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Associations between consumption of dietary fibers and the risk of cardiovascular diseases, cancers, type 2 diabetes, and mortality in the prospective NutriNet-Santé cohort

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SHORT RUNNING HEAD

Dietary fiber, chronic diseases and mortality

ABBREVIATIONS

BMI, body-mass index; CépiDc, Centre d'épidémiologie sur les causes médicales de décès ; CI, confidence interval ; CVD, cardiovascular disease; DF, dietary fiber; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; HR, hazard ratio; IF, insoluble fiber; PCA, principal component analysis; SF, soluble fiber; TDF, total dietary fiber; T2D, type 2-diabetes.

TRIAL REGISTRY

The NutriNet-Santé protocol is registered under ClinicalTrials.gov (NCT03335644 - <https://clinicaltrials.gov/ct2/show/NCT03335644?term=NCT03335644&rank=1>).

DATA SHARING

Data described in the manuscript (limited to summary data per participant consent), code book, and analytic code will be made available upon reasonable request pending application and approval.

1 **ABSTRACT**

2 **Background**

3 Mounting evidence – yet with varying levels of proof – suggests that dietary fibers (DFs) may
4 exert a protective role against various chronic diseases, but this might depend on the DF
5 type and source.

6 **Objective**

7 Our objectives were to assess the associations between the intake of DFs of different types
8 (total (TDF), soluble (SF), insoluble (IF)) and from different sources (fruits, vegetables, whole
9 grains, legumes, potatoes-tubers) and the risk of cardiovascular diseases (CVD), cancer,
10 type 2 diabetes (T2D), and mortality in the large-scale NutriNet-Santé prospective cohort
11 (2009-2019).

12 **Design**

13 Overall, 107,377 participants were included. Usual DF intake was estimated from validated
14 repeated 24-hour dietary records over the two first years following inclusion in the cohort.
15 Associations between sex-specific quintiles of DF intake and the risk of chronic diseases and
16 mortality were assessed using multi-adjusted Cox proportional hazards models.

17 **Results**

18 T2D risk was inversely associated with TDFs (HR for quintile 5 vs quintile 1: 0.59 (95%CI:
19 0.42,0.82), P-trend<0.001), SFs (HR: 0.77 (0.56,1.08); P-trend=0.02) and IFs (HR: 0.69
20 (0.50,0.96); P-trend=0.004). SFs were associated with a decreased risk of CVD (HR: 0.80
21 (0.66,0.98); P-trend=0.01) and colorectal cancer (HR: 0.41 (0.21,0.79); P-trend=0.01). IFs
22 were inversely associated with mortality from cancer or cardiovascular diseases (HR: 0.65
23 (0.45,0.94); P-trend=0.02). TDF intake was associated with a decreased risk of breast cancer
24 (HR: 0.79 (0.54,1.13); P for trend=0.04). DF intakes from fruit associated with the risk of
25 several chronic diseases.

26 **Conclusions**

27 Our results suggest that DF intake – especially SFs and DFs from fruits – was inversely
28 associated with the risk of several chronic diseases and with mortality. Further studies are
29 needed, involving different types and sources of fiber. Meanwhile, more emphasis should be
30 put on DFs in public health nutrition policies, as DF intake remains below the recommended
31 levels in many countries.

32 **Keywords**

33 Dietary fibers, cardiovascular diseases, cancers, type 2-diabetes, mortality, prospective
34 cohort

35 INTRODUCTION

36 Non-communicable diseases (e.g., cardiovascular diseases (CVD), cancer, type 2 diabetes
37 (T2D)) are estimated to be responsible for 70% of deaths worldwide, thus representing the
38 leading cause of mortality. In a recent study, the Global Burden of Diseases (GBD)
39 consortium concluded that suboptimal diet is responsible for more deaths than any other risk
40 factor globally, including tobacco smoking (1). Promoting the consumption of dietary
41 components for which intakes are less than the optimal level was thus suggested to be an
42 efficient way to mitigate the disease burden related to dietary risks (1).

43 In this context, dietary fibers (DFs) represent a highly promising target: the intake of DFs has
44 indeed consistently been reported as inadequate when compared to the recommended
45 intakes, regardless the country (2). Consumption of DFs has been associated with a variety
46 of health benefits, on both the short- (e.g. reduction of intestinal transit time, reduction of
47 post-prandial blood glucose level (2)), and the longer term, with mounting evidence
48 suggesting a role of DFs in the prevention of mortality (2,3) and chronic diseases such as
49 CVDs (1,4) and T2D (5,6). Regarding cancer, the current evidence supports a “probable”
50 inverse relationship between DFs and colorectal cancer, but is less clear regarding other
51 cancer types, as stated in the latest World Cancer Research Fund/American Institute for
52 Cancer Research (WCRF/AICR) report (7).

53 The generic term “dietary fibers” refers to a heterogeneous group of highly diversified
54 compounds which vary in terms of structure and physicochemical characteristics (e.g.,
55 solubility, viscosity, fermentability) (2,8). Overall, previous studies suggest that DFs may be
56 differentially associated with health outcomes depending on their solubility or sources (9–16)
57 and this may be related to corresponding differential physiological effects. For instance,
58 some SFs form a viscous gel in the intestinal tract; in contrast, IFs do not exhibit viscosity but
59 are characterized by a fecal-bulking ability (8). Likewise, the main sources of DFs – fruit,
60 vegetables, whole grains, potatoes, tubers, and legumes (17) each provide a distinctive mix
61 of different types of DF compounds with their specific properties (2,8).

62 In that context, our objectives were to assess the associations between the intake of dietary
63 fibers of different types (total dietary fibers (TDFs), SFs, and IFs) and from different sources
64 (fruits, vegetables, whole grain cereals, potatoes and tubers, and legumes), and the risk of
65 CVD, cancer, T2D and mortality, in a large prospective cohort of French adults.

66 **SUBJECTS, MATERIAL, AND METHODS**

67 **Study population**

68 This study was based on the NutriNet-Santé cohort, a web-based prospective study with
69 primary aim to investigate the associations between nutrition and health, as well as dietary
70 behaviors and their determinants. The recruitment of participants aged at least 18 years old,
71 speaking fluent French and having regular access to the Internet started in May 2009
72 through vast multimedia campaigns and is still ongoing (open cohort). Participants were
73 asked to register online on the dedicated web interface. More details on the study rationale,
74 design, and methods can be found elsewhere (18). The NutriNet-Santé study is conducted
75 according to the Declaration of Helsinki guidelines and was approved by the institutional
76 review board of the French Institute for Health and Medical Research (IRB Inserm
77 0000388FWA00005831) and the *Commission Nationale de l'Informatique et des Libertés*
78 (CNIL 908450/909216). The protocol is registered at ClinicalTrials.gov (NCT03335644).
79 Electronic informed consent is obtained from each participant.

80 **Data collection**

81 Participants are regularly invited to fulfill questionnaires directly on the study website. More
82 specifically, at inclusion, participants were required to fill in questionnaires collecting
83 information related to socio-demographic and lifestyle factors (e.g. educational level,
84 smoking status), anthropometrics (height, weight), physical activity (measured through the
85 French version of the validated International Physical Activity Questionnaire (IPAQ) (19)),
86 and health status (e.g. personal and family medical history, medical treatments, reproductive
87 life for women). Upon inclusion and every 6 months thereafter, dietary data was collected
88 through 3 non-consecutive web-based 24-hour dietary records (validated against traditional

89 methods and biomarkers (20–22)), randomly assigned over a 2-week period (2 weekdays
90 and 1 weekend day). For each dietary record, participants were asked to list all subsequent
91 foods and beverages ingested, from midnight to midnight, through main meals (breakfast,
92 lunch, dinner) and any other eating occasion. Participants then estimated the portion size for
93 all items previously listed using photographs from a validated picture booklet (23), or through
94 standard measurements (home containers, grams indicated on the package, etc.). Dietary
95 intakes (in energy, alcohol, macro- and micronutrients, etc.) were inferred using the
96 published NutriNet-Santé food composition database (24) which is regularly updated, and
97 currently comprises nutritional values for more than 3,500 food items. DF composition in
98 TDFs, SFs, and IFs for all food items (TDFs = SFs + IFs) was inferred using Finnish *Fineli*
99 and Turkish *Türkomp* databases as well as reference books (25–27) following an additional
100 ad hoc literature search.

101 In this prospective study, mean dietary intakes from all 24-hour dietary records available
102 during the first 2 years following participant's inclusion in the cohort (between 2 and 15
103 records) were considered as baseline usual dietary intakes.

104 **Case ascertainment**

105 Participants were asked to declare CVD or cancer events through the yearly health
106 questionnaire, through a quarterly specific questionnaire, or at any time using a specific
107 interface on the study website. Upon the declaration of such health event, the study
108 physicians started a validation process to confirm the event: participants were invited to send
109 all medical records and anatomic pathology reports corroborating the diagnosis; if necessary,
110 physicians from the NutriNet-Santé study contacted the participants' physicians or relevant
111 medical structures to collect additional information. Besides, data collected within the
112 NutriNet-Santé study were linked to the SNIIRAM database (medico-administrative
113 database) from the French national health insurance system (Caisse Nationale de
114 l'Assurance Maladie), which limits potential bias for participants who may not report their
115 disease to the study investigators. CVD and cancer cases were classified according to the

116 International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10).
117 All cancers except basal-cell carcinomas were included, and the CVDs included acute
118 coronary syndrome (ACS), angina pectoris, angioplasty, myocardial infarction (MI), stroke,
119 and transitory ischemic attack (TIA). CVDs were further classified into coronary heart
120 diseases (MI, ACS, angina pectoris, and angioplasty) and cerebrovascular diseases (stroke
121 and TIA). All T2D cases were primarily detected through the declaration by the participants of
122 a T2D diagnosed by a physician and/or of diabetes medication use in the quarterly and
123 yearly health questionnaires. Data from the SNIIRAM database (reimbursement of T2D
124 medication detected or not) were also considered for confirmation (ICD-10 codes E11). More
125 details regarding CVD, cancer and T2D case ascertainment are available in Supplementary
126 methods.

127 Data on participants' deaths were retrieved from the French National cause-specific mortality
128 registry (CépiDC) which includes both dates and causes of death and is accessible freely for
129 all French citizens. Mortality from cancer (ICD codes C00-C97 and D37-D48) or cardio- and
130 cerebrovascular diseases (ICD codes I00-I99) was more specifically considered.

131 All first incident cancers, CVDs and T2D, as well as deaths occurring between baseline (end
132 of completion of dietary data, two years after entry in the cohort) and February 2019 were
133 considered as cases.

134 **Statistical analysis**

135 To be included in the present work, participants needed to have provided at least 2 24-hour
136 dietary records during the first 2 years following their entry in the NutriNet-Santé cohort and
137 not to be classified as energy under-reporters (investigated using the method described by
138 Black (28), see more details in Supplementary methods). For each disease-specific analysis,
139 prevalent cases of the corresponding disease were excluded. A Flowchart is shown in
140 **Figure 1**. In the T2D track, prevalent and incident cases of type 1-diabetes were also
141 excluded. For all covariates except physical activity, <5% of values were missing. For
142 physical activity, the proportion of missing values was 14%. These missing data were

143 handled using Multiple Imputation by Chained Equations (MICE) by fully conditional
144 specification (FCS, 20 imputed datasets) for the following variables: body-mass index,
145 physical activity and educational level (29).
146 DF intakes (TDFs, SFs, IFs, as well as DFs from fruits, vegetables, legumes, and potatoes
147 and tubers) were computed as sex-specific quintiles to ensure the same sex-ratio between
148 all quintiles and limit a potential residual confounding due to sex (since women tend to eat
149 less than men and for this reason would tend to be more often found in the lowest quintiles).
150 For DF intake from legumes and whole grains, sex-specific quintiles could not be created
151 due to limited number of consumers; a non-consumer category was set, and sex-specific
152 quartiles were computed in consumers. P for trends were derived from tests performed with
153 the median of DF intake within each category. Cox proportional hazards models were used
154 to evaluate the association between DF intakes and the incidence of CVD (overall, coronary
155 heart diseases (CHD) and cerebrovascular diseases), cancers (overall, breast, prostate, and
156 colorectal cancers), T2D, and mortality from all causes and from cancer or cardio- and
157 cerebrovascular diseases. Participants contributed person-time from 2 years after their
158 inclusion in the cohort (allowing to disjoint the follow-up period from the diet assessment
159 period) until the date of the studied health event, the date at which the last questionnaire was
160 completed, the date of death, or February 22nd 2019, whichever occurred first. In specific
161 cancer or CVD models, participants were censored upon the declaration of another cancer or
162 CVD type than the one studied (e.g. breast cancer in the colorectal cancer model) and were
163 not considered as cases. For each model, hazard ratios (HR) and 95% confidence intervals
164 (CI) were computed. Age was used as the primary time-scale, and main models were
165 adjusted for the following potential confounders (established or suspected risk factors for the
166 studied health outcomes that also relate to diet) pertaining to socio-demographic
167 characteristics: age, sex, educational level (<high-school degree, <2 years of higher
168 education, ≥2 years of higher education); lifestyle: physical activity (low, moderate, high;
169 following IPAQ guidelines (19)), smoking status (current smoker, ex-smoker, non-smoker),
170 alcohol intake (in g/d), energy intake (in kcal/d); anthropometrics: body-mass index (BMI, in

171 kg/m²), height (for cancer analyses, in cm); study design: number of 24-hour dietary records
172 (continuous); family history of diseases (yes/no): CVD (for CVD and mortality analyses),
173 cancer (for cancer and mortality analyses) and T2D (for T2D analyses); and personal history
174 of CVD, cancer, and T2D (for mortality analyses, yes/no). When dealing with DF from
175 different sources, models were further adjusted for the intake of DF from all other sources
176 than the one under study. Schoenfeld residuals were computed in order to confirm risk
177 proportionality assumptions (Supplementary Figure 1). Spearman correlation coefficients
178 confirmed the absence of collinearity between the continuous variables included in the
179 models (Supplementary Table 1). Potential non-linear associations were assessed using
180 restricted cubic spline analyses (SAS %macro developed by Desquilbet et al. (30)). P for
181 non-linear associations are shown in Supplementary Table 5.

182 Sensitivity analyses were performed to test the robustness of our results. Model 2 was
183 further adjusted for metabolic risk factors (dyslipidemia, hypertriglyceridemia, hypertension
184 and prevalent T2D at inclusion (yes/no) and their related medications (yes/no). Further
185 adjustments for the quality of the diet were tested in model 3 (intakes of saturated fatty acids
186 (in g/d), sodium (in mg/d), and added sugars (in g/d)), model 4 (intakes of vitamin C (in
187 mg/d), vitamin E (in mg/d), zinc (in mg/d), and selenium (in mg/d)) and model 5 (“healthy”
188 and “Western” dietary patterns derived by principal component analysis on 20 food groups;
189 see further details in Supplementary methods). Model 6 excluded participants providing less
190 than 3 24-hour dietary records during the first two years of follow-up to improve the overall
191 accuracy of the dietary data. Model 7 excluded participants with prevalent CVD, cancer or
192 T2D at inclusion, to limit a potential reverse causality bias. Finally, model 8 excluded
193 participants with missing data on covariates (“complete cases” analysis). In the CVD track,
194 an additional analysis was run in which TIA and angina pectoris were not considered as CVD
195 cases. Indeed, TIA and angina pectoris have not always been considered as ‘major’ CVD
196 events in previous studies as they are lighter events than myocardial infarction or stroke, not
197 necessarily leading to a hospitalization and more likely to be missed/undiagnosed and
198 therefore not reported.

199 Interactions were tested between DF intake (TDF, SF, IF) and the following variables on all
200 outcomes: sex, age, BMI, “healthy” and “Western” dietary patterns. P for interaction was
201 obtained as the P-value of the product of the corresponding two variables introduced in the
202 model. For statistically significant interactions, corresponding subgroup analyses were
203 performed.

204 SAS 9.4 (SAS Institute) was used for the analyses, and tests were considered statistically
205 significant when p-value was <0.05.

206 RESULTS

207 Description of the study population

208 A total of 107,377 participants were eligible, from which were excluded prevalent cases of
209 the disease under study as well as participants with less than two years of follow-up.

210 Characteristics of these participants according to quintiles of TDF intakes are presented in

211 **Table 1**. The mean \pm SD age at inclusion was 42.8 ± 14.6 years. Mean number of dietary
212 records per participant was 6 (range: 2-15). On average, DF intakes were 19.5 ± 7.2 g/day for
213 TDFs, 5.7 ± 2.6 g/day for SFs, and 13.8 ± 5.1 g/day for IFs. Distributions of the consumption of
214 TDFs, IFs, and SFs, in the sample as well as their seasonal variations are presented in
215 Supplementary Figure 2. Strikingly, 92.5% of individuals (85.4% of men and 94.4% of
216 women) did not meet the French daily recommended TDF intake (i.e. 30 g of DFs per day).

217 Associations between DF intakes and mortality or the risk of chronic diseases

218 In mortality analyses, median follow-up (starting 2 years post-inclusion in the cohort) was 5.0
219 years (418,009 person-years) and 635 deaths occurred – among which 408 were attributed
220 to cancer or cardio- and cerebrovascular diseases. No association was observed for all-
221 cause mortality (**Table 2**). However, IF intake was inversely associated with mortality from
222 cancer or cardio- and cerebrovascular diseases (HR for quintile 5 vs quintile 1: 0.65; 95% CI:
223 0.45, 0.94; P for trend=0.02), even when adjusted for SF intake (**Table 2**).

224 In the CVD track, 131 MIs, 114 strokes, 54 ACSs, 678 angioplasties, 620 TIAs and 303
225 angina pectoris – representing 1554 first incident cases – occurred during follow-up. SFs
226 were inversely associated with the risk of overall CVD (HR_{Q5 vs Q1}: 0.80; 0.66, 0.98; P for
227 trend=0.01, median follow-up: 4.7 years, 385,028 person-years; **Table 2**), even when
228 adjusted for IF intake. This association was still observed when TIA and angina pectoris were
229 not considered as CVD cases (HR_{Q5 vs Q1}: 0.70; 0.54, 0.91; P for trend=0.005; data not
230 tabulated) and was more particularly observed for the risk of CHD (HR_{Q5 vs Q1}: 0.74; 0.58,
231 0.96; P for trend=0.004, median follow-up: 4.8 years, 387,199 person-years; **Table 2**). DFs
232 from fruit (**Figure 2**) were associated with a tendency for a decreased risk of overall CVD

233 (HR_{Q5 vs Q1}: 0.83; 0.69, 1.01; P for trend=0.07; HR_{per 1-SD increment}: 0.93; 0.88, 0.98, P for
234 trend=0.009), and of cerebrovascular diseases (HR_{Q5 vs Q1}: 0.71; 0.54, 0.92, P for trend=0.07;
235 HR_{per 1-SD increment}: 0.90; 0.83, 0.98, P for trend=0.02, median follow-up: 4.8 years, 388,487
236 person-years).

237 In the cancer track, 1,711 first incident cancers occurred, among which 529 breast, 218
238 prostate, and 127 colorectal cancer cases. No association was detected between any type
239 and source of DFs and overall cancer or prostate cancer (Table 2). SFs were associated with
240 a decreased risk of colorectal cancer (HR_{Q5 vs Q1}: 0.41; 0.21, 0.79; P for trend=0.01, median
241 follow-up: 4.7 years, 368,402 person-years), even when adjusted for IF intake (**Table 2**), and
242 as were DFs from fruit (HR_{Q5 vs Q1}: 0.42; 0.21, 0.81; P for trend=0.01; Figure 2;
243 Supplementary Table 2). TDFs were associated with a decreased risk of breast cancer (HR
244 _{Q5 vs Q1}: 0.79; 0.54, 1.13; P for trend=0.04; HR_{per 1-SD increment}: 0.86; 0.75, 0.97, P for trend=0.02
245 median follow-up: 4.7 years, 288,015 person-years; Table 2), as were IFs (HR_{Q5 vs Q1}: 0.93;
246 0.64, 1.35; P for trend=0.10; HR_{per 1-SD increment}: 0.85; 0.75, 0.96, P for trend=0.01; Table 2),
247 even when adjusted for soluble fiber intake. These associations were more particularly
248 observed for pre-menopausal breast cancer (Supplementary Table 3).

249 In the T2D track, 544 incident cases of T2D occurred during follow-up. A decreased risk of
250 T2D (median follow-up: 4.8 years, 388,205 person-years) was observed for TDFs (HR_{Q5 vs Q1}:
251 0.59; 0.42, 0.82; P for trend<0.001), SFs (HR_{Q5 vs Q1}: 0.77; 0.56, 1.08; P for trend=0.02), but
252 not when adjusted for IF intake, and IFs (HR_{Q5 vs Q1}: 0.69; 0.50, 0.96; P for trend=0.004),
253 even when adjusted for SF intake (**Table 2**). T2D risk was also inversely associated with DF
254 intake from fruit (HR_{Q5 vs Q1}: 0.68; 0.50, 0.92; P for trend=0.004; **Figure 2**).

255 Results were overall robust across all sensitivity analyses (Supplementary Table 4).

256 No interaction was detected except for T2D between IF intake and age (P for
257 interaction=0.02), with a stronger association in older participants (≥ 41.5 y, i.e. the median;
258 HR_{Q5 vs Q1}: 0.63; 0.44, 0.91; P for trend<0.001 versus HR_{Q5 vs Q1}: 1.32; 0.57, 3.04; P for
259 trend=0.44 for younger participants); and between IF intake and the “healthy” dietary pattern
260 score (P for interaction=0.01), with a stronger association for participants with a score above

261 the median (≥ -0.068 , i.e. a diet more likely to be “healthy”; HR_{Q5 vs Q1}: 0.44; 0.26, 0.74; P for
262 trend=0.01 versus HR_{Q5 vs Q1}: 0.76; 0.35, 1.66; P for trend=0.73 for participants with a score
263 below the median).

264 **DISCUSSION**

265 In this large prospective cohort of French adults, a higher intake of dietary fibers was
266 associated with a decrease in chronic disease incidence and mortality. Specifically, TDFs,
267 SFs and IFs were inversely associated with T2D risk, TDFs were also inversely associated
268 with breast cancer risk, SFs with the risk of CVD (overall and CHD) and colorectal cancer,
269 and IFs with mortality from cancer or cardio- and cerebrovascular diseases. Amongst the
270 different sources of DFs, DFs from fruit were inversely associated with the risk of CVD,
271 colorectal cancer and T2D.

272 Recent meta-analyses of prospective studies concluded that higher intakes of DFs were
273 inversely associated with mortality from all cause and from cancer or CVD (6,12,31). Inverse
274 associations were also reported for both IFs and SFs with CVD mortality (6,12,31), for DF
275 from cereals and mortality from all causes and cancer (6,12), for DF from cereals, fruit and
276 legumes and mortality from CVD (6,12), for DF from fruit and vegetables and mortality from
277 CHD (6,12). Beyond DFs, the consumption of whole grains was also associated with overall
278 mortality, cardiovascular, and cancer mortality (6). In our study, associations with DFs were
279 only observed for mortality from cancer or cardio- and cerebrovascular diseases, consistent
280 with their established sensitivity to nutritional factors (1), and only for IFs.

281 With regard to CVDs, meta-analyses of cohort studies reported inverse associations between
282 TDF, IF and SF intakes and the risk of overall CVD (6,13), CHD (6,13,15) or stroke (6), and
283 between DF from cereals, fruit and vegetables and the incidence of CVD (6,13), CHD
284 (6,13,15) or stroke (6). In our study, we report inverse associations between SFs and the risk
285 of CVD (overall and CHD), and between DFs from fruit and the risk of CVD (tendency for
286 associations for overall and cerebrovascular diseases), but not with TDF, IF or DF from
287 cereals or vegetables. Interestingly, SF were strongly inversely associated with CHD risk,
288 with or without adjustment for IF. In contrast, results on IF tended to be reinforced by
289 adjustment for SF. This suggests that SF may be an important confounder in this association
290 and that it is important to assess the link between IF and CHD at similar levels of SF intakes.
291 These results can be further discussed in light of a meta-analysis of randomized controlled

292 trials, which concluded that SF supplementation was significantly associated with a reduction
293 of both systolic and diastolic blood pressures (32), which are risk factors for CVDs.

294 The current body of evidence links DF intake with a decreased risk of colorectal cancer with
295 a strong level of proof (6,7,33). Still, evidence is needed on potential distinct associations
296 according to DF types (SFs and IFs) or sources, with a recent meta-analysis suggesting a
297 role for DFs from cereals (6). In the present work, we observed an inverse association
298 between the intake of SFs (P -trend=0.07 for TDFs) and DFs from fruit and the risk of
299 colorectal cancer. Regarding other cancer types, TDFs were associated with a decreased
300 breast cancer risk in meta-analyses of epidemiological studies (6,34). In particular, analyses
301 conducted by our group within the SU.VI.MAX cohort observed inverse associations between
302 DFs from vegetables, but not TDFs, and breast cancer risk (9), and between TDFs, IFs, and
303 DFs from legumes and prostate cancer risk (10). However, the evidence linking breast or
304 prostate cancers to DFs remain unclear, preventing the WCRF/AICR to reach a conclusion in
305 its latest report (7). Here we observed an inverse association between TDFs and breast
306 cancer, supporting previous results, but no association with prostate cancer.

307 Finally we reported here that all 3 types of DF, as well as DFs from fruit were inversely
308 associated with the risk of T2D, echoing several meta-analyses of prospective studies where
309 the intakes of TDFs, IFs and DFs from cereals (6,11,16), SFs (6) and DFs from fruit (6,16)
310 were inversely associated with the risk of T2D.

311 Overall, our findings were consistent with current knowledge suggesting that higher intakes
312 of DFs were associated with decreased risk of chronic diseases and mortality, while adding
313 to the body of evidence (limited so far) regarding SFs or IFs and DFs from several dietary
314 sources. Still, our results only partially reproduced the conclusions from prior meta-analyses,
315 as some associations were not observed. This could be linked to population differences
316 (sociodemographic, country, age, sex ratio, etc.), and therefore differences in food
317 consumption patterns and contribution of the sources to DF intake. In addition, the level of
318 DF intake in our population was quite low, and possibly below the amounts providing clear
319 health benefits (corresponding to the recommended 30g/d of TDFs, reached by only a limited

320 proportion of participants in our cohort) which may have weakened the associations. Finally,
321 the number of available studies included in the meta-analyses on different DF types and
322 sources was limited, DF from cereals being the most studied. More studies dissecting these
323 associations are therefore required.

324 The interactions observed in our study suggested that DF may be an important component of
325 a “healthy” dietary pattern for T2D prevention; interaction between IF and age was likely
326 explained by the fact that older participants were more at risk compared to younger ones.

327 DFs are not consumed alone but are rather brought by several sources (fruit, vegetables,
328 legumes, cereals) also providing other compounds of interest (e.g. antioxidants, etc.) and are
329 also usually part of healthy dietary patterns. Adjusting for antioxidant vitamins and minerals
330 (vitamins C and E, selenium and zinc) or overall dietary patterns in our study did not modify
331 the findings, arguing for a specific effect of dietary fibers. Additionally, several mechanistic
332 hypotheses support our results. DFs are indeed associated with improved blood glucose
333 levels (increased viscosity of the intestinal bulk and decreased transit time thus limiting the
334 nutrient absorption rate (35)), improved insulin response (36–39) and a reduction of total and
335 LDL serum cholesterol (37,40,41). Besides, the bulk-increasing capability of DFs may dilute
336 fecal carcinogens and reduce transit time and thus, duration of exposure to these
337 carcinogens (42). Finally, the potential protective role of DFs for the prevention of chronic
338 diseases could be mediated by the gut microbial production of short-chain fatty acids
339 (SCFAs) from the fermentation of undigestible DFs reaching the colon (43–45). SCFAs may
340 play a role in maintaining the metabolic health of the human host through local and systemic
341 effects on gut barrier integrity, inflammatory and immune response in the gut, glucose
342 homeostasis and lipid metabolism in several tissues (46,47). Differential associations
343 observed according to DF solubility or sources may reflect the specific properties of the
344 various compounds coined as ‘dietary fibers’ (2). For instance, SF, especially when viscous,
345 are recognized for their blood-glucose lowering or blood lipid-modifying effects and may be
346 more quickly fermented into SCFAs. These properties are also particularly recognized for
347 DFs characteristic of fruit, such as pectin (2).

348 In addition to its prospective design and the large sample size, the main strength of our study
349 pertained to the detailed collection of dietary and nutrient intake, collected through repeated
350 validated 24 hour-dietary records based on an extensive database comprising 3,500 food
351 items. This allowed us to examine the associations between different types and sources of
352 DFs and a variety of chronic conditions. However, some limitations should be acknowledged.
353 Although our models were adjusted for a variety of potential confounders, residual
354 confounding cannot be entirely ruled out. Still, the sensitivity analyses we performed
355 confirmed the overall robustness of our results. In our study, the detection of diseases was
356 primarily based on self-report, with a validation procedure based on medical records and/or
357 linkage to national databases. Despite this robust approach, misclassification bias cannot be
358 ruled out, especially when cases may not be reported: e.g., in the case of under-diagnosis for
359 diseases such as T2D (20% in France (48)) or in the case of a lack of awareness in the
360 population for diseases such as peripheral arterial disease (consequently not included as
361 CVD in our study). Yet, given the prospective design, such bias is unlikely to be differential
362 and would therefore result in weakened associations. Furthermore, the statistical power was
363 limited for colorectal cancer analyses and was too limited to perform separate analyses for
364 other cancer locations than the one reported here. Finally, compared to the general French
365 population, participants had higher socio-professional and educational levels (49) and
366 healthier lifestyle and dietary habits (50). This may limit the generalizability of our findings
367 and might also have resulted in an underrepresentation of cases compared to the general
368 French population (for instance, at inclusion, 5.7% of prevalent cancer, 2.4% of prevalent
369 CVD and 1.4% of prevalent T2D in our sample compared to national data: prevalence of
370 cancer of 7.2% (51), of CVD of 4.9% (52,53) and of T2D of around 5% (54)), and a smaller
371 contrast in dietary intakes between compared groups, thus a loss of statistical power.
372 Nonetheless, the average TDF intake in our study (19.5 ± 7.2 g/day) was comparable to the
373 average TDF intake of 19.6 ± 7.4 g/day observed in a French nationally representative study
374 (17).

375 Overall, this large prospective study supports a potential benefit of dietary fiber intake,
376 especially soluble fibers and fibers from fruits, in the prevention of various chronic diseases
377 and mortality, consistently with mechanistic data. Dietary fiber intake is still far below
378 recommended levels in many Western countries and thus represent a key target for public
379 health nutrition policies, with appropriate actions needed to foster the consumption of DFs
380 through a large variety of sources in the population.

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387 **CONFLICT OF INTERESTS**

388 The authors declare that they have no competing interests.

389 **AUTHORS' CONTRIBUTIONS**

390 The authors' contributions were as follows: VP, MD, BS, MT, designed the research; SH, PG,
391 MT, EKG, CJ, LF, NDP, LQM, MLA, DD, OL, MI Consortium: conducted the research; BS,
392 VP, performed data curation; VP: performed statistical analysis and wrote the original draft;
393 MD: revised the manuscript (statistical analyses and writing); MT: supervised statistical
394 analyses and manuscript writing; all authors: contributed to data interpretation and revised
395 each draft for important intellectual content; MT had primary responsibility for the final
396 content. All authors read and approved the final manuscript.

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Table 1. Characteristics of the study population at inclusion in the NutriNet-Santé cohort, according to sex-specific quintiles of total dietary fiber intakes, France, 2009-2019.

	All (N=107,377)	Quintiles of total dietary fiber intake ¹				
		Quintile 1 (N=21,474)	Quintile 2 (N=21,476)	Quintile 3 (N=21,476)	Quintile 4 (N=21,476)	Quintile 5 (N=21,475)
	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD
Age at inclusion (y)	42.8±14.6	37.5±13.7	41±14.4	43.5±14.5	45.7±14.3	46.6±14.2
Sex						
Male	22838 (21.3)	4567 (21.3)	4568 (21.3)	4568 (21.3)	4568 (21.3)	4567 (21.3)
Female	84539 (78.7)	16907 (78.7)	16908 (78.7)	16908 (78.7)	16908 (78.7)	16908 (78.7)
BMI (kg/m ²)	23.7±4.5	23.7±4.6	23.8±4.4	23.9±4.5	23.8±4.4	23.3±4.4
Educational level						
< High-school diploma	18774 (17.5)	4312 (20.1)	3688 (17.2)	3709 (17.3)	3691 (17.2)	3374 (15.7)
< 2 years of higher education	18372 (17.1)	4679 (21.8)	3883 (18.1)	3441 (16.0)	3220 (15.0)	3149 (14.7)
≥ 2 years of higher education	70231 (65.4)	12483 (58.1)	13905 (64.8)	14326 (66.7)	14565 (67.8)	14952 (69.6)
Smoking status						
Current smoker	18362 (17.1)	5969 (27.8)	4119 (19.2)	3286 (15.3)	2761 (12.9)	2227 (10.4)
Ex-smoker	35400 (33)	5737 (26.7)	6845 (31.9)	7184 (33.5)	7750 (36.1)	7884 (36.7)
Non-smoker	53615 (49.9)	9768 (45.5)	10512 (49)	11006 (51.3)	10965 (51.1)	11364 (52.9)
Physical activity level (IPAQ) ²						
High	30164 (28.1)	4846 (22.6)	5379 (25.1)	5923 (27.6)	6430 (29.9)	7586 (35.3)
Moderate	39680 (37)	7224 (33.6)	7949 (37)	8157 (38)	8240 (38.4)	8110 (37.8)
Low	22585 (21)	5567 (25.9)	5003 (23.3)	4448 (20.7)	4150 (19.3)	3417 (15.9)
Family history of CVD, yes	34044 (31.7)	5813 (27.1)	6343 (29.5)	6937 (32.3)	7375 (34.3)	7576 (35.3)
Family history of cancer, yes	40783 (38.0)	6949 (32.4)	7622 (35.5)	8315 (38.7)	8820 (41.1)	9077 (42.3)
Family history of T2D, yes	22774 (21.2)	4402 (20.5)	4441 (20.7)	4612 (21.5)	4729 (22.0)	4590 (21.4)
Prevalent CVD, yes	2573 (2.4)	646 (3.0)	503 (2.3)	448 (2.1)	479 (2.2)	497 (2.3)
Prevalent cancer, yes	6099 (5.7)	1109 (5.2)	1029 (4.8)	1218 (5.7)	1317 (6.1)	1426 (6.6)
Prevalent T2D, yes	1542 (1.4)	219 (1.0)	301 (1.4)	338 (1.6)	346 (1.6)	338 (1.6)
Total dietary fiber intake (g/d)	19.5±7.2	11.3±2.2	15.5±1.4	18.6±1.6	22.1±2	30.1±6.6
Soluble fiber intake (g/d)	5.7±2.6	3.1±1.1	4.4±1.1	5.4±1.3	6.5±1.5	9.0±2.8
Insoluble fiber intake (g/d)	13.8±5.1	8.2±1.7	11.1±1.4	13.2±1.6	15.6±1.9	21.0±4.8
Fruit fiber intake (g/d)	3.6±2.9	1.4±1.2	2.5±1.6	3.3±1.9	4.3±2.2	6.4±3.9
Vegetable fiber intake (g/d)	4.9±2.8	2.6±1.5	3.9±1.7	4.7±1.9	5.7±2.2	7.6±3.5
Whole grain fiber intake (g/d)	2±2.6	0.6±1	1.1±1.5	1.6±1.8	2.3±2.3	4.1±3.9
Legume fiber intake (g/d)	0.7±1.4	0.2±0.6	0.4±0.8	0.6±1	0.7±1.2	1.4±2.2
Potato and tuber fiber intake (g/d)	0.9±0.9	0.7±0.7	0.8±0.8	0.9±0.8	0.9±0.8	1.0±1.1
Energy intake (kcal/d)	1902±469	1631±395	1822±393	1914±418	1998±441	2145±522
Alcohol intake (g/d)	7.8±11.9	8.6±14.2	8.6±12.5	8.2±11.6	7.5±10.6	6.2±9.9
Total carbohydrate intake (g/d)	198.1±57.5	158.6±45.2	184.6±44.7	198.1±47.5	211.4±51	238±64.1
Added sugar intake (g/d)	38.4±23.7	36.9±24.5	39±23.1	39.3±22.9	38.8±22.9	38.1±24.9
Total fatty acid intake (g/d)	81.5±25.3	72.4±22.4	79.5±22.4	82.4±23.6	84.8±24.9	88.5±29.4
Saturated fatty acid intake (g/d)	33.2±12.1	30.5±10.9	33.4±11.1	34.2±11.6	34.4±12.2	33.4±14
Total protein intake (g/d)	78.8±21.5	69.9±20.3	76±18.8	79.4±19.5	82.6±20.3	86.4±24.4
Sodium intake (mg/d)	2718±886	2318±770	2610±768	2761±818	2881±863	3020±1020
Vitamin C intake (mg/d)	116.1±72.5	79±68.4	101.3±60.2	114.3±55.6	129.1±71.3	157.1±79.7
Vitamin E intake (mg/d)	11.7±4.7	9.1±3.8	10.5±3.7	11.4±3.8	12.5±4.1	15.1±5.6
Selenium intake (mg/d)	69.1±24.8	57.9±21.6	64.9±21.3	69.2±22.1	73.3±23.4	80.1±28.9
Zinc intake (mg/d)	10.7±3.3	9.1±3.1	10.1±2.9	10.6±3	11.2±3.1	12.3±3.7

¹ Cut-offs for the sex-specific quintiles of total dietary fiber intake were 15.7/19.3/22.9/27.9 g/day for men and 13.4/16.4/19.4/23.4 g/day for women.

² Available for 92,429 participants.

P-values for the comparisons of covariables across quintiles, from χ^2 test (categorical variables) or ANOVA (continuous variable), were all <0.001 (except for sex, P=1.00)

Table 2. Associations between consumption of total, soluble and insoluble dietary fibers, mortality (all cause and from chronic diseases) and the risk of cardiovascular diseases (overall, coronary heart diseases, cerebrovascular diseases), cancer (overall, colorectal, breast and prostate cancer), and type 2 diabetes, from multi-adjusted Cox proportional hazard models¹, NutriNet-Santé cohort, France, 2009-2019

	Quintiles ²					P-trend	Per 1-SD increment	P-value
	Q1	Q2	Q3	Q4	Q5			
Mortality, all causes								
Total dietary fibers, N cases / person-years	98/68,722	130/83,161	133/88,651	132/90,291	142/87,183		635 / 418,009	
Main model	1.00 (ref)	1.03 (0.79,1.35)	0.95 (0.72,1.25)	0.86 (0.64,1.15)	0.98 (0.72,1.33)	0.69	1.01 (0.91,1.12)	0.81
Soluble fibers, N cases / person-years	81/68,681	117/81,976	135/87,655	144/91,031	158/88,666		635 / 418,009	
Main model	1.00 (ref)	1.03 (0.77,1.37)	1.01 (0.76,1.34)	0.92 (0.69,1.23)	1.04 (0.77,1.41)	0.90	1.01 (0.93,1.11)	0.76
Main model, adjusted for insoluble fiber intake	1.00 (ref)	1.02 (0.77,1.37)	1.00 (0.75,1.34)	0.92 (0.68,1.24)	1.04 (0.74,1.44)	0.96	1.01 (0.91,1.13)	0.79
Insoluble fibers, N cases / person-years	115/69,595	126/84,012	136/88,413	127/90,214	131/85,775		635 / 418,009	
Main model	1.00 (ref)	0.95 (0.73,1.23)	0.95 (0.73,1.23)	0.84 (0.63,1.10)	0.90 (0.67,1.21)	0.38	1.01 (0.91,1.11)	0.87
Main model, adjusted for soluble fiber intake	1.00 (ref)	0.94 (0.72,1.22)	0.93 (0.71,1.21)	0.81 (0.60,1.08)	0.84 (0.60,1.18)	0.25	1.00 (0.89,1.13)	0.99
Mortality from cancer or cardio- and cerebrovascular diseases								
Total dietary fibers, N cases / person-years	71/68,722	86/83,161	80/88,651	88/90,291	83/87,183		408 / 418,009	
Main model	1.00 (ref)	0.94 (0.68,1.30)	0.77 (0.55,1.08)	0.76 (0.54,1.08)	0.74 (0.51,1.09)	0.10	0.91 (0.80,1.04)	0.18
Soluble fibers, N cases / person-years	55/68,681	77/81,976	86/87,655	97/91,031	93/88,666		408 / 418,009	
Main model	1.00 (ref)	0.98 (0.69,1.40)	0.95 (0.67,1.35)	0.91 (0.64,1.30)	0.89 (0.61,1.29)	0.46	0.95 (0.85,1.07)	0.43
Main model, adjusted for insoluble fiber intake	1.00 (ref)	1.00 (0.70,1.43)	0.99 (0.69,1.41)	0.97 (0.67,1.39)	0.99 (0.66,1.51)	0.95	1.00 (0.87,1.15)	0.99
Insoluble fibers, N cases / person-years	83/69,595	86/84,012	80/88,413	84/90,214	75/85,775		408 / 418,009	
Main model	1.00 (ref)	0.87 (0.64,1.19)	0.73 (0.53,1.01)	0.71 (0.51,1.00)	0.65 (0.45,0.94)	0.02	0.91 (0.80,1.04)	0.15
Main model, adjusted for soluble fiber intake	1.00 (ref)	0.86 (0.63,1.18)	0.72 (0.52,1.01)	0.70 (0.49,0.99)	0.63 (0.41,0.95)	0.03	0.91 (0.78,1.06)	0.23
Cardiovascular diseases, overall								
Total dietary fibers, N cases / person-years	207/62892	278/76694	349/81546	381/83563	339/80333		1554 / 385,028	
Main model	1.00 (ref)	0.91 (0.76,1.10)	0.96 (0.80,1.15)	0.94 (0.78,1.14)	0.86 (0.70,1.06)	0.19	0.93 (0.87,1.00)	0.04
Soluble fibers, N cases / person-years	194/63269	292/75491	336/80876	375/83827	357/81565		1554 / 385,028	
Main model	1.00 (ref)	0.97 (0.80,1.16)	0.90 (0.75,1.08)	0.85 (0.71,1.03)	0.80 (0.66,0.98)	0.01	0.90 (0.85,0.96)	0.001
Main model, adjusted for insoluble fiber intake	1.00 (ref)	0.97 (0.80,1.16)	0.90 (0.75,1.08)	0.85 (0.70,1.03)	0.80 (0.64,0.99)	0.02	0.89 (0.82,0.96)	0.002
Insoluble fibers, N cases / person-years	225/63464	284/77503	347/81571	361/83556	337/78934		1554 / 385,028	
Main model	1.00 (ref)	0.92 (0.77,1.10)	1.01 (0.84,1.20)	0.96 (0.80,1.15)	0.95 (0.78,1.15)	0.77	0.96 (0.90,1.03)	0.25
Main model, adjusted for soluble fiber intake	1.00 (ref)	0.96 (0.80,1.15)	1.08 (0.90,1.30)	1.07 (0.88,1.30)	1.14 (0.91,1.42)	0.13	1.03 (0.96,1.12)	0.40
Coronary heart diseases								
Total dietary fibers, N cases / person-years	120/63164	169/77034	209/82095	243/84012	204/80895		945 / 387,199	
Main model	1.00 (ref)	0.97 (0.77,1.24)	1.01 (0.80,1.28)	1.06 (0.83,1.35)	0.91 (0.70,1.19)	0.51	0.93 (0.86,1.02)	0.11
Soluble fibers, N cases / person-years	120/63497	182/75863	212/81331	222/84378	209/82130		945 / 387,199	
Main model	1.00 (ref)	0.97 (0.76,1.22)	0.91 (0.72,1.15)	0.80 (0.63,1.02)	0.74 (0.58,0.96)	0.004	0.88 (0.81,0.95)	0.001
Main model, adjusted for insoluble fiber intake	1.00 (ref)	0.96 (0.76,1.21)	0.89 (0.70,1.13)	0.78 (0.61,1.00)	0.70 (0.53,0.92)	0.002	0.84 (0.76,0.92)	<0.001
Insoluble fibers, N cases / person-years	131/63765	165/77894	216/82038	222/84029	211/79474		945 / 387,199	
Main model	1.00 (ref)	0.94 (0.74,1.18)	1.11 (0.88,1.39)	1.05 (0.83,1.33)	1.05 (0.82,1.36)	0.54	0.98 (0.90,1.07)	0.65
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.00 (0.79,1.26)	1.23 (0.97,1.55)	1.23 (0.96,1.57)	1.38 (1.04,1.84)	0.01	1.09 (0.99,1.20)	0.09
Cerebrovascular diseases								
Total dietary fibers, N cases / person-years	102/63295	127/77332	169/82386	176/84399	160/81074		734 / 388,487	
Main model	1.00 (ref)	0.82 (0.63,1.07)	0.90 (0.69,1.17)	0.85 (0.65,1.11)	0.79 (0.59,1.06)	0.22	0.93 (0.84,1.02)	0.13
Soluble fibers, N cases / person-years	88/63651	133/76131	143/81750	191/84643	179/82313		734 / 388,487	
Main model	1.00 (ref)	0.95 (0.73,1.26)	0.83 (0.63,1.09)	0.95 (0.72,1.24)	0.89 (0.67,1.18)	0.59	0.94 (0.85,1.03)	0.16

Main model, adjusted for insoluble fibers	1.00 (ref)	0.97 (0.74,1.28)	0.85 (0.64,1.13)	0.99 (0.75,1.31)	0.97 (0.71,1.33)	0.88	0.96 (0.86,1.07)	0.44
Insoluble fibers, N cases / person-years	106/63941	149/78093	159/82398	165/84351	155/79704		734 / 388,487	
Main model	1.00 (ref)	1.00 (0.77,1.28)	0.94 (0.73,1.22)	0.89 (0.69,1.17)	0.89 (0.66,1.18)	0.30	0.94 (0.85,1.03)	0.18
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.01 (0.78,1.31)	0.97 (0.74,1.26)	0.94 (0.71,1.24)	0.96 (0.69,1.33)	0.70	0.96 (0.85,1.08)	0.51
Type 2–diabetes								
Total dietary fibers, N cases / person-years	84/63477	119/77209	115/82230	121/84133	105/81155		544 / 388,205	
Main model	1.00 (ref)	0.94 (0.70,1.25)	0.69 (0.51,0.93)	0.61 (0.45,0.84)	0.59 (0.42,0.82)	<0.001	0.81 (0.72,0.92)	<0.001
Soluble fibers, N cases / person-years	70/63836	115/76024	118/81521	121/84509	120/82315		544 / 388,205	
Main model	1.00 (ref)	1.06 (0.78,1.43)	0.84 (0.62,1.14)	0.69 (0.51,0.95)	0.77 (0.56,1.08)	0.02	0.85 (0.76,0.95)	0.005
Main model, adjusted for insoluble fiber intake	1.00 (ref)	1.09 (0.81,1.48)	0.90 (0.66,1.23)	0.77 (0.56,1.08)	0.95 (0.65,1.37)	0.40	0.92 (0.80,1.05)	0.19
Insoluble fibers, N cases / person-years	88/64061	126/77950	110/82230	112/84088	108/79875		544 / 388,205	
Main model	1.00 (ref)	1.03 (0.78,1.36)	0.73 (0.55,0.99)	0.64 (0.47,0.87)	0.69 (0.50,0.96)	0.004	0.83 (0.74,0.93)	0.002
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.07 (0.81,1.42)	0.78 (0.58,1.06)	0.70 (0.50,0.97)	0.81 (0.56,1.17)	0.09	0.87 (0.76,1.01)	0.06
Cancer, overall								
Total dietary fibers, N cases / person-years	88/64061	126/77950	110/82230	112/84088	108/79875		544 / 388,205	
Main model	1.00 (ref)	1.03 (0.86,1.24)	1.10 (0.92,1.31)	1.09 (0.91,1.31)	0.97 (0.79,1.18)	0.49	0.99 (0.93,1.05)	0.65
Soluble fibers, N cases / person-years	201/61627	294/72845	368/77675	419/79519	429/76735		1711 / 368,402	
Main model	1.00 (ref)	0.94 (0.78,1.13)	0.94 (0.79,1.13)	0.93 (0.78,1.11)	0.94 (0.78,1.13)	0.65	0.97 (0.92,1.03)	0.39
Main model, adjusted for insoluble fiber intake	1.00 (ref)	0.94 (0.78,1.13)	0.94 (0.79,1.13)	0.93 (0.77,1.12)	0.93 (0.76,1.15)	0.66	0.97 (0.90,1.04)	0.34
Insoluble fibers, N cases / person-years	217/61760	323/74555	382/77455	412/79552	377/75080		1711 / 368,402	
Main model	1.00 (ref)	1.09 (0.92,1.30)	1.16 (0.97,1.38)	1.12 (0.93,1.33)	1.06 (0.87,1.28)	0.95	1.00 (0.94,1.06)	0.88
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.10 (0.92,1.32)	1.18 (0.99,1.41)	1.15 (0.95,1.38)	1.11 (0.90,1.38)	0.57	1.02 (0.94,1.10)	0.67
Colorectal cancer								
Total dietary fibers, N cases / person-years	16/61127	30/74245	30/77701	24/79259	27/76070		127 / 368,402	
Main model	1.00 (ref)	1.14 (0.61,2.12)	0.92 (0.49,1.74)	0.62 (0.31,1.23)	0.68 (0.33,1.39)	0.08	0.81 (0.64,1.04)	0.10
Soluble fibers, N cases / person-years	19/61627	23/72845	28/77675	32/79519	25/76735		127 / 368,402	
Main model	1.00 (ref)	0.66 (0.35,1.22)	0.61 (0.33,1.12)	0.57 (0.31,1.04)	0.41 (0.21,0.79)	0.01	0.73 (0.58,0.93)	0.009
Main model, adjusted for insoluble fiber intake	1.00 (ref)	0.65 (0.35,1.21)	0.60 (0.32,1.11)	0.55 (0.29,1.03)	0.38 (0.18,0.80)	0.02	0.69 (0.53,0.91)	0.01
Insoluble fibers, N cases / person-years	17/61760	27/74555	34/77455	23/79552	26/75080		127 / 368,402	
Main model	1.00 (ref)	1.12 (0.60,2.08)	1.23 (0.67,2.26)	0.72 (0.37,1.41)	0.83 (0.41,1.68)	0.25	0.90 (0.72,1.14)	0.40
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.25 (0.67,2.33)	1.46 (0.78,2.74)	0.94 (0.46,1.90)	1.29 (0.59,2.83)	0.85	1.11 (0.85,1.46)	0.45
Breast cancer								
Total dietary fibers, N cases / person-years	59/48022	99/58219	130/60691	136/62101	105/58981		529 / 288,015	
Main model	1.00 (ref)	1.08 (0.78,1.50)	1.17 (0.85,1.61)	1.04 (0.75,1.45)	0.79 (0.54,1.13)	0.04	0.86 (0.75,0.97)	0.02
Main model with further adjustments ³	1.00 (ref)	1.08 (0.78,1.50)	1.17 (0.85,1.61)	1.05 (0.75,1.46)	0.79 (0.55,1.14)	0.04	0.86 (0.76,0.97)	0.02
Soluble fibers, N cases / person-years	58/48361	101/57105	108/60889	137/61968	125/59692		529 / 288,015	
Main model	1.00 (ref)	1.10 (0.79,1.52)	0.92 (0.67,1.28)	1.02 (0.74,1.41)	0.89 (0.63,1.25)	0.30	0.91 (0.81,1.03)	0.13
Main model, adjusted for insoluble fiber intake	1.00 (ref)	1.14 (0.82,1.59)	0.99 (0.71,1.39)	1.14 (0.81,1.60)	1.10 (0.75,1.61)	0.74	1.00 (0.87,1.15)	0.99
Main model with further adjustments	1.00 (ref)	1.10 (0.79,1.52)	0.92 (0.67,1.28)	1.02 (0.74,1.41)	0.89 (0.63,1.26)	0.30	0.91 (0.81,1.03)	0.13
Insoluble fibers, N cases / person-years	56/48346	112/58556	127/60635	133/62168	101/58310		529 / 288,015	
Main model	1.00 (ref)	1.37 (0.99,1.90)	1.35 (0.97,1.87)	1.23 (0.88,1.72)	0.93 (0.64,1.35)	0.10	0.85 (0.75,0.96)	0.01
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.39 (1.00,1.93)	1.39 (0.99,1.94)	1.28 (0.90,1.83)	1.00 (0.66,1.52)	0.31	0.85 (0.73,0.99)	0.04
Main model with further adjustments	1.00 (ref)	1.37 (0.99,1.90)	1.36 (0.98,1.88)	1.23 (0.88,1.73)	0.94 (0.65,1.36)	0.10	0.85 (0.75,0.97)	0.01
Prostate cancer								
Total dietary fibers, N cases / person-years	17/13104	42/16026	46/17010	61/17158	52/17089		218 / 80,387	
Main model	1.00 (ref)	1.44 (0.81,2.55)	1.27 (0.71,2.26)	1.43 (0.80,2.55)	1.19 (0.64,2.23)	0.92	1.01 (0.86,1.18)	0.94
Soluble fibers, N cases / person-years	18/13267	37/15740	44/16787	54/17550	65/17043		218 / 80,387	
Main model	1.00 (ref)	1.02 (0.58,1.81)	0.91 (0.52,1.60)	0.90 (0.52,1.58)	1.11 (0.63,1.97)	0.55	1.03 (0.89,1.18)	0.70
Main model, adjusted for insoluble fiber intake	1.00 (ref)	1.03 (0.58,1.83)	0.93 (0.53,1.63)	0.93 (0.53,1.65)	1.18 (0.64,2.18)	0.47	1.05 (0.88,1.24)	0.59

Insoluble fibers, N cases / person-years	22/13414	39/15999	48/16820	56/17384	53/16770		218 / 80,387	
Main model	1.00 (ref)	1.24 (0.73,2.12)	1.33 (0.79,2.24)	1.36 (0.80,2.30)	1.27 (0.71,2.26)	0.61	0.99 (0.85,1.16)	0.91
Main model, adjusted for soluble fiber intake	1.00 (ref)	1.24 (0.72,2.11)	1.31 (0.77,2.24)	1.34 (0.77,2.31)	1.24 (0.66,2.31)	0.70	0.96 (0.80,1.16)	0.70

¹ For all outcomes, the main model was adjusted for age (timescale), sex, educational level, body-mass index, physical activity, smoking status, alcohol intake, energy intake and number of 24-hour dietary records. For mortality outcomes, the main model was additionally adjusted for the family history of cancer and CVD, and the personal history of cancer, CVD and T2D. For CVD outcomes, the main model was additionally adjusted for the family history of CVD. For cancer outcomes, the main model was additionally adjusted for the family history of cancer; For T2D, the main model was additionally adjusted for the family history of diabetes

² Cut-offs for sex-specific quintiles were as follows: for TDFs 15.7/19.3/22.9/27.9 in men and 13.4/16.4/19.4/23.4 in women, for SFs 4.10/5.48/6.86/8.72 in men and 3.47/4.57/5.67/7.16 in women, for IFs 11.0/13.6/16.1/19.6 in men 9.5/11.7/13.8/16.6 in women

³ The following further adjustments were included in the main model: number of biological children (continuous), menopausal status (premenopause/postmenopause), use of hormonal replacement therapy (yes/no) and use of contraceptive pill (yes/no)

FIGURE LEGENDS

Figure 1. Participants flow-chart. NutriNet-Santé cohort, France, 2009-2019.

Figure 2. Associations between consumption of dietary fibers from different sources and (A) mortality (all cause and from cancer or cardio- and cerebrovascular diseases; N=89,896), (B) cardiovascular disease risk (overall, coronary heart diseases, cerebrovascular diseases; N=87,278), (C) cancer risk (overall and colorectal cancer; N=83,877), and (D) the risk of type 2 diabetes (N=87,295), from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009-2019. Diamond points and associated horizontal line represent the HR and 95%CI for quintile 5 vs quintile 1 of the intake from the corresponding fiber source. For legume and whole grain fibers, sex-specific quintiles could not be created due to limited number of consumers. The displayed HR and 95%CI are therefore for quartile 4 in consumers (sex-specific) vs non-consumers. All HR and 95% CI are shown in Supplementary Table 2. Significant P for trend across quintiles are indicated with an asterisk (*)