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An overview and update on the epidemiology of flavonoid intake and cardiovascular disease risk

Short title: Flavonoid intake and cardiovascular disease risk

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Abstract

There is an accumulating body of literature reporting on dietary flavonoid intake and the risk of cardiovascular disease (CVD) in prospective cohort studies. This makes apparent the need for an overview and update on the current state of the science. To date, at least 27 prospective cohorts (in 44 publications) have evaluated the association between estimated habitual flavonoid intake and CVD risk. At this time, the totality of evidence suggests long-term consumption of flavonoid-rich foods may be associated with a lower risk of fatal and non-fatal ischemic heart disease (IHD), cerebrovascular disease, and total CVD; disease outcomes which are principally, though not exclusively, composed of cases of atherosclerotic CVD (ASCVD). To date, few studies have investigated outcome specific ASCVD, such as peripheral artery disease (PAD) or ischemic stroke. Of the flavonoid subclasses investigated, evidence more often implicates diets rich in anthocyanins, flavan-3-ols, and flavonols in lowering the risk of CVD. Although inferences are restricted by confounding and other inherent limitations of observational studies, causality appears possible based on biological plausibility, temporality, and the relative consistency of the reported associations. However, whether the associations observed represent a benefit of the isolated bioactives per se, or are a signal of the bioactives acting in concert with the co-occurring nutrient matrix within flavonoid-bearing foods, are issues of consideration. Thus, the simple interpretation, and the one most relevant for dietary advice, is that consumption of flavonoid-rich foods or diets higher in flavonoids, appear nutritionally beneficial in the prevention of CVD.

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1. Introduction

The 2017 Global Burden of Disease study observed that nutrition is a major contributor to cardiovascular morbidity and mortality, both in developed and developing countries.² This highlights the need to shift global dietary trends for the health of humanity.^{1,2} Overall dietary patterns, generally higher in fruits, vegetables, wholegrains, nuts, seeds, legumes, seafood and yoghurt; moderate to modest in poultry, milk, cheese, eggs, alcohol and unprocessed red meat; and low to absent in processed meat, refined grains, and ultra-processed foods; have been identified as providing cardio-metabolic benefits, which translate into a lower risk of developing cardiovascular disease (CVD).³ The contribution of other regularly consumed items, such as tea and coffee, to cardio-metabolic health appears less certain.³ Attempts to determine the contribution of specific nutritive components, underpinning the benefits of such dietary patterns rich in plant foods, is underway. In addition to vitamins, minerals, and macro-nutrients, plant foods contain a wide variety of bioactive agents, such as (poly)phenols, terpenoids, and nitrogen containing compounds that might confer health benefits.⁴ Flavonoids, a class of (poly)phenolics, have gained specific interest as findings from epidemiological studies throughout the 1990's and 2000's indicate they may be responsible, at least in part, for the cardiovascular-protective benefits of diets rich in plant-foods.

In 1993, the first prospective study to evaluate the cardio-protective benefits of flavonoids observed that participants with the highest flavonoid intakes had a lower risk of ischemic heart disease (IHD) mortality.⁵ Since this time, a rapidly accumulating body of epidemiological evidence, supported by growing evidence from human intervention studies, has emerged. Comprehensively reviewed in 2005 by Arts and Hollman,⁶ as well as by Graf *et al.*,⁷ and again in 2012 by Peterson *et al.*,⁸ we have sought to provide an overview and update on the epidemiological evidence regarding the association between habitual flavonoid intake and CVD incidence and mortality in prospective cohorts. We begin by covering the dietary occurrence and intake of flavonoids. First, we describe the different flavonoid subclasses and

111 their food sources before continuing with an overview of global consumption trends and intake
112 differences between populations. The quantification of flavonoid intake follows, describing
113 advances in composition databases, how these have changed over the years, and the potential
114 impact this has for cohort studies. An overview of biological mechanisms, by which flavonoids
115 mitigate CVD initiation and progression, precedes the synthesis of epidemiological evidence
116 regarding the association of flavonoid intake with CVD risk. Here, we focus on total flavonoid
117 intake and consumption of major flavonoid subclasses and their association with total CVD
118 and CVD of atherosclerotic origin, before discussing major findings from outcome-specific
119 prospective cohort studies on IHD, cerebrovascular disease and peripheral artery disease
120 (PAD) spanning 1993 to March 2020. Following the update on the current state of the art, the
121 discussion addresses broader issues of importance to flavonoid epidemiology research. We
122 discuss the central hypothesis, its evidence and limitations, that flavonoid-rich dietary intake
123 mediates intermediate endpoints of CVD, which modulates the trajectory of chronic CVD.
124 Thereafter, we highlight critical gaps and needs for advancing flavonoid epidemiology,
125 including the use of objective intake measures, cumulative measures of exposure, and the
126 rationale for targeting ASCVD rather than all-cause CVD. Concluding the review is a
127 summary of progress in the field over the past ~25 years and major future pathways for its
128 continued development.

129 **2. Dietary occurrence and intake of flavonoids**

130 Flavonoids are the most common group of plant phenolics occurring ubiquitously throughout
131 food plants and their products.⁹ To this end, a recent report estimates over 15,000 different
132 flavonoids have been identified throughout the plant Kingdom,¹⁰ with at least several hundred
133 occurring in edible components.¹¹ In plants, flavonoids occur as secondary metabolites, which
134 are not essential to the growth or life of the plant.^{12,13} Instead, flavonoids contribute to the
135 protection of plants against pests and herbivores, as well as plant disease, season and climate,

136 geography, and other local challenges, to increase the plant's overall ability to survive.^{12,13}
137 Flavonoids, found in edible plants and their food products, are part of the human diet.^{13,14} They
138 are not essential constituents in the classic nutrition sense; rather, they are non-nutrients, which
139 can exert biologically relevant effects *in vivo*.^{13,14} Based on their underlying structure,
140 flavonoids can be subdivided into six major subclasses, namely, the flavonols, flavones,
141 flavanones, isoflavones, flavan-3-ols, and anthocyanins.¹⁵ Collectively, dietary sources are
142 quite diverse and range from nuts, seeds, wholegrains, and legumes to fruits, herbs, and
143 vegetables, and also include oils, tea, wine, and beer.

144 In foods, the flavonols, flavones, flavanones, isoflavones and anthocyanins occur mostly as
145 glycosides (i.e., attached to a sugar moiety) rather than as aglycones (i.e., as free form
146 compounds).^{16,17} Flavan-3-ol monomers on the other hand, are generally not present as
147 glycosides; instead they occur most often in free form or as gallic acid esters.^{16,17} As the
148 glycosidic flavonoids may be linked with many different sugars,^{17,18} to simplify analyses, these
149 flavonoids are often quantified and reported as aglycone equivalents (abbreviated herein as
150 AE). This is achieved by hydrolysing the flavonoid from their attached sugars and measuring
151 the total content of the flavonoid aglycone present in a single food.¹⁷⁻¹⁹ Gallic acid esters of
152 flavan-3-ols however, are often reported as such, without any conversion to aglycones; in turn,
153 these values are often incorporated in total flavonoid intake calculations, while other subclasses
154 are included as AE.^{19,20} When quantified exclusively as AE, it becomes apparent that only
155 several dozen flavonoids are relatively common among foods and dietary intake.^{13,21} For
156 example, in the French observational study SUplémentation on VItamines et Minéraux
157 AntioXydants (SU.VI.MAX), across the 4,942 participants, >180 different flavonoids were
158 consumed by the cohort as part of their normal dietary intake, of which, 80% occurred as
159 glycosides; the remainder occurring as aglycones or esters.²¹ Yet, when quantified entirely as
160 AE, only 47 aglycones were commonly consumed.²¹

161 While the flavonoid subclass and compound make-up of plant foods differs within and between
162 their genus, across species (e.g., apple varieties), the flavonoid subclasses present are more or
163 less consistent.¹³ However, the absolute concentration of individual flavonoids in foods is
164 strongly influenced by their growing, storage, and processing conditions.¹³ The flavonols are
165 the most widely occurring of the flavonoids, being found in almost all fruits and vegetables.¹⁷
166 The richest flavonol sources include onions (>20 mg/100 g AE) and spinach (>10 mg/100 g
167 AE); although, black tea (>3 mg/100 ml AE) and apples (>2 mg/100 g AE with skin), are
168 usually the more important dietary sources, as they are generally consumed in greater
169 quantities.^{17,20} Anthocyanins are uniquely concentrated in berries (e.g., blueberries typically
170 contain >100 mg/100 g AE) however, are present in a several other foods (e.g., plum >40 to
171 >500 mg/100 g AE depending on species; kidney beans cooked >3 mg/100 g AE).^{17,20} On the
172 other hand, flavones are found in very limited quantities throughout foods.¹⁷ Examples of
173 flavone food sources include whole grain wheat flour (e.g., sorghum flour >2 mg/100 g AE),
174 orange juice (>5 mg/100 ml AE) and extra virgin olive oil (>1 mg/100 ml AE).²⁰ Flavanones
175 are mostly concentrated in citrus fruits (e.g., orange >40 mg/100 g AE) and their juices.¹⁹
176 Isoflavones are found in trace quantities throughout vegetables and grains; their only rich
177 sources include soy bean products (e.g., edamame >40 mg/100 g AE).^{19,23} Lastly is the flavan-
178 3-ol subclass, which consist of several sub-groups including monomers (also termed
179 catechins), as well as oligomers and polymers (also termed proanthocyanidins). Flavan-3-ols
180 are also found in black tea in various oxidized oligomeric and polymeric forms, such as
181 theaflavins and thearubigins, formed during tea leaf fermentation.²⁴⁻²⁶ Catechins and
182 proanthocyanidins are present in high concentrations in dark chocolate (>200 mg/100 g),
183 apples (>100 mg/100 g), red wine (>50 mg/100 ml), nuts (e.g., almonds >150 mg/100 g) and
184 berries (e.g., blueberry >300 mg/ 100 g) while, black tea is uniquely high in monomers,
185 theaflavins and thearubigins (>100 mg/100 ml).^{17,20,27} However, the measurement of
186 thearubigins is often inaccurate,²¹ and thus, they are often not included in intake estimates

187 despite contributing most tea flavan-3-ols.²⁰ As an aside, coffee is not a rich source of
188 flavonoids (<0.5 mg/100 ml AE total flavonoids), however, it is abundant in phenolic acids.¹⁷
189 Ultimately, an individual's flavonoid exposure is dependent on their routine diet.

190 Globally, the average intake of total flavonoids is estimated at ~400 mg/day (calculated
191 principally as AE though, not including thearubigins).²⁸ However, dietary patterns and regional
192 food consumption differs greatly between countries and continents so there can be large
193 variability in the daily intake of flavonoids across the globe.²⁸ While limitations exist in diet
194 data collection methods and the estimation of flavonoid intake,¹³ some general estimates can
195 be made. Yet, to preface these estimates, researchers tend to broadly estimate total flavonoid
196 intake in terms of AE, however, this includes free form flavan-3-ols and sometimes esterified
197 flavan-3-ols as well. In the United States of America, the mean intake of total flavonoids varies
198 from ~250 to ~400 mg/day AE (including thearubigins) while, in the United Kingdom, the
199 average intake is reported to be >1000 mg/day AE (including thearubigins), which is more
200 similar to intakes reported in Australia AE (~650 to ~700 mg/day including thearubigins).^{13,28}
201 The differences likely reflect a high intake of black tea in the latter two countries where black
202 tea may provide 60 to 80% of total flavonoid intake.^{13,28} Across mainland Europe, in
203 Mediterranean countries (defined here as Greece, Spain, Italy, and Southern France), the mean
204 intake of total flavonoids is ~250 to ~400 mg/day AE (not including thearubigins); the major
205 contributor being fruit.²⁸ In Nordic countries, such as Finland, average total flavonoid intake is
206 ~200 to ~250 mg/day AE (not including thearubigins) while, to the Far East in China, ~225
207 mg/day AE (not including thearubigins) is generally consumed; the major contributor being
208 tea,²⁸ of which, green tea is a popular variety.²⁹

209 As total daily flavonoid intake varies across the globe, so too does the consumption of
210 flavonoid subclasses and their respective individual compound make-up. That being, in
211 general, the flavan-3-ols are the most commonly consumed subclass, typically contributing

212 upwards of ~80% towards total flavonoid intake, followed by flavanones (~8–10%),
213 anthocyanins (~7–10%), flavonols (~7–9%), flavones (~1–2%), and isoflavones which, at the
214 population level, are generally (except in Asia) consumed in trace quantities.²⁸ Yet, even within
215 populations, differences in flavonoid intake occurs among subgroups. For example, in the
216 European Prospective Investigation into Cancer, across Europe, higher flavonoid intake was
217 associated with increasing age, education and physical activity as well as being female and a
218 health-food consumer.³⁰ Thus, across geographic regions and socio-demographic
219 characteristics, differences in both the quantity and proportion of flavonoid-rich foods
220 consumed results in a wide variability of flavonoid exposure among populations.²⁸

221 **3. Calculation of flavonoid intake and how this has changed over the years**

222 Flavonoid intake in nutritional epidemiology has historically been estimated from food
223 frequency questionnaires (FFQ) and diet histories using food composition tables. By the mid-
224 1970's, emerging composition data, detailing a small range of foods, were used to calculate the
225 first estimate of daily flavonoid intake from dietary origin.^{31,32} However, advances in analytical
226 methods by the early 1990's enabled a more accurate measure of the flavonoid content of foods
227 and up-dated composition tables were published by Hertog *et al.* in 1992 and 1993.^{18,33,34} These
228 tables provide information on AEs of two flavones (i.e., luteolin and apigenin) and three
229 flavonols (i.e., quercetin, myricetin and kaempferol) across ~60 foods and beverages.^{18,33,34}

230 The food composition tables by Hertog *et al.* were used to estimate flavonoid intake in the
231 Zutphen Elderly cohort in order to examine the association between flavonoid intake and CVD
232 risk—the first prospective cohort study with this aim.⁵ This prompted an interest in assessing
233 associations between habitual flavonoid consumption and CVD health outcomes and the data
234 on flavonoid intakes developed by Hertog *et al.* were used as the cornerstone to estimate
235 flavonoid intake in several prospective studies on CVD throughout the later 90's and early
236 2000's.^{35–42} Interest in flavonoids other than flavones or flavonols was building, yet, at the turn

237 of the century (1999 to 2000), accurate data on the flavan-3-ol content of foods was largely
238 unavailable.⁴³ At this time, Arts *et al.* measured the content of six flavan-3-ol monomers found
239 in >60 foods and beverages.^{43,44} This spurred the investigation of flavan-3-ol intake and CVD
240 risk in several prospective cohorts.^{45,46} However, a database detailing the gamut of flavonoids
241 was lacking and studies were starting to integrate several smaller reports on the flavonoid
242 composition of foods into their analyses.⁴⁷

243 In 2003 the United States Department of Agriculture (USDA) released their database on the
244 flavonoid content of 225 foods and beverages covering 26 of the most commonly occurring
245 flavonoids (expressed as AE, except for flavan-3-ols which were reported as free form
246 aglycones and esters without conversion) throughout five subclasses (i.e., flavonols, flavones,
247 flavanones, anthocyanins and flavan-3-ols (including catechins, theaflavins and
248 thearubigins)).¹⁶ Around the same time, they also released their database on the isoflavone
249 content of 128 foods covering three aglycones (i.e., daidzein, genistein, and glycitein) and in
250 2004 they released their database on the proanthocyanidin content of 205 foods.^{27,48} Following
251 their initial release, the USDA databases have undergone several major updates. In 2007, the
252 flavonoids database was updated to include 392 foods (Release 2.0), and in 2011, again
253 expanded to include 500 foods (Release 3.0), although no other monomeric compounds were
254 incorporated.²⁰ In 2008, the isoflavone database was updated to contain 557 foods (Release
255 2.0),²³ and in 2015 the proanthocyanidin database (Release 2.0) was updated to contain 283
256 foods; again neither incorporating further compounds.²⁸ In 2014 the USDA released their
257 extended database, which covers ~2900 foods and six major flavonoid subclasses except
258 proanthocyanidins.⁴⁹ Since their initial release, the USDA databases have been used regularly
259 for estimating flavonoid intake in prospective cohort studies.^{50–57} However, different flavonoid
260 glycosides are known to vary in their biological activity and a database detailing the range of
261 flavonoids naturally occurring in foods was thus developed.

262 The Phenol-Explorer database was released online in 2009.¹⁹ This database differs to the
263 USDA databases in that it contains information on individual flavonoids as they are found in
264 food (i.e., mainly as glycosides).¹⁹ Phenol-Explorer also contains information on other
265 (poly)phenol classes, such as stilbenes, lignans and phenolic acids in addition to several other
266 subclasses (e.g., curcuminoids), collectively providing information on 502 (poly)phenols in
267 452 foods.¹⁹ With regards to flavonoids, Phenol-Explorer compiles data that was (largely)
268 measured utilising chromatography without hydrolysis (in which each individual flavonoid
269 form, as found in food, is quantified) while, the USDA databases (are generally) compiled from
270 analysis utilising chromatography after hydrolysis (which removes the glycosides enabling
271 total quantification of the aglycones).^{16,19} To obtain AE using Phenol-Explorer, the user
272 converts the glycoside or ester via molecular weight conversion into total aglycones.²¹
273 Alternatively, Phenol-Explorer also contains content values as measured by chromatography
274 after hydrolysis,¹⁹ but, these data have been seldom used in cohort studies.

275 The first release of Phenol-Explorer contained information on >270 unique flavonoids.¹⁹
276 Importantly, unlike the USDA database, Phenol-Explorer does not include data on thearubigins
277 however, both contain information on theaflavins. Phenol-Explorer was updated in 2012
278 (version 2.0) and again in 2013 (version 3.0) to contain information on flavonoid
279 pharmacokinetics as well as the effect of food processing on flavonoid retention throughout
280 food preparation.^{58,59} Like the USDA databases, Phenol-Explorer has been widely used to
281 estimate flavonoid intake in epidemiological studies.^{60–64} Of note, Knaze *et al.* used Phenol-
282 Explorer to calculate the flavonoid content of foods and meals consumed in the European
283 Prospective Investigation into Cancer;⁶⁵ using retention factors, they generated the
284 (poly)phenol composition of 19,899 raw and prepared, generic and multi-ingredient food
285 items—the database of which is accessible online.⁶⁵ While other databases detailing the
286 flavonoid content of foods exist (e.g., EuroFIR-BASIS),⁶⁶ these have been much less frequently
287 incorporated in epidemiological research.⁶⁷

288 While there has been substantial advances in the completeness of flavonoid databases, such
289 food composition tables are known to be limited by their coverage of food items and nutrients
290 within foods.¹³ In addition, the flavonoid composition of foods is variable as they are dependent
291 on their variety, growing, storage, and processing or cooking conditions; thus such data are
292 generally regarded as approximations of the contents of food.^{13,68} To this end, limited attention
293 has been paid to the potential differences between flavonoid databases and the impact this may
294 have on flavonoid intake estimates. In a recent method-comparison study, Ivey *et al.* studied
295 the congruence between Phenol-Explorer (version 2.1) and both the USDA database for
296 estimating flavonoid (Release 3.1) and proanthocyanidin (Release 1.0) consumption.⁶⁹ From
297 FFQs, flavonoid intake was estimated in AE, using all databases.⁶⁹ The USDA and Phenol-
298 Explorer databases were highly correlated for total flavonoid intake and all subclasses ($r =$
299 >0.8 , $P < 0.001$) except flavones ($r = 0.34$, $P < 0.001$).⁶⁹ However, the absolute mean intake
300 values were significantly different between databases across all subclasses and total
301 flavonoids.⁶⁹ Despite these differences, when participants were classified as low, moderate and
302 high consumers as estimated using both databases, in general, participants fell into the same
303 intake categories.⁶⁹ Thus, in epidemiology research, these issues need to be considered in
304 systematic reviews and meta-analyses of data.

305 Regardless of the database used to calculate flavonoid intake, estimates can only be as accurate
306 as the assessment tools used to quantify habitual diet. The quantification of habitual intake is
307 complex and difficult because individuals eat a wide variety of different foods, in different
308 combinations, in different amounts, in different frequencies.⁷⁰ Until recent years, only a few
309 main methods of assessing dietary intake have been available: the food diary, diet history, 24-
310 hr recall and FFQ.^{70,71} Of these, the FFQ is the most efficient and therefore most widely
311 used.^{13,70} However, most FFQs used in prospective cohort investigations to date were
312 constructed prior to the development of the USDA flavonoid databases and were not
313 specifically designed for the measurement of flavonoid intake.¹³ As such, they may not

314 optimally reflect the variability in flavonoid intake, due to the omission of some flavonoid-
315 bearing foods or the group of similar food items within the same question (e.g., berries), making
316 it impossible to discern which specific food type/s the individual eats.¹³ Performance and
317 validation studies of FFQs, specifically in regards to flavonoid intake, have seldom been
318 conducted; while an FFQ may have been validated for other nutrients or food groups, this does
319 not necessarily imply that it can reasonably assess intake of flavonoids. In this context, the
320 extrapolation of absolute values from FFQs as accurate measures of intake is not usually
321 justified. However, they may still provide a rank of usual consumption, allowing researchers
322 to roughly separate out irregular (lower) vs regular (higher) consumers, in large samples, given
323 the FFQ contains ample questions on major flavonoid bearing items. Ultimately, inaccurate
324 dietary assessment biases results towards the null as noise in the data increases; the implications
325 are that true associations are likely stronger than those reported.⁷² In more recent years,
326 validation studies of FFQs for flavonoid intake have begun to emerge,^{73,74} however, it is hoped
327 that nutrition science will look to shift to emerging technologies, such as biomarkers or smart-
328 phone methods, which may allow for a more robust assessment of dietary intake in the future.⁷⁵

329 As described above, with advances in both knowledge and technology, methods used to
330 estimate flavonoid intake in cohorts with data on habitual diet have changed over the last ~25
331 years (**Figure 1**). Prior to 2003 and the development of the USDA database and later, Phenol-
332 Explorer, total flavonoid intake reported in cohort studies (~3 to 25 mg/day) was calculated
333 from the estimated intake of 5 to 10 compounds spanning 2 to 4 subclasses (flavonols, flavones,
334 flavan-3-ols monomers and flavanones)^{5,36,46,47,76} This underestimation of flavonoid intake
335 (and conceivable misclassification of participants) is a critical limitation of these early studies
336 often not recognized in the literature. More recent studies present results for 5 to 7 flavonoid
337 subclasses and have an average flavonoid intake ranging from approximately 130 to 700
338 mg/day.^{50,54,55,67,77,78} Further, flavonoid intake values between studies may not be directly
339 comparable as the studies used different dietary assessment tools that were not necessarily

340 validated for measuring flavonoids. These differences in calculating flavonoid intake must be
341 kept in mind; comparing findings from studies prior to development of the USDA and Phenol-
342 Explorer databases, to findings from studies post their release, is inherently difficult. In this
343 review, we refer to a study as estimating total flavonoid intake, only if the estimate is a
344 composite of ≥ 5 subclasses; often, studies do not include isoflavones in their composite scores
345 due to their low dietary occurrence in most populations. Where a study has estimated the sum
346 of ≤ 4 subclasses, we describe the sum of subclasses (e.g., intake of flavones plus flavonols
347 etc.).

348 [Insert Figure 1]

349 **Figure 1.** Timeline of development of landmark flavonoid-food composition databases and the
350 cumulative number of prospective cohort publications reporting on the intake of flavonoid
351 subclasses and/or total consumption and cardiovascular disease risk. USDA, United States
352 Department of Agriculture.

353 4. Biological mechanisms of flavonoids in cardiovascular disease

354 Following their digestion and absorption, flavonoid metabolites enter the blood stream where
355 they may interact with molecular mechanisms mediating CVD.^{14,15,79} Over 170 biological
356 effects have been reported for flavonoids and flavonoid-rich foods, reviewed recently by
357 Williamson *et al.*¹⁴ Regarding their CVD-protective actions, the most recognized activity of
358 flavonoids is their positive effects on the vasculature. In randomised controlled trials (RCTs),
359 flavonoids and flavonoid-rich foods have been shown to lower blood pressure,⁸⁰ improve
360 endothelial function,⁸¹ and augment arterial stiffness.⁸² Most evidence from RCTs is for the
361 flavan-3-ol subclass, which, in most populations, is the greatest contributor to total flavonoid
362 intake.^{51,83,84}

363 Meta-analyses of human RCTs have shown beneficial effects of flavonoids on major CVD risk
364 factors. Blood pressure is one well-established risk factor for CVD.⁸⁵ A meta-analysis of 91

365 RCTs comparing the effect of a flavan-3-ol intervention with a control on blood pressure
366 showed a significant decrease in SBP (−1.46 mm Hg, 95% CI: −2.27, −0.65 mmHg) and DBP
367 (−0.99 mm Hg, 95% CI: −1.50, −0.45 mm Hg).⁸⁶ Another independent risk factor of CVD,
368 endothelial dysfunction (impaired nitric oxide-mediated vasodilation), predicts
369 atherothrombotic clinical events.⁸⁷ Aside from impaired vasodilation, a dysfunctional
370 endothelium may be permeable to atherogenic lipoproteins and secrete vascular adhesion
371 molecules; critical initial steps in the development of an atherosclerotic lesion.⁸⁸ A meta-
372 analysis comparing the effects of flavan-3-ols with controls showed a significant increase in
373 acute FMD response measured from 1 to 6 h (1.70%, 95% CI: 1.31%, 2.08%; 24 RCTs) and a
374 significant improvement in chronic FMD measured after a few weeks of intervention (1.21%,
375 95% CI: 0.70%, 1.73%; 23 RCTs).⁸⁶ Additionally, several RCTs have reported a decrease in
376 arterial stiffness after a flavonoid-based intervention, independent of blood pressure changes.⁸²
377 The exact mechanisms behind these improvements are yet to be established but may include
378 enhanced nitric oxide bioavailability,⁸⁹ increased expression of heme oxygenase-1,⁹⁰ and
379 inhibition of angiotensin-converting enzyme activity.⁹¹

380 Quantifying the effect of flavonoids on atherosclerosis itself in RCTs is inherently difficult due
381 to slow disease initiation and progression. However, flavonoid interventions have been
382 reported to lower LDL-cholesterol and triglycerides, and increase HDL-cholesterol in human
383 studies,⁸⁶ while animal and *in vitro* studies provide evidence that flavonoids improve
384 inflammatory-status via the interference of pro-oxidant enzyme-signalling cascades or
385 adhesion molecule expression.⁹² Unfortunately, fluctuations in background cytokine
386 production and difficulty in detecting subtle changes in inflammatory status make this very
387 difficult to assess in human intervention studies; a meta-analysis of RCTs on inflammatory
388 biomarkers found no difference between flavan-3-ols and controls.⁸⁶ Thus, in the absence of
389 long-term clinical trials allowing for the long preclinical phase or quantifiable progression of

390 atherosclerosis, observational prospective cohort studies provide us with the strongest evidence
391 for the protective role of habitual flavonoid intakes in the manifestation of CVD.

392 **5. Flavonoid intake and cardiovascular disease risk: epidemiological evidence**

393 **a. Total cardiovascular disease**

394 *Disease overview.* Currently, the global burden of CVD accounts for approximately one third
395 of all deaths and is the leading cause of mortality and disability worldwide.^{93,94} Total CVD is
396 an umbrella term for a broad range of diseases of the heart and circulatory system, of which,
397 the main underlying pathology is atherosclerosis.^{95,96} The major clinical manifestations of
398 atherosclerotic CVD (ASCVD) include IHD, PAD, and ischemic stroke.⁹⁷ Other CVDs, not
399 aetiologically linked to atherosclerosis, include: structural heart disease, congenital heart
400 disease, rheumatic heart disease, arrhythmias, and other disease of the arterial and venous
401 system.⁹⁸ In 2015, the Global Burden of Disease study estimated the worldwide prevalence of
402 CVD for the most common causes of CVD death.⁹⁴ They found there was ~422.7 million
403 prevalent cases of CVD worldwide, of which, ASCVD was the main contributor with ~154.7
404 million cases of PAD (~36.6%), ~110.5 million cases of IHD (~26.2%) and ~24.9 million cases
405 of ischemic stroke (~5.9%); the other ~31.3% of prevalent cases constituted haemorrhagic and
406 other strokes, hypertensive heart disease, cardiomyopathy, atrial fibrillation, endocarditis and
407 other cardiovascular and circulatory diseases.⁹⁴ In the same year, ~17.9 million people died
408 from CVD, wherein, it is estimated that ~66% died from ischemic stroke and IHD.⁹⁴ In high-
409 income countries, such as within the continent of North America, the proportion of the
410 population dying of IHD and ischemic stroke, reaches as high as ~75% of total CVD.⁹⁴ A range
411 of *in vitro* and *in vivo* studies suggest that flavonoids exert beneficial effects on the arterial
412 vascular system suggesting that CVDs of atherosclerotic origin may be particularly amenable
413 to a flavonoid intervention.^{79,99,100} While the bulk of existing literature on flavonoid intake and

414 risk of total CVD includes CVDs of both atherosclerotic and non-atherosclerotic origins, as
415 highlighted above, cases are dominated by ASCVD.

416 *Cohort characteristics.* To date, at least 19 prospective cohorts (in 21 publications) have
417 estimated flavonoid intake and the risk of total CVD incidence and/or mortality (**Table 1**).
418 Nearly all studies reporting on CVD incidence defined this as the first non-fatal or fatal event.
419 However, one study restricted outcomes to first time events resulting in hospitalisation,⁶² while
420 another defined incidence as the first non-fatal event only.⁶⁷ Around half of the studies defined
421 total CVD as any type of CVD, mostly using the International Classification of Diseases (ICD)
422 9th Revision, codes 390–459, and their equivalent ICD-10 codes I00–I99 to identify case events
423 ($n = 10$ publications). However, all such studies reported on mortality outcomes—which is
424 dominated by ASCVD (Table 1). At the same time, studies reporting on total CVD incidence,
425 tend to restrict analysis to events of cerebrovascular disease and IHD,^{51,60,101–103} with some
426 further incorporating death from any CVD (Table 1).^{43,66,89} Thus, they too are principally
427 reporting on ASCVD. However, given this outcome definition, studies on CVD incidence tend
428 to overlook non-fatal events of PAD; although PAD is the most prevalent ASCVD, a large
429 proportion of PAD goes undiagnosed and therefore, in a cohort study, PAD usually represents
430 proportionally less events. Other studies exclusively analysed events of ASCVD,^{62,63} while two
431 studies did not provide complete outcome definitions.^{67,78} At least one study presented analyses
432 of total CVD as per several outcome definitions, of which we report the most relevant for this
433 review.⁴² Effectively, while the definition of total CVD is somewhat heterogeneous, the cases
434 are primarily, but not exclusively, ASCVD-related.

435 Other cohort characteristics were also heterogeneous. The cohorts vary in size (from 774 to
436 98,469 participants) as well as their follow-up timeframe (from 4.3 to 25 years) and location
437 (United States of America ($n = 5$), Australia ($n = 2$), Asia ($n = 2$), and Europe ($n = 10$)). Most
438 cohorts recruited middle-aged participants (e.g., ~50 years), while some recruited older

439 individuals (e.g., 65+ years). Habitual diet has been mainly assessed using FFQs ($n = 14$
440 cohorts) and flavonoid intake mostly estimated using the USDA ($n = 9$ publications) and/or
441 Phenol-Explorer ($n = 6$ publications) databases (Table 1). Only one study indicated flavonoid
442 intake was estimated as glycosides (and other naturally occurring structures);⁶⁰ all others
443 appear to report intake as AE (including free form and potentially esterified flavan-3-ols).

444 *Total flavonoids.* As previously mentioned, in this review, we discuss a study as assessing total
445 flavonoid intake, only if this estimate was a composite of ≥ 5 subclasses. The association
446 between such total flavonoid intake and total CVD incidence has been studied in at least five
447 cohorts, while at least nine cohorts report on total CVD mortality. In 2017, Grosso *et al.* meta-
448 analysed five of these cohorts reporting on total CVD mortality ($n = 137,629$, with 5,351 CVD
449 deaths), and found a trend towards a lower risk of death with higher total flavonoid intake
450 (multivariable adjusted risk estimate for highest vs lowest intake category: 0.83, 95% CI: 0.68,
451 1.03).¹⁰⁵ While high heterogeneity was observed among these studies ($I^2 = 67\%$), a subsequent
452 sensitivity analysis (by systematic exclusion of cohorts) reduced heterogeneity ($I^2 = 20\%$, $P =$
453 0.29) and highlighted a significant association between total flavonoid intake and CVD
454 mortality ($n = 4$ cohorts, $n = 136,566$, $n = 5,273$ deaths; multivariable adjusted risk estimate
455 for highest vs lowest intake category: 0.88, 95% CI: 0.79, 0.98).¹⁰⁵ The excluded study by Ivey
456 *et al.* reported the strongest association of all studies (multivariable adjusted risk estimate for
457 highest vs lowest intake category: 0.32, 95% CI: 0.16, 0.61).⁷⁷ Ivey *et al.* undertook analysis
458 in the oldest cohort in the meta-analysis ($n = 1,063$, mean age: 80 ± 3 years at baseline) with
459 ~30% of the sample experiencing pre-existing CVD at baseline, which may explain why such
460 a strong association was observed. That is, participants would have been at very high risk of
461 dying of CVD (7.3% died of CVD).⁷⁷ The Grosso *et al.* meta-analysis found no evidence of
462 publication bias, which was supported by a similar meta-analysis published in the same year.¹⁰⁶
463 However, this finding may not be overly convincing as both meta-analyses included a relatively
464 small number of cohorts.¹⁰⁶ Grosso *et al.* also found an association, albeit non-significant,

465 between CVD mortality and total flavonoid intake when the meta-analysis was confined
466 exclusively to studies adjusting for dietary confounders in addition to sociodemographic
467 factors ($n = 3$ studies; multivariable adjusted risk estimate for highest vs lowest intake category:
468 0.71, 95% CI: 0.33, 1.51; $I^2 = 79\%$). Consequently, confounding from unmeasured nutritional
469 components may have biased results, although conclusions are limited due to a small sample
470 size and wide confidence intervals.¹⁰⁵ Since the Grosso *et al.* meta-analysis, a further three
471 studies on total flavonoid intake and CVD mortality have been published with results trending
472 towards a lower associated risk of CVD mortality with higher flavonoid intake.^{51,52,61} Unlike
473 for total CVD mortality, a meta-analysis on total flavonoid intake and CVD incidence has not
474 been published. However, significant inverse relationships emerge in three of the five cohorts
475 reporting on this outcome. While other meta-analyses in the field have pooled heterogeneous
476 flavonoid exposures and outcome measures, overall their findings suggest that flavonoid-rich
477 dietary patterns are associated with a lower risk of CVD events.^{107,108}

478 *Flavonoid subclasses.* The impact of individual flavonoid subclasses on total CVD risk has
479 been studied across incidence ($n = 9$ cohorts) and mortality ($n = 14$ cohorts) outcomes. The
480 results typically report an inverse association reaching statistical significance for all subclasses
481 in at least one or more cohorts (Table 1). Grosso *et al.* meta-analysed several of the cohorts
482 reporting on CVD mortality.¹⁰⁵ A significantly lower risk of death was found for the highest
483 compared to the lowest intake categories of anthocyanins ($n = 5$ cohorts; RR = 0.89, 95% CI:
484 0.83, 0.95; $I^2 = 0\%$), catechins (termed flavan-3-ols in their manuscript; $n = 7$ cohorts; RR =
485 0.82, 95% CI: 0.71, 0.95; $I^2 = 53\%$), proanthocyanidins ($n = 4$ cohorts; RR = 0.89, 95% CI:
486 0.81, 0.97; $I^2 = 0\%$), flavonols ($n = 6$ cohorts; RR = 0.79, 95% CI: 0.63, 0.99; $I^2 = 67\%$),
487 flavones ($n = 5$; RR = 0.85, 95% CI: 0.75, 0.96; $I^2 = 25\%$), and flavanones ($n = 5$ cohorts; RR
488 = 0.84, 95% CI: 0.73, 0.96; $I^2 = 34\%$) but not isoflavones ($n = 6$ cohorts; RR = 1.01, 95% CI:
489 0.94, 1.08; $I^2 = 0\%$) in multivariable adjusted models.¹⁰⁵ The high heterogeneity observed for
490 flavonols and catechins was reportedly due to a study by Mursu *et al.*,⁵⁵ which after removal,

491 reduced heterogeneity without any material impact on the results. These findings were in
492 agreement with two other recent meta-analyses on CVD mortality risk and intake of
493 anthocyanins and flavan-3-ols.^{86,109} Since these meta-analyses, at least three further prospective
494 cohorts have been published on each subclass (except isoflavones); results typically trending
495 towards a beneficial association, though, reaching significance only for anthocyanin intake and
496 lower CVD mortality risk in one cohort (Table 1). While less research has focused on CVD
497 incidence, it is suspected that outcomes would echo CVD mortality findings.

498 *Dose-response.* The intake of flavonoids associated with significant benefit has been the
499 subject of investigation. In a dose-response meta-analysis, Grosso *et al.* report a 4% lower risk
500 of CVD mortality for every ~100 mg/day increment in total flavonoid intake ($n = 5$ cohorts, n
501 $= 137,629$, total CVD deaths $= 5,351$; multivariable adjusted risk estimate: 0.96, 95% CI: 0.92,
502 1.00; $I^2 = 68\%$).¹⁰⁵ While a significant linear relationship emerged over the range of intakes
503 studied ($P_{\text{linearity}} < 0.001$) it is unlikely that the true relationship maintains linearity indefinitely.
504 It is more plausible that there is a plateau in the trend somewhere, where further consumption
505 affords no added benefit, although the point of plateau likely differs in populations with
506 different underlying risk. Nonetheless, it appears that only moderate intakes may be needed to
507 positively affect health outcomes, and that higher intakes likely afford no added benefit. Results
508 supporting this assertion can be seen in analyses from the Cancer Prevention Study II Nutrition
509 Cohort ($n = 98,469$),⁵⁴ and the Danish Diet Cancer and Health Cohort ($n = 56,048$),⁶¹ both of
510 which show nonlinear dose-response thresholds, somewhere around ~250 to ~500 mg/day AE
511 of total flavonoid intake. However, extrapolation of absolute values from FFQs is not usually
512 possible unless a study has validation data.¹¹⁰

513 *Effect modification.* As indicated, the beneficial associations of dietary patterns high in
514 flavonoids might differ, in different population subgroups. It has previously been hypothesized
515 that the association between flavonoid intake and CVD mortality may be stronger in persons

516 at a higher risk of CVD. Early findings of a study by Mink *et al.* weakly supported this
517 hypothesis.⁵⁰ In their analysis, significant inverse associations between flavanone intake (but
518 not other subclasses or total intake) and CVD mortality were found in ever-smokers, but not
519 never-smokers following multivariable adjustment for age and energy.⁵⁰ Bondonno *et al.*, then
520 showed a lower risk of all-cause mortality (31% were CVD-related) for higher flavonoid
521 intakes only amongst participants with at least one early mortality risk factor (smoking, high
522 alcohol consumption, no regular exercise or obesity).⁵¹ Following on from this, more results
523 by Bondonno *et al.* show clear effect modification by smoking status and alcohol intake at
524 baseline although, not for sex, physical activity, or diabetes following multivariable adjustment
525 for lifestyle factors.⁶¹ That is, the inverse association between total flavonoid intake and total
526 CVD mortality appeared to differ in smokers in contrast to non-smokers as well as in high
527 alcohol over low alcohol consumers suggesting dietary flavonoid intake may partially mitigate
528 harmful effects of such activities (although, the smoking and high alcohol intake groups would
529 remain at higher overall risk of CVD compared to their counterparts). Given this finding, it
530 stands to reason that associations between flavonoid intake and CVD may appear to be stronger
531 in cohorts that have a higher proportion of smokers and high alcohol consumers. It is also
532 plausible that further unidentified effect modifiers exist, such as in racial or ethnic populations,
533 which warrants further investigation. However, as “at risk” populations have a higher
534 underlying risk of CVD, these findings require investigation on an absolute, as well as, a
535 relative scale.

Table 1. Summary of prospective cohort studies investigating the association of flavonoid intake with total cardiovascular disease incidence and mortality

Author, year	Country (cohort)	n (population)	Base-line age (yrs)	Follow-up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Total CVD incidence ^c			Total CVD mortality		
										n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend	n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend
Bondonno 2019 ⁶¹	Denmark (Danish Diet, Cancer & Health study)	56,048 (M & F)	56	23	ICD-10 I00–I99	FFQ/ PE	Hazard ratio by quintiles	Anthocyanidin:	<9.6 vs ≥53.2	—	—	—	3,981	0.90 (0.82, 0.99)	—
								Catechin:	<20.5 vs ≥281.4	—	—	—		0.97 (0.89, 1.06)	—
								PA + theaflavin:	<136 vs ≥360	—	—	—		0.94 (0.85, 1.03)	—
								Flavanone:	<6.0 vs ≥49.0	—	—	—		0.96 (0.88, 1.05)	—
								Flavone:	<3.0 vs ≥8.8	—	—	—		0.97 (0.88, 1.06)	—
								Flavonol:	<20.5 vs ≥82.5	—	—	—		0.95 (0.87, 1.05)	—
Bondonno 2019 ⁵¹	Australia (Blue Mountains Eye Study)	2,349 (M & F)	65	14	ICD-9 410–414 & 430–438	FFQ/ USDA	Hazard ratio by tertiles	Total:	<250.8 vs ≥908.5	—	—	—	213	0.97 (0.88, 1.06)	—
								Anthocyanidin:	<3.8 vs ≥9.2	—	—	—		0.80 (0.53, 1.18)	—
								Catechin + ODC:	<310.5 vs ≥747.9	—	—	—		0.96 (0.67, 1.39)	—
								PA:	<85.9 vs ≥155.5	—	—	—		1.00 (0.69, 1.45)	—
								Flavanone:	<10.3 vs ≥38.9	—	—	—		0.87 (0.61, 1.25)	—
								Flavone:	<0.72 vs ≥1.32	—	—	—		0.80 (0.56, 1.15)	—
Dalgaard 2019 ⁶²	Denmark (Danish Diet, Cancer & Health study)	53,552 (M & F)	56	23	Hospital admission for atherosclerotic CVD; ICD-10 I20–I25, I63 & I70–I74	FFQ/ PE	Hazard ratio by quintiles	Flavonol:	<25.0 vs ≥42.3	—	—	—	—	1.01 (0.71, 1.44)	—
								Isoflavone:	<0.81 vs ≥1.23	—	—	—		1.16 (0.81, 1.66)	—
								Total:	<599.9 vs ≥1106	—	—	—		0.98 (0.68, 1.41)	—
								Anthocyanidin:	<9 vs ≥53	8,773	1.02 (0.95, 1.09)	—		—	—
								Catechin:	<21 vs ≥282	—	0.91 (0.86, 0.97)	—		—	—
								PA + theaflavin:	<137 vs ≥435	—	0.87 (0.81, 0.93)	—		—	—
Mendonca 2019 ¹⁰⁴	Spain (SUN cohort)	17,065 (M & F)	37	10	MI, stroke or death from CVD causes	FFQ/ PE	Hazard ratio by quintile	Flavanone:	<6 vs ≥50	—	0.97 (0.90, 1.04)	—	—	—	—
								Flavone:	<3 vs ≥9	—	0.95 (0.88, 1.02)	—		—	—
								Flavonol:	<21 vs ≥83	—	0.88 (0.82, 0.94)	—		—	—
								Total:	<253 vs ≥912	—	0.90 (0.85, 0.97)	—		—	—
								Total:	$\bar{x}$ =186 vs $\bar{x}$ =772	113	0.53 (0.29, 0.98)	0.09		—	—
Adriouch 2018 ⁶⁰	France (Nutrinet-Santé)	84,158 (M & F)	44	5	Stroke, MI, acute coronary syndrome, or angioplasty	3 x 24 hr diet record/ PE***	Hazard ratio by tertiles	Anthocyanin:	$\bar{x}$ =27.5 vs $\bar{x}$ =55.0	602	0.67 (0.53, 0.85)	0.0007	—	—	—
								Catechin:	$\bar{x}$ =75.4 vs $\bar{x}$ =178	—	0.76 (0.62, 0.94)	0.01		—	—
								Theaflavin:	$\bar{x}$ =10.3 vs $\bar{x}$ =24.5	—	0.89 (0.67, 1.18)	0.41		—	—
								PA:	$\bar{x}$ =33.7 vs $\bar{x}$ =71.7	—	0.85 (0.68, 1.01)	0.05		—	—
								Flavanone:	$\bar{x}$ =30.1 vs $\bar{x}$ =30.7	—	0.99 (0.81, 1.24)	0.93		—	—
								Flavone:	$\bar{x}$ =23.3 vs $\bar{x}$ =27.6	—	1.12 (0.90, 1.40)	0.32		—	—
Ivey 2017 ⁵²	USA (NHS II)	93,145 (F)	36	18	ICD-8 390–458 & ICD-9 390–459	FFQ/ USDA	Hazard ratio by quintiles	Flavonol:	$\bar{x}$ =46.5 vs $\bar{x}$ =86.3	—	0.77 (0.61, 0.98)	0.02	189	—	—
								Isoflavone:	$\bar{x}$ =4.5 vs $\bar{x}$ =11.5	—	0.98 (0.80, 1.20)	0.89		—	—
								Anthocyanidin:	<3 vs ≥17	—	—	—		0.85 (0.50, 1.43)	—
								Catechin:	<12 vs ≥86	—	—	—		0.75 (0.49, 1.16)	—
								PA:	<79 vs ≥356	—	—	—		0.77 (0.49, 1.20)	—
								Flavanone:	<9 vs ≥51	—	—	—		1.10 (0.69, 1.76)	—
								Flavone:	<0.7 vs ≥2.2	—	—	—	1.15 (0.72, 1.83)	—	
								Flavonol:	<9 vs ≥26	—	—	—	0.91 (0.58, 1.41)	—	
								Total:	<138 vs ≥518	—	—	—	0.83 (0.53, 1.29)	—	

Table 1. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with total CVD incidence and mortality

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Total CVD incidence ^c			Total CVD mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Dower 2016 ¹¹¹	Netherlands (Zutphen)	774 (M)	65 to 84	25	ICD-9 390–459 & 798.2	Diet history/Arts <i>et al.</i> ^{43,44}	Hazard ratio by tertiles	Catechin	<9.4 vs ≥19.5	—	—	—	329	0.79 (0.58, 1.08)	—
Ivey 2015 ⁷⁷	Australia (CAIFOS)	1,063 (post- menopause women)	>75	5	ICD-9 390–459 & ICD-10 I00–I99	FFQ/ PE and USDA	Hazard ratio by tertiles	Total (USDA): Total (PE):	<547 vs ≥813 <525 vs ≥788	—	— —	—	78	0.34 (0.17, 0.69) 0.32 (0.16, 0.61)	—
Jacques 2015 ⁵³	USA (Framingham Offspring Cohort)	2,880 (M & F)	54	14.9	Stroke, TIA, CHD, heart failure or peripheral vascular disease	FFQ/ USDA	Relative risk for each 2.5-fold ↑ in daily intake	Anthocyanidin: Catechin: PA + ODC: Flavanone: Flavone: Flavonol: Total:	— — — — — — —	518 — — — — — —	0.95 (0.86, 1.05)† 0.97 (0.88, 1.05)† 0.93 (0.84, 1.02)† 1.00 (0.92, 1.09)† 1.00 (0.82, 1.21)† 0.89 (0.75, 1.06)† 0.93 (0.82, 1.06)†	0.30 0.43 0.13 0.97 0.99 0.20 0.26	— — — — — — —	— — — — — — —	
Ponzo 2015 ⁶⁷	Italy (no cohort name)	1,658 (M & F)	45 to 64	12	Mortality: ICD-9 390–459 & 798.1; no codes specified for incidence	FFQ/ Mostly USDA	Hazard ratio by tertiles	Anthocyanidin: Catechin + ODC: PA: Flavanone: Flavone: Flavonol: Isoflavone: Total:	— — — — — — — Total: <191.5 vs ≥322.3	125 — — — — — — —	0.56 (0.36, 0.89)* 0.42 (0.26, 0.68)* 0.43 (0.27, 0.70)* 0.48 (0.29, 0.77)* 0.66 (0.40, 1.09)* 0.53 (0.34, 0.83)* 0.77 (0.49, 1.21)* 0.46 (0.28, 0.75)*	— — — — — — — —	84 — — — — — — —	0.67 (0.38, 1.18) 0.72 (0.41, 1.26) 0.80 (0.44, 1.46) 0.66 (0.37, 1.17) 0.83 (0.45, 1.52) 0.72 (0.41, 1.27) 0.74 (0.41, 1.36) 0.83 (0.46, 1.51)	— — — — — — — —
Vogiatz- ogloua 2015 ¹⁰³	UK (EPIC)	M: 11,252 F: 13,633	40 to 75	11.1	ICD-9 410–448 & ICD-10 I10–I79	7-day diary/ Flaviola Flavanol Database	Hazard ratio by quintiles	<i>Males:</i> Total flavan-3-ol: <i>Females:</i> Total flavan-3-ol:	̄x=198 vs ̄x=2008 ̄x=179 vs ̄x=1828	4,403 4,060	0.90 (0.81, 0.99) 1.01 (0.91, 1.13)	0.176 0.364	1,154 833	0.95 (0.74, 1.20) 0.81 (0.60, 1.09)	0.607 0.166
Talaei 2014 ¹¹²	Singapore (Singapore Chinese Health Study)	63,257 (M & F)	45 to 74	14.7	ICD-9 390–459	FFQ/ Singapore Composition Database ¹¹³	Hazard ratio by quartile	Isoflavone:	̄x=5.4 vs ̄x=36.1	—	—	—	4,780	1.00 (0.91, 1.10)	0.83
Tresserra- Rimbau 2014 ⁶⁴	Spain (PREDIMED)	7,172 (M & F)	~67	4.3	MI, stroke or death from CVD causes	FFQ/PE	Hazard ratio by quintiles	Anthocyanin: Total flavan-3-ol: Flavanone: Flavone: Flavonol: Total:	11.8 vs 74.6 90 vs 263 28 vs 247 20 vs 67 56 vs 124 273 vs 1170	273 — — — — —	0.67 (0.39, 1.13) 0.40 (0.23, 0.72) 1.09 (0.68, 1.74) 1.07 (0.64, 1.80) 0.69 (0.40, 1.19) 0.71 (0.43, 1.18)	0.05 0.003 0.54 0.72 0.08 0.16	— — — — — —	— — — — — —	

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Table 1. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with total CVD incidence and mortality

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Total CVD incidence ^c			Total CVD mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Ivey 2013 ⁶³	Australia (CAIFOS)	1,063 (post- menopaus al women)	>75	5	ICD-9 410–414, 428, 433– 438 & 440–444	FFQ/ USDA	Odds ratio by tertile	Anthocyanidin:	<23 vs >41	—	—	—	64	0.67 (0.33, 1.34)	0.35
								Catechin + ODC:	<296 vs >563	—	—	—		0.34 (0.17, 0.70)	0.01
								PA:	<140 vs >229	—	—	—		0.62 (0.32, 1.20)	0.22
								Flavanone:	<32 vs >61	—	—	—		0.55 (0.28, 1.09)	0.16
								Flavone:	<2 vs >3	—	—	—		0.56 (0.29, 1.12)	0.20
								Flavonol:	<24 vs >35	—	—	—		0.27 (0.13, 0.59)	0.01
								Isoflavone:	<3 vs >4	—	—	—		0.87 (0.46, 1.64)	0.51
Zamora- Ros 2013 ⁷⁸	Spain (EPIC)	40,622 (M & F)	29 to 69	13.6	ICD-9 & ICD-10 (no codes specified)	Diet history/ Mix of USDA, PE and others	Hazard ratio for each 2- fold ↑ in daily intake	Anthocyanidin:	—	—	—	—	416	0.96 (0.88, 1.03)†	—
								Total flavan-3-ol:	—	—	—	—		0.94 (0.87, 1.01)†	—
								Catechin:	—	—	—	—		0.99 (0.94, 1.04)†	—
								PA:	—	—	—	—		0.90 (0.83, 0.97)†	—
								Flavanone:	—	—	—	—		0.93 (0.88, 0.98)†	—
								Flavone:	—	—	—	—		0.91 (0.82, 1.00)†	—
								Flavonol:	—	—	—	—		0.84 (0.72, 0.99)†	—
Mc- Cullough 2012 ⁵⁴	USA (Cancer Prevention Study II)	98,469 (M & F)	~69	7	ICD-9 390–459 & ICD-10 I20–I99	FFQ/ USDA	Rate ratios by quintile	Isoflavone:	—	—	—	—	2,771	1.00 (0.85, 1.16)†	—
								Total:	—	—	—	—		0.87 (0.77, 0.98)†	—
								Anthocyanidin:	<5.5 vs ≥16.7	—	—	—		0.86 (0.76, 0.97)	0.04
								Catechin:	<9.5 vs ≥37.2	—	—	—		0.83 (0.74, 0.93)	0.02
								PA:	<71.6 vs ≥253.6	—	—	—		0.87 (0.77, 0.98)	0.02
								Flavanone:	<7.0 vs ≥35.4	—	—	—		0.90 (0.80, 1.01)	0.5
								Flavone:	<0.5 vs ≥2.1	—	—	—		0.82 (0.72, 0.92)	0.001
Mursu 2008 ⁵⁵	Finland (Kuopio IHD study)	1,950 (M)	42 to 60	15.2	ICD-9 390–459 & ICD-10 I00–I99	4-day diary/USDA	Relative risk by quartiles	Flavonol:	<8.5 vs ≥20.6	—	—	—	102	0.84 (0.75, 0.94)	0.03
								Isoflavone:	<0.03 vs ≥0.14	—	—	—		0.92 (0.81, 1.05)	0.1
								Total:	<121.5 vs ≥359.7	—	—	—		0.82 (0.73, 0.92)	0.01
								Anthocyanidin:	—	—	—	—		0.99 (0.62, 1.85)	0.193
								Catechin + ODC:	—	—	—	—		1.06 (0.64, 1.65)	0.694
								Flavanone:	—	—	—	—		0.54 (0.32, 0.92)	0.266
								Flavone:	—	—	—	—		0.65 (0.40, 1.05)	0.333
Kokubo 2007 ¹⁰¹	Japan (Japan Public Health Study Cohort I)	40,462 (M & F + post- menopause sub-group)	40 to 59	12	ICD-10 I21–I23, I46, I60–I61, I63 & I693	FFQ/ Local database ¹¹⁴	Hazard ratio by quintiles	Flavonol:	—	—	—	—	175	1.26 (0.75, 2.14)	0.622
								Total:	$\bar{x}=9.5$ vs $\bar{x}=435.0$	—	—	—		1.25 (0.74, 2.11)	0.730
								<i>Males:</i>							
								Isoflavone:	<16.4 vs ≥39.6	550	1.14 (0.82, 1.59)	0.884		1.27 (0.66, 2.43)	0.391
								<i>Females:</i>					57		
								Isoflavone:	<16.2 vs ≥37.7	226	0.39 (0.25, 0.60)	<0.001		0.87 (0.29, 2.52)	0.103
								<i>Post-menopause:</i>					—		
								Isoflavone:	<16.2 vs ≥37.7	148	0.25 (0.14, 0.45)	<0.001		—	—

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Table 1. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with total CVD incidence and mortality

Author, year	Country (cohort)	n (population)	Base-line age (yrs)	Follow-up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Total CVD incidence ^c			Total CVD mortality		
										n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend	n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend
Mink 2007 ⁵⁰	USA (Iowa WHS)	34,489 (post-menopause women)	55 to 69	16	ICD-9 390–459	FFQ/USDA	Rate ratio by quintiles (except antho-cyanidin by 2 groups)	Anthocyanidin:	<0 vs ≥0.01	—	—	—	2,316	0.91 (0.83, 0.99)	0.032
								Catechin + ODC:	<6.8 vs ≥135.7	—	—	—		0.95 (0.83, 1.09)	0.395
								PA:	<89.5 vs. ≥343.2	—	—	—		0.93 (0.81, 1.07)	0.332
								Flavanone:	<16.1 vs ≥72.8	—	—	—		0.88 (0.77, 1.01)	0.054
								Flavone:	<0.02 vs ≥1	—	—	—		0.95 (0.83, 1.10)	0.136
								Flavonol:	<5.4 vs ≥14.6	—	—	—		0.91 (0.79, 1.05)	0.779
								Isoflavone:	<0.1 vs ≥0.5	—	—	—		1.05 (0.91, 1.21)	0.210
van der Schouw 2005 ¹⁰²	Netherlands (Prospect-EPIC)	16,165 (F)	49 to 70	6.25	ICD-9 410–414, 427.5 & 430–438	FFQ/Self-developed database	Hazard ratio by quartiles	Total:	<133.2 vs ≥425.3	—	—	—	—	0.93 (0.81, 1.07)	0.628
								Isoflavone:	—	518	0.97 (0.74, 1.27)	—		—	—
Sesso 2003 ⁴²	USA (WHS)	38,445 (F)	>45	6.9	MI, heart bypass, PTCA stroke & CVD death	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	$\bar{x}$ =8.8 vs $\bar{x}$ =47.4	729	0.88 (0.68, 1.14)	0.63	—	1.05 (0.62, 1.78)	0.12

^a Diet data capture method/Major flavonoid database used. ^b Subclass composition and calculations of flavonoid intake may differ between studies; the term ‘Total’ is used to denote the sum of 5 or more flavonoid subclasses. ^c Incidence is defined as the first fatal or non-fatal event unless otherwise indicated. ^d The model with the most covariate adjustments in each manuscript is reported; covariates differ between manuscripts. *Includes non-fatal events only. ***Flavonoid intake estimated as found in food (i.e., mostly glycosides). †Represents the association for a proportional difference in flavonoid intake (see corresponding analysis description). Abbreviations: CAIFOS, Calcium Intake Fracture Outcome Age Related Extension Study; CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; ICD, International Classification of Disease; IHD, ischemic heart disease; M, male; MI, myocardial infarction; NHS, Nurses’ Health Study; ODC, other derived compounds (e.g. theaflavins and/or thearubigins); PA, proanthocyanidin; PE, Phenol-Explorer; PREDIMED, Prevención con Dieta Mediterránea; PTCA, percutaneous transluminal coronary angioplasty; SUN, Seguimiento Universidad de Navarra; TIA, transient ischemic attack; USA, United States of America; USDA, United States Department of Agriculture; UK, United Kingdom; WHS, Women’s Health Study; $\bar{x}$, mean; $\bar{x}$, median.

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569 **b. Ischemic heart disease**

570 *Disease overview.* Globally, IHD is the main cause of death accounting for ~9 million fatalities
571 in 2015.⁹⁴ Collectively, IHD is the term for a group of clinical syndromes characterized by
572 myocardial ischemia, most often due to atherosclerosis.^{98,115} Atherosclerosis can cause
573 narrowing of the coronary arteries (stenosis) which can lead to angina pectoris, marked by
574 paroxysms of chest pain. Secondly, atherosclerosis can cause thrombus formation in the
575 coronary arteries, interrupting the blood supply to the heart and causing necrosis of the
576 myocardium, in addition to several other manifestations such as coronary aneurysms.¹¹⁶ A
577 growing body of mechanistic research suggests flavonoids could lower the risk of IHD by
578 mitigating atherosclerosis and its risk factors such as hypertension, hypercholesterolemia, and
579 endothelial dysfunction.^{79,99,100} Thus, the following describes findings from studies examining
580 the association of flavonoid intake with IHD (also referred to as coronary heart disease) or its
581 distinct disease sequelae such as myocardial infarction.

582 *Cohort characteristics.* Since 1993, at least 21 prospective cohorts (in 28 publications) have
583 reported on flavonoid intake and the risk of IHD incidence and/or mortality (**Table 2**). As an
584 aside, one other prospective study has reported on flavonoids and IHD risk, but it had an
585 ecological study design, which differs from the other studies and is thus, not presented in table
586 two.¹¹⁷ Of the publications presented, some report on the same study over different years of
587 follow-up. For example, the Zutphen Elderly Study reports on flavone and flavonol intake and
588 IHD risk at five and 10 years of follow-up,^{5,118} as well as catechin intake and IHD risk after 10
589 and 25 years of exposure.^{45,111} Other cohorts report on different classes of flavonoid intake
590 across multiple papers, reflecting the timeline of development of several key flavonoid
591 databases. For example, the Iowa Women's Health Study first reported on IHD risk and intake
592 of flavones and flavonols in 1999 using tables by Hertog *et al.* to estimate consumption, then
593 in 2001 on catechin intake using tables by Arts *et al.* to estimate exposure, then again in 2007

594 using the USDA database to estimate all flavonoid subclasses and total intake; in each instance,
595 they used updated follow-up time frames.^{39,46,50}

596 Of the cohorts investigating flavonoid intake and IHD to date, most were conducted in Europe
597 ($n = 10$) and the United States of America ($n = 8$) with only a minority being conducted in
598 other parts of the world (Australia ($n = 1$) and Asia ($n = 2$)). A total of 18 studies report on
599 IHD mortality while, 19 report on IHD incidence (with nine reporting on both incidence and
600 mortality). Nearly all studies reporting on IHD incidence defined this as the first non-fatal or
601 fatal event. However, incidence was occasionally defined as the first non-fatal event only.^{40,76}
602 Some authors presented results using both definitions (of which we present the former in Table
603 2).⁴² Approximately half of the studies reporting on incidence restricted analysis to case events
604 of myocardial infarction.^{5,40–42,45,56,76,101,118,119} Studies reporting on IHD mortality tended to
605 identify events more broadly using ICD-9 codes 410–414, or their equivalent. Some authors
606 presented results for total IHD as well as selected IHD subtypes, for which we present the
607 results of the broader definition in Table 2.³⁷ Most cohorts recruited middle aged adults,
608 although they varied in their demographic characteristics as well as sample size (from 755 to
609 98,469 participants) and follow-up periods (from 4.9 to 28 years). Habitual diet was mainly
610 assessed using FFQs ($n = 17$ publications) and the source used to estimate flavonoid exposure
611 varied from the tables by Hertog *et al.* ($n = 10$ publications) to the USDA databases ($n = 7$
612 publications), tables by Arts *et al.* ($n = 3$ publications), Phenol-Explorer ($n = 2$ publications),
613 the Singapore Composition Database ($n = 1$ publication), and several other methods ($n = 5$).
614 All studies appear to report intake as AEs (including free form and potentially esterified flavan-
615 3-ols), except for one cohort, which reports flavonoids expressed as glycosides (and their other
616 naturally occurring structures).⁶⁰

617 *Total flavonoids.* The association between total flavonoid intake (estimated as ≥ 5 subclasses)
618 and IHD incidence has been studied in at least four cohorts while mortality rates have been

619 studied in at least three. Of these studies, significant findings were only observed in the Danish
620 Diet, Cancer & Health study which examined first time events of hospitalisation for IHD
621 (multivariable adjusted hazard ratio for highest vs lowest intake category: 0.91, 95% CI: 0.85,
622 0.98).⁶² This study had a large sample size ($n = 53,552$), high number of cases ($n = 5,323$) and
623 long follow-up period (23 years). While no meta-analyses have focused exclusively on total
624 flavonoid intake and IHD, a 2017 meta-analysis pooled heterogeneous flavonoid exposures
625 and examined their association with IHD mortality.¹⁰⁶ Here, Liu *et al.* describe a trend towards
626 a lower risk of IHD death with higher flavonoid intake ($n = 4$ cohorts; multivariable adjusted
627 risk estimate for highest vs lowest intake category: 0.74, 95% CI: 0.54, 1.02; $P = 61\%$).¹⁰⁶
628 However, these results differ to a prior meta-analysis by Jiang *et al.*, who also pooled 4 cohorts
629 reporting on flavonoid intake and IHD death, yet a clearly lowered risk with higher flavonoid
630 exposure was reported (multivariable adjusted risk estimate for highest vs lowest intake
631 category: 0.82, 95% CI: 0.74, 0.90; $P = 22\%$).¹²⁰ The reasons for these disparities are not clear,
632 although may have arisen from study selection criteria. Jiang *et al.* further pool 15 cohorts
633 reporting on IHD mortality ($n = 4$), IHD incidence ($n = 10$) and total CVD mortality ($n = 1$),
634 examining any flavonoid exposure, including total intake ($n = 3$), single subclass estimates (n
635 $= 5$) or other subclass combinations ($n = 7$).¹²⁰ In this analysis, a significantly lower risk of
636 IHD events for persons with a higher flavonoid intake was observed ($n = 452,564$; $n = 7,233$
637 cases; multivariable adjusted risk estimate for highest vs lowest intake category: 0.85, 95% CI:
638 0.79, 0.91, $P = 26\%$).¹²⁰ Thus, while the body of evidence lends support to a beneficial
639 association between higher flavonoid intake and IHD risk, additional research to further the
640 granularity of evidence may be beneficial.

641 *Flavonoid subclasses.* The association between individual flavonoid subclasses and IHD
642 incidence has been studied in at least 16 cohorts (in 19 publications), while mortality events
643 have been studied in at least 11 cohorts (across 18 publications). Across cohorts, a lower risk
644 of IHD tends to emerge, reaching significance in at least one or more studies, but not in more

than half, for each individual subclass, except isoflavones for which no significant associations have been observed (Table 2). In 2003, Huxley and Neil pooled seven cohorts reporting on intakes of flavonols and risk of IHD mortality (although, some of the included studies additionally included flavones in their intake estimates).¹²¹ The authors observed a significantly lower risk of IHD mortality with higher exposures ($n = 105,737$; multivariable adjusted risk estimate for highest vs lowest intake category: 0.80, 95% CI: 0.69, 0.93).¹²¹ More recently, Kimble *et al.* pooled studies reporting on intakes of anthocyanins (or berries as surrogate indicators of intake) and both IHD incidence and mortality.¹⁰⁹ Overall, this analysis observed an association in favour of a lower risk with higher intakes and minimal publication bias was apparent ($n = 5$ studies, $n = 58,638$; multivariable adjusted risk estimate for highest vs lowest intake category: 0.91, 95% CI: 0.83, 0.99; $I^2 = 12.0\%$).¹⁰⁹ Kimble *et al.* also restricted the meta-analysis to events of myocardial infarction (including incidence and mortality), yet observed no association with anthocyanin/berry intake ($n = 3$ studies, $n = 175,656$; multivariable adjusted risk estimate for highest vs lowest intake category: 1.00, 95% CI: 0.68, 1.46, $I^2 = 78.1\%$).¹⁰⁹ Raman *et al.* reported a meta-analysis of two studies on IHD incidence and total flavan-3-ol intake finding an inverse association ($n = 41,563$; multivariable adjusted risk estimate for highest vs lowest intake category: 0.81, 95% CI: 0.66, 0.99; $I^2 = 60.8\%$) although, no association was for observed monomer exposure ($n = 2$ studies, $n = 44,514$; multivariable adjusted risk estimate for highest vs lowest intake category: RR = 1.00 95% CI: 0.76, 1.32).⁸⁶ Seemingly, across subclasses, evidence appears stronger for anthocyanin, flavanol and flavan-3-ol intake in lowering risk of IHD.

Effect modification. Modification of the relationship between flavonoid intake and IHD has been explored in a limited number of studies. Goetz *et al.* explored effect modification of flavonoids on IHD by age, sex, race (non-Hispanic white and black Americans), educational attainment, smoking, and physical activity in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.⁵⁷ The authors enrolled 16,678 black and white males

671 and females (≥ 45 yrs old, 42% black, 55% female) living throughout the United States of
672 America.⁵⁷ After 6.0 ± 1.9 years of follow-up, 589 IHD incidences occurred however, the effect
673 of flavonoids did not vary by the tested factors; confirmation of these findings in a larger
674 sample would be of interest.⁵⁷ Cassidy *et al.* examined the associations between anthocyanin
675 intake and incidence of myocardial infarction among strata of age (participants < 65 or ≥ 65
676 years old), the presence of type 2 diabetes mellitus and hypertension, in the Health
677 Professionals Follow-Up Study ($n = 43,880$).¹¹⁹ After 24 years of following the all-male cohort,
678 they found no effect modification by age at baseline, nor diabetes. However the inverse
679 association between anthocyanin intake and myocardial infarction was stronger in participants
680 who were not hypertensive (HR: 0.81; 95% CI: 0.69, 0.96) compared to participants diagnosed
681 with hypertension (HR: 1.05; 95% CI: 0.79, 1.39; $P_{\text{interaction}} = 0.03$).¹¹⁹ Cassidy *et al.* suggest
682 this may have occurred because medication use may have exceeded the capacity for flavonoids
683 to lower the risk of CVD.¹¹⁹ In the Nurses' Health Study II ($n = 93,600$; all females), Cassidy
684 *et al.* also identified risk factors that may modify the relationship between flavonoid intake and
685 myocardial infarction.¹¹⁹ They tested for effect modification by age, smoking, physical activity,
686 prevalent hypertension, type 2 diabetes mellitus, alcohol intake, and body mass index.¹¹⁹ No
687 significant interactions emerged.¹¹⁹

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Table 2. Summary of prospective cohort studies investigating the association of flavonoid intake with ischemic heart disease

Author, year	Country (cohort)	<i>n</i> (population)	Base-line age (yrs)	Follow-up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	IHD incidence ^c			IHD mortality			
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	
Dalgaard 2019 ⁶²	Denmark (Danish Diet, Cancer & Health study)	53,552 (M & F)	56	23	Hospital admission for ICD-10 I20-I25	FFQ/ PE	Quintile one vs 1000 mg	Total:	$\bar{x}$ =174 vs 1000	5,323	0.91 (0.85, 0.98)	—	—	—	—	
Adriouch 2018 ⁶⁰	France (Nutrinet-Santé)	84,158 (M & F)	44.1	4.9	MI, acute coronary syndromes, & angioplasty	3 x 24 hr diet record/ PE***	Hazard ratio by tertiles	Anthocyanin:	$\bar{x}$ =27.5 vs $\bar{x}$ =55.0	309	0.74 (0.53, 1.03)	0.07	—	—	—	
								Catechin:	$\bar{x}$ =75.4 vs $\bar{x}$ =178	0.85 (0.63, 1.14)	0.26	—	—	—		
								Theaflavin:	$\bar{x}$ =10.3 vs $\bar{x}$ =24.5	0.90 (0.70, 1.17)	0.44	—	—	—		
								PA:	$\bar{x}$ =33.7 vs $\bar{x}$ =71.7	0.84 (0.61, 1.17)	0.26	—	—	—		
								Flavanone:	$\bar{x}$ =30.1 vs $\bar{x}$ =30.7	1.20 (0.90, 1.62)	0.21	—	—	—		
								Flavone:	$\bar{x}$ =23.3 vs $\bar{x}$ =27.6	1.15 (0.84, 1.56)	0.39	—	—	—		
								Flavonol:	$\bar{x}$ =46.5 vs $\bar{x}$ =86.3	0.93 (0.68, 1.28)	0.65	—	—	—		
Bondonno 2018 ⁵¹	Australia (Blue Mountains Eye Study)	2,349 (M & F)	64.7	14	ICD-9 410–414 & ICD-10 I21–I25.9	FFQ/ USDA	Hazard ratio by tertiles	Isoflavone:	$\bar{x}$ =4.5 vs $\bar{x}$ =11.5	1.12 (0.84, 1.50)	0.45	—	—	—	—	
								Anthocyanidin:	<3.8 vs ≥9.2	—	—	143	0.90 (0.56, 1.45)	—	—	
								Catechin + ODC:	<310.5 vs ≥747.9	—	—	1.00 (0.64, 1.56)	—	—		
								PA:	<85.9 vs ≥155.5	—	—	1.23 (0.77, 1.94)	—	—		
								Flavanone:	<10.3 vs ≥38.9	—	—	0.87 (0.57, 1.33)	—	—		
								Flavone:	<0.72 vs ≥1.32	—	—	0.87 (0.57, 1.34)	—	—		
								Flavonol:	<25.0 vs ≥42.3	—	—	0.97 (0.63, 1.49)	—	—		
Cassidy 2016 ¹¹⁹	USA (Health Professionals Follow-Up)	43,880 (M)	32 to 81	24	MI	FFQ/ Mostly USDA	Hazard ratio by quintiles	Isoflavone:	<0.81 vs ≥1.23	1.23 (0.79, 1.91)	0.65	—	—	—	—	
								Total:	<599.9 vs ≥1106	—	—	1.02 (0.65, 1.59)	—	—		
								Anthocyanidin:	$\bar{x}$ =1.9 vs $\bar{x}$ =26.3	4,046	0.97 (0.87, 1.07)	0.44	1,816	1.10 (0.94, 1.28)	0.56	—
								Flavanone:	$\bar{x}$ =7.5 vs $\bar{x}$ =103.9	0.98 (0.88, 1.08)	0.87	0.95 (0.81, 1.11)	0.22	—		
								Catechin:	<9.4 vs ≥19.5	—	—	—	—	0.74 (0.47, 1.16)	—	—
								Anthocyanidin:	≤5.8 vs ≥18.6	589	0.73 (0.55, 0.96)	0.05	—	—	—	
								Catechin + ODC:	≤25 vs ≥279	1.05 (0.82, 1.34)	0.39	—	—	—		
Goetz 2016 ⁵⁷	USA (REGARDS)	16,678 (M & F)	≥45	6	MI & CHD death	FFQ/ USDA	Hazard ratio by quintiles	PA:	≤59 vs ≥137	0.66 (0.51, 0.85)	0.03	—	—	—	—	
								Flavone:	≤0.51 vs ≥1.46	0.97 (0.73, 1.28)	0.78	—	—	—		
								Flavanone:	≤10 vs ≥46	1.03 (0.80, 1.33)	0.62	—	—	—		
								Flavonol:	≤9 vs ≥28	0.98 (0.75, 1.27)	0.98	—	—	—		
								Total:	≤149 vs ≥478	0.93 (0.71, 1.19)	0.86	—	—	—		
								Anthocyanidin:	—	261	0.98 (0.86, 1.12)†	0.76	—	—	—	
								Catechin:	—	1.01 (0.89, 1.14)†	0.86	—	—	—		
Jacques 2015 ⁵³	USA (Framingham Offspring Cohort)	2,880 (M & F)	54	14.9	MI, angina pectoris, coronary insufficiency and CHD death	FFQ/ USDA	Relative risk for each 2.5-fold ↑ in daily intake	PA + ODC:	—	0.97 (0.84, 1.12)†	0.68	—	—	—	—	
								Flavanone:	—	0.94 (0.85, 1.06)†	0.32	—	—	—		
								Flavone:	—	0.83 (0.64, 1.09)†	0.18	—	—	—		
								Flavonol:	—	0.96 (0.76, 1.22)†	0.76	—	—	—		
								Total:	—	0.96 (0.80, 1.14)†	0.63	—	—	—		

696 **Table 2.** Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with ischemic heart disease

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	IHD incidence ^c			IHD mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Vogiatz- ogloua 2015 ¹⁰³	UK (EPIC)	M: 11,252 F: 13,633	40 to 75	11.1	ICD-9 410–414 or ICD-10 I20–I25	7-day diary/ Flaviola Flavanol Food Database	Hazard ratio by quintiles	<i>Males:</i> Total flavan-3-ol: <i>Females:</i> Total flavan-3-ol: Isoflavone:	$\bar{x}$ =198 vs $\bar{x}$ =2008 $\bar{x}$ =179 vs $\bar{x}$ =1828 $\bar{x}$ =5.4 vs $\bar{x}$ =36.1	2,335	0.88 (0.77, 1.01)	0.338	—	—	—
										1,325	0.96 (0.80, 1.17)	0.810	—	—	—
Talaei 2014 ¹¹²	Singapore (Singapore Chinese Health Study)	63,257 (M & F)	45 to 74	14.7	ICD-9 410–414	FFQ/Singapore Composition Database ¹¹³	Hazard ratio by quartile			—	—	—	2,697	0.97 (0.81, 1.16)	0.41
Cassidy 2013 ⁵⁶	USA (NHS II)	93,600 (F)	25 to 42	18	MI	FFQ/ USDA	Hazard ratio by quintiles	Anthocyanidin:	2.5 vs 25.1	405	0.68 (0.49, 0.96)	0.047	—	—	—
								Catechin:	13.4 vs 610.2	—	0.82 (0.61, 1.11)	0.37	—	—	—
								PA + ODC:	65.4 vs 578.6	—	0.83 (0.62, 1.11)	0.051	—	—	—
								Flavanone:	6.6 vs 71.1	—	0.91 (0.66, 1.26)	0.96	—	—	—
								Flavone:	0.6 vs 2.9	—	1.00 (0.72, 1.40)	0.75	—	—	—
								Flavonol:	7.8 vs 33.2	—	0.79 (0.58, 1.08)	0.08	—	—	—
								Total:	117.4 vs 804.7	—	0.83 (0.61, 1.12)	0.09	—	—	—
Mc- Cullough 2012 ⁵⁴	USA (Cancer Prevention Study II)	98,469 (M & F)	~69	7	ICD-9 410–414 & 492.2	FFQ/ USDA	Rate ratios by quintiles	Anthocyanidin:	<5.5 vs ≥16.7	—	—	—	1,286	0.79 (0.67, 0.94)	0.06
								Catechin:	<9.5 vs ≥37.2	—	—	—	—	0.87 (0.74, 1.04)	0.5
								PA:	<71.6 vs ≥253.6	—	—	—	—	0.94 (0.79, 1.12)	0.2
								Flavanone:	<7.0 vs ≥35.4	—	—	—	—	0.89 (0.76, 1.06)	0.5
								Flavone:	<0.5 vs ≥2.1	—	—	—	—	0.75 (0.62, 0.90)	0.0009
								Flavonol:	<8.5 vs ≥20.6	—	—	—	—	0.85 (0.72, 1.01)	0.1
								Isoflavone:	<0.03 vs ≥0.14	—	—	—	—	0.88 (0.73, 1.07)	0.08
Kokubo 2007 ¹⁰¹	Japan (Japan PHS Cohort I)	40,462 (M & F)	40 to 59	12	ICD-10 I21–I23 & I46	FFQ/Local database ¹¹⁴	Hazard ratio by quintiles	<i>Males:</i> Isoflavone:	<16.4 vs ≥39.6	242	0.77 (0.47, 1.24)	0.614	—	—	—
								<i>Females:</i> Isoflavone:	<16.2 vs ≥37.7	66	0.37 (0.14, 0.98)	0.006	—	—	—
								Flavone + flavonol:	≤9.6 vs ≥30.9	938	1.05 (0.85, 1.29)*	0.55	324	0.81 (0.57, 1.16)	0.29
Lin 2007 ⁷⁶	USA (NHS)	66,360 (F)	30 to 55	12	Incidence: MI Mortality: ICD -9 410–414	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles								
Mink 2007 ⁵⁰	USA (Iowa WHS)	34,489 (post- menopau- sal women)	55 to 69	16	ICD-9 410–414 & 429.2	FFQ/ USDA	Rate ratio by quintiles (except antho- cyanidin by 2 groups)	Anthocyanidin:	0 vs ≥0.01	—	—	—	1,329	0.88 (0.78, 0.99)	0.031
								Catechin + ODC:	<6.8 vs ≥135.7	—	—	—	—	1.02 (0.86, 1.21)	0.113
								PA:	<89.5 vs ≥343.2	—	—	—	—	0.91 (0.76, 1.10)	0.489
								Flavanone:	<16.1 vs ≥72.8	—	—	—	—	0.78 (0.65, 0.94)	0.010
								Flavone:	<0.02 vs ≥1	—	—	—	—	0.95 (0.78, 1.14)	0.147
								Flavonol:	<5.4 vs ≥14.6	—	—	—	—	0.95 (0.79, 1.14)	0.965
Marniemi 2005 ¹²²	Finland (no study name)	755 (M & F)	65 to 99	10	ICD-9 410, 412 & 414	Diet history/ Nutrica database	Relative risk by tertiles	Isoflavone:	<0.1 vs ≥0.5	—	—	—	—	1.00 (0.83, 1.19)	0.425
								Total:	<133.2 vs ≥425.3	—	—	—	—	0.94 (0.78, 1.13)	0.980
								Flavone + flavonol:	—	130	0.79 (0.51, 1.24)	—	—	—	—

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Table 2. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with ischemic heart disease

Author, year	Country (cohort)	<i>n</i> (population)	Base-line age (yrs)	Follow-up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	IHD incidence ^c			IHD mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
van der Schouw 2005 ¹⁰²	Netherlands (Prospect EPIC)	16,165 (F)	49 to 70	6.25	ICD-9 410–414, 427.5	FFQ/self-developed database	Hazard ratio by quartiles	Isoflavone:	—	372	0.94 (0.68, 1.30)	—	—	—	—
Sesso 2003 ⁴²	USA (WHS)	38,445 (F)	>45	6.9	MI using WHO criteria	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	$\bar{x}$ =8.8 vs $\bar{x}$ =47.4	—	0.82 (0.51, 1.33)	0.89	—	—	—
Knekt 2002 ⁴⁷	Finland (Finnish Mobile Clinic)	9,131 (M & F)	54	28	ICD-8 410–414	Diet history/ Mostly local analysis	Relative risk by quartiles	Flavone + flavonol + flavanone:	—	—	—	—	681	0.93 (0.74, 1.17)	0.30
Geleijnse 2002 ⁴¹	Netherlands (Rotterdam Study)	4,807 (M & F)	≥55	5.6	ICD-10 I21	FFQ/ Hertog <i>et al.</i> ^{38,39}	Relative risk by tertiles	Flavonol:	$\bar{x}$ =16.8 vs $\bar{x}$ =40.0	146	0.76 (0.49, 1.18)	—	30	0.35 (0.13, 0.98)	—
Arts 2001 ⁴⁵	Netherlands (Zutphen)	806 (M)	65 to 84	10	Incidence: MI Mortality: ICD -9 410–414	Diet history/ Arts <i>et al.</i> ^{43,44}	Risk ratio by tertiles	Catechin:	<49.0 vs ≥85.9	90	0.49 (0.27, 0.88)	0.017	90	0.70 (0.39, 1.26)	0.232
Arts 2001 ⁴⁶	USA (Iowa WHS)	34,492 (F)	55 to 69	13	ICD-9 410–414 & 429.2	FFQ/Mostly Arts <i>et al.</i> ^{43,44}	Risk ratio by quintile	Catechin:	$\bar{x}$ =3.7 vs $\bar{x}$ =52.7	—	—	—	767	0.85 (0.67, 1.07)	—
Hirvonen 2001 ⁴⁰	Finland (ATBC Study)	25,372 (M smokers)	50 to 69	6.1	Incidence: MI Mortality: ICD -9 410–414	Diet history/ Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	$\bar{x}$ =3.9 vs $\bar{x}$ =17.8	1,122	0.77 (0.64, 0.93)*	—	815	0.89 (0.71, 1.11)	—
Yochum 1999 ³⁹	USA (Iowa WHS)	34,492 (post-menopause women)	~61	10	ICD-9 410–414 & 429.2	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	<5.7 vs ≥18.7	—	—	—	438	0.62 (0.44, 0.87)	0.11
Hertog 1997 ¹¹⁸	Netherlands (Zutphen)	804 (M)	65 to 84	10	Incidence: MI Mortality: ICD -9 410–414	Diet history/ Hertog <i>et al.</i> ^{38,39}	Relative risk by tertiles	Flavone + flavonol:	<19 vs ≥29.9	92	0.62 (0.24, 1.05)	0.078	90	0.47 (0.27, 0.82)	0.006
Hertog 1997 ³⁸	UK (Caerphilly Study)	1,900 (M)	45 to 59	14	MI & IHD death	FFQ/ Hertog <i>et al.</i> ^{38,39}	Relative risk by quartiles	Flavonol:	<19 vs >34	186	1.1 (0.6, 1.6)	0.996	131	1.6 (0.9, 2.9)	0.119
Rimm 1996 ³⁷	USA (Health Professional Follow-up)	34,789 (M)	40 to 75	6	MI & Revascularization or CHD death	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	$\bar{x}$ =7.1 vs $\bar{x}$ =40.0	373	0.94 (0.68, 1.31)	—	140	0.77 (0.45, 1.35)	—

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Table 2. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with ischemic heart disease

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	IHD incidence ^c			IHD mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Knekt 1996 ³⁶	Finland (Finnish Mobile Clinic)	M: 2,748 F: 2,385	30 to 69	26	ICD-8 410–414	Diet history/ Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quartiles	<i>Males:</i> Flavone + flavanol: <2.1 vs >4.8	—	—	—	—	324	0.67 (0.44, 1.00)	0.12
								<i>Females:</i> Flavone + flavanol: <2.4 vs >5.5							
Hertog 1993 ³	Netherlands (Zutphen)	805 (M)	65 to 84	5	Incidence: MI Mortality: ICD -9 410–414	Diet history/ Hertog <i>et al.</i> ^{38,39}	Relative risk by tertiles	Flavone + flavanol:	<19 vs ≥29.9	38	0.52 (0.22, 1.23)	0.15	149	0.73 (0.41, 1.32)	0.21
													43	0.32 (0.15, 0.71)	0.003

^a Diet data capture method/Major flavonoid database used. ^b Subclass composition and calculations of flavonoid intake may differ between studies; the term ‘Total’ is used to denote the sum of 5 or more flavonoid subclasses. ^c Incidence is defined as the first fatal or non-fatal event unless otherwise indicated. ^d The model with the most covariate adjustments in each manuscript is reported; covariates differ between manuscripts. *Includes non-fatal events only. ***Flavonoid intake estimated as found in food (i.e., mostly glycosides). †Represents the association for a proportional difference in flavonoid intake (see corresponding analysis description). Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD, coronary heart disease; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; ICD, International Classification of Disease; IHD, ischemic heart disease; M, male; MI, myocardial infarction; NHS, Nurses’ Health Study; ODC, other derived compounds (e.g. theaflavins and/or thearubigins); PA, proanthocyanidin; PE, Phenol-Explorer; PHS, Public Health Study; REGARDS, The REasons for Geographic and Racial Differences in Stroke; USA, United States of America; USDA, United States Department of Agriculture; UK, United Kingdom; WHS, Women’s Health Study; WHO, World Health Organisation; $\bar{x}$, mean; $\tilde{x}$, median.

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722 **c. Cerebrovascular disease**

723 *Disease overview.* Cerebrovascular disease is the second leading cause of death and the leading
724 cause of adult long-term disability.¹²³ Cerebrovascular disease is the collective term for a broad
725 range of conditions that adversely affect cerebral blood supply including stroke, transient
726 ischemic attacks, other intracranial vascular disorders as well as late effects of stroke or its
727 sequelae.¹²⁴ Stroke is the primary sub-type of cerebrovascular disease and is characterised by
728 a sudden onset of neurological dysfunction.^{125,126} It is typically caused by an occlusion in the
729 cerebral vasculature resulting in an ischemic stroke and, less often, vessel rupture producing a
730 haemorrhagic stroke.¹²⁷ In high income countries, such as within North America, death from
731 ischemic stroke accounts for as high as 67.9% of stroke mortality.⁹⁴ Likewise, the prevalence
732 of ischemic stroke dominates hemorrhagic strokes in Australasia and Western and Central
733 Europe, reaching as high as 74.3% of stroke cases in North America.⁹⁴ Vessel occlusion,
734 occurring in ischemic stroke, is mostly a consequence of atherosclerosis,¹²⁵ either locally,
735 producing luminal narrowing precipitating obstruction, or from atherosclerotic thrombus or
736 emboli, which form elsewhere in the body, dislodge and travel to the cerebrovasculature, where
737 they cause significant vascular ischemia.¹²⁶ As flavonoids have shown anti-atherogenic and
738 anti-thrombotic properties,¹²⁸ they are thought to play a role in mitigating the pathogenesis and
739 progression of stroke from atherosclerotic origins.^{79,99,100} While most literature on flavonoid
740 intake and cerebrovascular events has included the broad range of cerebrovascular disease in
741 their assessment of outcome cases, as highlighted above, these are principally ASCVD related.

742 *Cohort characteristics.* At least 18 prospective cohorts (in 21 publications) have reported on
743 flavonoid intake and risk of cerebrovascular disease incidence and/or mortality (**Table 3**).
744 Some of these cohorts are reported across multiple publications, such as the Zutphen Elderly
745 study and Iowa Women's Health Study, reflecting either the examination of certain flavonoids
746 after different lengths of follow-up, or the examination of different flavonoids, in different

manuscripts. Across all studies, incidence was defined as the first non-fatal or fatal event. One study restricted analyses to first time events resulting in hospitalisation.⁶² Outcome events were mostly defined as all cerebrovascular disease using ICD-9 codes 430–438 or their equivalent, to identify cases. Though, some studies reported exclusively on ischemic stroke.^{55,62,129,130} Others reported across multiple types of cerebrovascular disease, for which we present findings for ischemic stroke in Table 3, as flavonoids appear most relevant to ASCVD.^{35,47,119,131} Overall, cohorts were conducted in Europe ($n = 10$), the United States of America ($n = 6$), and Asia ($n = 2$), and they vary in size (from 552 to 98,469 participants) and follow-up periods (from 4.9 to 28 years). Flavonoid intake was mostly estimated from FFQs ($n = 12$ publications) and diet histories ($n = 6$ publications) using the USDA database ($n = 6$ publications), Phenol-Explorer ($n = 2$ publications), tables by Hertog *et al.* ($n = 3$ publications) and Arts *et al.* ($n = 2$ publications), among a variety of other sources. Across all studies, only one indicated that flavonoid intake was estimated as glycosides (and other naturally occurring compounds);⁶⁰ all other studies appear to report intake as AE (including free form and potentially esterified flavan-3-ols).

Total flavonoids. Total flavonoid intake (estimated as ≥ 5 subclasses) has been examined in 6 cohorts for an association with cerebrovascular disease incidence or mortality. In most cohorts there was a trend towards a lower cerebrovascular disease risk with higher consumption. However, none reached statistical significance in the highest exposure category. In 2016, Tang *et al.* published a meta-analysis which pooled 11 cohorts ($n = 356,627$; $n = 5,154$ cases), reporting across incidence and mortality measures of cerebrovascular disease ($n = 8$ cohorts) and ischemic stroke ($n = 3$ cohorts), with any flavonoid exposure; from total intake ($n = 3$ cohorts), to specific subclasses or their combinations ($n = 8$ cohorts).¹³² In their main analysis, the authors report a significantly lower risk of cerebrovascular disease for persons with higher flavonoid intake (multivariable adjusted risk estimate for highest vs lowest intake category:

0.89, 95% CI: 0.82, 0.97; $I^2 = 0\%$).¹³² In their sub-analysis of ischemic stroke, the association was not as clear ($n = 3$ cohorts, $n = 98,069$; multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 0.93, 95% CI: 0.80, 1.07; $I^2 = 0\%$).¹³² However, these results are limited by the number of cohorts pooled.¹³² Consequently, while the body of evidence suggests an association between flavonoid intake and cerebrovascular disease risk, further research re-orientated towards disease sub-types, such as ischemic stroke, may help facilitate a better granularity of evidence.

Flavonoid subclasses. Individual flavonoid subclasses have been examined for associations with cerebrovascular disease incidence ($n = 15$ cohorts across 16 publications) and mortality ($n = 4$ cohorts across 6 publications). Across cohorts, a trend towards a lower risk of cerebrovascular disease emerges, reaching significance in at least one or more cohorts, for all subclasses, except flavones (Table 3). By 2010, Hollman *et al.* had pooled 6 cohorts ($n = 111,067$, $n = 2,155$ cases), reporting intake combinations of flavonols, flavones and flavanones, and outcomes events of cerebrovascular disease and ischemic stroke, across incidence and mortality measures.¹³³ They found, overall, a lower risk of cerebrovascular disease in those participants consuming the highest compared to the lowest estimated intakes (multivariable adjusted risk estimate: 0.80, 96% CI: 0.65, 0.98). However, heterogeneity ($I^2 = 54\%$) and publication bias (Eggers test = 0.01) was present.¹³³ In 2014, Wang *et al.* conducted an updated systematic review and meta-analysis, similar that of Hollman *et al.*, including two further cohorts, which substantially increased the sample size and number of cases ($n = 280,174$, $n = 5,228$ cases).¹³⁴ Again a significantly lower risk was observed (multivariable adjusted risk estimate for highest vs lowest intake category: 0.86, 96% CI: 0.75, 0.99) though, again, publication bias was indicated (Eggers test = 0.005).¹³⁴ Wang *et al.* further conducted sub-analyses, finding a trend towards a lower risk of ischemic stroke events ($n = 4$ cohorts; multivariable adjusted risk estimate for highest vs lowest intake category: 0.86, 95% CI: 0.71,

1.04; $I^2 = 48\%$), and unsurprisingly, given disease aetiology, this trend was less apparent for haemorrhagic stroke events ($n = 3$ cohorts; multivariable adjusted risk estimate: 0.90, 95% CI: 0.61, 1.32; $I^2 = 50\%$).¹³⁴ In 2019, Kimble *et al.* pooled ten cohorts reporting incidence or mortality outcomes of cerebrovascular disease or specific stroke sub-types, finding no clear association with higher intake of anthocyanins or berries which were used as a surrogate indicator of anthocyanin intake (multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 1.00, 95% CI: 0.93, 1.07; $I^2 = 15.1\%$).¹⁰⁹ When analysed by disease sub-type, there was a trend towards a lower risk of ischemic stroke with higher anthocyanin/berry consumption ($n = 4$ cohorts; multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 0.90, 95% CI: 0.79, 1.03; $I^2 = 0\%$).¹⁰⁹ However, no such association was apparent between anthocyanin intake and haemorrhagic stroke ($n = 2$ cohorts; multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 1.01, 95% CI: 0.75, 1.35; $I^2 = 0\%$).¹⁰⁹ A meta-analysis has also been performed on cohort studies reporting on flavan-3-ol intake and incident cerebrovascular disease; while no association was found, the analysis is limited by the number of included cohorts ($n = 2$ cohorts; multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 0.95; 95% CI: 0.80, 1.12; $I^2 = 0.0\%$).⁸⁶ However, higher flavan-3-ol monomer intake was associated with a significantly lower risk of cerebrovascular disease ($n = 4$ cohorts; multivariable adjusted risk estimate for highest vs lowest flavonoid intake category: 0.82; 95% CI: 0.68, 0.99; $I^2 = 0.0\%$).⁸⁶ Thus, at this time, additional research is needed to clearly delineate the role of all flavonoid subclasses on cerebrovascular disease risk and its distinct disease sub-types.

Effect modification. The beneficial association between flavonoid-rich diets and cerebrovascular disease might differ across population subgroups. Goetz *et al.* evaluated 20,024 participants in the REGARDS study and tested for effect modification of flavonoids on incidence of ischemic stroke by race (non-Hispanic white and black Americans) and sex.¹²⁹

822 After 6.5 years of follow-up (and 524 cases) no significant effect modification by race or sex
823 was observed for any flavonoid exposure including all major subclasses and their total intake;
824 though corroboration of these findings in further samples is needed.¹²⁹ In the Nurses' Health
825 Study ($n = 69,622$) effect modification by hypertension and aspirin use was tested ($n = 1,803$
826 cases) and no interactions were observed after 14 years of follow-up.¹³¹ In contrast, in the
827 Health Professionals Follow-Up Study, after 24 years of following 43,880 participants,
828 significant effect modification by age occurred, wherein higher flavanone intake was
829 associated with a lower risk of incidence ischemic stroke in men aged >65 years (HR: 0.71,
830 95% CI: 0.54, 0.92) compared with men ≤ 65 y (HR: 1.0, 95% CI: 0.66, 1.51; $P_{\text{interaction}} =$
831 0.04),¹¹⁹ presumably due to a higher rate of death among the more elderly.

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Table 3. Summary of prospective cohort studies investigating the association of flavonoid intake with cerebrovascular disease

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Cerebrovascular disease incidence ^c			Cerebrovascular disease mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Dalgaard 2019 ⁶²	Denmark (Danish Diet, Cancer & Health study)	53,552 (M & F)	56	23	Hospital admission for ICD-10 I63	FFQ/ PE	Quintile one vs 1000 mg	Total: $\bar{x}$ =174 vs 1000		2,920	0.91 (0.82, 1.01)	—	—	—	—
Adriouch 2018 ⁶⁰	France (Nutrinet- Santé)	84,158 (M & F)	44.1	4.9	Stroke	3 x 24 hr diet record/ PE***	Hazard ratio by tertiles	Anthocyanin: $\bar{x}$ =27.5 vs $\bar{x}$ =55.0		293	0.61 (0.43, 0.85)	0.007	—	—	—
								Catechin: $\bar{x}$ =75.4 vs $\bar{x}$ =178			0.69 (0.51, 0.93)	0.01	—	—	—
								Theaflavin: $\bar{x}$ =10.3 vs $\bar{x}$ =24.5			0.90 (0.68, 1.18)	0.44	—	—	—
								PA: $\bar{x}$ =33.7 vs $\bar{x}$ =71.7			0.86 (0.62, 1.18)	0.32	—	—	—
								Flavanone: $\bar{x}$ =30.1 vs $\bar{x}$ =30.7			0.82 (0.60, 1.12)	0.25	—	—	—
								Flavone: $\bar{x}$ =23.3 vs $\bar{x}$ =27.6			1.09 (0.79, 1.50)	0.61	—	—	—
								Flavonol: $\bar{x}$ =46.5 vs $\bar{x}$ =86.3			0.64 (0.45, 0.89)	0.01	—	—	—
Cassidy 2016 ¹¹⁹	USA (Health Professionals Follow-Up)	43,880 (M)	32 to 81	24	National Survey of Stroke criteria for ischemic stroke	FFQ/ mainly USDA	Hazard ratio by quintiles	Isoflavone: $\bar{x}$ =4.5 vs $\bar{x}$ =11.5			0.90 (0.68, 1.19)	0.48	—	—	—
								Anthocyanidins: $\bar{x}$ =1.9 vs $\bar{x}$ =26.3		200	0.93 (0.75, 1.15)	0.51	—	—	—
								Flavanones: $\bar{x}$ =7.5 vs $\bar{x}$ =103.9			0.78 (0.62, 0.97)	0.059	—	—	—
Dower 2016 ¹¹¹	Netherlands (Zutphen)	774 (M)	65 to 84	25	ICD-9 430–438	Diet history/ Arts <i>et al.</i> ^{43,44}	Hazard ratio by tertiles	Catechin: $\bar{x}$ <9.4 vs $\bar{x}$ ≥19.5		—	—	—	—	0.73 (0.39, 1.38)	—
Goetz 2016 ¹²⁹	USA (REGARDS)	20,024 (M & F)	≥45	6.5	Medical records & National Death Index for ischemic stroke	FFQ/ USDA	Hazard ratio by quintiles	Anthocyanidin: $\bar{x}$ ≤4.8 vs $\bar{x}$ ≥18.5		524	0.94 (0.71, 1.25)	0.67	—	—	—
								Catechin + ODC: $\bar{x}$ ≤12.4 vs $\bar{x}$ ≥119.7			0.97 (0.74, 1.28)	0.93	—	—	—
								PA: $\bar{x}$ ≤46.8 vs $\bar{x}$ ≥141.4			0.93 (0.67, 1.28)	0.80	—	—	—
								Flavone: $\bar{x}$ ≤0.3 vs $\bar{x}$ ≥1.6			0.97 (0.72, 1.31)	0.88	—	—	—
								Flavanone: $\bar{x}$ ≤3.9 vs $\bar{x}$ ≥48.0			0.72 (0.55, 0.95)	0.03	—	—	—
								Flavonol: $\bar{x}$ ≤8.9 vs $\bar{x}$ ≥27.8			1.19 (0.88, 1.61)	0.79	—	—	—
								Isoflavone: $\bar{x}$ ≤0.18 vs $\bar{x}$ ≥1.03			1.06 (0.84, 1.59)	0.11	—	—	—
Vogiatz- ogloua 2015 ¹⁰³	UK (EPIC Norfolk cohort)	M: 11,252 F: 13,633	40 to 75	11.1	ICD-9 430–438 & ICD-10 I60–I69	7-day diary/ Flaviola Flavanol Food Database	Hazard ratio by quintiles	Total: $\bar{x}$ ≤109.6 vs $\bar{x}$ ≥347.0			0.74 (0.55, 1.01)	0.19	—	—	—
								<i>Males:</i> Total flavan-3-ol: $\bar{x}$ =198 vs $\bar{x}$ =2008		595	1.08 (0.82, 1.43)	0.727	—	—	—
								<i>Females:</i> Total flavan-3-ol: $\bar{x}$ =179 vs $\bar{x}$ =1828		605	0.89 (0.68, 1.19)	0.384	—	—	—
Talaei 2014 ¹¹²	Singapore (Singapore Chinese Health Study)	63,257 (M & F)	45 to 74	14.7	ICD-9 430–438	FFQ/ Singapore Composition Database ¹¹³	Hazard ratio by quartile	Isoflavone: $\bar{x}$ =5.4 vs $\bar{x}$ =36.1		—	—	—	1,298	0.97 (0.81, 1.16)	0.41

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Table 3. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with cerebrovascular disease

Author, year	Country (cohort)	<i>n</i> (population)	Base-line age (yrs)	Follow-up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Cerebrovascular disease incidence ^c			Cerebrovascular disease mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Cassidy 2012 ¹³¹	USA (NHS)	69,622 (F)	30 to 55	14	National Survey of Stroke criteria for ischemic stroke	FFQ/ USDA	Relative risk by quintiles	Anthocyanidin:	<5.4 vs >20.2	943	0.89 (0.72, 1.11)	0.59	—	—	—
								Catechin:	<12.3 vs >75.8	—	0.87 (0.72, 1.06)	0.59	—	—	—
								PA + ODC:	<77.1 vs >306.4	—	0.90 (0.73, 1.11)	0.36	—	—	—
								Flavone:	<0.94 vs >2.7	—	0.88 (0.72, 1.08)	0.26	—	—	—
								Flavanone:	<13.7 vs >63.0	—	0.81 (0.66, 0.99)	0.10	—	—	—
								Flavonol:	<10.2 vs >25.1	—	0.96 (0.79, 1.17)	0.94	—	—	—
Mc-Cullough 2012 ⁵⁴	USA (Cancer Prevention Study II)	98,469 (M & F)	~69	7	ICD-9 430–438 & ICD-10 I60–I69	FFQ/ USDA	Hazard rate ratios by quartiles	Anthocyanidin:	<5.5 vs ≥16.7	—	—	—	573	0.95 (0.75, 1.20)	0.7
								Catechin:	<9.5 vs ≥37.2	—	—	—	0.90 (0.71, 1.14)	0.2	
								PA:	<71.6 vs ≥253.6	—	—	—	0.88 (0.70, 1.10)	0.8	
								Flavanone:	<7.0 vs ≥35.4	—	—	—	0.84 (0.67, 1.06)	0.4	
								Flavone:	<0.5 vs ≥2.1	—	—	—	0.88 (0.69, 1.11)	0.3	
								Flavonol:	<8.5 vs ≥20.6	—	—	—	0.93 (0.74, 1.16)	0.9	
Mursu 2008 ⁵⁵	Finland (Kuopio IHD study)	1,950 (M)	42 to 60	15.2	ICD-9 433–434 & ICD-10 I63	4-day diary/ USDA	Relative risk by quartiles	Isoflavone:	<0.03 vs ≥0.14	—	—	—	1.00 (0.78, 1.28)	0.8	
								Total:	<121.5 vs ≥359.7	—	—	—	0.83 (0.66, 1.04)	0.5	
								Anthocyanidin:	—	102	0.88 (0.47, 1.62)	0.813	—	—	—
								Catechin + ODC:	—	—	0.59 (0.30, 1.14)	0.102	—	—	—
								Flavone:	—	—	1.30 (0.69, 2.47)	0.181	—	—	—
								Flavanone:	—	—	0.89 (0.49, 1.63)	0.870	—	—	—
Kokubo 2007 ¹⁰¹	Japan (Japan PHS Cohort I)	40,462 (M & F)	40 to 59	12	ICD-10 I60–I61, I63 & I693	FFQ/Local database ¹¹⁴	Hazard ratio by quintiles	Males:	—	—	—	—	—	—	
								Isoflavone:	<16.4 vs ≥39.6	308	1.21 (0.84, 1.74)	0.053	—	—	—
								Females:	—	—	—	—	—	—	—
								Isoflavone:	<16.2 vs ≥37.7	160	0.35 (0.21, 0.59)	0.015	—	—	—
								Anthocyanidin:	<0 vs ≥0.01	—	—	—	469	1.01 (0.83, 1.24)	0.896
								Catechin + ODC:	<6.8 vs ≥135.7	—	—	—	0.95 (0.71, 1.28)	0.724	
Mink 2007 ⁵⁰	USA (Iowa WHS)	34,489 (post-menopausal women)	55 to 69	16	ICD-9 430–438	FFQ/ USDA	Rate ratio by quintiles (except antho-cyanidin by 2 groups)	PA:	<89.5 vs ≥343.2	—	—	—	1.02 (0.74, 1.39)	0.983	
								Flavanone:	<16.1 vs ≥72.8	—	—	—	0.94 (0.69, 1.27)	0.846	
								Flavone:	<0.02 vs ≥1	—	—	—	0.92 (0.68, 1.25)	0.664	
								Flavonol:	<5.4 vs ≥14.6	—	—	—	0.92 (0.67, 1.24)	0.984	
								Isoflavone:	<0.1 vs ≥0.5	—	—	—	1.23 (0.89, 1.69)	0.27	
								Total:	<133.2 vs ≥425.3	—	—	—	0.94 (0.69, 1.29)	0.796	
Marniemi 2005 ¹²²	Finland (no name)	755 (M & F)	65 to 99	10	ICD-9 431, 433, 434 & 436	Diet history/ Nutrica	Relative risk by tertiles	Flavone + flavonol:	—	70	0.65 (0.34, 1.23)	—	—	—	
								Isoflavone:	—	147	1.05 (0.64, 1.70)	—	—	—	
van der Schouw 2005 ¹⁰²	Netherlands (Prospect-EPIC)	16,165 (F)	49 to 70	6.25	ICD-9 430–438	FFQ/self-developed database	Hazard ratio by quartiles	Isoflavone:	—	147	1.05 (0.64, 1.70)	—	—	—	

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Table 3. Continued: Summary of prospective cohort studies investigating the association of flavonoid intake with cerebrovascular disease

Author, year	Country (cohort)	<i>n</i> (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	Cerebrovascular disease incidence ^c			Cerebrovascular disease mortality		
										<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend	<i>n</i>	Fully adjusted estimate (95% CI) [high vs low] ^d	<i>P</i> for trend
Sesso 2003 ⁴²	USA (WHS)	38,445 (F)	>45	6.9	Stroke	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavanol:	$\bar{x}$ =8.8 vs $\bar{x}$ =47.4	—	0.70 (0.46, 1.07)	0.43	—	—	—
Vokó 2003 ¹³⁰	Netherlands (Rotterdam study)	5,197 (M & F)	67.6	6.4	Review by neurologist for ischemic stroke	FFQ/ Composite of older sources	Relative risk by tertiles	Flavonoid (undefined):	—	227	0.79 (0.66, 2.12)	—	—	—	—
Knekt 2002 ⁴⁷	Finland (Finnish Mobile Clinic)	9,131 (M & F)	39.3	28	ICD-8 for thrombotic stroke	Diet history/ mostly local analysis	Relative risk by quartiles	Flavone + flavanol + flavanone:	—	423	0.73 (0.54, 0.98)	0.004	—	—	—
Arts 2001 ⁴⁵	Netherlands (Zutphen)	806 (M)	65 to 84	10	ICD-9 430–438	Diet history/ Arts <i>et al.</i> ^{43,44}	Risk ratio by tertiles	Catechin:	<49.0 vs ≥85.9	88	0.92 (0.51, 1.68)	0.749	47	0.81 (0.36, 1.83)	0.606
Hirvonen 2000 ³⁵	Finland (ATBC Study)	26,593 (M smokers)	50 to 69	6.1	ICD-8 for cerebral infarction	Diet history/ Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quartiles	Flavone + flavanol:	$\bar{x}$ =4.2 vs $\bar{x}$ =16.4	736	0.98 (0.80, 1.21)	0.81	—	—	—
Yochum 1999 ³⁹	USA (Iowa WHS)	34,492 (post- menopause women)	~61	10	ICD-9 430–438	FFQ/Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavanol:	<5.7 vs ≥18.7	—	—	—	438	1.18 (0.70, 2.00)	0.83
Keli 1996 ¹³⁵	Netherlands (Zutphen)	552 (M)	50 to 69	15	ICD-8 430–438	Diet history/ Netherlands food table	Relative risk by tertile	Flavone + flavanol:	<18.3 vs ≥28.6	42	0.27 (0.11, 0.70)	0.004	—	—	—

^a Diet data capture method/Major flavonoid database used. ^b Subclass composition and calculations of flavonoid intake may differ between studies; the term ‘Total’ is used to denote the sum of 5 or more flavonoid subclasses. ^c Incidence is defined as the first fatal or non-fatal event unless otherwise indicated. ^d The model with the most covariate adjustments in each manuscript is reported; covariates differ between manuscripts. ***Flavonoid intake estimated as found in food (i.e., mostly glycosides). Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; ICD, International Classification of Disease; IHD, ischemic heart disease; M, male; NHS, Nurses’ Health Study; ODC, other derived compounds (e.g, theaflavins and/or thearubigins); PA, proanthocyanidin; PE, Phenol-Explorer; PHS, Public Health Study; REGARDS, The REasons for Geographic and Racial Differences in Stroke; USA, United States of America; USDA, United States Department of Agriculture; UK, United Kingdom; WHS, Women’s Health Study; $\bar{x}$, mean; $\bar{x}$, median.

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859 **e. Peripheral artery disease**

860 *Disease overview.* It is estimated that PAD is the most prevalent CVD globally, though PAD
861 mortality accounted for a mere ~0.3% of total CVD-related death in 2015.^{94,136} In general PAD
862 refers to acute or chronic obstruction of the arteries supplying the lower/upper extremities,
863 excluding those supplying the heart or brain.^{137,138} The most common cause of PAD is
864 atherosclerosis, which accounts for >90% of cases.¹³⁹ Individuals with PAD have a higher risk
865 of coronary and cerebral atherosclerosis, and are several times more likely to experience
866 myocardial infarction or ischemic stroke than individuals without PAD.¹⁴⁰ The clinical
867 spectrum of PAD is wide, including people who are asymptomatic (~50% of those affected);
868 to those experiencing intermittent claudication (~10 to 30% of PAD patients), wherein pain in
869 the calves occurs on exercise and is relieved by rest.^{141,142} The most severe progression of PAD
870 is critical limb ischemia, which develops in ~1 to 2% of PAD patients, leading to ulceration
871 and gangrene requiring amputation in ~30% of patients, and ultimately causing death in 25%
872 of those affected within one year.^{142,143} Evidence suggests flavonoids attenuate
873 pathophysiological processes involved in PAD,^{79,99,100} and consequently, we sought to report
874 on cohorts describing the association of flavonoids with risk of PAD.

875 *Cohort characteristics and findings.* To our knowledge, only two prospective cohorts (in three
876 publications), have investigated the association of flavonoid intake with PAD risk. As early as
877 2004, Hirvonen *et al.* evaluated the risk of intermittent claudication, after 4.1 years of follow-
878 up, in 25,041 male smokers, recruited to the Alpha-Tocopherol, Beta-Carotene Cancer
879 Prevention Study.¹⁴⁴ The authors observed a significant inverse association in their age-
880 adjusted, and lifestyle-adjusted models, yet, upon further adjustment for intake of vitamins C,
881 E and carotenoids, significance was attenuated, yet a trend towards a lower risk of intermittent
882 claudication, with higher intakes of flavonols plus flavones remained (**Table 4**).¹⁴⁴ More
883 recently, Bondonno *et al.* studied the risk of hospitalisation for PAD in the Danish Diet, Cancer
884 & Health study of >50,000 people, over >20 of follow-up (*in press*). In their earlier manuscript,

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885 PAD is reported as a secondary outcome, and a comparison between total flavonoid intake of
886 175 mg/day (quintile one) and 1000 mg/day is made, showing a statistically significantly lower
887 associated risk of PAD (multivariable adjusted HR: 0.68, 95% CI: 0.60, 0.78).⁶² In their latter
888 manuscript (*in press*), the authors went on to study PAD in its entirety. In the same cohort, after
889 adjustment for lifestyle and dietary factors, a lower risk of PAD was observed, across all
890 subclasses, reaching significance for intake of anthocyanin, catechins, proanthocyanidins,
891 flavonols and total flavonoids (Table 4). The non-linear association between total flavonoid
892 intake and PAD hospitalizations plateaued at ~750 to 1000 mg/day after which no added benefit
893 was observed. Moreover, across secondary endpoints, compared to a total flavonoid intake of
894 174 mg/day, for intakes of 1000 mg/day and 500 mg/day respectively, a lower risk of
895 revascularizations/endovascular surgery [HR: 0.57 (95% CI 0.46, 0.69)], and amputations [HR:
896 0.56 (95% CI 0.43, 0.74)] was observed. Furthermore, on both a relative and an absolute scale,
897 the greatest benefits observed for higher flavonoid intakes were in current or former smokers.
898 Overall, evidence is sparse yet promising, that higher intake of flavonoid rich foods lowers risk
899 of PAD.

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904 **Table 4.** Summary of prospective cohort studies investigating the association of flavonoid intake with peripheral artery disease

Author, year	Country (cohort)	n (population)	Base- line age (yrs)	Follow- up (yrs)	Outcome assessment	Flavonoid intake estimate ^a	Analysis	Exposure ^b	Intake (low vs high) mg/day	PAD incidence ^c			PAD mortality		
										n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend	n	Fully adjusted estimate (95% CI) [high vs low] ^d	P for trend
Bondonno 2020	Denmark (Danish Diet, Cancer & Health study)	56,048 (M & F)	56	23	Hospital admission for ICD-10 I70- I74	FFQ/ PE	Hazard ratio by quintiles	Anthocyanidin:	<10 vs ≥53	2,131	0.86 (0.76, 0.98)	—	—	—	—
								Catechin:	<21 vs ≥282		0.80 (0.71, 0.91)				
								PA + theaflavin:	<136 vs ≥434		0.69 (0.60, 0.80)				
								Flavanone:	<6 vs ≥49		0.95 (0.83, 1.09)				
								Flavone:	<3 vs ≥9		0.88 (0.76, 1.02)				
								Flavonol:	<21 vs ≥83		0.73 (0.63, 0.83)				
Dalgaard 2019 ⁶²	Denmark (Danish Diet, Cancer & Health study)	53,552 (M & F)	56	23	Hospital admission for ICD-10 I70- I74	FFQ/ PE	Quintile one vs 1000 mg	Total:	<251 vs ≥909		0.75 (0.65, 0.86)				
								Total:	̄x=174 vs 1000	1,867	0.68 (0.60, 0.78)	—	—	—	—
Hirvonen 2004 ¹⁴⁴	Finland (ATBC Study)	25,041 (M to 69 smokers)	50	4.1	IC using Rose questionnaire	Diet history/ Mostly Hertog <i>et al.</i> ^{38,39}	Relative risk by quintiles	Flavone + flavonol:	—	2,412	0.93 (0.81, 1.08)	0.12	—	—	—

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905 ^a Diet data capture method/Major flavonoid database used. ^b Subclass composition and calculations of flavonoid intake may differ between studies; the term ‘Total’ is used to denote the sum of 5 or more flavonoid
906 subclasses. ^c Incidence is defined as the first fatal or non-fatal event unless otherwise indicated. ^d The model with the most covariate adjustments in each manuscript is reported; covariates differ between manuscripts.
907 Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; F, female; FFQ, food frequency questionnaire; ICD, International Classification of Disease; IC, intermittent claudication, M, male; ODC,
908 other derived compounds (e.g. theaflavins and/or thearubigins); PA, proanthocyanidin; PAD, peripheral artery disease; PE, Phenol-Explorer; **̄x, median.**
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6. Discussion: current evidence—future epidemiological frontiers

In the absence of long-term RCTs, the prospective cohort studies conducted to date offer critical information on the typical foods and beverages consumed by populations, their relative flavonoid contents, and the long-term association with CVD incidence and mortality. Over the past three decades, at least 27 prospective cohorts (in 44 publications) have evaluated the relationship between estimated flavonoid intake and CVD risk. While inconsistencies in findings are observed between studies, meta-analyses of these cohorts tend to suggest a common significant association, wherein, habitual, long-term intakes of flavonoid-rich diets may be associated with a lower risk of IHD, cerebrovascular disease, and total CVD. Less evidence is available for PAD. Of the flavonoid subclasses investigated, epidemiological evidence more often supports diets rich in anthocyanins, flavan-3-ols, and flavonols in lowering the risk of chronic CVD. At the same time, several mechanisms have been investigated by which flavonoids might modulate the causal pathway of major CVD. To this end, short-term RCTs provide evidence that flavonoids lower blood pressure,⁸⁶ improve endothelial function,⁸⁶ improve arterial stiffness,⁸² reduce dyslipidaemia,⁸⁶ and mediate inflammatory responses.¹⁴⁵ As these mechanisms are collectively implicated in atherosclerosis, they are thought, among other possible mechanisms, to conjointly influence the trajectory of chronic CVD, particularly, ASCVD.^{79,99,100} Seemingly, converging evidence of the effects of flavonoids on intermediate endpoints and their association with hard clinical outcomes is suggestive that flavonoid-rich foods, may be protective against CVD. If confirmed, food policy strategies incorporating evidence of the benefits of flavonoid-rich diets may have important implications for health care services and public health outcomes.

While meta-analyses tend to suggest a significant inverse association between flavonoid intake and CVD risk, some inconsistencies in findings between the cohort studies seem apparent. There are multiple potential reasons for these discrepancies, including differences in demographic

characteristics or study settings, differences in the actual absolute intake between populations, the length of follow-up, the varying definition of outcomes, accuracy of covariate assessment, heterogeneous covariate adjustments, the sample size (and number of cases) and consequently, adequate statistical power for meaningful conclusions.¹⁴⁶ Moreover, U-shaped associations have been seen, wherein participants with moderate intakes have a significantly lower risk of CVD, but for those in the highest intake category, this association is not significant. The reason for this finding is not entirely clear, but fewer individuals with these high intakes means less certainty (wider confidence intervals), and findings must be interpreted with caution. In addition, the studies used different flavonoid databases at varying stages of their 'development' which may have also contributed to varying outcomes; to this end, the known limitations of using databases to calculate dietary intake also apply.^{13,68} Further, dietary assessment tools also contribute to measurement error in the exposure.¹³ Many of the studies summarised in this review used FFQs, and many of these FFQs have not been validated specifically for flavonoids. Though, even if they were, such self-reported dietary data would still contain measurement error and this has long been acknowledged.^{147,148} Such uncertainty in exposure data translates into uncertainty of outcomes and biases associations towards the null raising the possibility of false-negatives. Thus, null findings may not necessarily predicate no association. Indeed, in meta-analyses of prospective cohorts, although often accompanied by statistically significant heterogeneity (likely from some of the aforementioned causes), an overall link between flavonoid-rich diets and IHD, cerebrovascular disease and total-CVD emerges.

As the temporal relationship between the exposures and outcomes reveals that reverse causality is unlikely attributable, this supports the presence of a beneficial association in favour of flavonoid intake. However, whether the associations represent a benefit of the isolated bioactives per se, or a signal of the bioactives working in concert with the co-occurring nutrient matrix within flavonoid-bearing foods, are issues of consideration.^{4,149–152} Moreover, whether beneficial associations between total flavonoid intake and CVD is driven by flavan-3-ols, the

966 principal subclass consumed in most populations, or whether it represents the breakdown of
967 several subclasses into common downstream bioactive metabolites, must be considered. Even
968 the biological rationale for examining individual subclasses is somewhat tenuous as differences
969 in the bioavailability and bioactivity of individual compounds within the same subclass is
970 observed. Indeed, a central limitation of quantifying flavonoid intake based on aglycones is
971 that the varying effects of different glycosides¹⁰ cannot be taken into consideration; this is best
972 investigated in clinical trials and animal studies. Thus, while the calculation and correlation of
973 aglycones with endpoints might be useful to obtain a broad overview of the relationships, there
974 are several caveats with this approach. Thus, the simple interpretation of the data to date, and
975 the one most relevant for dietary advice, is that consumption of flavonoid-rich foods or diets
976 higher in flavonoids, appear nutritionally beneficial in the prevention of CVD.

977 Although, if persons with higher flavonoid intakes tend to have other positive dietary habits,⁶¹
978 one may question whether associations observed can be attributable to flavonoid-rich foods or
979 whether these diets are simply a marker of higher diet quality overall. To address this issues,
980 one approach has been to add potential dietary confounders as covariates in multivariable
981 adjusted models, or to adjust for a “diet-quality” index. While the former approach is sensible
982 when the dietary confounders are not also a source of flavonoids, risk estimates arising from
983 models adjusting for flavonoid sources, such as fruits and vegetables, become difficult to
984 interpret. Using a different approach, Bondonno *et al.* report evidence of an association
985 between total flavonoid intake and all-cause mortality amongst participants in the highest fruit
986 and vegetable intake tertile, suggesting that there may be a benefit to recommending a diet rich
987 in flavonoids, above and beyond a diet rich in fruits and vegetables.⁶¹ This is reasonable as it
988 is possible to have a diet low in fruits and vegetables but high in flavonoids and vice versa.

989 Thus, the observed associations may not necessarily be a mere marker of higher overall diet
990 quality, although, we are unable to rule out this hypothesis. Yet, to this end, we postulate that

991 higher intakes of flavonoid-rich foods are likely one factor of a healthy diet, which when
992 coupled with other beneficial dietary habits, are likely to produce the greatest health benefits.

993 Comprehensive knowledge on the current state of the science is a prerequisite for hypothesis
994 formulation and the design and conduct of further research. This review traces the development
995 and advances of flavonoid epidemiology providing a broad overview and update on the current
996 state of the science. To the best of our knowledge we include all major studies (written in
997 English) and our general conclusions are in alignment with other reviews in the field, however,
998 we limit our scope to intake of total flavonoids and major subclasses and selected CVD
999 outcomes. To this end, a growing body of studies have also addressed individual flavonoid
1000 compounds and their relationship to CVD.^{61,153} These compounds may warrant further
1001 research, where intake is sufficiently variable and at potentially biologically relevant quantities
1002 in the populations being studied. To this end, a growing body of cohort studies have also
1003 recently addressed flavonoid intake and other CVDs or related risk factors, including, yet not
1004 limited to, risk of hypertension,^{154–156} type 2 diabetes,¹⁵⁷ and overweight and obesity,^{158,159}
1005 which in general, show a protective association across such non-communicable conditions
1006 related to CVD.

1007 In considering the design of further research, careful selection of lifestyle confounders is an
1008 issue of importance. This is because dietary intake may relate in a complicated manner to other
1009 social and behavioural determinants of disease. To date, most investigators have adjusted for
1010 age, sex (in mixed cohorts), body mass index, physical activity, and smoking history while,
1011 sometimes, indices of cardio-metabolic health, such as blood pressure, cholesterol and/or
1012 diabetes were incorporated. Not all studies adjusted for indices of socioeconomic status (SES),
1013 be it via education, income or profession. As flavonoid intake appears to be associated with
1014 SES, which is in turn associated with CVD,¹⁶⁰ there is reason to consider adjustment for SES
1015 in future studies. Though of course, confounders within cohorts will depend on the specific

1016 population recruited. Most authors adjusted for total energy intake, via either a standard
1017 multivariable model or another method (e.g. nutrient residual).¹⁶¹ However some authors
1018 presented models without energy adjustment, as it is thought that absolute consumption
1019 (adjusted for body size), may be more relevant than energy-adjusted values.^{51,61,62} Although
1020 these studies tended to additionally conduct sensitivity analysis with energy included.
1021 Adjusting for energy intake made no difference, however, the interpretation of the result
1022 changes. Considerable heterogeneity is found in the current literature with regards to the
1023 adjustment of other dietary factor, with many authors not considering dietary cofounders at all.
1024 Thus, residual confounding in this regard likely to vary between studies.

1025 Several knowledge gaps exist in the current evidence base; such gaps may need to be addressed
1026 if flavonoid epidemiology research is to inform dietary guidelines.^{70,162,163} There are only a few
1027 studies available on flavonoid intake and ischemic stroke as well as PAD and, as such, there is
1028 a need for further study in these areas. Moreover, although included under the umbrella of total
1029 CVD, flavonoid intake does not appear to be associated with atrial fibrillation,¹⁶⁴ or
1030 haemorrhagic stroke;¹³⁴ investigations targeting total ASCVD may be more appropriate than
1031 all-cause CVD, as flavonoids appear most relevant to CVDs with atherosclerotic origins.
1032 Including atrial fibrillation, which has a relatively high prevalence,¹⁶⁵ within total CVD
1033 outcomes plausibly dilutes the association with flavonoid intake. Findings from the Danish
1034 Diet Cancer and Health Study cohort also suggest that a high flavonoid intake may be most
1035 beneficial to populations at risk of CVD, namely smokers and high alcohol consumers.^{61,62}
1036 Although similar effect modification by smoking or alcohol intake was not observed in the
1037 Nurses' Health Study II or the REGARDS cohort;^{57,119} these analyses were specifically
1038 conducted in relation to IHD in contrast to total atherosclerotic CVD which was looked at in
1039 the Danish Diet Cancer and Health Study. A limitation of the Danish cohort is that the Danish
1040 population is more homogenous than many other countries, with most of the participants being
1041 Caucasian, limiting the generalizability of the findings to other ethnicities. Thus, further studies

1042 are warranted to determine whether similar associations exist in other ethnic groups. As the
1043 inverse association between flavonoid intake and CVD may be stronger in subgroups of
1044 smokers and high alcohol consumers, the associations between flavonoid intake and CVD may
1045 differ in cohorts that have a higher proportion of these individuals. To this end, modification
1046 of the flavonoid-CVD association by other potential effect modifiers has been explored in a
1047 limited number of cohorts. No effect modification was found by sex, race, physical activity,
1048 education, aspirin use, type 2 diabetes mellitus, or body mass index, however, at least one study
1049 reported effect modification by age.^{57,61,119,129,131} As a result, it is also likely that the
1050 associations between flavonoid intake and CVD may appear stronger in cohorts that have a
1051 higher proportion of older individuals. Other differences which may also affect the association,
1052 such as length of follow-up or geographical region, are of interest. However, a recent meta-
1053 analysis found no difference in results, when subgroup analysis was performed on studies with
1054 these differing attributes (i.e., studies with less or greater than 10 years of follow-up and
1055 Mediterranean compared to non-Mediterranean countries) however, the number of studies
1056 included was small (n = 5).¹⁰⁵ Corroboration of these findings in further samples is needed as
1057 is the examination of other potential effect modifiers.

1058 In the context of advancing flavonoid research, the prospective cohort study appears to be the
1059 most feasible design realistically available for examining dietary exposures with long-term
1060 disease outcomes.^{70,166,167} Though of course, large-scale RCTs, where-ever viable, would
1061 immensely facilitate progress in this field. One long-awaited RCT, involving >20,000
1062 participants, is the COcoa Supplement and Multivitamin Outcomes Study, which aims to
1063 examine the effect of flavan-3-ol intake on CVD outcomes, over 5 years of follow-up.¹⁶⁸
1064 Moving forward, the use of nutritional biomarkers or other innovative measures of flavonoid
1065 intake, in both RCTs and observational studies, provides a major future pathway for
1066 strengthening the investigation of flavonoids, by providing objective assessments of dietary
1067 intake or, in the case of biomarkers, further allowing for calibrated adjustment of subjective

1068 intake values.^{169–171} There is a crucial need for quality biomarkers of intake as a means of
1069 overcoming well-known FFQ and food database limitations.¹⁷² As well as being subjective and
1070 restricted, the use of FFQs to estimate flavonoid exposure does not allow for differences in
1071 metabolism between individuals to be taken into consideration. This is crucial as metabolism
1072 affects the levels of circulating bioactive downstream metabolites and may be key in explaining
1073 why some individuals benefit from the consumption of flavonoid-rich foods whilst others do
1074 not. Furthermore, many cohort studies do not have FFQ data. Indeed, several recent meta-
1075 analyses of prospective cohorts using (poly)phenol biomarkers and assessing CVD outcomes,
1076 have shown a paucity of studies using this approach.^{173,174} With the ever-growing progress in
1077 identifying biomarkers of flavonoid exposure,^{68,170} this approach is likely to usher in a new era
1078 of research, with a combination of dietary data and biomarkers likely being the most favourable
1079 approach. One recent example is a case-control study by Murphy *et al.*, whom used a newly
1080 developed method for quantifying 38 dietary (poly)phenols in plasma—seemingly the most
1081 comprehensive method for (poly)phenol biomarker assessment developed to date.^{175,176}
1082 Another important advantage of using biomarkers is their potential ability to capture exposure
1083 to foods and/or flavonoids, not included in food composition databases, such as food additives
1084 or dietary supplements.¹⁶⁷ However, biomarkers are not without their own limitations and
1085 readers are directed to several key reviews for further discussion.^{68,170,171}

1086 Future studies addressing several other limitations may also provide a more robust basis for
1087 evaluating the association between flavonoid intake and CVD. In prospective cohort studies
1088 lasting many years, repeated measures of dietary intake and other covariates would allow for
1089 cumulative exposures to be included, reducing regression dilution bias resulting from
1090 measurement error, and increasing confidence in the findings. One example can be seen in the
1091 Nurses' Health Study II by Cassidy *et al.*, where FFQs were collected every 4 years (as well as
1092 covariate data biennially) providing better estimates of average habitual flavonoid exposure
1093 (and covariate status) over the 18 year follow-up timeframe.^{56 56} Other improvements include

1094 increasing the reliability of the evidence base. Given the rising threat of the reproducibility
1095 crisis, cherry-picking and p-hacking,^{177–179} meta-analysis authors are encouraged to test for bias
1096 across all exposure-outcome assessments and are advised to include technical flavonoid experts
1097 on their team. While results of meta-analyses to date generally indicate that publication bias
1098 appears less prevalent in flavonoid research, both Hollman *et al.*,¹³³ and Wang *et al.*,¹³⁴ found
1099 evidence of publication bias, and thus caution is needed in interpreting the results on
1100 cerebrovascular disease. To facilitate improvements, epidemiologists are urged to adopt
1101 reporting guidelines for cohort studies,¹⁸⁰ and flavonoid-specific research,¹⁸¹ as well as
1102 consider open access databases, and the pre-registration of analysis plans for cohort studies,
1103 thereby improving transparency and the reproducibility of research practices.¹⁸²

1104 7. Conclusion

1105 Nutrition plays a critical role in preserving cardiovascular health and lowering the risk of major
1106 CVD. In the early 1990's, prospective studies began to emerge, reporting beneficial
1107 associations between a higher dietary flavonoid intake and a lower risk of CVD. Since this time
1108 a large volume of literature has accumulated. During the last ~25 years, the completeness of
1109 flavonoid-food composition databases have advanced substantially, although this brings with
1110 it inherent difficulty when cross-comparing (old and new) studies. This could explain some of
1111 the discrepancies between cohort studies, however difference in other cohort characteristics
1112 have likely also contributed. Differences in outcome definitions and the inclusion of total CVD
1113 cases, rather than those specifically of ASCVD, may have attenuated results, based on what is
1114 known on proposed flavonoid mechanism and atherosclerosis. Despite these limitations, the
1115 evidence from prospective cohort studies, when combined in meta-analyses, suggests, habitual,
1116 long-term moderate consumption of flavonoid-rich diets may be associated with lower risk of
1117 CVD. Specifically, the totality of evidence suggests a protective association between flavonoid
1118 intake and IHD, cerebrovascular disease and total CVD; disease outcomes which are

1119 principally, though not exclusively, composed of cases of ASCVD. Limited available evidence
1120 also suggests a role of flavonoids in mitigating the risk of PAD and ischemic stroke although,
1121 further research is required. Of the subclasses investigated, evidence for a protective
1122 association appears strongest for diets rich in anthocyanin, flavan-3-ol, and flavonol intake. If
1123 confirmed, these findings have important clinical and public health implications as flavonoids
1124 are common in foods and CVD is of major public health concern. A major future pathway in
1125 studies of flavonoid intake is the use of nutritional biomarkers, in combination with traditional
1126 food intake approaches. Future epidemiological research re-orientated towards the
1127 investigation of ASCVD may enhance the evidence base as flavonoids are primarily
1128 hypothesised to lower the risk of CVD of atherosclerotic origins.

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