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.

ABSTRACT

Background

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

Objective

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

Design

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

Results

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

Conclusions

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

Keywords

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

INTRODUCTION

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

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

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

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

SUBJECTS, MATERIAL, AND METHODS

Study population

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

Data collection

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

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

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

Case ascertainment

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

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

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

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

Statistical analysis

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

handled using Multiple Imputation by Chained Equations (MICE) by fully conditional specification (FCS, 20 imputed datasets) for the following variables: body-mass index, physical activity and educational level (29).

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

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

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

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

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

RESULTS

Description of the study population

A total of 107,377 participants were eligible, from which were excluded prevalent cases of the disease under study as well as participants with less than two years of follow-up. Characteristics of these participants according to quintiles of TDF intakes are presented in **Table 1**. The mean ± SD age at inclusion was 42.8±14.6 years. Mean number of dietary records per participant was 6 (range: 2-15). On average, DF intakes were19.5±7.2 g/day for TDFs, 5.7±2.6 g/day for SFs, and 13.8±5.1 g/day for IFs. Distributions of the consumption of TDFs, IFs, and SFs, in the sample as well as their seasonal variations are presented in Supplementary Figure 2. Strikingly, 92.5% of individuals (85.4% of men and 94.4% of women) did not meet the French daily recommended TDF intake (i.e. 30 g of DFs per day).

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

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

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

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

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

In the T2D track, 544 incident cases of T2D occurred during follow-up. A decreased risk of T2D (median follow-up: 4.8 years, 388,205 person-years) was observed for TDFs (HR $_{Q5\ vs\ Q1}$: 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 not when adjusted for IF intake, and IFs (HR $_{Q5\ vs\ Q1}$: 0.69; 0.50, 0.96; P for trend=0.004), even when adjusted for SF intake (**Table 2**). T2D risk was also inversely associated with DF intake from fruit (HR $_{Q5\ vs\ Q1}$: 0.68; 0.50, 0.92; P for trend=0.004; **Figure 2**).

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

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

DISCUSSION

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

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

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

These results can be further discussed in light of a meta-analysis of randomized controlled

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

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

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

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

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

The interactions observed in our study suggested that DF may be an important component of a “healthy” dietary pattern for T2D prevention; interaction between IF and age was likely explained by the fact that older participants were more at risk compared to younger ones. DFs are not consumed alone but are rather brought by several sources (fruit, vegetables, legumes, cereals) also providing other compounds of interest (e.g. antioxidants, etc.) and are also usually part of healthy dietary patterns. Adjusting for antioxidant vitamins and minerals (vitamins C and E, selenium and zinc) or overall dietary patterns in our study did not modify the findings, arguing for a specific effect of dietary fibers. Additionally, several mechanistic hypotheses support our results. DFs are indeed associated with improved blood glucose levels (increased viscosity of the intestinal bulk and decreased transit time thus limiting the nutrient absorption rate (35)), improved insulin response (36–39) and a reduction of total and LDL serum cholesterol (37,40,41). Besides, the bulk-increasing capability of DFs may dilute fecal carcinogens and reduce transit time and thus, duration of exposure to these carcinogens (42). Finally, the potential protective role of DFs for the prevention of chronic diseases could be mediated by the gut microbial production of short-chain fatty acids (SCFAs) from the fermentation of undigestible DFs reaching the colon (43–45). SCFAs may play a role in maintaining the metabolic health of the human host through local and systemic effects on gut barrier integrity, inflammatory and immune response in the gut, glucose homeostasis and lipid metabolism in several tissues (46,47). Differential associations observed according to DF solubility or sources may reflect the specific properties of the various compounds coined as ‘dietary fibers’ (2). For instance, SF, especially when viscous, are recognized for their blood-glucose lowering or blood lipid-modifying effects and may be more quickly fermented into SCFAs. These properties are also particularly recognized for DFs characteristic of fruit, such as pectin (2).

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

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

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

The authors' contributions were as follows: VP, MD, BS, MT, designed the research; SH, PG, MT, EKG, CJ, LF, NDP, LQM, MLA, DD, OL, MI Consortium: conducted the research; BS, VP, performed data curation; VP: performed statistical analysis and wrote the original draft; MD: revised the manuscript (statistical analyses and writing); MT: supervised statistical analyses and manuscript writing; all authors: contributed to data interpretation and revised each draft for important intellectual content; MT had primary responsibility for the final 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 models[1], NutriNet-Santé cohort, France, 2009-2019

	Quintiles[2]						Per 1-SD increment	P-value
	Q1	Q2	Q3	Q4	Q5	P-trend		
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	75/85775		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 (*)