit the external validity of our findings. Third, meta-regression and calculation of small study effect were not possible due to the relatively small number of studies. Fourth, patients with a prior history of heart disease, stroke and cancer were excluded in two studies [14,15]. Fifth, heterogeneity ( $I^2$ ) was found to be high which was due to different proportions of CP consumers versus rare/non-consumers in the included studies. Additionally, the potential biases (selection, information or recall and residual confounding among the included studies) could affect the individual study results. However, the authors of the individual studies performed multivariate adjustment for these factors.

## 5. Conclusion

In this contemporary meta-analysis, CP consumption was associated with a statistically significant relative reduction in all-cause, cardiovascular, and cancer-related mortalities. This suggests that CP consumption and/or supplementation of one of its bioactive components may provide significant health benefits. It is a relatively inexpensive, widely available dietary ingredient. Future studies to better understand the mechanisms mediating these potential health benefits, as well as to characterize the optimal amount, type, and frequency of CP consumption are needed.

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None relevant.

Online supplemental (OS) 1: Search strategy for the systematic review and meta-analysis.

OS 2: Adjustment for various cardiovascular risk factors among the studies included in the meta-analysis.

OS 3: Hazard ratio (random effects with Sidik-Jonkman estimator) of chili pepper intake versus no pepper intake for deaths due to (a) cardiac causes HR: 0.78 [0.75; 0.81],  $p = 0.0013$ ;  $I^2=0\%$  (b) cerebrovascular accidents HR: 0.87 [0.11; 7.05],  $p = 0.55$ ;  $I^2=39\%$ .

OS 4: Newcastle-Ottawa Scale for evaluating quality of the evidence for cohort studies.

### CRedit authorship contribution statement

**Manpreet Kaur:** Data curation, Writing – original draft. **Beni R Verma:** Writing – original draft, Methodology, Software. **Leon Zhou:** Data curation, Writing – review & editing. **Hassan Mehmood Lak:** Data curation, Writing – review & editing. **Simrat Kaur:** Data curation, Writing – review & editing. **Yasser M Sammour:** Writing – review & editing. **Samir R Kapadia:** Supervision, Writing – review & editing. **Brian P Griffin:** Supervision, Writing – review & editing. **Bo Xu:** Conceptualization, Methodology, Supervision, Writing – review & editing.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2021.100301.

## References

- [1] Kim H, Caulfield LE, Garcia-Larsen V, Steffen LM, Coresh J, Rebholz CM. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. *J Am Heart Assoc* 2019;8(16). doi:10.1161/JAHA.119.012865.
- [2] Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr* 2014;144(6):881–9. doi:10.3945/jn.113.189407.
- [3] Sotos-Prieto M, Bhupathiraju SN, Mattei J, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med* 2017;377(2):143–53. doi:10.1056/NEJMoa1613502.
- [4] Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Vol 140; 2019. 2019. doi:10.1161/CIR.0000000000000678.
- [5] Anand SS, Hawkes C, De Souza RJ, et al. Fast food consumption and its impact on CVD: importance of solutions focused on the globalized food system. *J Am Coll Cardiol* 2016;66(14):1590–614. doi:10.1016/j.jacc.2015.07.050.
- [6] Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2224–60. doi:10.1016/S0140-6736(12)61766-8.
- [7] Roth DE, Abrams SA, Aloia J, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann N Y Acad Sci* 2018;1430:44–79. doi:10.1111/nyas.13968.
- [8] Aburto NJ, Abudou M, Candeias V, Tiexiang Wu P. Effect and safety of salt iodization to prevent iodine deficiency disorders: a systematic review with meta-analyses WHO Library Cataloguing-in-Publication Data. WHO eLibrary Evid Nutr Actions 2014:91–3.
- [9] Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. *Lancet Glob Heal* 2013;1(1):16–25. doi:10.1016/S2214-109X(13)70001-9.
- [10] Kraft KH, Brown CH, Nabhan GP, et al. Multiple lines of evidence for the origin of domesticated chili pepper, *Capsicum annuum*, in Mexico. *Proc Natl Acad Sci U S A* 2014;111(17):6165–70. doi:10.1073/pnas.1308933111.
- [11] Zimmer AR, Leonardi B, Miron D, Schapoval E, De Oliveira JR, Gosmann G. Antioxidant and anti-inflammatory properties of *Capsicum baccatum*: from traditional use to scientific approach. *J Ethnopharmacol* 2012;139(1):228–33. doi:10.1016/j.jep.2011.11.005.
- [12] Bogusz S, Libardi SH, Dias FFG, et al. Brazilian *Capsicum* peppers: capsaicinoid content and antioxidant activity. *J Sci Food Agric* 2018;98(1):217–24. doi:10.1002/jsfa.8459.
- [13] Dairam A, Fogel R, Daya S, Limson JL. Antioxidant and iron-binding properties of curcumin, capsaicin, and S-allylcysteine reduce oxidative stress in rat brain homogenate. *J Agric Food Chem* 2008;56(9):3350–6. doi:10.1021/jf0734931.
- [14] Hashemian M, Poustchi H, Murphy G, et al. Turmeric, pepper, cinnamon, and saffron consumption and mortality. *J Am Heart Assoc* 2019;8(18). doi:10.1161/jaha.119.012240.
- [15] Lv J, Qi L, Yu C, et al. Consumption of spicy foods and total and cause specific mortality: population based cohort study. *BMJ* 2015;351:1–10. doi:10.1136/bmj.h3942.
- [16] Bonaccio M, Di Castelnuovo A, Costanzo S, et al. Chili pepper consumption and mortality in Italian adults. *J Am Coll Cardiol* 2019;74(25):3139–49. doi:10.1016/j.jacc.2019.09.068.
- [17] Chopan M, Littenberg B. The association of hot red chili pepper consumption and mortality: a large population-based cohort study. *PLoS ONE* 2017;12(1):1–10. doi:10.1371/journal.pone.0169876.
- [18] Sharma SK, Vij AS, Sharma M. Mechanisms and clinical uses of capsaicin. *Eur J Pharmacol* 2013;720(1–3):55–62. doi:10.1016/j.ejphar.2013.10.053.
- [19] Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:1–6. doi:10.1186/1472-6947-7-16.
- [20] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7). doi:10.1371/journal.pmed.1000097.
- [21] De Masi L, Siviero P, Castaldo D, Cautela D, Esposito C, Laratta B. Agronomic, chemical and genetic profiles of hot peppers (*Capsicum annuum* spp.). *Mol Nutr Food Res* 2007;51(8):1053–62. doi:10.1002/mnfr.200600233.

- [22] Snitker S, Fujishima Y, Shen H, et al. Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. *Am J Clin Nutr* 2009;89(1):45–50. doi:10.3945/ajcn.2008.26561.
- [23] Ludy MJ, Mattes RD. The effects of hedonically acceptable red pepper doses on thermogenesis and appetite. *Physiol Behav* 2011;102(3–4):251–8. doi:10.1016/j.physbeh.2010.11.018.
- [24] Janssens PLHR, Hursel R, Martens EAP, Westerterp-Plantenga MS. Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. *PLoS ONE* 2013;8(7):e67786. doi:10.1371/journal.pone.0067786.
- [25] Yoshioka M, St-Pierre S, Suzuki M, Tremblay A. Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. *Br J Nutr* 1998;80(6):503–10. doi:10.1017/s0007114598001597.
- [26] Wang P, Yan Z, Zhong J, et al. Transient receptor potential vanilloid 1 activation enhances gut glucagon-like peptide-1 secretion and improves glucose homeostasis. *Diabetes* 2012;61(8):2155–65. doi:10.2337/db11-1503.
- [27] Zahner MR, Li DP, Chen SR, Pan HL. Cardiac vanilloid receptor 1-expressing afferent nerves and their role in the cardiogenic sympathetic reflex in rats. *J Physiol* 2003;551(2):515–23. doi:10.1113/jphysiol.2003.048207.
- [28] Sexton A, McDonald M, Cayla C, Thiemermann C, Ahluwalia A. 12-Lipoxygenase-derived eicosanoids protect against myocardial ischemia/reperfusion injury via activation of neuronal TRPV1. *FASEB J* 2007;21(11):2695–703. doi:10.1096/fj.06-7828com.
- [29] Raghavendra RH, Naidu KA. Spice active principles as the inhibitors of human platelet aggregation and thromboxane biosynthesis. *Prostaglandins Leukot Essent Fat Acids* 2009;81(1):73–8. doi:10.1016/j.plefa.2009.04.009.
- [30] Harper AGS, Brownlow SL, Sage SO. A role for TRPV1 in agonist-evoked activation of human platelets. *J Thromb Haemost* 2009;7(2):330–8. doi:10.1111/j.1538-7836.2008.03231.x.
- [31] Kang C, Wang B, Kaliannan K, Godoy-Vitorino F, Dominguez Bello MG, et al. Gut microbiota mediates the protective effects of dietary capsaicin against chronic low-grade inflammation and associated obesity induced by high-fat diet. *MBio* 2017;8(3):1–15. doi:10.1128/mBio.00470-17.
- [32] Tang WHW, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. *Circ Res* 2017;120(7):1183–96. doi:10.1161/CIRCRESAHA.117.309715.
- [33] Janeiro MH, Ramírez MJ, Milagro FI, Martínez JA, Solas M. Implication of trimethylamine n-oxide (TMAO) in disease: potential biomarker or new therapeutic target. *Nutrients* 2018;10(10). doi:10.3390/nu10101398.
- [34] Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell* 2016;165(1):111–24. doi:10.1016/j.cell.2016.02.011.
- [35] Tang WHW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;368(17):1575–84. doi:10.1056/NEJMoa1109400.
- [36] Li XS, Wang Z, Cajka T, et al. Untargeted metabolomics identifies trimethyllysine, a TMAO-producing nutrient precursor, as a predictor of incident cardiovascular disease risk. *JCI insight* 2018;3(6). doi:10.1172/jci.insight.99096.
- [37] Balducci Stefano, Sacchetti Massimo, Haxhi Jonida, Orlando Giorgio, D'Errico Valeria, Fallucca Sara, Menini Stefano, Pugliese G. Mediterranean diet and type 2 diabetes. *Diabetes Metab Res Rev* 2014;32(30):13–23. doi:10.1002/dmrr.
- [38] Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health: a critical review. *Circ Res* 2019;124(5):779–98. doi:10.1161/CIRCRESAHA.118.313348.
- [39] Woo J, Woo KS, Leung SS, et al. The Mediterranean score of dietary habits in Chinese populations in four different geographical areas. *Eur J Clin Nutr* 2001;55(3):215–20. doi:10.1038/sj.ejcn.1601150.
- [40] Hendrychova T, Vytrisalova M, Alwarafi A, et al. Fat- and fiber-related diet behavior among type 2 diabetes patients from distinct regions. *Patient Prefer Adherence* 2015;9:319–25. doi:10.2147/PPA.S71373.
- [41] Kornitzer M, De Backer G, Dramaix M, Thilly C. Regional differences in risk factor distributions, food habits and coronary heart disease mortality and morbidity in Belgium. *Int J Epidemiol* 1979;8(1):23–31. doi:10.1093/ije/8.1.23.
- [42] Pettinger C, Holdsworth M, Gerber M. “All under one roof?” Differences in food availability and shopping patterns in Southern France and Central England. *Eur J Public Health* 2008;18(2):109–14. doi:10.1093/eurpub/ckm037.