Nut and legume consumption and human health: an umbrella review of observational studies

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Nut and legume consumption and human health: an umbrella review of observational studies

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Nut and legume consumption and human health: an umbrella review of observational studies

Keywords: nut; legume; meta-analysis; umbrella review; evidence; non-communicable diseases; cardiovascular disease; cancer; coronary heart disease; stroke; colon cancer

Abstract

Consumption of nuts and legumes has been associated with several health benefits. The aim of this study was to systematically review existing meta-analyses of observational studies on nut and legume consumption and various health outcomes. The level of evidence for their association on health was assessed. Out of the 21 meta-analyses, a possible association with decreased risk of colorectal adenoma and coronary heart disease was assessed for higher legume consumption, and a decreased risk of cardiovascular and cancer mortality, colon cancer, hypertension and ischaemic stroke for higher nut consumption; the association between legume consumption and CVD, as well as nut consumption and risk of cancer, cardiovascular diseases incidence, and mortality from all causes was deemed as “limited” due to heterogeneity between results and/or potential confounding factors. General benefit toward better health can be observed for both nut and legume consumption; further studies are needed to better elucidate potential confounding factors.

Introduction

The scientific community agrees that a dietary pattern rich in plant-derived foods might exert beneficial effects on human health (Angelino et al. 2019). The global burden of disease has been shown to be strongly affected by nutritional risk factors and addressing malnutrition would impact global mortality and years of life lived with disability (GBD 2017 Diet Collaborators 2019; GBD 2019 Risk Factors Collaborators 2020). Traditional healthy dietary patterns have gained large interest due to their content in fruit and vegetables, but also in legumes and nuts: considered key features for a balanced healthy diet, these food groups are globally accessible and easily embeddable in any sort of diet worldwide (Mocciaro et al. 2018). Several overviews of the scientific literature emphasized on the potential benefits of nut and legume consumption, especially toward age-related diseases (Bouchenak & Lamri-Senhadjji 2013; Grosso & Estruch 2016). Nuts and legumes, among other foods, characterize the pillars of traditional Mediterranean dietary pattern, which has been associated with a number of health benefits (Grosso et al. 2017) being characterized by a high consumption of plant-based foods (i.e. wholegrain, fruit and vegetables, legumes, nuts) moderate amounts of animal-foods, and extra-virgin olive oil as dressing and main source of monounsaturated fatty acids (MUFA). Among the plant-based foods characterizing the Mediterranean diet, nuts and legumes play an important role due to their favourable nutrient profile.

The term “nuts” include a wide range of different products such as chestnut, brazil nut, and hazelnut, that are true nuts also from a botanical point of view, but also almond, cashew, and peanut, and other seeds, which are energy and nutrient dense foods characterized by high content of protein, fats, vitamins, minerals. Legumes, also known as pulses, also comprehend a wide list of products such as peas, beans, chickpeas and many others, generally high in protein, low in fats (except for soy), and good sources of fibre and some micronutrients.

Moreover, both nuts and legumes are good sources of phytochemicals like polyphenols that are often investigated for explaining part of the preventive role associated with the consumption of these two food groups (Godos et al. 2017; Marino et al. 2020).

With a various extent, the content in fiber, phytochemicals, and optimal fatty acid profile of nuts and legumes provide indeed an ideal mix of nutrients and antioxidants potentially leading their role in decreasing non-communicable diseases (Martini 2019; Dinu et al. 2020).

Previous studies discussed the potential for a decreased risk of cardiovascular disease (CVD) and certain cancers associated with consumption of nuts and legumes, but a comprehensive assessment of the level of evidence is lacking. Thus, the aim of the present umbrella review was to systematically review existing meta-analyses on nut and legume consumption and all available outcomes and to evaluate the level of evidence for their impact on disease risk.

Methods

Study selection

We performed a systematic review of existing meta-analyses of prospective cohort studies on nut and legume consumption and various health outcomes in Medline and Embase electronic databases until January 2017. The search strategy included: [(pulse OR pulses OR bean OR beans OR lentil OR lentils OR legume OR legumes OR pea OR peas OR chickpea OR chickpeas tree nuts OR tree nut OR nuts OR nut OR almond OR almonds OR pecan OR pecans OR brazil nuts OR hazelnut OR hazelnuts OR macadamia OR pine nuts OR pistachio OR pistachios OR walnut OR walnuts OR peanut OR peanuts OR cashew OR cashews) AND (meta-analysis OR meta-analyzed OR pooled analysis)]. Only meta-analyses of prospective cohort studies on legume or nut consumption as the variable of exposure were included for evaluation. Studies on soy or isoflavones were not included. Meta-analyses of RCTs with

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outcomes of intermediary biomarkers of disease (i.e., blood lipids, blood pressure, etc.) or intermediary clinical conditions (i.e., variation in body weight/BMI, etc.), and systematic reviews without quantitative evaluation of the association between exposure and outcome were not included for evaluation. Hand searching of reference lists was also undertaken. Any discrepancy on the inclusion/exclusion decision was solved through discussion.

Data extraction

From each meta-analysis included, the following information was extracted: name of the first author and year of publication, outcome, number of studies included in the meta-analysis, study design of included studies (i.e., case-control/cross-sectional and prospective), total number of population, number of cases, type of exposure, measure of exposure [including highest versus lowest (reference) category of exposure or dose-response incremental servings per day (linear)], effect sizes [risk ratio (RR), odds ratio (OR), or hazard ratio (HR)].

Data evaluation and evidence synthesis

Where more than one meta-analysis was conducted on the same outcome, including the same study design, and the same population group, the concordance for the main outcome of interest, including direction and magnitude (overlapping confidence interval) of the association was evaluated. For further analyses, the most recent/exhaustive study was considered. The pooled analyses of the highest versus the lowest (reference) category of exposure and dose-response analyses were evaluated. Direction and magnitude of the association, heterogeneity (I²) of results, and subgroup/stratified analyses for potential confounding factors were considered to have indication of level of evidence. Criteria used for evidence categorization were modified from the Joint WHO/FAO Expert Consultation (Degrees of evidence by the Joint WHO/FAO Expert Consultation).

http://www.who.int/nutrition/topics/5_population_nutrient/en/#diet 5.1.2 Accessed November 2015) (Table 1). Briefly, the relation between exposure and outcomes was categorized as following: suggestive/limited/contrasting evidence, when there was availability of solely meta-analyses of case-control studies, limited prospective cohort studies included in meta-analyses ($n < 3$), or evident contrasting results from meta-analyses with the same level of evidence; possible evidence, when there was availability of meta-analyses with lack of information on/significant heterogeneity ($I^2 > 50\%$) or identification of potential confounding factors (i.e., different findings in subgroups); probable association, when there was availability of meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained (and evidence of dose-response relation further investigated); convincing association, when there was concordance between meta-analyses of RCTs and observational studies. Lack of fulfillment of the previous criteria was considered as insufficient evidence.

Results

Study selection

Of 139 articles identified through the database search, 54 were excluded based on title and after abstract evaluation (Figure 1). Twenty-one studies were further excluded because meta-analyses of RCT ($n = 11$), narrative/systematic reviews without quantitative evaluation of the association between exposure and outcome ($n = 2$), pooled analysis of prospective cohort studies ($n = 1$), investigating biomarkers ($n = 2$), having different exposure (i.e., soy, soy isoflavones; $n = 5$). Thus, a total number of 6 studies on legume consumption (Wang et al. 2013; Afshin et al. 2014; Shi et al. 2014; Zhu et al. 2015; Marventano et al. 2017; Zhong et al. 2018) and 15 on nut consumption (Afshin et al. 2014; Luo et al. 2014; Zhou et al. 2014;

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Ma et al. 2014; Shi et al. 2014; Guo et al. 2015; Zhang et al. 2015; Grosso et al. 2015; van den Brandt & Schouten 2015; Wu et al. 2015; Mayhew et al. 2016; Weng et al. 2016; Shao et al. 2016; Wu et al. 2016; Aune et al. 2016) and various health outcomes was selected for evaluation.

Characteristics of the studies on legume consumption and health outcomes

The main characteristics of the studies exploring the risk associated to high vs. low legume consumption for 5 unique outcomes from 3 non-overlapping meta-analyses and the risk associated to linear legume consumption for 4 unique outcomes from 1 non-overlapping meta-analysis are shown in Figure 2 and Supplementary Table 1, respectively. A decreased risk of CVD, CHD, and colorectal adenoma was observed for higher vs. lower intake of legume (Figure 2). One meta-analysis (Zhong et al. 2018) on a limited number of prospective cohort studies (<3) and case-control studies also reported a potential inverse association between high legume intake and endometrial cancer risk. Limited information on potential confounding factors showed that results on colorectal cancer risk were significant only when considering Asian cohorts (Marventano et al. 2017).

Characteristics of the studies on nut consumption and health outcomes

An overview of the main characteristics of the studies included and the risk estimates of various health outcomes for the highest versus the lowest category of nut consumption are reported for 15 unique outcomes extracted from 9 non-overlapping meta-analyses in Figure 3 and the risk estimates of 10 outcomes from 5 non-overlapping meta-analyses for linear consumption of nuts are reported in Supplementary Table 2. A significant inverse association between nut consumption and CVD risk (including subtypes CHD and stroke) and mortality, as well as all-cause mortality and total and colorectal cancer was found: however, the meta-

analysis on risk of CVD reported significant heterogeneity and a study specifically exploring myocardial infarction reported null results (Figure 3). The results on CVD mortality and cancer risk were in line with those estimated for increasing consumption (linear) of nuts (Supplementary Table 2). Two non-overlapping meta-analyses conducted on a limited number of prospective cohort studies (<3) or case-control studies reported null results on individual types of cancers (Wu et al. 2015) and stroke (hemorrhagic) (Zhang et al. 2015). When controlling for potential confounding factors, results were only relatively consistent, since significance in studies on CVD outcomes varied by geographical region (i.e., a decreased risk for higher nut consumption was stably observed in US cohorts but not consistently in European ones), as well as results on stroke (total) were significant only in women while those on cancer (any) and CVD risk only in men. When controlling for stability of findings over time, a previous study on cancer risk reported non-significant results (Wu et al. 2015).

Summary of evidence

The strength of the evidence was evaluated through checking for the pre-selected criteria as reported in Supplementary Table 3. A possible association with decreased risk of colorectal adenoma and CHD was assessed for higher legume consumption, and a decreased risk of CVD and cancer mortality, colon cancer, hypertension and ischemic stroke for higher nut consumption; the association between legume consumption and CVD, as well as nut consumption and risk of cancer, CVD, CHD (fatal), stroke, and mortality from all causes was deemed as limited mostly due to heterogeneity between results and/or potential residual confounding. No probable nor convincing associations were found. Limited or insufficient evidence has been reported for all other outcomes investigated (Table 1).

Discussion

The findings of this umbrella review emphasize on the convincing role of nut and legume consumption in affecting cardiovascular and, probably, on general cancer risk. Despite with great differences between nut and legume types, these foods are rich in nutrients, such as protein, unsaturated fatty acids, fiber, vitamins, minerals, as well as a number of phytochemicals, including polyphenols and phytosterols (Ros 2010). Several mechanisms have been hypothesized to explain the reduced CVD risk associated with nut consumption. The protein content of nuts accounts for about 10-25% and includes aminoacids, such as L-arginine, which is involved in the production of nitric oxide (NO) and an endogenous vasodilator that may play a role in regulating blood pressure (Brufau et al. 2006). The fat content includes monounsaturated fatty acids (MUFA), such as oleic acid in most of nuts, and polyunsaturated fatty acids (PUFA), such as alpha-linolenic acid in pine nuts and walnuts; MUFA and PUFA are able to reduce serum concentrations of the vasoconstrictor thromboxane 2, which might influence blood pressure regulation. Together with polyphenols and group B vitamins and folate, nuts may prevent oxidative stress by scavenging or neutralizing reactive oxidant species and improve inflammatory status by reducing circulating levels of soluble cellular adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, which are released from the activated endothelium and circulating monocytes (Segura et al. 2006). Moreover, content in fiber and polyphenols of nuts and legumes may play a role in modulating the profile of gut microbiome exerting favourable effects toward systemic inflammation (Salvucci 2019; Mena & Bresciani 2020). Finally, the presence of mineral such as magnesium, potassium, and calcium, may play a role on blood pressure through the production NO, prostacyclin and calcium channel blockade, the reduction of the extracellular

fluid volume modulating the activity of the renin-angiotensin system, and the inhibition of the parathyroid hormone that induces hypertension (Casas-Agustench et al. 2011).

From a clinical point of view, nut consumption has been revealed to be effective in reducing cardiovascular risk factors. A pooled analysis of RCTs showed a potential role of nuts in reducing blood lipids: a diet supplemented with a daily consumption of 67 g of nuts reduced total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), ratio of LDL-C to HDL-C, and ratio of TC to HDL-C concentration (Sabaté et al. 2010). Similar findings have been reported also for specific types of nuts: for instance, a meta-analysis on diets supplemented with walnuts led to reduction of TC and LDL-C (Guasch-Ferré et al. 2018); another meta-analysis on diets supplemented with almonds showed reduction of TC and a non-significant trend in LDL-C reduction (Del Gobbo et al. 2015); no general effects on high-density lipoprotein-cholesterol (HDL-C) and triglycerides concentrations have been reported. Also a meta-analysis on RCT investigating the effects of legumes on blood lipids showed that diets including legumes led to reduction in TC and LDL-C (Bazzano et al. 2011). Regarding blood pressure, a meta-analysis of RCTs showed that diets supplemented with nuts reduced SBP and DBP, despite the effect was relevant only in individuals without T2DM (Mohammadifard et al. 2015). Similarly, results from another meta-analysis of RCTs showed that dietary pulses, exchanged isocalorically for other foods, significantly lowered SBP and DBP (Jayalath et al. 2014). Contrasting results have been found regarding glycemic control: despite no evidence from observational studies has been concluded, a meta-analysis of RCTs on the effects of nut consumption in diabetic individuals showed an improvement in glycemic control, including lowering HbA1c and fasting glucose but not fasting insulin and homeostatic model assessment (Viguioliouk et al. 2014). Similarly, also a meta-analysis of RCTs on legumes showed lowering of fasting blood glucose and insulin, despite most of

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results were stronger when considering legume consumption in the context of low-glycaemic index or high-fiber diets (Sievenpiper et al. 2009).

Nuts and legumes have been proposed as foods potentially playing a role as anticancer agents. Their components may synergistically exert antioxidative and anti-inflammatory properties that may contribute to the prevention of processes leading to tumor initiation, invasion, and intravasation into blood and lymphatics vessels, a process further enhanced by the inflammatory status, such as vascular permeability induced by tumor necrosis factor and prostaglandin production (Falasca et al. 2014). Certain polyphenols contained in plant-derived foods, including nuts and legumes, have been shown to affect various cellular processes involved in cancer development and progression, including cell survival, cell proliferation, cell invasion, and angiogenesis (Falasca & Casari 2012). With special regard to colon cancer, nuts and legumes are also a dietary source of fiber, well-known to play a role in lower gastrointestinal cancer prevention (González & Salas-Salvadó 2006). Finally, nuts and legumes may indirectly exert anticancer activity through their ability to alter lipid profiles and cell metabolism (Grosso et al. 2013; Tárraga López et al. 2014).

The present study should be considered in light of some limitations. The results pooled from different cohort studies may have different methods for dietary exposure estimation and lack of general identification of type of nuts or legumes, which might play a role for the different effect on health. Moreover, it has been pointed out that plant-food consumption is a health-conscious choice (Grosso et al. 2015), thus confounding from background variables potentially leading to effect modification should be taken into account.

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3 In conclusions, given the validity of the presented findings from observational studies and the
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5 agreement of results with clinical trials, we can conclude that a diet containing nuts and
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7 legumes reduces the risk of CVD. Despite convincing evidence of an association has been
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9 observed also for cancer outcomes, further studies in clinical settings are needed to better
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11 understand the potential mechanisms underlying the aforementioned relation.
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23 24 **Declaration of interests**

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26 The authors declare no conflicts of interest.
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Figure legend

Figure 1. Flow chart of study selection.

Figure 2. Summary results from meta-analyses of prospective cohort studies on legume consumption on various health outcomes included in umbrella review.

Figure 3. Summary results from meta-analyses of prospective cohort studies on nut consumption on various health outcomes included in umbrella review.

Table legend

Table 1. Level of evidence for the association between nut and legume consumption and health outcomes.

Supplementary material legend

Supplementary Table 1. Summary results from meta-analyses investigating continuous linear exposure to legume consumption and health outcomes.

Supplementary Table 2. Summary results from meta-analyses investigating continuous linear exposure to nut consumption and health outcomes.

Supplementary Table 3. Variables investigated to address the strength of evidence from selected meta-analyses on legume and nut consumption and health outcomes.

Table 1. Level of evidence for the association between nut and legume consumption and health outcomes.

Level of evidence*	Criteria§	Legume consumption	Nut consumption
Convincin g	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassified as possible].	None.	None.
Probable	Meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassified as possible].	None.	None.
Possible	Meta-analysis of prospective cohort studies with no heterogeneity and lack of information on potential confounding factors.	Association with decreased risk of adenoma (colorectal) and CHD.	Association with decreased risk of cancer (colon), hypertension, mortality (cancer, CVD), stroke (ischemic)
Limited	Meta-analysis of prospective cohort studies with presence of significant heterogeneity ($I^2 > 50\%$) or identification of potential confounding factors (i.e., different findings in subgroups).	Association with decreased risk of CVD (any)*.	Association with decreased risk of cancer (total)*, CHD (fatal)*, CVD (any)*, mortality (all-cause)*, stroke (total)*
Insuffici ent	Meta-analysis of case-control studies, limited prospective cohort studies included in meta-analyses (n < 3), or evident contrasting results from meta-analyses with the	None.	Association with cancer (acute myeloid leukemia, endometrial, gastric, glioma, hepatocellular carcinoma, leukemia, lymphoma, ovarian, pancreatic,

	same level of evidence.		prostate, stomach, upper areo-digestive)
No evidence	Non-significant results from meta-analyses of either prospective or case-control studies.	No association with cancer (colorectal), stroke, type-2 diabetes.	No association with cancer (breast), myocardial infarction, type-2 diabetes.
all the associations should be biologically plausible; potential confounding factors should be taken into account. \$ modified from the Joint WHO/FAO Expert Consultation * presence of potential confounding factors

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Supplementary Table 1. Summary results from meta-analyses investigating continuous linear exposure to legume consumption and health outcomes.

Outcome	Number of Studies	Exposure (increment)	RR (95% CI)	I2	Reference
CHD	4	4 servings/w (100g/w)	0.86 (0.78, 0.94)	0,2%	Afshin, 2014
Stroke	6	4 servings/w (100g/w)	0.98 (0.84, 1.14)	32%	Afshin, 2014
Diabetes	2	4 servings/w (100g/w)	0.78 (0.50, 1.24)	94,6%	Afshin, 2014
Ischemic stroke	4	4 servings/w (100g/w)	1.07 (0.77, 1.50)	60,1%	Afshin, 2014
Hemorrhagic stroke	4	4 servings/w (100g/w)	1.23 (0.91, 1.66)	0%	Afshin, 2014

Abbreviations: CHD (coronary heart disease).

Supplementary Table 2. Summary results from meta-analyses investigating continuous linear exposure to nut consumption and health outcomes.

Outcome	Number of Studies	Exposure (increment)	RR (95% CI)	I ²	Reference
Cancer (total)	9	1 serving (28g)/d	0.85 (0.76, 0.94)	42%	Aune 2016
Breast cancer	3	1 serving (28g)/d	0.96 (0.84, 1.09)	0%	Wu 2016
CHD	12	1 serving (28g)/d	0.71 (0.63, 0.80)	47%	Aune 2016
CVD	12	1 serving (28g)/d	0.79 (0.70, 0.88)	60%	Aune 2016
CVD mortality	5	1 serving (28g)/d	0.61 (0.42, 0.91)	75%	Grosso 2015
Hypertension	3	1 serving/w	0.97 (0.83, 1.13)	69%	Guo 2015
All cause mortality	15	1 serving (28g)/d	0.78 (0.72, 0.84)	66%	Aune 2016
Stroke ischemic	7	12g/d	0.86 (0.79, 0.94)	NA	Shao 2016
Stroke	11	1 serving (28g)/d	0.93 (0.83, 1.05)	14%	Aune 2016
T2DM	6	1 serving/w	1.00 (0.95, 1.04)	0%	Guo 2015

Abbreviations: CHD (coronary heart disease), CVD (cardiovascular disease), T2DM (type-2 diabetes mellitus).

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Supplementary Table 3. Variables investigated to address the strength of evidence from selected meta-analyses on legume and nut consumption and health outcomes.

Reference	Outcome	Heterogeneity	Dose-response analysis	Agreement over time	Potential confounding	Reference
Legumes						
Marventano, 2016	CHD	∅	⊕	⊕	⊕	Marventano, 2016
Marventano, 2016	Stroke (total)	⊕	⊕	⊕	∅	Marventano, 2016
Marventano, 2016	CVD (total)	∅	⊕	○	∅	Marventano, 2016
Zhu, 2015	Cancer (colorectal)	∅	○	○	⊕	Zhu, 2015
Wang, 2013	Adenoma (colorectal)	∅	○	○	○	Wang, 2013
Afshin, 2014	Stroke (ischemic)*	⊕	⊕	○	○	Afshin, 2014
Afshin, 2014	Stroke (hemorrhagic)*	∅	⊕	○	○	Afshin, 2014
Nuts						
Aune 2016	Cancer (any)	⊕	⊕	∅	⊕	Aune 2016
Wu 2016	Cancer (breast)	∅	⊕	⊕	○	Wu 2016
Wu 2015	Cancer (colon)	∅	○	○	○	Wu 2015
Aune 2016	CHD	∅	⊕	⊕	⊕	Aune 2016
Mayhew 2016	CHD (fatal)	∅	○	⊕	⊕	Mayhew 2016
Aune 2016	CVD	∅	⊕	⊕	⊕	Aune 2016
Grosso 2015	Mortality (CVD)	∅	⊕	⊕	○	Grosso 2015
Guo 2015	Hypertension	∅	⊕	⊕	○	Guo 2015
Ma 2014	MI	⊕	○	○	○	Ma 2014
Aune 2016	Mortality (all-cause)	∅	⊕	⊕	⊕	Aune 2016
Van den Brandt, 2015	Mortality (cancer)	∅	○	⊕	○	Van den Brandt, 2015
Shao 2016	Stroke (ischemic)	∅	⊕	∅	○	Shao 2016
Mayhew 2016	Stroke (mortality)	∅	○	⊕	∅	Mayhew 2016
Aune 2016	Stroke (total)	∅	⊕	⊕	⊕	Aune 2016
Guo 2015	T2DM	⊕	⊕	⊕	∅	Guo 2015

*only dose-response meta-analysis.
CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; T2DM, type-2 diabetes.
○ (denotes lacking information); ∅ (denotes “no”); ⊕ (denotes “yes”).