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2 **A prospective diet-wide association study for risk of colorectal cancer in EPIC**

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85 **Abstract** (max 260 words, structured)

86 **BACKGROUND & AIMS:** Evidence regarding the association of dietary exposures with  
87 colorectal cancer (CRC) risk is not consistent with a few exceptions. Therefore, we conducted  
88 a diet-wide association study (DWAS) in the European Prospective Investigation into Cancer  
89 and Nutrition (EPIC) to evaluate the associations between several dietary exposures with CRC  
90 risk.

91 **METHODS:** The association of 92 food and nutrient intakes with CRC risk was assessed in  
92 386,792 participants, 5,069 of whom developed incident CRC. Correction for multiple  
93 comparisons was performed using the false discovery rate, and emerging associations were  
94 examined in the Netherlands Cohort Study (NLCS). Multiplicative gene-nutrient interactions  
95 were also tested in EPIC based on known CRC-associated loci.

96 **RESULTS:** In EPIC, alcohol, liquor/spirits, wine, beer/cider, soft drinks, and pork were  
97 positively associated with CRC, whereas milk, cheese, calcium, phosphorus, magnesium,  
98 potassium, riboflavin, vitamin B6, beta-carotene, fruit, fibre, non-white bread, banana, and total  
99 protein intakes were inversely associated. Of these 20 associations, 13 were replicated in  
100 NLCS, for which a meta-analysis was performed, namely alcohol (summary HR per 1 SD  
101 increment in intake: 1.07; 95%CI:1.04-1.09), liquor/spirits (1.04; 1.02-1.06), wine (1.04;1.02-  
102 1.07), beer/cider (1.06;1.04-1.08), milk (0.95;0.93-0.98), cheese (0.96;0.94-0.99), calcium  
103 (0.93;0.90-0.95), phosphorus (0.92;0.90-0.95), magnesium (0.95;0.92-0.98), potassium  
104 (0.96;0.94-0.99), riboflavin (0.94;0.92-0.97), beta-carotene (0.96;0.93-0.98), and total protein  
105 (0.94;0.92-0.97). None of the gene-nutrient interactions were significant after adjustment for  
106 multiple comparisons.

107 **CONCLUSIONS:** Our findings confirm a positive association for alcohol and an inverse  
108 association for dairy products and calcium with CRC risk, and also suggest a lower risk at

109 higher dietary intakes of phosphorus, magnesium, potassium, riboflavin, beta-carotene and  
110 total protein.

111 **KEYWORDS:** nutrition; cohort study; colorectal cancer; epidemiology

112 **ABBREVIATIONS:** BMI: Body mass index; CI: Confidence interval; CRC: Colorectal  
113 cancer; EPIC: European Prospective Investigation into Cancer and Nutrition; FDR: False  
114 discovery rate; GWAS: Genome-wide association study; HR: Hazard ratio; MR: Mendelian  
115 Randomization; NLCS: the Netherlands Cohort Study; DWAS: Diet-wide association study;  
116 SNP: Single nucleotide polymorphism; WCRF: World Cancer Research Fund; WGS: Whole-  
117 genome sequencing.

118 Colorectal cancer (CRC) is the third most common type of cancer worldwide with over  
119 1.8 million new cases and over 800,000 deaths in 2018<sup>1</sup>. The incidence rates are higher in high  
120 income countries, but there has been a recent large increase in the rates in low- and middle-  
121 income countries potentially due to the “westernization” of these societies<sup>1</sup>. Several aspects of  
122 the Western lifestyle such as obesity and lack of physical activity are well-established risk  
123 factors of CRC<sup>2, 3</sup>, but evidence regarding diet, and in particular the association of specific  
124 foods and nutrients with CRC is not consistent, with a few exceptions<sup>4</sup>. The World Cancer  
125 Research Fund (WCRF) third Expert Report identified strong evidence that consuming  
126 processed meat, red meat, and alcohol increases risk of CRC, whereas consumption of whole-  
127 grains, foods containing dietary fibre, and dairy products lowers CRC risk<sup>4</sup>. Associations for  
128 other foods and nutrients and CRC risk exist, but are inconsistent and currently provide limited  
129 evidence according to WCRF<sup>4</sup>.

130 The aim of this study was to systematically examine the associations between a wide  
131 set of dietary factors and risk of CRC in the European Prospective Investigation into Cancer  
132 and Nutrition (EPIC) and the Netherlands Cohort Study (NLCS), by conducting a diet-wide  
133 association study (DWAS)<sup>5</sup>. The DWAS takes an analogous strategy to that of a genome-wide  
134 association study (GWAS) by separately estimating associations for each food and nutrient,  
135 using adjustments for multiple comparisons, and replicating promising associations in an  
136 independent study.

## 137 **Methods**

### 138 **Study populations**

139 EPIC is a large European multicentre prospective cohort that consists of 521,324  
140 participants, mostly aged between 35 and 70 years, recruited between 1992 and 2000 from 23



141 centres across 10 European countries<sup>6</sup>. A total of 386,792 participants (71% women) were  
142 included in the present analysis after pertinent exclusions (supplementary methods).

143 NLCS is a prospective cohort study of 120,852 participants, aged between 55 and 69  
144 years and recruited in 1986 from 204 computerised population registries across the Netherlands  
145 that uses a case-cohort approach<sup>7</sup>. Of the 5,000 subcohort participants, 3,893 were included in  
146 the current analysis after pertinent exclusions (supplementary methods).

### 147 **Assessment of dietary factors**

148 In EPIC, consumption of foods over the last 12 months was assessed at baseline using  
149 validated country-specific food questionnaires<sup>6</sup>. In total, 92 dietary factors (63 foods and 29  
150 nutrients) were included in the current analysis.

151 In NLCS, information on dietary intake over the preceding 12 months was assessed at  
152 baseline using a semi-quantitative 150-item food frequency questionnaire, which has been  
153 validated and tested for reproducibility<sup>8</sup> (supplementary methods).

### 154 **Identification of colorectal cancer cases**

155 In EPIC and NLCS, incident CRC cases were identified by record linkage with  
156 population-based cancer registries or a combination of registries, insurance records and active  
157 follow up of the study participants or their relatives. More details are provided in the  
158 supplementary methods.

### 159 **Statistical analyses**

160 In EPIC, separate Cox proportional hazards regression models were used to investigate  
161 the associations between each of the dietary factors with CRC risk. In NLCS, given the case-  
162 cohort design, Prentice weighted Cox proportional hazards regression models with robust  
163 standard error estimation were implemented<sup>9</sup>. All of the models were adjusted for: total energy  
164 intake; smoking; body mass index (BMI); physical activity; diabetes history; level of education

165 and family history of CRC (in NLCS only) and further stratified by sex, age and in EPIC also  
166 by centre.

167 To account for multiple comparisons, the false discovery rate (FDR) adjusted *P* values  
168 (or *q* values) were estimated for each association analysed<sup>10</sup>. The dietary factors with an FDR  
169 less than 0.05 were subsequently selected for replication in NLCS, and fixed-effects meta-  
170 analysis was performed to combine the results from the two cohorts when heterogeneity was  
171 low or moderate (*P* value for heterogeneity>0.1 and/or  $I^2 \leq 50\%$ ). To further investigate the  
172 robustness of the associations that were replicated in NLCS, a mutual adjustment model was  
173 used. Presence of non-linear associations was investigated using restricted cubic spline models.  
174 More details on the statistical analyses methods are provided in the supplementary methods.

175

## 176 **Results**

### 177 **Study characteristics**

178 After a mean follow up of 14.1 (SD:3.9) years, a total of 5,069 (56.8% in women)  
179 incident malignant CRC cases were identified among the 386,792 included EPIC participants,  
180 of which 3,143 were identified as colon (1,495 proximal; 1,435 distal; 213 unspecified) and  
181 1,715 as rectal cancers. In NLCS, 3,765 cases (42.8% female) with incident and  
182 microscopically confirmed CRC were included in the present analysis, of which 2,612 were  
183 colon (1,348 proximal; 1,187 distal) and 801 were rectal cancers.

184 The main baseline characteristics of the study participants are shown in **Supplementary**  
185 **Table 1**. In EPIC, approximately 30% of the participants were men, and 47% were overweight  
186 or obese. About 50% of the participants were never smokers, and 47% were physically active.  
187 More than half of the NLCS subcohort participants were male (54%), 47% were overweight or  
188 obese, one third (33%) were never smokers, and 48% spent more than 60 minutes/day on non-  
189 occupational physical activities.

190 **DWAS in EPIC**

191 Of the 92 dietary factors that were examined in EPIC, 20 were associated with CRC  
192 risk (FDR<0.05) (**Figure 1; Supplementary Table 2**). Higher intakes of alcohol, liquor/spirits,  
193 wine, beer/cider, soft drinks, and pork were positively associated with CRC, whereas higher  
194 milk, cheese, calcium, phosphorus, magnesium, potassium, riboflavin, vitamin B6, beta-  
195 carotene, fruit, fibre, non-white bread, banana, and total protein intakes were associated with a  
196 lower CRC risk.

197 After conducting the analysis by tumour subsite, evidence of heterogeneity between  
198 colon and rectal cancer was observed for intakes of magnesium, potassium, vitamin B6 and  
199 banana, with associations being inverse for colon cancer and null for rectal cancer  
200 (**Supplementary Table 3**). Regarding proximal versus distal colon subsites, only total alcohol  
201 and wine had heterogeneous results, whereby the associations were positive only for distal  
202 colon cancer (**Supplementary Table 4**). Additionally, heterogeneous associations were  
203 observed by sex, for total alcohol and spirits, magnesium, fibre, and non-white bread, where  
204 the associations were only observed in men (**Supplementary Table 5**). When we investigated  
205 the association of red and processed meat with CRC risk by follow-up duration, a trend towards  
206 smaller HRs was observed as follow-up increased (**Supplementary Figure 1**). There was some  
207 evidence for non-linearity ( $P$  value = 0.028) in the association of alcohol intake and CRC risk  
208 (**Supplementary Figure 2**).

209 **Replication analysis in NLCS**

210 Of the 20 associations with an FDR<0.05 in EPIC, four associations reached nominal  
211 statistical significance ( $P$  value < 0.05) in the NLCS cohort in the analysis for CRC (***Figure 2;***  
212 **Supplementary Table 6**), namely alcohol and liquor/spirits (positively), milk and calcium  
213 intake (inversely). An additional four associations, namely phosphorus, magnesium, riboflavin

214 and total protein, had a borderline inverse association in NLCS, and the point estimates were  
215 almost identical to the ones calculated in EPIC.

216 In a separate analysis by tumour subsite in the NLCS, we found that most associations  
217 were consistent across the different subsites with heterogeneous associations only evident for  
218 phosphorus, potassium, vitamin B6, beta-carotene and total protein in the analysis for colon  
219 versus rectal cancer (*Supplementary Tables 7-8*). Little heterogeneity was observed by sex for  
220 CRC risk (*Supplementary Table 9*).

### 221 **Meta-Analysis of EPIC and NLCS**

222 The associations for most of the 20 dietary variables with CRC risk were homogeneous  
223 between EPIC and NLCS, except for soft drinks, vitamin B6, fruit, fibre, non-white bread,  
224 banana, and pork ( $P$  value for heterogeneity  $< 0.1$  and/or  $I^2 > 50\%$ ), where the associations were  
225 null in NLCS and therefore a meta-analysis was not performed. The remaining 13 associations  
226 yielded a nominally significant summary finding: alcohol (HR per 1 SD increment in intake  
227 per day: 1.07; 95% CIs: 1.04-1.09), liquor/spirits (1.04; 1.02-1.06), wine (1.04; 1.02-1.07),  
228 beer/cider (1.06; 1.04-1.08), milk (0.95; 0.93-0.98), cheese (0.96; 0.94-0.99), calcium (0.93;  
229 0.90-0.95), phosphorus (0.92; 0.90-0.95), magnesium (0.95; 0.92-0.98), potassium (0.96; 0.94-  
230 0.99), riboflavin (0.94; .92-0.97), beta-carotene (0.96; 0.93-0.98), and total protein (0.94; 0.92-  
231 0.97) (*Figure 2*; *Supplementary Table 6*).

### 232 **Pairwise correlations and Mutual-adjustment analysis**

233 Most of the pair-wise correlation coefficients for the 20 FDR-significant foods/nutrients  
234 in EPIC were weak and ranged from -0.25 to 0.79 (*Figure 3*).

235 When alcohol, milk, cheese, calcium, phosphorus, magnesium, potassium, riboflavin,  
236 beta-carotene and total protein were included in a single multivariable-adjusted model in EPIC,

237 only alcohol remained significantly associated with CRC risk (1.05; 1.03-1.11) Supplementary  
238 Table 10).

### 239 **Gene-Nutrient interaction analysis**

240 Of the 73×20 gene-nutrient multiplicative interactions that were tested, using the  
241 Bonferroni adjusted *P* value threshold of  $3.4 \times 10^{-5}$ , no interaction remained significant  
242 (Supplementary Table 11).

### 243 **Discussion**

244 We used the DWAS approach to systematically evaluate the association between  
245 dietary intakes of 92 foods and nutrients and risk of CRC in EPIC and NLCS. We confirmed  
246 well-described associations in the literature for alcoholic beverages (positive), milk and  
247 calcium (inverse) with risk of CRC. In addition, our analysis showed that higher intakes of  
248 phosphorus, magnesium, potassium, riboflavin, beta-carotene, and total protein were  
249 associated with a lower risk of CRC.

250 **Alcohol** consumption was positively associated with risk of CRC in EPIC and NLCS,  
251 and this association was not different between colon and rectal cancer subsites or by type of  
252 alcoholic beverage. In agreement, the WCRF third Expert Report has graded the quality of this  
253 evidence as strong<sup>11</sup>. Persons with higher total alcohol consumption had a higher risk of CRC  
254 (summary HR per SD increment in intake/day: 1.07; 1.04-1.09), colon, and rectal cancer in the  
255 meta-analysis of EPIC and NLCS. When we evaluated this association by proximal vs. distal  
256 colon cancer and by sex, we found heterogeneous associations in EPIC, with associations only  
257 present for distal colon cancer and in men, but these findings were not confirmed in NLCS.  
258 The majority of the literature agrees that the positive association of alcohol consumption with  
259 CRC risk is consistent by anatomical subsite and sex<sup>12, 13</sup>. Acetaldehyde, as a metabolite of  
260 ethanol oxidation, can be carcinogenic in colonocytes<sup>14</sup>. Mendelian randomization (MR)

261 studies have failed to demonstrate an association between genetically proxied alcohol  
262 consumption and CRC risk, but this analysis was underpowered to detect relatively small  
263 effects<sup>15</sup>.

264 Our study also confirmed the inverse association between intake of dairy products and  
265 calcium with risk of CRC, where individuals with higher calcium consumption had a 7% lower  
266 risk of CRC per 334.5 mg increment in intake/day. One of the most prominent mechanisms by  
267 which calcium is thought to act to reduce CRC risk is by its ability to bind unconjugated bile  
268 acids and free fatty acids, diminishing their potential toxic effects on the colorectum<sup>16</sup>..  
269 Heterogeneity by anatomical subsite or sex was not observed, in agreement with the WCRF  
270 meta-analysis and a more recent publication in the Nurses' Health Study<sup>11, 12</sup>. Dairy products  
271 are also a rich source of **phosphorus**, which was also inversely associated with CRC risk in  
272 our study but has been infrequently studied in other publications. A previous analysis of  
273 nutrient patterns in EPIC identified a pattern characterised by total protein, riboflavin,  
274 phosphorus and calcium that was associated with a 4% decreased CRC risk<sup>17</sup>. All these  
275 nutrients were analysed independently in our analysis and yielded inverse associations in EPIC  
276 that were robust after correcting for multiple testing and were replicated in NLCS. Since several  
277 of these nutrients share common sources of intake, a correlation of approximately 0.50-0.70  
278 was observed in EPIC, which makes it challenging to distinguish their independent effects<sup>18</sup>.  
279 Evidence from MR studies suggests that genetically proxied milk consumption is associated  
280 with a reduced CRC risk, but failed to demonstrate an association for genetically proxied  
281 calcium or phosphorus concentrations<sup>19,20</sup>. Additionally, although previous RCTs have showed  
282 null associations for calcium supplementation in relation to CRC risk, a 13% decreased risk of  
283 colorectal adenoma recurrence has been reported in a meta-analysis of four RCTs, with daily  
284 doses of calcium ranging from 1200 to 2000 mg<sup>21</sup>.

285 Many studies have investigated the association between **red meat or processed meat**  
286 consumption and risk of CRC. A dose-response meta-analysis by the WCRF third Expert  
287 Report concluded that there is strong evidence that consuming red meat (including beef, pork,  
288 lamb and goat from domesticated animals) or processed meat (meat preserved by smoking,  
289 curing, salting or addition of chemical preservatives) increases the risk of CRC by 12% per 100  
290 gram/day increment for red meat and 16% per 50 gram/day for processed meat<sup>4</sup>. A combination  
291 of mechanisms may contribute to the higher risk of colorectal tumourigenesis among  
292 individuals consuming larger amounts of red and/or processed meat. Cooking meat at high  
293 temperatures may lead to the formation of heterocyclic amines (HCA) and polycyclic aromatic  
294 hydrocarbons (PAHs), which have been associated with colorectal carcinogenesis in  
295 experimental studies<sup>22</sup>. Red meat also contains haem iron at high levels that may stimulate the  
296 endogenous formation of carcinogenic N-nitroso compounds, which promote colorectal  
297 tumourigenesis<sup>23</sup>. Additionally, processed meat can be an exogenous source of N-nitroso  
298 compounds. Although accumulated evidence supports that higher intakes of red or processed  
299 meat are associated with higher risk of CRC, these findings were not replicated in our analysis  
300 in EPIC (HR per 36.2 grams of red meat intake daily: 1.02; 0.98-1.05; HR per 31.5 grams of  
301 processed meat intake daily: 1.04; 1.00-1.08). An earlier report from EPIC in 2005, with a  
302 mean follow-up of 4.8 years and 1,329 incident CRC cases, observed a positive association  
303 between red and processed meat consumption with CRC risk<sup>24</sup>. A potential reason for this  
304 discrepancy is that EPIC, as most other cohorts, has assessed meat consumption only during  
305 recruitment in the 1990s; thus, the current analysis assumes that consumption has stayed stable  
306 over two decades. However, a notable decrease in bovine meat consumption between 2000 and  
307 2013 has been noticed in Europe, which was accompanied by an analogous increase in cheese,  
308 fish, dairy and poultry consumption. In the current paper, we observed a trend towards smaller  
309 HRs in the association of red and processed meat with CRC risk as follow-up increased. A

310 recent time-varying exposure analysis in the Nurses' Health Study and the Health Professionals  
311 Follow-up Study showed that a decrease in red meat consumption and simultaneous increases  
312 in healthy alternative food choices over time were associated with a lower risk of all-cause  
313 mortality<sup>25</sup>.

314 The current DWAS study observed an inverse association of **magnesium** intake with  
315 risk of CRC, which agreed with the results of a recent meta-analysis of seven observational  
316 studies<sup>26</sup>. One purported mechanism by which magnesium may be implicated in lower CRC  
317 risk is by its potential to inhibit *c-myc* oncogene expression in colon cancer cells<sup>27</sup>.  
318 Furthermore, magnesium has been shown to improve insulin sensitivity and lower plasma  
319 insulin concentrations, which may have an impact on CRC development<sup>28</sup>. No association of  
320 genetically proxied circulating concentrations of **magnesium** was found in a recent MR study<sup>20</sup>

321 We also observed an inverse association between intake of **beta-carotene** and risk of  
322 CRC, but few other studies have investigated this association<sup>29</sup>. Our findings agree with a  
323 previous report from EPIC in 2014<sup>29</sup>. However, a cohort analysis in the Alpha-Tocopherol,  
324 Beta-Carotene Cancer Prevention (ATBC) trial, comprising of 26,951 middle-aged male  
325 smokers, showed no association between dietary beta-carotene and risk of CRC<sup>30</sup>. No evidence  
326 of association between genetically proxied circulating concentrations of **beta-carotene** and  
327 CRC have been reported in MR studies<sup>20</sup>.

328 Vitamins B2 and B6 are among the micronutrients that play a pivotal role in one-carbon  
329 metabolism, which has been related to carcinogenesis because of its involvement in the  
330 synthesis of purines and pyrimidines for subsequent DNA synthesis and in the synthesis of  
331 methionine for DNA methylation<sup>31</sup>. Inverse associations between **riboflavin** (vitamin B2) and  
332 **vitamin B6** intake and CRC risk were observed in EPIC, but only the association with  
333 riboflavin was replicated in the NLCS. Previous studies on the association between riboflavin  
334 intake and CRC risk are scarce<sup>32</sup>. Results from the Women's Health Initiative Observational



335 Study indicated a 25% decreased CRC risk for the highest compared to the lowest quartile of  
336 total riboflavin intake, but was not statistically significant when only dietary intake of  
337 riboflavin was considered<sup>32</sup>. A meta-analysis of eight studies did not show an association  
338 between vitamin B6 intake and CRC risk, but blood levels of its active form, pyridoxal 5'-  
339 phosphate, were associated with lower CRC risk<sup>33</sup>.

340 Little is known on the role that **potassium** may play in relation to CRC risk, and  
341 epidemiological evidence thus far is limited<sup>34</sup>. We cannot rule out the possibility that the  
342 inverse association observed in our study may mirror the effect of other nutrients, such as  
343 vitamin B6 or dietary fibre, which share common dietary sources with potassium.

344 **Strengths** of this study include its large size and long follow-up duration and the  
345 DWAS approach that involved a comprehensive assessment of foods and nutrients whilst  
346 accounting for multiplicity of tests and replication of findings in an independent cohort.  
347 Another strength was the ability to explore associations according to different anatomical  
348 subsites as well as by sex. The primary **limitation** was that the analysis relied on a single dietary  
349 assessment at recruitment, not allowing to capture potential changes in dietary habits over time.  
350 In addition, intercorrelations between dietary exposures and overall dietary patterns were not  
351 accounted for. Intercorrelations between dietary exposures may have led to low precision of  
352 the estimates, even though variance inflation factors were relatively small, which might explain  
353 that none of the dietary factors remained in the multivariable adjusted model. Furthermore, it  
354 is possible that there might be an association for foods or nutrients that were not included in  
355 this analysis. Additionally, the data derived from the Dutch food composition table were not  
356 checked against the use of ENDB for nutrient calculation, so discrepancies may have occurred,  
357 hence it is possible that some of the discrepancies observed between the two cohorts for some  
358 dietary exposures, are in part due to poor reproducibility in measurements. Among the  
359 exposures for which heterogeneity was observed between EPIC and NLCS, correlation

360 between the baseline FFQs and 24-hour diet recalls has been reported to be good for fruit, fibre,  
361 vitamin B6 and beverage consumption in NLCS and fairly good for fibre and fruit across most  
362 EPIC centres, but for exposures like non-white bread or vitamin B6 no information was  
363 available<sup>8, 35</sup>. Finally, we cannot exclude the possibility of residual confounding, although we  
364 adjusted for several potential confounders.

365           In **conclusion**, our study confirmed the well-established positive association for alcohol  
366 consumption and inverse association for dairy products and calcium intake with CRC risk. The  
367 study further suggested that higher intakes of magnesium, phosphorus, potassium, riboflavin,  
368 beta-carotene and total protein are associated with lower CRC risk.

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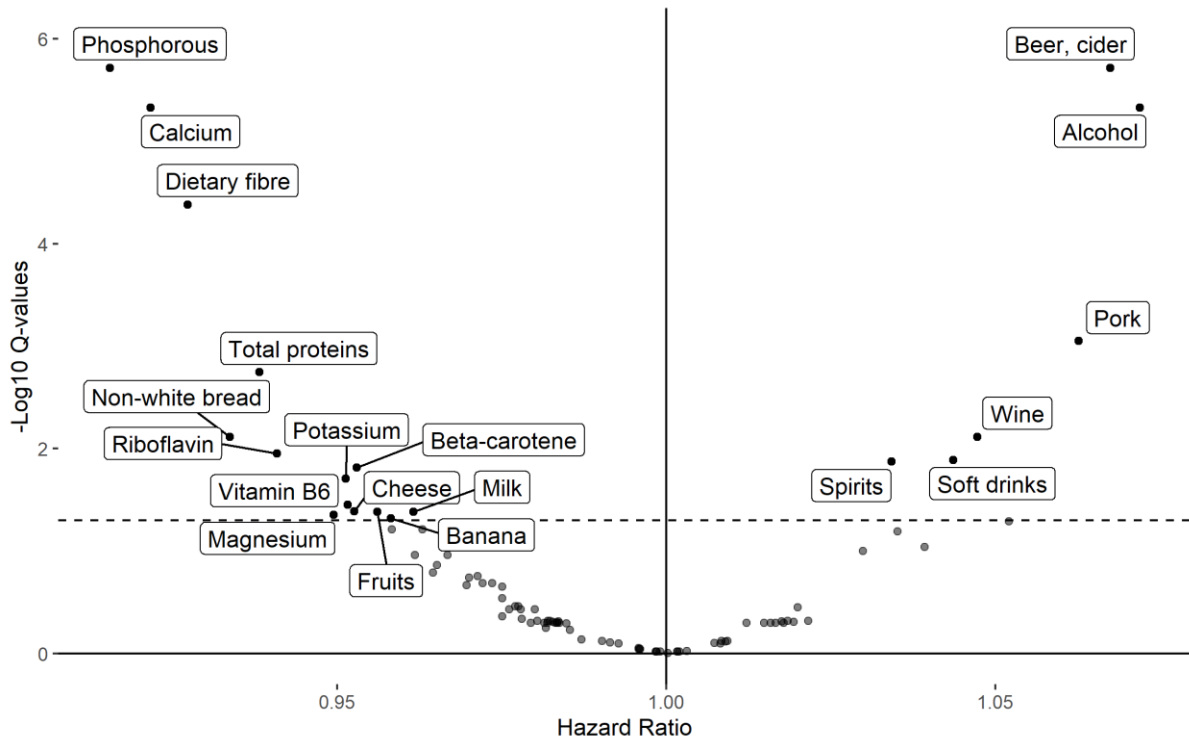
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395 Research on Cancer / World Health Organization, the authors alone are responsible for the  
396 views expressed in this article and they do not necessarily represent the decisions, policy or  
397 views of the International Agency for Research on Cancer / World Health Organization.

398 **Data availability:** The EPIC study data can be accessed via an application to the EPIC  
399 Steering Committee (<https://epic.iarc.fr/access/index.php>). Further information is available  
400 from the corresponding author upon request.

401 **References**

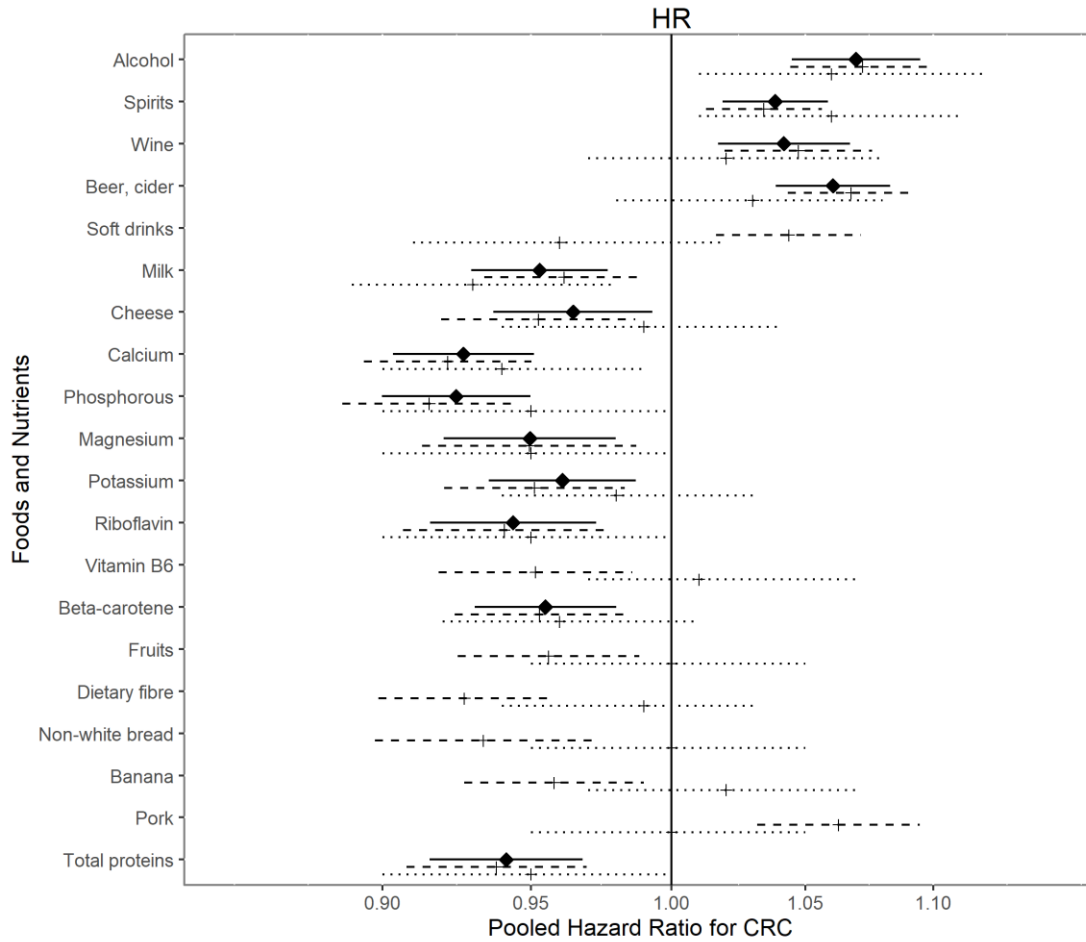
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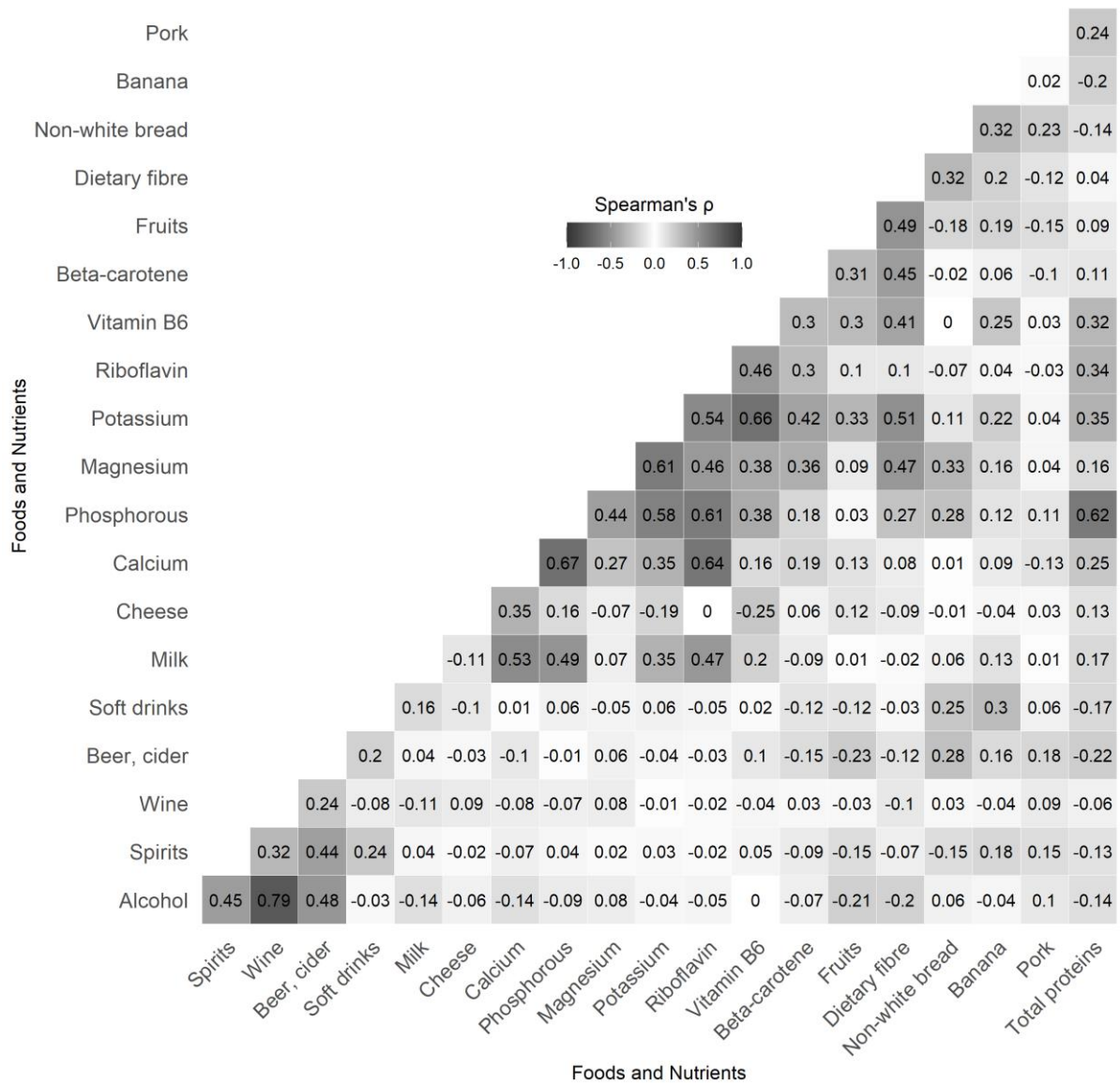
505 **Figure 1. Volcano plot showing results from the DWAS regarding the association between**  
 506 **92 dietary factors and CRC risk in EPIC.** The Y-axis shows the false discovery rate (FDR)  
 507 adjusted *P* values in  $-\log_{10}$  scale from the Cox proportional hazards models for each dietary  
 508 factor. The X-axis shows the estimated HR for each dietary factor per 1 SD increase in daily  
 509 consumption. The dashed horizontal line represents the level of significance corresponding to  
 510 FDR of 5%.



511

512 **Figure 2. Forest plot showing the hazard ratios and 95% confidence intervals for the 20**  
 513 **FDR significant associations (FDR<5%), in EPIC (---) and NLCS (···), as well as the**  
 514 **results from a meta-analysis (MA) (—). The X-axis shows the estimated HR for each dietary**  
 515 **factor for 1 SD increase in daily consumption. The diamond and the solid line represent the**  
 516 **pooled HR and 95%CI of the MA. MA was not performed when heterogeneity was high.**





517

518 **Figure 3.** Pairwise partial correlation coefficients (Spearman's  $\rho$ ) of the 20 FDR-significant  
 519 foods/nutrients in EPIC, adjusting for age, sex and centre.