1 **VEGETARIANISM AND VEGANISM VERSUS MENTAL HEALTH AND COGNITIVE**

2 **OUTCOMES. A SYSTEMATIC REVIEW AND META-ANALYSIS**

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29 **Abstract**

30 **Context:** Vegetarian and vegan diet become more popular. Although these diets are known to

31 ameliorate health, certain deficiencies might put these people at higher risk. Cognitive and mental health

32 are related diseases with high economic burden.

33 **Objective:** A meta-analysis on the relation of vegan or vegetarian diets with cognitive and mental

34 health.

35 **Data Sources:** PubMed, Scopus, Science Direct and Proquest databases were examined from the

36 beginning to July 2018.

37 **Study Selection**: Only original observational or interventional human studies on pure vegan/vegetarian

38 diets (excluding case-reports, studies without omnivorous control group, multi-lifestyle interventions

39 and eating disorders) were selected by two independent reviewers.

40 **Data Extraction:** Raw mean and standard deviation was taken for continuous outcomes while number

41 of events for categorical outcomes.

42 **Results:** From 1,249 hits, 13 articles were included on total 17,809 individuals. Most studies were

43 cross-sectional, two prospective and three interventional. Six studies included vegetarians, two vegans

44 and five both. Study quality was rather medium. No significant association was found for the continuous

45 depression score (n=9), stress (n=5), well-being (n=4) or cognitive impairment (n=3).

46 Vegans/vegetarians were at increased depression risk (odds ratio= 2.142[1.105, 4.148], n=2) and had

47 lower anxiety scores (mean difference=-0.847[-1.677, -0.018], n=7). Heterogeneity was large, thus

48 subgroup analyses showed a lot of contrasting significances with higher mental risks mainly in those

49 under 26y and in higher quality studies but no difference whether vegans versus vegetarians were

50 included.

51 **Conclusions:** More studies (especially on cognitive health) with overall better quality (e.g. adjusting

52 for confounders) are needed to make clear positive/negative associations.

53

54 **Keywords:** vegetarian diet, vegan, depression, anxiety, stress, memory, well-being, mental health,

55 cognition, dementia.

56 **Systematic Review Registration:** PROSPERO registration no. CRD42018097204

Introduction

Cognitive and mental disorders are critical public health issues.[1, 2] Among cognitive disorders, dementia is a worldwide problem with a current prevalence of 47.5 million people and the number will double every 20 years.[3] Among mental disorders, depression affects more than 300 million people and it is also linked with cognitive dysfunction and a higher risk for anxiety, stress and many other mental health issues. A poor mental health not only negatively affects a person's emotional and physical health but also productivity with more absenteeism, unemployment, and lower income. Mental health disorders accounted for a total economic burden of more than $1 trillion per year and dementia for $818 billion every year.[2]

Diet has been hypothesized to have an important role not only on physical health but also in cognitive and mental health issues.[4] For example, following a Mediterranean diet can reduce and even prevent cardiovascular disease, breast cancer, depression or cognitive decline.[5, 6] Vegetarian and vegan diets have also been widely associated with physical health outcomes, including a lower incidence and/or mortality from ischemic heart disease and incidence from total cancer[7] due to its high content of fiber, folic acid, vitamins C and E, potassium, magnesium, and many phytochemicals and a more unsaturated fat content.[8] Nevertheless, vegetarian and mainly vegan diets, might be deficient in vitamins B12, creatine and omega-3 fatty acids,[9-11] which have been found to be associated with neurodegenerative disease, cognitive impairment and poor mental health.[12-14] Also, the bioavailability of iron and zinc in vegetarian diets is poor because of their higher content of absorption inhibitors such as phytate and polyphenols and the absence of flesh foods.[15] Such deficiencies might lead to a lower mental health in vegetarians and vegans.[16]

Results in literature have been found to be controversial,[17-29] with some investigations showing positive associations of vegetarian and vegan diets with different mental health and cognitive outcomes[17, 19-21] and other studies showing an inverse association.[18, 25, 29, 30] Equivocal results in studies can be partially due to different definitions used to describe vegetarian and vegan diets (with some of the studies including the consumption of fish or chicken also as vegetarian); the special characteristics of the groups studied with a healthier lifestyle (i.e. Seventh Day Adventist)[31] or the variation in the years adopting a vegetarian or vegan diet.

85 Although the number of vegetarians and vegans worldwide is still low (except for India where around

86 one-third of the population is vegetarian),[32] most recent surveys have shown an increasing number of

87 vegetarians and vegans mostly in high income countries. In fact, the percentage of vegetarians or vegans

88 represents more than 10% of the total population in countries such as Australia, New Zealand, Israel or

89 Sweden.[33] Taking into account the rise of people adhering to these dietary practices and the

90 controversial literature on mental and cognitive outcomes, we aim to conduct a systematic review and

91 meta-analysis investigating the associations of vegetarianism or veganism with mental and cognitive

92 outcomes.

93

94 **Methods**

95 **Search strategy**

96 The present systematic review and meta-analysis was registered in the PROSPERO database (ID:

97 CRD42018097204) and followed the systematic review methodology proposed in the "Preferred

98 Reporting Items for Systematic reviews and Meta-analyses" (PRISMA) statement (Table S1 in the

99 Supporting Information online).[34, 35] A specific question was constructed according to the PICOS

100 (Participants, Interventions, Control, Outcomes, Study Design) principle (Table 1).[36]

101 A systematic search of the literature was carried out using PubMed, Scopus, Science Direct and

102 Proquest databases (from database inception to July 2018). When possible, the search included

103 Thesaurus (MESH terms in Pubmed). Firstly, the diet terms were combined as follows, "vegetarian"

104 OR "Vegan" OR "Vegetarians" OR "Diet, Vegetarian" OR "Diet, Vegan". Secondly, the mental and

105 cognitive outcome terms were combined as follows, "Cognition" OR "Cognitive" OR "Depression" OR

106 "Executive Function" OR "Anxiety" OR "Memory" OR "Mental health" OR "Psychological stress" OR

107 "Emotion". Finally, both the diet and the mental and cognitive outcome terms were combined with

108 "AND". In Scopus and Science Direct and Proquest these terms had to appear in the title, abstract or

109 keywords. The filters "humans", "articles" and "in English, Spanish, French, Italian and Portuguese"

110 were applied when possible. Two reviewers independently (I.I and N.M) examined each database to

111 obtain publications. Agreement between reviewers was found in 90% of the publications while

112   remaining inter-reviewer discrepancies were resolved by consensus. Relevant articles were obtained in

113   full and assessed against the inclusion and exclusion criteria described below.

114

115   **Inclusion criteria**

116   The inclusion criteria were as follows: 1) original studies; 2) studies performed in humans; 3) studies

117   written in English, Spanish, French, Italian or Portuguese; 4) studies including vegetarian (lacto-ovo-

118   vegetarian; ovo-vegetarian or lacto-vegetarian) or vegan diets as exposures; 5) studies including raw

119   data on mental or cognitive outcomes (i.e. mean and standard deviation for continuous variables and

120   cases and events for categorical outcomes). In the present study, vegetarians and particularly lacto-ovo-

121   vegetarians were defined as those who excluded meat, fish and seafood but not milk and dairy products

122   from their diet; vegans were defined as those who excluded any kind of animal product.

123

124   **Exclusion criteria**

125   The exclusion criteria were as follows: 1) articles that did not provide original data (e.g. systematic

126   reviews, meta-analysis, literature reviews); 2) case reports; 3) articles that did not present data regarding

127   the control group (omnivores), and 4) studies in which several interventions were carried out (i.e.

128   vegetarian or vegan diet combined with an increase in physical activity levels) making it impossible to

129   separate the individual effect of diet and 5) studies with eating disorders as an outcome due to causality.

130

131   **Data extraction**

132   After reviewing all the relevant literature, depression, anxiety, stress, mental-health/well-being and

133   mood disturbances for mental health and dementia/memory impairment for cognitive measurements

134   were identified as outcomes for the present meta-analysis. For each study that included a mental health

135   or cognitive outcome, relevant data was extracted (see Table 2)[17] including number of participants, sex,

136   mean age, type of diet (e.g. vegetarian, vegan or omnivores diet), instruments used to assess the

137   outcomes, study design and quality assessment. Instruments to assess the outcomes were self-reported

138   or diagnosed by a specialist, with different tools to evaluate **depression**: Depression Anxiety Stress

139   Scales, DASS-Depression (DASS-D), Center for Epidemiologic Studies Depression (CESD), Hamilton

140   Rating Scale for Depression (HRSD) and Edinburgh Post Natal Depression Scales (EPDS); **anxiety**:

141   DASS-Anxiety (DASS-A), State-Trait Anxiety Inventory (STAI); **stress**: DASS-Stress (DASS-S) or

142   36-Item Short Form Health Survey (SF-36), used to assess depression, anxiety and mental health; **mood**

143   **disturbances**: Profile of Mood States (PMHS); **mental health**: Positive Mental Health Scale (PMHS)

144   and **dementia/memory impairment**: Mini-Mental Status Examinations (MMSE). Other information

145   extracted was whether the papers included any confounders or used raw data; possible differences

146   between groups in relevant confounders (i.e. vegan and vegetarians were usually more physically active,

147   had a lower Body Mass Index (BMI) and a higher education and were less likely to be married than

148   omnivores); the period of time for which the vegetarian or vegan diet had been followed; country or

149   countries in which the study took place and predominant ethnicity if reported.

150   Mean and standard deviation (SD) was taken for continuous outcomes while number of events in each

151   group (i.e. number of depressions diagnosed in vegetarian and vegan vs. omnivores) for categorical

152   outcomes. Only raw data (unadjusted) was used to perform the meta-analyses as only two papers in the

153   present meta-analysis included adjusted data.[23, 29] Reporting unadjusted estimates also reduces the bias

154   of selective reporting of adjusted estimates in primary studies and the risk of over-adjustment with

155   multiple confounders. When a study offered information about matched and non-matched data the

156   matched data was taken for our analysis.

157

158   **Quality assessment**

159   Depending of the study design, the "Quality Assessment Tool for Observational Cohort and Cross-

160   Sectional Studies"[37] or the "Quality Assessment Tool of Controlled Intervention Studies"[38] provided by

161   the National Heart, Lung, and Blood Institute was used to assess the quality of the included studies.

162   Two reviewers (I.I and N.M) independently assessed and thereafter discussed the quality of the studies.

163   Agreement between reviewers was found in 90% of the publications and inter-reviewer discrepancies

164   were resolved by consensus.

165   **Search summary**

166   A total of 1,249 articles were extracted from Pubmed, Scopus, Proquest and Science Direct. After

167   eliminating all the duplicates, 911 manuscripts were evaluated. Thereafter, 857 records were excluded

168   by title and abstract reading and 54 full-text articles were assessed for eligibility (see Figure 1): 13

169   articles were discarded because they did not include a pure vegetarian or vegan diet (i.e. flexitarians or

170   self-reported vegetarians reporting to eat fish)[13, 30, 39-49]; 11 studies had a different objective than the one

171   of our meta-analysis[50-60]; 6 did not include a control group (omnivorous group) to compare the mental

172   or cognitive outcome[61-66]; 4 had eating disorders as a mental health outcome[67-70]; 3 were conducted in

173   unhealthy subjects (i.e. papers in which participants reported to have eating disorders before starting

174   the diet)[71-73], 1 did not provide raw data to extract[60, 74]; 2 were not pure diet interventions in which we

175   could separate individual dietary effects[75, 76]; 1 was not an original article.[77] The main author was

176   contacted in case the manuscript did not provide raw or adjusted data and to clarify blurred definitions

177   of diets. Also, the main author was contacted in case mixed diets had been reported in the same group

178   to ask for the separated data if available (i.e. vegetarian, vegan and pescatarian were reported in the

179   same group), which was possible for one study that was included.[29]

180

181   **Statistical analyses**

182   All analyses were performed using Open Meta [Analyst] software. For continuous outcomes,

183   information on sample size, mean and standard deviation (SD) was taken and for categorical outcomes

184   number of events in each group mean and SD were extracted for meta-analysis. When the SD was not

185   reported in the study, the authors were first contacted and if no response[19], the following formula were

186   applied: Standard Error=SD/$\sqrt{n}$; SD=interquartile range/1.35. When the mean was not reported in the

187   studies, the median was used.[20] The mean difference (MD) and the relative risks (RRs) or odds ratio

188   (OR) with a 95% CI were calculated for continuous and categorical data respectively. DerSimonian and

189   Laird estimators using random effects models were applied for continuous and categorical data. Effect

190   sizes were calculated for each outcome. When possible, subgroup analyses were conducted.

191   Sources of heterogeneity were investigated by subgroup analyses comparing results based on age (<=25

192   years old, 26-45 years old or >45, or NR -not reported-); sex (women, men, mainly women, men and

193   women); the period of time for which the vegetarian or vegan diet had been followed (short term period:

194   <1 year, long term: ≥1 year or NR); diet (vegetarians or vegans), instrument used to assess the mental

195   or cognitive outcome and quality assessment when information was available (<50 score versus >=50

196   score). The heterogeneity of the studies was tested using the I^2 statistic.[78] This statistic describes the

197   variance between studies as a proportion of the total variance. A value <25% indicated low

198   heterogeneity, from 25 to 50% moderate, from 50 to 75 high heterogeneity, and >75% very high

199   heterogeneity. The associated p-value of the heterogeneity of the studies was also calculated, with a

200   non-significant result indicating absence of heterogeneity.

201   To investigate publication bias, we conducted funnel plots using RevMan (version 5.2). Additionally,

202   publication bias was assessed by Egger's linear regression test following the indications provided by

203   Peters et al.[79] Therefore, funnel plots and tests were carried out when the meta-analysis had above ten

204   studies because a small number of studies lowers test power to a point where it is too low to distinguish

205   chance from real asymmetry.[80]

206

207   **Results**

208

209   **Description of the included studies**

210   After applying the exclusion criteria, a total of 13 articles[17-29] was included in this review: 11 covered

211   outcomes of depression (9 as continuous and 2 as categorical); 8 outcomes of anxiety (7 as continuous

212   and 1 as categorical); 5 on stress; 4 included mental health/well-being outcomes (continuous), 3

213   outcomes of memory impairment/Alzheimer (categorical); 2 outcomes of mood disturbances

214   (continuous), 1 outcomes of neuropsychiatric problems (categorical), 1 outcomes of personality change

215   (Figure 1)[17-29].

216   The present meta-analysis encloses 17,809 individuals. The mean age of the participants varied from

217   18 to 80 years old and most of the studies equally distributed the sample between omnivores and

218   vegetarians/vegans. Most of the studies considered both women and men (although with a higher

219   participation of women than men) or only women. Of all eligible studies, 46% (6/13) included

220   vegetarians, 15% (2/13) were conducted in vegans and 38% (5/13) included both vegetarians and

221   vegans. Most studies (62%, 8/13) were conducted in the United States, 1 in Australia, 1 in Pakistan, 1

222   in Finland, 1 in Puerto Rico, 1 included both countries Germany and China. The study design was

223   mostly cross-sectional (62%, 8/13), 2 were prospective, 2 were randomized clinical trials and 2 were

224   non-randomized trials (Table 2). Most of the studies in the present meta-analysis were of medium

225   quality with points varying between 28 and 64 on a scale of 100 (Table S2 and S3).

226

227   **Mental health differences between vegetarians/vegans and omnivores**

228   Figure 2 to 7[17-29] show the individual study results and plot the global effect of vegetarianism/veganism

229   on mental health and cognitive outcomes as well as several subgroup analyses. Several specific sub-

230   group analyses were not performed due to a lack of studies (subgroups with only 1 or 2 studies in one

231   of the groups).

232

233   **Depression (continuous)**

234   As shown in Figure 2a, no statistically significant differences were found between vegetarian or vegan

235   diets and omnivores regarding the incidence of depression (MD = -0.532; 95% CI: -2.047, 0.984).

236   Heterogeneity among studies for depression was very high (I^2 =92.53; p = 0.040).

237   Results of the subgroup analysis showed a statistically significant higher depression level in

238   vegetarians/vegans under 26 years old (MD= 1.737; 95% CI: 0.757, 2.717; Figure 2b), in female

239   vegetarians/vegans (MD= 2.910; 95% CI: 0.876, 4.944; Figure 2c) or studies with higher quality (MD=

240   1.418; 95% CI: 0.473, 2.363; Figure 2g). Subgroup analyses on period following the diet (Figure 2d),

241   vegan vs vegetarian (Figure 2e), or used instrument (Figure 2f) did not show significant differences in

242   comparison with the control group. Heterogeneity was more pronounced in those over 25 years old (I^2

243   =93.22; p<0.001), in studies that included mainly women (I^2 =94.29; p<0.001), short-term studies (I^2

244   =97.87; p<0.001), studies including vegans (I^2 =95.10; p<0.001), when using instruments different from

245   DASS or CESD (I^2 =98.12; p<0.001) and lower quality studies (I^2 =93.62; p<0.001).

246

247   **Depression (categorical)**

248   As shown in Figure 3a, vegetarians and vegans had a higher risk of depression when using a categorical

249   variable (OR = 2.142; 95% CI: 1.105, 4.148) but heterogeneity among studies was high (I^2 =65.4; p =

250   0.089).

251

Anxiety (continuous)

Vegetarian and vegan diets were associated with lower levels of anxiety (MD = -0.847; 95% CI: -1.677, -0.018) but heterogeneity among studies was very high (I^2 =92.08; p = 0.001) (Figure 4a).

Results of the subgroup analysis confirmed these lower anxiety levels in vegetarians/vegans 26-45 years old (MD= -3.144; 95% CI: -4.728, -1.561; Figure 4b), in studies including predominantly women (MD= -0.744; 95% CI: -1.461, -0.026; Figure 4c), when not using DASS-A as instrument (MD= -5.940; 95% CI: -7.704, -4.175; Figure 4f) or in lower quality studies (MD= -3.144; 95% CI: -4.728, -1.561; Figure 4g). In contrast, higher levels of anxiety were detected in vegetarian/vegans younger than 26 years (MD= 0.901; 95% CI: 0.143, 1.658; Figure 4b) and higher quality studies (MD= 0.909; 95% CI: 0.158, 1.660; Figure 4g). Subgroup analyses on period of following the diet or vegan versus vegetarian did not show any significant differences with the control group (Figure 4d, Figure 4e). Heterogeneity was more pronounced in those under 26 years old (I^2 =92.27; p<0.001), in studies that included women and men (I^2 =93.86; p<0.001), in studies that did not report the period following the diet (I^2 =94.94; p<0.001), studies including vegetarians (I^2 =93.35; p<0.001), when using DASS as an assessment instrument (I^2 =98.12; p<0.001) and higher quality studies (I^2 =89.79; p<0.001).

Stress (continuous)

Vegetarian and vegan diets did not show any statistically significant associations with stress (MD = -0.422; 95% CI: -1.823, 0.979). Heterogeneity among studies for stress was very high (I^2 =82.71; p = 0.001) (Figure 5a).

Results of the subgroup analysis showed lower stress levels in vegetarians/vegans 26 to 45 years old in comparison with omnivores (MD= -2.178; 95% CI: -3.538, -0.818), and in low quality studies (MD= -2.178; 95% CI: -3.538, -0.818; Figure 5f). In contrast, higher stress levels were found in younger vegetarians/vegans compared to omnivores (MD=1.033; 95% CI: 0.478, 1.587; Figure 5b) and in higher quality studies (MD= 1.005; 95% CI: 0.452, 1.559; Figure 5f). The results did not differ by sex (Figure 5c), the period following the diet (Figure 5d) or by vegan versus vegetarian (Figure 5e). Subgroup analyses by instrument were not conducted because all studies used DASS-S.

279   Heterogeneity was more pronounced in adults from 26 to 45 years old (I^2 =49.24; p = 0.139), in studies

280   that included mainly women (I^2 =83.14; p<0.001), in studies that did not report the period following the

281   diet (I^2 =89.31; p<0.001), studies including vegetarians (I^2 =78.17; p = 0.001) and low quality studies

282   (I^2 =49.24; p = 0.139).

283

284   **Mental health/well-being (continuous)**

285   As shown in Figure 6a, being a vegetarian or vegan was not statistically significantly associated with

286   levels of well-being (MD= -1.319; 95% CI: -2.834, 0.197) and heterogeneity among studies was high

287   (I^2 =73.62; p = 0.004).

288   Based on subgroup analyses, lower mental health/well-being levels were found in vegetarians/vegans

289   under 26 years old (MD= -1.967; 95% CI: -2.924, -1.011; Figure 6b), when the studies included both

290   men and women (MD= -1.480; 95% CI: -2.134, -0.826; Figure 6c), when the years of diet adherence

291   was not specified (MD= 1.967; 95% CI: -2.924, -1.011; Figure 6d) and in higher quality studies (MD=

292   1.967; 95% CI: -2.924, -1.011; Figure 6d).

293   Heterogeneity was more pronounced in those participants under 26 years old (I^2 =55.22; p = 0.107), in

294   studies that included mainly women (I^2 =83.14; p<0.001), in studies that did not report the period

295   following the diet (I^2 =55.22; p = 0.107), studies including vegans (I^2 =81.44; p = 0.005) and in low

296   quality studies (I^2 =84.93; p = 0.001).

297

298   **Other mental health outcomes**

299   A meta-analysis was not conducted on other mental health outcomes due to the insufficient quantity of

300   studies (n=1 or 2). However, Beezhold et al. concluded that vegetarians reported significantly less

301   negative emotion than omnivores.[19, 20] On the contrary, Kapoor et al. reported higher neuropsychiatric

302   problems (psychosis and personality change) in young vegetarians compared to omnivores and Baines

303   found that vegetarians had significantly higher panic attacks or palpitations, deliberate self-harm and

304   other psychosomatic problems.[25]

305

306   **Memory impairment/dementia**

307 Vegetarian and vegan diets did not show any statistically significant associations with memory

308 impairment when compared to omnivores (OR = 0.825; 95% CI: 0.242, 2.809) and heterogeneity among

309 studies was very high (I^2 =63.13; p = 0.066) (Figure 7a).

310

311 **Publication Bias**

312 No indication for publication bias was found for studies including depression (Egger *P*=0.230) and

313 anxiety (Egger *P*=0.324). Also, visual inspection of the funnel plot did not suggest publication bias for

314 neither depression nor anxiety as the studies were distributed symmetrically (i.e. inverted funnel shape)

315 around the summary effect size (Supplementary Figure 1 and 2).

316

317 **Discussion**

318 **Overall findings**

319 To date no previous systematic review or meta-analysis has been conducted on the associations between

320 vegetarianism or veganism and mental and cognitive outcomes. We could not find a significant effect

321 of being vegetarian/vegan for the continuous depression score (n=9), stress (n=5), well-being (n=4) or

322 cognitive impairment (n=3) but vegans/vegetarians were at increased depression risk (OR = 2.142; 95%

323 CI: 1.105, 4.148, n=2) and showed higher levels of anxiety in this younger age while older adults had

324 lower anxiety scores (MD = -0.847; 95% CI: -1.677, -0.018, n=7). Heterogeneity was large, thus

325 subgroup analyses showed a lot of contrasting significances. For all tested outcomes, higher mental

326 risks were found in those under 26y and in higher-quality studies. Concerning the instruments used,

327 often no differences existed and only lower anxiety levels were found when not using the specific

328 DASS-A. Inconsistent sex-patterns appeared: more depression symptoms were seen only in female

329 vegetarians/vegans, while lower anxiety symptoms were shown only in studies including predominantly

330 women above the age of 26. Lower wellbeing was only seen in studies including both men and women.

331 Finally, no differences were detected depending on whether vegans versus vegetarians were included

332 or on the amount of years diet adherence.

333 Vegetarian and vegan diets have been found to be a protecting factor for many chronic diseases such as

334 heart disease, hypertension, type 2 diabetes, obesity, and some cancers such as colorectal and prostate[81].

335 This might be because of the healthier diet intake with higher fiber, polyunsaturated fats, vitamin C,

336 bioactive molecules and a lower intake of saturated fats. All these nutrients act directly or indirectly

337 (via other diseases) to an anti-inflammatory status.[82] Moreover, vegetarians and vegans seem to have a

338 healthier lifestyle: higher levels of physical activity and lower levels of sedentarism, alcohol and

339 tobacco consumption.[83] Nevertheless, our meta-analyses indicated the potential of negative mental

340 health outcomes in a vegetarian/vegan diet. Despite of benefits, several investigations have indeed

341 identified nutrient deficiencies among vegetarians and vegans[18, 84, 85] that are related to poorer mental

342 health outcomes.[18, 22, 25, 26]

343 Subgroup analyses showed clear age-dependent patterns with negative effects at a young age while

344 opposite effects in those older than 25. This might reflect that young people are more vulnerable to

345 deficiencies since their brain and personality are still in development.[86] While women are often more

346 sensitive to mental problems, no such consistent sex-patterns appeared in our study. Similarly, vegan

347 subjects often have more difficulties in preventing nutrient deficiencies but no higher risk for vegans

348 versus vegetarians was detected in subgroup analyses. Since information on the duration of diet

349 adherence was often lacking or imprecise, the lack of subgroup differences depending on diet adherence

350 duration is not surprising.

351

352 **Possible mechanisms involved in these associations between vegetarian/vegan diets and mental**

353 **health outcomes**

354 Large heterogeneity was found in the link of vegetarianism and veganism with mental health outcomes:

355 several non-significant findings, lower risk for anxiety but higher risk for depression and age dependent.

356 In general, higher quality studies and studies in populations <25y suggested a higher risk of all types of

357 mental problems in vegetarians and vegans compared to omnivores.

358 A first possible explanation for these associations is a reverse causal relationship between vegetarianism

359 or veganism and mental health outcomes: individuals who have psychosocial disorders are more eager

360 to follow a vegetarian or vegan diet in order to improve their mental health. Based on age of diet

361 adoption in a German study, the adoption of vegetarian diets was after the onset of mental disorders

362 thus confirming the possibility of reverse causation.[42] Still, one intervention study found an

13

363　improvement in depression, anxiety and mood after following a vegan diet,[17, 20] while another found

364　only improvements in stress but no significant changes in depression, anxiety or mood.[19] These

365　interventions, however, have been conducted for only a short period (less than 4 months) and effects

366　during a longer period have not yet been investigated. As mental health problems often develop at young

367　age, our subgroup analysis showing higher risk in those younger than 25 might reflect this reverse

368　causation, apart from the fact that young people are more vulnerable to deficiencies. Other possible

369　explanations yielded in the literature are the nutrient deficiencies that are common in vegan diets (such

370　as some amino acids, long chain omega 3 fatty acids, vitamin B6 and B12, zinc and creatine and even

371　too low cholesterol) that could accelerate or worsen pre-existing mental conditions.[8] All these

372　deficiencies have been found to be linked with a higher risk of mental health problems[87, 88]. Several

373　amino-acids like methionine, tryptophan, lysine, arginine, beta-alanine and tryptophan can have a

374　protective effect on depression and on anxiety[89, 90] as derived neurotransmitters like dopamine and

375　serotonin are important neurotransmitters in mood regulation.[91] Still the story is more nuanced since

376　the levels of methionine, tryptophan and tyrosine were highest in fish-eaters and vegetarians, followed

377　by meat-eaters, but lowest in vegans.[92] Thus the amino-acid deficiencies would mainly be an

378　explanation for health effects in vegans only.

379　Another possible explanation could be that vegetarians or vegans belong to a minority group (at least

380　until recently since the prevalence is skyrocketing the last years) and being a minority can induce

381　feelings of lower well-being.[22]

382

383　**Possible mechanism of the results found in cognitive outcomes**

384　We did not find a statistically significant result between following a vegetarian/vegan diet and cognitive

385　outcomes in the two existing studies, while Giem et al. found a trend toward delayed onset of dementia

386　in vegetarians,[23] Kapoor et al. found higher neuropsychiatric and neurological problems such as

387　memory impairment, personality change, and psychosis in vegetarians. Studies that were not included

388　(because of vegetarian definition problems) were also conflicting: Xu et al. found a higher risk of

389　memory impairment and dementia in vegetarians,[48] while in another study vegetarians responded better

390　than meat-eaters in memory tasks but for other cognitive domains no differences were observed,[14] and

macrobiotic (similar to vegan diets but fish eaten occasionally) adolescents performed worse on most cognitive tests than omnivores.[13]

The apparently contradictory results might be explained by differences in vitamin B12 values. Vegetarians had lower vitamin B12 (and 50% had a deficiency) compared to omnivores in Kapoor's study where higher cognitive risks for vegetarians were found. In the macrobiotic study, vitamin B12 levels were indeed associated with lower performance for certain cognitive tests and not all macrobiotic subjects had deficiency. The other studies did not report serum vitamin B12 profiles.[23,48] A second possible mechanism cited in the literature is the role that phytoestrogens play in cognitive function. Phytoestrogens are the most bioactive components of soy (a product mainly eaten by vegetarians and vegans) that seem to have a neuroprotective effect.[93] Creatine is another nutrient that plays a critical role in brain development and function. Some papers have hypothesized that it aids cognition by improving energy supply and neuroprotection. Creatine is a peptide found mostly in meat, fish and other animal products, and the levels of muscle creatine are known to be lower in vegetarians. After supplementation of creatine, the memory of vegetarians was better than that of meat-eaters. However, at baseline, memory did not differ depending on dietary style, so any hypothesised creatine deficiency in vegetarians did not influence memory, rather it was found that vegetarians were more sensitive to supplementation with creatine.[51]

Strengths and weaknesses of this meta-analysis

To the best of the authors' knowledge, this is the first meta-analysis to examine the association between vegetarianism/veganism and mental health and cognitive outcomes. An advantage is that these outcomes were interpreted quite broadly while both categorical as well as continuous variables were considered. This study also included many subgroup analyses (by diet, age, sex, instrument, period following the diet and quality assessment score) to detect heterogeneity that might reflect more vulnerable subgroups and methodological issues. This allowed us to estimate the total effect size of the vegan and vegetarian diets on mental health and cognitive outcomes with a larger sample size despite the large heterogeneity in the included studies.

418 A first limitation is that there are no studies including children and most of the studies included a higher

419 percentage of women than men. Secondly, there were only a few interventional studies and some of

420 them with a low-quality score had a short intervention period (i.e. 2 weeks) hindering the detection of

421 long-term consequences on cognition or mental health. Although many studies have described

422 important differences in lifestyle among vegetarians and vegans compared to omnivores (lower BMI,

423 higher levels of physical activity and lower levels of sedentarism, alcohol and tobacco consumption),

424 only two studies took into account key potential confounders.[23, 29] Consequently, the meta-analysis was

425 conducted on raw data only. Nevertheless, adjustment for confounders did not drastically change results

426 in these two studies. Moreover, many relevant articles were finally discarded since they wrongly used

427 the term vegan or vegetarian (i.e. they ate fish or poultry) or they self-reported to be vegetarians or

428 vegans but in the food frequency questionnaire meat and fish were occasionally eaten.[30, 40, 42, 48] The

429 large variety in used instruments/approaches to define vegetarian/vegan limits comparability and power

430 to find significant relationships. Although it might be interesting to test the situation in pesco-

431 vegetarians (to see whether outcomes might be due to fish omission), only 3 studies identified pesco-

432 vegetarians and this was always a minority group mixed with those having a pure vegetarian diet.

433 Another group that was discarded in our systematic review was eating disorders as mental health

434 outcome. Although vegetarians and vegans were more likely to suffer from eating disorders compared

435 to omnivores in some studies[39, 68], we discarded these due to the fact that vegetarian/vegan diets can be

436 a camouflage of an existing eating disorder.[94] Finally, subgroup analyses were based on a small quantity

437 of studies and might thus be biased or lack power.

438

439 **Implications for public health**

440 The necessary protein, fat, carbohydrate, vitamin and mineral intake within vegetarian and vegan diets

441 for optimal health is still under investigation. Vegetarians and particularly vegans may require

442 supplementation as the nutrients may not be adequately available from plant sources. Some supplements

443 (such as vitamin B12, zinc or creatine) to improve short term memory and intelligence/reasoning may

444 help in very restricted diets. Otherwise, a well-chosen plant-based diet provides all the necessary

445 protein, fats, carbohydrates, vitamins and minerals for optimal health. Apart from the strict omission of

16

animal-based protein, dietary patterns can also be considered on a continuous scale where the amount of animal-based protein is just limited.[95] The terms semi-vegetarians, flexitarians, and plant-based diets reflect the decrease of animal-based proteins[96], which might perhaps bring the advantages without the difficulties of preventing deficiencies in a vegetarian diet. A 6-19% reduction in the risk of all-cause mortality and cardiovascular disease mortality was found by replacing 3% of energy from animal protein with plant protein.[97]

Implications for further research

Drawing conclusions is difficult when there is a lack of studies, when different instruments/definitions are used or when study quality is low. A major flaw in current literature on this topic is the adjustment for confounders. Future studies should adjust for sociodemographics, physical activity, alcohol and tobacco consumption, weight status and medical history. To draw causal conclusions, well-designed intervention studies are needed as we could only find 3 interventions where often participants differed at baseline, there was low intervention adherence and only short-term interventions. In finding causal pathways, studies should measure nutrient status as deficiencies are frequent in vegetarian/vegan diets. Moreover, different gradients of plant-based diet should be examined e.g. the role of fish (with omega-3 fats), milk, eggs and quality of plant-based foods (omission of meat or any other animal-product does not guarantee high-nutritious choices). Herein, the duration of diet adherence is seldom examined.

Conclusion

Based on our meta-analysis, following a vegan or vegetarian diet was associated with a higher depression risk and in those under 26y with higher anxiety scores but no differences for the other outcomes were found. Subgroup analyses showed a lot of contrasting significances with higher mental risks mainly in those under 26y and in higher quality studies. Large heterogeneity impeded us to draw definitive conclusions. More studies in mental health and especially on cognitive outcomes with overall better quality are needed to derive clear positive/negative associations.

Acknowledgments

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