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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TITLE

ASSOCIATIONS BETWEEN CONSUMPTION OF DIETARY FIBERS AND THE RISK OF CARDIOVASCULAR DISEASES, CANCERS, TYPE 2-DIABETES, AND MORTALITY: RESULTS FROM THE PROSPECTIVE NUTRINET-SANTÉ COHORT

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ABSTRACT

Background

Mounting evidence suggests that dietary fibers (DF) may exert a protective role against a range of chronic diseases, which might depend on the type and source of DF. Various levels of proof have been reported. The objectives were to assess the associations between DF intakes (total (TDF), soluble (SF), insoluble (IF); fibers from fruits, vegetables, whole grains, legumes, potatoes and tubers) and mortality, cardiovascular diseases (CVD), cancers, and type 2-diabetes (T2D) risks in the large-scale NutriNet-Santé prospective cohort.

Design

Overall, 107,377 participants were included. Intakes of DF were estimated from validated repeated 24-hour dietary records. The associations between sex-specific tertiles of DF intake and the risks of mortality and chronic diseases were assessed using multi-adjusted Cox proportional hazards models. Associations between DF and gut microbiota composition (available for N=117) were also investigated.

Results

TDF were associated with chronic disease mortality (HR_{T3vT1};(95%IC)=0.69;(0.55-0.88), p_{trend}=0.002, 580 cases) and T2D risks (HR_{T3vT1};(95%IC)=0.75;(0.61-0.92), p_{trend}=0.006, 821 cases), so were IF (p_{trend}=0.0003 and 0.0007, respectively). SF were associated with chronic disease mortality (HR_{T3vT1};(95%IC)=0.77;(0.64-0.92), p_{trend}=0.004), T2D (HR_{T3vT1};(95%IC)=0.74;(0.61-0.90), p_{trend}=0.002), CVD (HR_{T3vT1};(95%IC)=0.87;(0.76-0.99), p_{trend}=0.02, 1952 cases) and colorectal cancer (HR_{T3vT1};(95%IC)=0.66;(0.44-1.01), p_{trend}=0.045, 182 cases) risks. Fibers from fruits were associated with the highest number of chronic conditions. Higher TDF intake was associated with increased gut microbiota α-diversity (Spearman's $\rho_{observed\ richness}$=0.20, p=0.03).

Conclusion

Our results support a protective role of DF – especially SF and DF from fruits – against several chronic conditions. DF intake is still below recommended levels in many countries and should represent a target for future public health nutrition policies.

Keywords

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

ABBREVIATIONS

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

INTRODUCTION

Non-communicable diseases are estimated to be responsible for 70% of deaths worldwide, thus representing the leading cause of death globally [1]. In a recent study, the Global Burden of Diseases consortium concluded that suboptimal diet is responsible for more deaths than any other risks globally, including tobacco smoking. It was suggested that promoting the consumption of dietary components for which intake is less than the optimal level might be an efficient way to mitigate the disease burden of dietary risks [2].

In this context, dietary fibers (DF) represent a highly promising nutrient target. The ingested amount of DF has indeed consistently been reported as inadequate when compared to the recommended intakes, regardless of the country considered [3]. Consumption of DF 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 [3], and the longer term. Mounting evidence indeed suggests a protective role of DF in mortality [3;4] and chronic diseases such as cardiovascular diseases (CVD) [2;5] and type 2-diabetes (T2D) [6;7]. Furthermore, evidence support a “probable” inverse relationship between DF and colorectal cancer, but controversy subsists regarding other cancer locations [8].

The generic term “dietary fibers” refers to a heterogeneous group of highly diversified compounds which vary in terms of structure and physicochemical properties [3;9]. For instance, soluble fibers differ from insoluble fibers in that the former turn into a viscous gel within the intestinal tract whereas the latter do not exhibit viscosity but can instead be characterized by their fecal-bulking ability [9]. Additionally, DF come from various sources (fruits, vegetables, whole grains, potatoes, tubers, and legumes being the principal sources of DF [10]). Overall, available studies suggest that DF might exert differential physiological effects depending on their solubility or sources [11-18]. Mounting evidence suggests that diet – and more specifically DF – exert an impact on gut microbiota [19-21]. The latter is now vastly recognized as a key player in human health and disease which might be involved in the development of chronic diseases [22-24].

In that context, our objective was to assess the associations between intake of dietary fibers based on their type (total dietary fibers (TDF), soluble fibers (SF), and insoluble fibers (IF)) and sources (TDF from fruits, vegetables, whole grain cereals, potatoes and tubers, and legumes) and the risk of CVDs, cancers, T2D – which are the leading causes of diet-related death [2] – and mortality, in a large prospective cohort of French adults with detailed nutritional exposure data. We also aimed at exploring associations between DF intakes and gut microbiota diversity in a subsample of this cohort.

MATERIAL & METHODS

Study population

This study was based on the NutriNet-Santé cohort, which has been initiated in May 2009, and for which the rationale, design, and methods have been extensively described elsewhere [25]. Briefly, NutriNet-Santé is a web-based prospective observational cohort which overall goal is to study the relationships between nutrition and health, as well as dietary behaviors and their determinants. Eligibility to engage in the study is conditional upon being at least 18 years old, speaking fluent French and having a regular access to the Internet – all questionnaires are indeed self-administered directly on the study website.

Data collection

At baseline, participants were required to fill in an “inclusion kit” collecting information related to socio-demographic [26] and lifestyle factors [27] (e.g. educational level, smoking status); anthropometrics (height, weight); physical activity (measured through the French version of the validated International Physical Activity Questionnaire (IPAQ) [28]; health status (e.g. personal and family medical history, medical treatments, reproductive life for women); and diet. Upon inclusion and every 6 months thereafter, dietary data was collected through 3 non-consecutive web-based 24-hour dietary records, randomly assigned over a 2-week period (2 weekdays and 1 weekend day) [29]. Validation studies comparing the dietary data collected within the NutriNet-Santé study to data obtained through interviews with a trained dietician [29] and to urinary and blood biomarkers [30;31] have been conducted and demonstrated

good consistency. For each dietary record, participants were asked to list all eating occasions (main meals – breakfast, lunch, dinner – plus any “other” eating occasion), and subsequent foods and beverages ingested, from midnight to midnight. Then, participants were required to estimate portion sizes for all items previously listed using photographs taken from a validated picture booklet [32], or through standard measurements (home containers, grams indicated on the package, etc.). Dietary intakes (energy, alcohol, macronutrients, micronutrients, etc.) were inferred using the published *NutriNet-Santé* composition database [33] which is regularly updated, and comprises nutritional values for more than 3,300 references. Additional ad hoc literature search was used to infer DF intakes (TDF, SF, IF). More precisely, Finnish *Fineli* [34] and Turkish *Türkomp [35]*, as well as reference books [36-38] were used. TDF intakes were also calculated based on the dietary sources (fruits, vegetables, whole grain, legumes, potatoes and tubers). Dietary under-reporting was investigated using the method described by Black [39], which uses the basal metabolic rate (calculated based on Schofield’s equations [40], as well as Goldberg’s cut-offs [41]). In this prospective study, mean dietary intakes from all the 24-hour dietary records available during the first 2 years of each participant’s follow-up (up to 15 records) were considered as baseline usual dietary intakes. Distributions of the consumption of TDF, IF, and SF in the sample are presented in **Supplemental figure 1**. In addition, biological and clinical data were collected for 19,772 participants of the cohort, including measures for fasting glycaemia.

Case ascertainment

Participants were asked to declare major health events through the yearly health questionnaire, through a quarterly specific questionnaire, or at any time through a specific interface on the study website. Upon the declaration of a health event, participants were invited to send all medical records and anatomopathological reports corroborating the diagnosis. If necessary, the study physicians contacted the participants' physicians or relevant medical structures to collect additional information and validate declared cases.

Besides, data collected within the NutriNet-Santé study is linked to the *SNIIRAM* database (medico-administrative database) from the *Caisse Nationale de l'Assurance Maladie*, which limits potential bias for participants who may not report their disease to the study investigators. Finally, additional and exhaustive information regarding deaths (date and cause of death) were obtained from the *Centre d'épidémiologie sur les causes médicales de Décès* (CépiDc) database. CVD and cancer cases were classified according to the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10), and cases were ascertained through reviewing of the medical data by a specific committee of physicians. T2D cases were ascertained using a multi-source approach, i.e. T2D declaration during follow-up along with declaration of the use of T2D medication (or a reimbursement of T2D medication detected from SNIIRAM), or hyperglycaemia in the biological data along with one T2D medication use. All first incident cancers, CVDs, T2D and deaths occurring between the inclusion and February 2019 were considered as cases. More precisely, all cancers except basal-cell carcinomas were included, and the CVDs considered were 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).

Gut microbiota sequencing

A subsample of 117 participants of the NutriNet-Santé study was also included in the Milieu Intérieur study, which primary objectives are to define the variability in a healthy population's immune phenotypes and to characterize the genetic and environment factors driving this variability [42]. To this end, the Milieu Intérieur Consortium has recruited a population-based sample of 1,000 French adults who have been extensively phenotyped. Notably, gut microbiota composition and systemic immune parameters have been determined and measured. More specifically, gut microbiota composition was determined through the sequencing of the V3–V5 region of the 16S ribosomal RNA gene in participants' stools upon inclusion. Detailed information regarding gut microbiota sequencing protocol (sampling, DNA

preparation, barcoding polymerase chain reaction protocol, sequencing, and computation of microbial diversity indexes) is provided in **Supplemental Method 1**.

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 of their follow-up. For each disease-specific analysis, prevalent cases of the corresponding disease were excluded. In the T2D track, prevalent and incident cases of type 1-diabetes were also excluded. Participants flow-chart is shown in **Figure 1**. For all covariates except physical activity, <5% of values were missing. These were therefore imputed to the modal value or to the median (for categorical or continuous variables, respectively). For physical activity however, the proportion of missing values was higher (14%), and a missing class was therefore introduced. Multiple imputation for missing data was also tested in sensitivity analyses using the MICE method [43].

DF intakes (TDF, SF, IF, as well as TDF from fruits, vegetables, whole grains, legumes, and potatoes and tubers) were computed as sex-specific tertiles. Cox proportional hazards models with age as the primary time-scale were used to evaluate the association between DF intakes and the incidence of CVD (overall, coronary heart diseases and cerebrovascular diseases), cancers (overall cancers, breast, prostate, and colorectal cancers), T2D, and mortality (overall and mortality from chronic diseases, which was not imputable to suicides, accidental reasons, or unknown reasons). Participants contributed person-time 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. For each model, hazard ratios (HR) and 95% confidence intervals (CI) were computed. Schoenfeld residuals were generated in order to confirm risk proportionality assumptions (**Supplemental figure 2**). Reference models (Model 1) were multi-adjusted for age (continuous, as time-scale), sex (male/female), body-mass index (BMI) (continuous, in kg.m^{-2}), physical activity (low, moderate, high), smoking status (current smoker, ex-smoker, non-smoker), alcohol intake (continuous, in g.d^{-1}), energy intake (continuous, in kcal.d^{-1}), number of 24-hour dietary

records (continuous), educational level (<high-school degree, <2 years of higher education, ≥2 years of higher education), and family history of the chronic pathology of interest (CVD, cancer, or T2D) for pathology models or family history of CVD and cancer for mortality models (yes/no). Cancer models were additionally adjusted for height (continuous, in cm). Further adjustments were performed to test for the potential influence of metabolic risk factors (model 2), the overall quality of the diet (models 3 and 4), and study design (model 5). Thus, model 2 was adjusted for baseline dyslipidemia, hypertriglyceridemia, hypertension (yes/no), as well as the baseline medical treatments associated with these conditions (yes/no). For CVD and cancer, model 2 was also adjusted for baseline T2D (yes/no) and baseline T2D medical treatment (yes/no). Model 3 was adjusted for saturated fat, sodium, and added sugar intakes (continuous, in $g.d^{-1}$). Model 4 was adjusted for the intakes of vitamin C, vitamin E, zinc, and selenium (continuous, in $g.d^{-1}$). To mitigate potential reverse causality, model 5 was carried out by excluding participants whose conditions were diagnosed or whose death occurred within 2 years after inclusion. For breast cancer, additional analyses were run by stratifying based on the menopausal status. In the premenopausal model – which was adjusted for the number of biological children (continuous) and the use of contraceptive pill (yes/no) – women were censored at the age of menopause; in the postmenopausal model – which was adjusted for the number of biological children (continuous) and the use of hormonal replacement therapy (yes/no) – women contributed person-time from their age of menopause onwards. For CVDs, an additional analysis was run excluding TIA and angina pectoris.

Unconstrained principal coordinate analysis (PCoA) of the Bray–Curtis dissimilarity matrix was plotted and color-coded based on tertiles of TDF consumption. The vector corresponding to TDF intake was fitted onto the subsequent ordination, and standard deviational ellipses were plotted. Associations between TDF, SF, and IF intakes and α-diversity indexes were tested using nonparametric Spearman correlations.

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

Out of the 118,290 participants of the NutriNet-Santé cohort with valid dietary data, 10,913 were excluded because of an insufficient number of 24-hour dietary records. Therefore, 107,377 participants were included in our study sample (i.e. “maximum” sample, which was used for the mortality analyses). Flow-chart is shown in **Figure 1**. Characteristics of the maximum sample according to tertiles of TDF intakes are presented in **Table 1**. Overall, 22,838 (21.3%) males and 84,539 (78.7%) females were included. Mean ± standard deviation (SD) age of participants at baseline was 42.8 ± 14.6 years. Mean ± SD DF intakes were 19.5 ± 7.2g for TDF, 5.7 ± 2.6g for SF, and 13.8 ± 5.1g for IF. Distributions of the consumption of TDF, IF, and SF in the sample are presented in **Supplemental figure 2**. Strikingly, 92.5% of individuals (85.4% of males and 94.4% of females) did not meet the French daily recommended TDF intake (i.e. 30 g of DF per day).

Associations between DF intakes and the risks of mortality and chronic diseases

Results of overall mortality, mortality attributed to chronic diseases, overall CVDs, coronary heart diseases, cerebrovascular diseases, overall cancers, colorectal cancer, and T2D are presented in **Table 2** for TDF, SF, and IF and **Table 3** for the different sources of dietary fibers. Corresponding associations for breast and prostate cancers are presented in **Supplemental Tables 1** and **2**.

In mortality analyses, median follow-up was 6.3 years (616,427 person-years) and 935 deaths occurred – of which 580 were attributed to chronic diseases. The risk of mortality attributed to chronic diseases was inversely associated with all 3 types of DF (p_{trend}=0.002 for TDF, 0.004 for SF and 0.0003 for IF), as well as with TDF from fruits (p_{trend}=0.02) and whole grains (p_{trend}=0.009).

In the CVD track, 89 ACSs, 841 angioplasties, 130 strokes, 164 MIs, and 760 TIAs – representing 1952 first incident cases – occurred during follow-up. SF were negatively associated with both the risk of overall CVDs (p_{trend}=0.02, median follow-up: 6.0 years,

579,099 person-years) and the risk of coronary heart diseases (p_{trend}=0.0005, median follow-up: 6.0 years, 581,374 person-years). TDF from fruits were associated with a decreased risk of overall CVDs (p_{trend}=0.01, median follow-up: 6.0 years, 579,099 person-years), as well as with a decreased risk of cerebrovascular diseases (p_{trend}=0.04, median follow-up: 6.0 years, 582,790 person-years).

Overall in the cancer track, 2503 first incident cancers occurred, among which 783 breast, 323 prostate, and 182 colorectal cancer cases. SF were associated with a decreased risk of colorectal cancer (p_{trend}=0.05, median follow-up: 6.0 years, 579,099 person-years). No associations were detected between any type or source of DF and overall cancers, breast cancer, or prostate cancer.

In the T2D track, 821 incident cases of T2D occurred during follow-up. TDF (p_{trend}=0.006) SF (p_{trend}=0.002), and IF (p_{trend}=0.0007) were all associated with a decreased risk of T2D (median follow-up: 6.0 years, 582,237 person-years). Besides, TDF from fruits were negatively associated with the risk of T2D (p_{trend}=0.0004).

Sensitivity analyses testing further adjustments for metabolic risk factors (model 2), beneficial and deleterious nutrient intakes (models 3 and 4), and excluding participants health events that occurred within 2 years after inclusion (models 5) provided similar results (**Supplemental Table 3**), although associations were slightly attenuated for SF and overall CVD risk (model 3), SF and colorectal cancer risk (models 3 and 4), SF and chronic disease mortality (model 5), and strengthened for TDF and overall CVD risk (model 5).

In the cardiovascular disease model, excluding the cases of TIA and angina pectoris did not modify the results: SF were significantly associated with a reduced risk of CVDs (HR_{T3vT1};(95%IC)=0.80;(0.67-0.95), p_{trend}=0.007, 821 cases), whereas TDF (HR_{T3vT1};(95%IC)=0.93;(0.77-1.11) and IF (HR_{T3vT1};(95%IC)=1.02;(0.85-1.21) were not.

Associations between TDF intake and gut microbiota composition

Overall, 117 participants of the NutriNet-Santé cohort also included in the Milieu Intérieur study had available gut microbiota composition. Unconstrained PCoA of the Bray-Curtis

dissimilarity matrix is shown in **Figure 2** and highlights grouping patterns along the gradient of TDF consumption. Observed richness was significantly associated with TDF (Spearman's $\rho = 0.20$, $p = 0.03$), and SF (Spearman's $\rho = 0.20$, $p = 0.03$). Chao1 richness estimate was significantly associated with TDF (Spearman's $\rho = 0.24$, $p = 0.01$), SF (Spearman's $\rho = 0.21$, $p = 0.02$), and IF (Spearman's $\rho = 0.22$, $p = 0.02$). No significant associations were detected between observed richness and IF (Spearman's $\rho = 0.17$, $p = 0.07$).

DISCUSSION

In this large prospective cohort of French adults, the results suggest a protective role of dietary fibers against several chronic conditions. Total dietary fibers were associated with the risks of mortality from chronic diseases and T2D, so were soluble and insoluble fibers. Soluble fibers were also associated with the risks of cardiovascular diseases and colorectal cancer. Fiber intakes from fruits were associated with the highest number of chronic conditions. Besides, higher dietary fiber intake was associated with increased gut microbiota α-diversity.

More precisely, we found that the risk of mortality from chronic diseases was inversely associated with all 3 types of DF (TDF, IF, and SF), as well as DF from fruits and whole grains, consistently with meta-analyses of prospective studies. Interestingly, a decreased risk of mortality (overall mortality [7], mortality from CVD [7;14;44]) was consistently associated with higher intakes of DF, but the investigation of the associations between the risk of mortality and DF intakes based on the type of fiber yielded more mixed results. A decreased risk of cardiovascular mortality was indeed significantly associated with higher intakes of IF and SF in the meta-analysis by Liu et al. [44], but not in the one by Kim et al. Regarding the dietary sources, DF from whole grains have been associated with a decreased risk of cardiovascular mortality [14], and the consumption of whole grains was negatively associated with overall mortality, cardiovascular, and cancer mortality [7]. Our results support such findings, and additionally suggest a protective effect of DF from fruits with regard to mortality from chronic diseases.

With regard to CVDs, meta-analyses of cohort studies reported negative associations between DF intakes and the risks of coronary heart diseases and stroke [7], between IF and SF and a lower risk of coronary heart diseases [17], and between IF alone and lower risks of overall CVDs [15]. Inverse associations between the risk of overall CVDs DF from cereals, fruits, and vegetables [15] and between the risk of coronary heart diseases and DF from cereals and fruits [17] were also reported in these meta-analyses. Consistently with these studies, we detected negative associations between SF and the risks of overall CVDs and coronary heart diseases, and between DF from fruits and the risks of overall CVDs and cerebrovascular diseases. These result can be further discussed in light of a meta-analysis of randomized controlled trials, which concluded that soluble fiber supplementation was significantly associated with a reduction of both systolic and diastolic blood pressures [45], which are risk factors for CVDs. Overall, our findings corroborate a beneficial role of DF in CVDs [2;5], and add to a mixed body of evidence. More studies dissecting these associations based on DF types and sources are required.

The current body of evidence links DF with a decreased risk of colorectal cancer [8;46;47], although distinct associations with DF types (SF and IF) remain to be extensively scrutinized. In the present work, we observed a negative association between the intake of SF and the risk of colorectal cancer. With regard to IF, we observed a protective trend, although the latter was not statistically significant. Overall, our findings support and extend the current knowledge suggesting a protective role of DF in colorectal cancer. Regarding other cancer locations, higher intakes of TDF were associated with a decreased risk of breast cancer in a systematic review and meta-analysis of epidemiological studies [48]. In prospective analyses conducted within the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) cohort our group observed negative associations between DF from vegetables – rather than TDF – and the risk of breast cancer [11], and between TDF, IF, and TDF from legumes and the risk of prostate cancer risk [12]. However, findings linking breast or prostate cancers to DF remain limited, as illustrated by the fact that the World Cancer Research Fund/American

Institute for Cancer Research did not come to an unequivocal conclusion [8], consistently with the results reported in the present study.

In the present study, all 3 types of DF, as well as DF from fruits were negatively associated with the risk of T2D, echoing various meta-analyses of prospective studies: the intakes of TDF [13;18], IF [18] and TDF from fruits [18] were indeed inversely associated with the risk of T2D. Other associations were suggested, which we did not detect – notably with DF from cereal [13;18] and from vegetables [13].

The potential beneficial effects of DF consumption suggested in this study could be linked not only to DF, but also to other nutritional compounds ingested along with DF (e.g. vitamins, minerals, antioxidants) since it is difficult to disentangle the effects of these various dietary components. Nonetheless, adjustment for antioxidants vitamins and minerals did not modify the findings, arguing for a specific effect of dietary fibers. Additionally, several mechanistic hypotheses have been proposed, which could explain our results. First, DF are associated to improvement of blood glucose levels. SF and IF were indeed demonstrated to decrease nutrient absorption (including simple carbohydrates) through increased viscosity of the intestinal bulk and decreased transit time, respectively [49]. Then, DF might have beneficial effects on insulin response, such as the stimulation of postprandial insulin release [50;51], the improvement of insulin sensitivity [52;53], and the reduction of insulin-like growth factor activity [54] – which has been linked to insulin resistance. Additionally, DF have be shown exert a modulatory impact on blood lipid profiles. More precisely, it appears that SF are associated to a reduction of serum cholesterol and LDL cholesterol through their ability to bind bile acids in the small intestine and therefore increasing lipid excretion in the feces [51;55;56]. Besides, beneficial effect of the bulk-increasing capability of DF include dilution of fecal carcinogens and reduction in transit time which allegedly decrease the contact with carcinogen compounds with the distal digestive tract [57]. Finally, mounting evidence shows that the protective effects of dietary fiber intake are probably mediated by gut microbiota. Gut bacterial metabolism produces short-chain fatty acids (SCFA) – acetate, propionate, and

butyrate are the 3 major SCFAs [58] – and abundant evidence supports the role of these compounds in maintaining health status of the human host. Notably, SCFA exert both local and systemic effects, ranging from supporting gut barrier integrity and controlling inflammatory and immune response the gut, to maintaining glucose homeostasis and regulating lipid metabolism in the adipose tissue, the liver, the muscle, etc. [58-60]. We observed that DF is positively associated with gut microbial diversity, consistently with the pioneer study by de Filippo et al., who compared the gut microbiota of rural African children to that of Italian children, and in which rural African children were not only reported to harbor a more diverse and functionally active gut microbiota, but also were the only ones harboring indigestible carbohydrates fermenters [21], which was imputed to huge differences in DF intakes (the African and Italian diets were notably characterized by high and low contents of DF respectively). Observational studies comparing the microbiotas of adult omnivores to that of adult vegans or vegetarians somehow confirmed that hypothesis [61;62]. Finally, mounting evidence suggests that the beneficial impact of DF could be mediated by the gut microbial production of SCFAs [63-66].

In addition to its prospective design, the main strength of our study pertained to the detailed nutritional phenotyping of a large sample size. The latter indeed allowed us to examine the associations between different types and sources of DF and a variety of chronic conditions. The dietary data we used was collected through validated repeated 24 hour-dietary records based on a detailed database comprising 3,300 food items. Additionally, we were able to investigate the cross-sectional associations between DF and gut microbiota composition for a subsample of participants. However, some limitations should be acknowledged. Although our models were adjusted for a variety of potential confounders, residual confounding cannot be ruled out. Besides, no causal relationships can be inferred from this observational study. To mitigate this, sensitivity analyses were performed, which confirmed the robustness of our results overall. Furthermore, statistical power was limited for certain pathologies, which may have affected our ability to detect previously reported associations. Finally, compared to the

general French population, participants of the NutriNet-Santé were younger, more often women, and with higher socio-professional and educational levels [67] and had healthier dietary habits [68]. This may limit the generalizability of our findings, and might also have resulted in an underrepresentation of cases and a smaller contrast in dietary intakes between compared groups, thus a loss of statistical power.

Overall, this large prospective study support a protective role of dietary fibers – especially soluble fibers and fibers from fruits – against various chronic diseases and mortality, consistently with mechanistic data. Dietary fiber intake is still far below recommended levels in many Western countries (in our study sample, 92.5% of the participants did not meet the French recommended DF intake) and should therefore represent a key target for future public health nutritional policies.

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Table 1. Baseline characteristics of the study population according to sex-specific tertiles of total dietary fiber intakes (n=107,377), NutriNet-Santé cohort, France, 2009-2019.

	All participants	Tertiles of total dietary fiber consumption[a]		
		Tertile 1	Tertile 2	Tertile 3
Age (y)	42.8 ± 14.6	38.6 ± 14.0	43.5 ± 14.5	46.4 ± 14.2
Sex				
Male	22838 (21.3)	7612 (21.3)	7613 (21.3)	7613 (21.3)
Female	84539 (78.7)	28179 (78.7)	28180 (78.7)	28180 (78.7)
BMI (kg/m^2)	23.7 ± 4.5	23.7 ± 4.6	23.9 ± 4.4	23.5 ± 4.4
Family history of CVD				
Yes	34044 (31.7)	9978 (27.9)	11476 (32.1)	12590 (35.2)
No	73333 (68.3)	25813 (72.1)	24317 (67.9)	23203 (64.8)
Family history of cancer				
Yes	40783 (38.0)	11921 (33.3)	13797 (38.6)	15065 (42.1)
No	66594 (62.0)	23870 (66.7)	21996 (61.5)	20728 (57.9)
Family history of T2D				
Yes	22774 (21.2)	7377 (20.6)	7598 (21.2)	7799 (21.8)
No	84603 (78.8)	28414 (79.4)	28195 (78.8)	27994 (78.2)
Educational level				
< High-school diploma	18774 (17.5)	6768 (18.9)	6169 (17.2)	5837 (16.3)
< 2 years of higher education	18372 (17.1)	7368 (20.6)	5732 (16.0)	5272 (14.7)
≥ 2 years of higher education	70231 (65.4)	21655 (60.5)	23892 (66.8)	24684 (69.0)
Smoking status				
Current smoker	18362 (17.1)	8808 (24.6)	5537 (15.5)	4017 (11.2)
Ex-smoker	35400 (33.0)	10242 (28.6)	12062 (33.7)	13096 (36.6)
Non-smoker	53615 (49.9)	16741 (46.8)	18194 (50.8)	18680 (52.2)
Physical activity level (IPAQ)				
High	30164 (28.1)	8364 (23.4)	9839 (27.5)	11961 (33.4)
Moderate	39680 (37.0)	12493 (34.9)	13567 (37.9)	13620 (38.1)
Low	22585 (21.0)	8944 (25.0)	7523 (21.0)	6118 (17.1)
Total dietary fibers (g.d^{-1})	19.5 ± 7.2	12.8 ± 2.6	18.6 ± 2	27.1 ± 6.4
Soluble fibers (g.d^{-1})	5.7 ± 2.6	3.6 ± 1.2	5.4 ± 1.3	8.1 ± 2.6
Insoluble fibers (g.d^{-1})	13.8 ± 5.1	9.2 ± 2.0	13.2 ± 1.8	19 ± 4.6
Total lipid intake (g.d^{-1})	81.5 ± 25.3	75.1 ± 29.6	82.3 ± 23.6	87.1 ± 27.9
Total carbohydrate intake (g.d^{-1})	198.1 ± 57.5	168.1 ± 46.3	198.2 ± 48.0	228.1 ± 60.6
Sodium intake (mg.d^{-1})	2718.0 ± 886.4	2425.0 ± 780.2	2759.2 ± 815.4	2969.8 ± 965.8
Vitamin C intake (mg.d^{-1})	116.1 ± 72.5	86.9 ± 66.9	114.7 ± 62.2	146.9 ± 74.9
Vitamin E intake (mg.d^{-1})	11.7 ± 4.7	9.6 ± 3.8	11.4 ± 3.8	14.2 ± 5.2
Selenium intake (mg.d^{-1})	69.1 ± 24.8	60.5 ± 21.8	69.1 ± 21.9	77.7 ± 27.2
Zinc intake (mg.d^{-1})	10.7 ± 3.3	9.5 ± 3.1	10.6 ± 3.0	11.9 ± 3.5
Energy intake (kcal.d^{-1})	1901.8 ± 469.1	1701.6 ± 402.7	1913.6 ± 417.9	2090.3 ± 497.5
Alcohol intake (g.d^{-1})	7.8 ± 11.9	8.6 ± 13.6	8.2 ± 11.6	6.7 ± 10.1

Values are N (%) or Mean ± SD.

[a]Sex specific tertiles of total dietary fibers. Sex-specific cut-offs for total dietary fiber were 18.2 g.d^{-1} and 24.2 g.d^{-1} in men and 15.5 g.d^{-1} and 20.5 g.d^{-1} in women.

Available for 92429 subjects. Subjects were categorized into the "high", "moderate" and "low" categories according to IPAQ guidelines (Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, and Oja P. 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. 35 (8): 1381-1395.)

Table 2. Associations between consumption of total, soluble and insoluble dietary fibers, and the risk of overall mortality, mortality attributed to chronic diseases, overall CVD, coronary heart diseases, cerebrovascular diseases, overall cancers, colorectal cancer, and type 2 diabetes from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009-2019

	Total dietary fibers				Soluble fibers				Insoluble fibers			
	Tertile[a]	N (of which cases)	HR (95%CI)[d]	p–trend[d]	Tertile[b]	N (of which cases)	HR (95%CI)[d]	p–trend[d]	Tertile[c]	N (of which cases)	HR (95%CI)[d]	p–trend[d]
Overall mortality[e]	T1	35,791 (290)	1.00		T1	35,791(288)	1.00		T1	35,791 (318)	1.00	
	T2	35,793 (322)	0.95 (0.80–1.12)	0.3	T2	35,793 (313)	0.81 (0.69–0.96)	0.004	T2	35,793 (301)	0.89 (0.76–1.06)	0.3
	T3	35,793 (323)	0.90 (0.75–1.09)		T3	35,793 (334)	0.77 (0.64–0.92)		T3	35,793 (316)	0.91 (0.76–1.10)	
Mortality attributed to chronic diseases[e]	T1	35,791 (194)	1.00		T1	35,791 (174)	1.00		T1	35,791 (216)	1.00	
	T2	35,793 (195)	0.79 (0.64–0.97)	0.002	T2	35,793 (204)	0.84 (0.68–1.03)	0.004	T2	35,793 (186)	0.75 (0.61–0.93)	0.0003
	T3	35,793 (191)	0.69 (0.55–0.88)		T3	35,793 (202)	0.71 (0.57–0.90)		T3	35,793 (178)	0.65 (0.52–0.82)	
Overall cardiovascular diseases[f]	T1	34,934 (479)	1.00		T1	34,934 (463)	1.00		T1	34,934 (512)	1.00	
	T2	34,936 (740)	1.04 (0.92–1.18)	0.2	T2	34,936 (727)	0.98 (0.87–1.10)	0.02	T2	34,936 (710)	1.05 (0.93–1.18)	1.0
	T3	34,935 (733)	0.92 (0.80–1.05)		T3	34,935 (762)	0.87 (0.76–0.99)		T3	34,935 (730)	1.01 (0.89–1.15)	
Coronary heart diseases[f]	T1	34,934 (302)	1.00		T1	34,934 (296)	1.00		T1	34,934 (314)	1.00	
	T2	34,936 (455)	1.04 (0.90–1.22)	0.6	T2	34,936 (468)	0.99 (0.85–1.16)	0.01	T2	34,936 (449)	1.11 (0.96–1.29)	0.4
	T3	34,935 (462)	0.97 (0.81–1.15)		T3	34,935 (455)	0.82 (0.70–0.97)		T3	34,935 (456)	1.08 (0.91–1.27)	
Cerebrovascular diseases[f]	T1	34,934 (209)	1.00		T1	34,934 (197)	1.00		T1	34,934 (235)	1.00	
	T2	34,936 (341)	1.04 (0.87–1.25)	0.1	T2	34,936 (304)	0.93 (0.77–1.12)	0.9	T2	34,936 (315)	0.96 (0.80–1.14)	0.3
	T3	34,935 (328)	0.87 (0.71–1.07)		T3	34,935 (377)	0.97 (0.80–1.18)		T3	34,935 (328)	0.91 (0.75–1.10)	
Overall cancers[g]	T1	33,759 (591)	1.00		T1	33,759 (571)	1.00		T1	33,759 (643)	1.00	
	T2	33,760 (914)	1.06 (0.95–1.18)	0.9	T2	33,760 (883)	0.97 (0.87–1.08)	0.6	T2	33,760 (916)	1.07 (0.96–1.19)	0.8
	T3	33,760 (998)	1.01 (0.89–1.13)		T3	33,760 (1049)	0.97 (0.87–1.09)		T3	33,760 (944)	0.99 (0.88–1.11)	
Colorectal cancer[g]	T1	33,759 (44)	1.00		T1	33,759 (45)	1.00		T1	33,759 (52)	1.00	
	T2	33,760 (77)	1.11 (0.76–1.64)	0.1	T2	33,760 (70)	0.87 (0.59–1.28)	0.045	T2	33,760 (72)	1.00 (0.69–1.45)	0.09
	T3	33,760 (61)	0.74 (0.47–1.15)		T3	33,760 (67)	0.66 (0.44–1.01)		T3	33,760 (58)	0.70 (0.46–1.08)	
Type 2–diabetes[h]	T1	34,901 (226)	1.00	0.006	T1	34,901 (210)	1.00	0.002	T1	34,901 (258)	1.00	0.0007

	T2	34,903 (292)	0.83 (0.69–1.00)	T2	34,903 (305)	0.88 (0.74–1.06)	T2	34,903 (273)	0.75 (0.63–0.90)
	T3	34,903 (303)	0.75 (0.61–0.92)	T3	34,903 (306)	0.74 (0.61–0.90)	T3	34,903 (290)	0.70 (0.58–0.86)

CI, confidence interval; HR, hazard ratio

For mortality models N=107,377. For cardiovascular disease models N=104,805. For cancer models, N=101,279. For type 2 diabetes models N=104,707

[a]Cut-offs for sex-specific tertiles of TDF consumption were 18.2g.d^{-1} and 24.2g.d^{-1} for men and 15.5g.d^{-1} and 20.5g.d^{-1} for women.

[b]Cut-offs for sex-specific tertiles of SF consumption were 5.0g.d^{-1} and 7.4g.d^{-1} for men and 4.2g.d^{-1} and 6.1g.d^{-1} for women.

[c]Cut-offs for sex-specific tertiles of IF consumption were 12.8g.d^{-1} and 17.1g.d^{-1} for men and 11.0g.d^{-1} and 14.6g.d^{-1} for women.

[d]HR (95%CI) and p-value were computed from Cox proportional hazard model, adjusted for age (timescale), sex, body-mass index, physical activity, smoking status, alcohol intake, energy intake, number of 24-hour dietary records, educational level, and family history of the chronic pathology of interest (CVD, cancer, or T2D) for pathology models or family history of CVD and cancer for mortality models. Cancer models were also adjusted for height.

[e]Mean follow-up time for mortality was 6.3 years, with 616,427 person-years.

[f]Mean follow-up times for overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases were all equal to 6.0y. Person-years were 579,099, 581,374, and 582,790 respectively.

[g]Mean follow-up times for overall cancers and colorectal cancer was 6.0y. Person-years was 579,099.

[h]Mean follow-up times for type 2-diabetes was 6.0y. Person-years was 582,237.

Table 3. Associations between consumption of dietary fibers from different sources, and the risk of overall mortality, mortality attributed to chronic diseases, overall CVD, coronary heart diseases, cerebrovascular diseases, overall cancers, colorectal cancer, and type 2 diabetes from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009-2019

	Total dietary fibers from fruits				Total dietary fibers from vegetables				Total dietary fibers from whole grains				Total dietary fibers from legumes				Total dietary fibers from potatoes & tubers			
	Tertile[a]	N (of which cases)	HR (95%CI)[f]	p–trend[f]	Tertile[b]	N (of which cases)	HR (95%CI)[f]	p–trend[f]	Tertile[c]	N (of which cases)	HR (95%CI)[f]	p–trend[f]	Tertile[d]	N (of which cases)	HR (95%CI)[f]	p–trend[f]	Tertile[e]	N (of which cases)	HR (95%CI)[f]	p–trend[f]
Overall mortality[g]	T1	35,791 (258)	1.00	0.07	T1	35,791 (251)	1.00	1.0	T1	36,011 (356)	1.00	0.004	T1	59,810 (513)	1.00	0.1	T1	35,793 (289)	1.00	0.4
	T2	35,793 (306)	0.88 (0.74–1.05)		T2	35,793 (326)	1.06 (0.90–1.26)		T2	35,573 (272)	0.80 (0.68–0.95)		T2	11,775 (95)	1.03 (0.82–1.3)		T2	35,763 (320)	1.14 (0.97–1.35)	
	T3	35,793 (371)	0.85 (0.71–1.01)		T3	35,793 (358)	1.01 (0.86–1.20)		T3	35,793 (307)	0.79 (0.68–0.93)		T3	35,792 (327)	1.12 (0.97–1.3)		T3	35,821 (326)	1.07 (0.91–1.26)	
Mortality attributed to chronic diseases[g]	T1	35,791 (159)	1.00	0.02	T1	35,791 (151)	1.00	0.7	T1	36,011 (217)	1.00	0.009	T1	59,810 (320)	1.00	0.8	T1	35,793 (187)	1.00	1.0
	T2	35,793 (201)	0.90 (0.73–1.12)		T2	35,793 (212)	1.10 (0.89–1.36)		T2	35,573 (175)	0.82 (0.67–1.01)		T2	11,775 (67)	1.13 (0.86–1.49)		T2	35,763 (192)	1.03 (0.84–1.27)	
	T3	35,793 (220)	0.77 (0.62–0.96)		T3	35,793 (217)	0.97 (0.78–1.20)		T3	35,793 (188)	0.77 (0.63–0.93)		T3	35,792 (193)	1.02 (0.85–1.23)		T3	35,821 (201)	1.00 (0.82–1.23)	
Overall cardiovascular diseases[h]	T1	34,934 (447)	1.00	0.01	T1	34,934 (475)	1.00	0.1	T1	35,102 (537)	1.00	0.4	T1	58,316 (928)	1.00	1.0	T1	34,922 (535)	1.00	1.0
	T2	34,936 (670)	0.90 (0.79–1.02)		T2	34,936 (723)	1.00 (0.89–1.12)		T2	34,770 (712)	1.04 (0.92–1.16)		T2	11,558 (270)	1.00 (0.87–1.15)		T2	34,935 (711)	0.99 (0.88–1.11)	
	T3	34,935 (870)	0.85 (0.75–0.97)		T3	34,935 (754)	0.92 (0.82–1.04)		T3	34,933 (703)	0.96 (0.85–1.07)		T3	34,931 (754)	1.00 (0.90–1.1)		T3	34,948 (706)	1.00 (0.89–1.12)	
Coronary heart diseases[h]	T1	34,934 (275)	1.00	0.09	T1	34,934 (283)	1.00	0.9	T1	35,102 (346)	1.00	0.3	T1	58,316 (576)	1.00	0.9	T1	34,922 (336)	1.00	0.9
	T2	34,936 (431)	0.96 (0.82–1.13)		T2	34,936 (463)	1.10 (0.94–1.28)		T2	34,770 (437)	0.99 (0.86–1.15)		T2	11,558 (176)	1.03 (0.87–1.23)		T2	34,935 (437)	0.97 (0.84–1.12)	
	T3	34,935 (513)	0.88 (0.75–1.03)		T3	34,935 (473)	1.01 (0.86–1.18)		T3	34,933 (436)	0.93 (0.81–1.08)		T3	34,931 (467)	1.01 (0.89–1.14)		T3	34,948 (446)	1.01 (0.87–1.17)	
Cerebrovas--cular diseases[h]	T1	34,934 (203)	1.00	0.04	T1	34,934 (218)	1.00	0.1	T1	35,102 (234)	1.00	0.6	T1	58,316 (414)	1.00	0.9	T1	34,922 (237)	1.00	0.9
	T2	34,936 (288)	0.80 (0.67–0.97)		T2	34,936 (321)	0.92 (0.77–1.1)		T2	34,770 (326)	1.06 (0.90–1.26)		T2	11,558 (117)	0.98 (0.79–1.21)		T2	34,935 (322)	0.98 (0.82–1.16)	
	T3	34,935 (387)	0.80 (0.67–0.97)		T3	34,935 (339)	0.85 (0.71–1.01)		T3	34,933 (318)	0.96 (0.81–1.14)		T3	34,931 (347)	1.01 (0.87–1.17)		T3	34,948 (319)	0.99 (0.83–1.17)	
Overall	T1	33,759	1.00	1.0	T1	33,759	1.00	0.9	T1	34,075	1.00	0.4	T1	56,418	1.00	0.7	T1	33,759	1.00	0.3

cancers[i]		(540)				(572)				(696)				(1184)				(717)		
	T2	33,760 (847)	0.97 (0.87–1.09)		T2	33,760 (923)	1.05 (0.94–1.17)		T2	33,445 (874)	0.97 (0.88–1.08)		T2	11,106 (361)	1.11 (0.98–1.25)		T2	33,761 (920)	0.99 (0.89–1.09)	
	T3	33,760 (1116)	0.99 (0.89–1.11)		T3	33,760 (1008)	1.01 (0.90–1.12)		T3	33,759 (933)	0.96 (0.87–1.06)		T3	33,755 (958)	1.02 (0.93–1.11)		T3	33,759 (866)	0.94 (0.85–1.05)	
Colorectal cancer[i]	T1	33,759 (36)	1.00	0.1	T1	33,759 (35)	1.00	0.7	T1	34,075 (49)	1.00	0.9	T1	56,418 (91)	1.00	0.4	T1	33,759 (52)	1.00	1.0
	T2	33,760 (75)	1.13 (0.75–1.69)		T2	33,760 (70)	1.24 (0.82–1.87)		T2	33,445 (63)	1.03 (0.70–1.5)		T2	11,106 (31)	1.30 (0.85–1.99)		T2	33,761 (65)	1.00 (0.69–1.45)	
	T3	33,760 (71)	0.77 (0.50–1.17)		T3	33,760 (77)	1.14 (0.76–1.72)		T3	33,759 (70)	0.99 (0.68–1.43)		T3	33,755 (60)	0.86 (0.61–1.20)		T3	33,759 (65)	1.00 (0.69–1.45)	
Type 2–diabetes[j]	T1	34,901 (215)	1.00	0.0004	T1	34,901 (218)	1.00	0.1	T1	35,100 (271)	1.00	0.06	T1	57,835 (412)	1.00	0.9	T1	34,900 (198)	1.00	0.1
	T2	34,903 (291)	0.90 (0.75–1.08)		T2	34,903 (281)	0.92 (0.77–1.11)		T2	34,704 (270)	0.85 (0.77–1.11)		T2	11,555 (109)	1.02 (0.82–1.27)		T2	34,904 (299)	1.18 (0.97–1.4)	
	T3	34,903 (315)	0.72 (0.60–0.87)		T3	34,903 (322)	0.87 (0.73–1.05)		T3	34,903 (280)	0.85 (0.73–1.05)		T3	34,905 (300)	0.99 (0.84–1.15)		T3	34,903 (324)	0.96 (0.82–1.13)	

CI, confidence interval; HR, hazard ratio

For mortality models N=107,377. For cardiovascular disease models N=104,805. For cancer models, N=101,279. For type 2 diabetes models N=104,707

[a]Cut-offs for sex-specific tertiles of TDF from fruits consumption were 2.1g.d^{-1} and 4.6g.d^{-1} for men and 2.0g.d^{-1} and 4.1g.d^{-1} for women.

[b]Cut-offs for sex-specific tertiles of TDF from vegetables consumption were 3.6g.d^{-1} and 5.9g.d^{-1} for men and 3.5g.d^{-1} and 5.6g.d^{-1} for women.

[c]Cut-offs for sex-specific tertiles of TDF from whole grains consumption were 0g.d^{-1} and 2.3g.d^{-1} for men and 0.3g.d^{-1} and 2.1g.d^{-1} for women.

[d]Cut-offs for sex-specific tertiles of TDF from legumes consumption were 0g.d^{-1} and 0.6g.d^{-1} for men and 0g.d^{-1} 0.4g.d^{-1} for women.

[e]Cut-offs for sex-specific tertiles of TDF from potatoes and tubers consumption were 0.5g.d^{-1} and 1.2g.d^{-1} for men and 0.4g.d^{-1} 1.0g.d^{-1} for women.

[f]HR (95%CI) and p-value were computed for Cox proportional hazard model, adjusted for age (timescale), sex, body-mass index, physical activity, smoking status, alcohol intake, energy intake, number of 24-hour dietary records, educational level, and family history of the chronic pathology of interest (CVD, cancer, or T2D) for pathology models or family history of CVD and cancer for mortality models. Cancer models were also adjusted for height.

[g]Mean follow-up time for mortality was 6.3 years, with 616,427 person-years.

[h]Mean follow-up times for overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases were all equal to 6.0y. Person-years were 579,099, 581,374, and 582,790 respectively.

[i]Mean follow-up time for overall cancers and colorectal cancer was 6.0y. Person-years was 579,099.

[j]Mean follow-up times for type 2-diabetes was 6.0y. Person-years was 582,237.

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

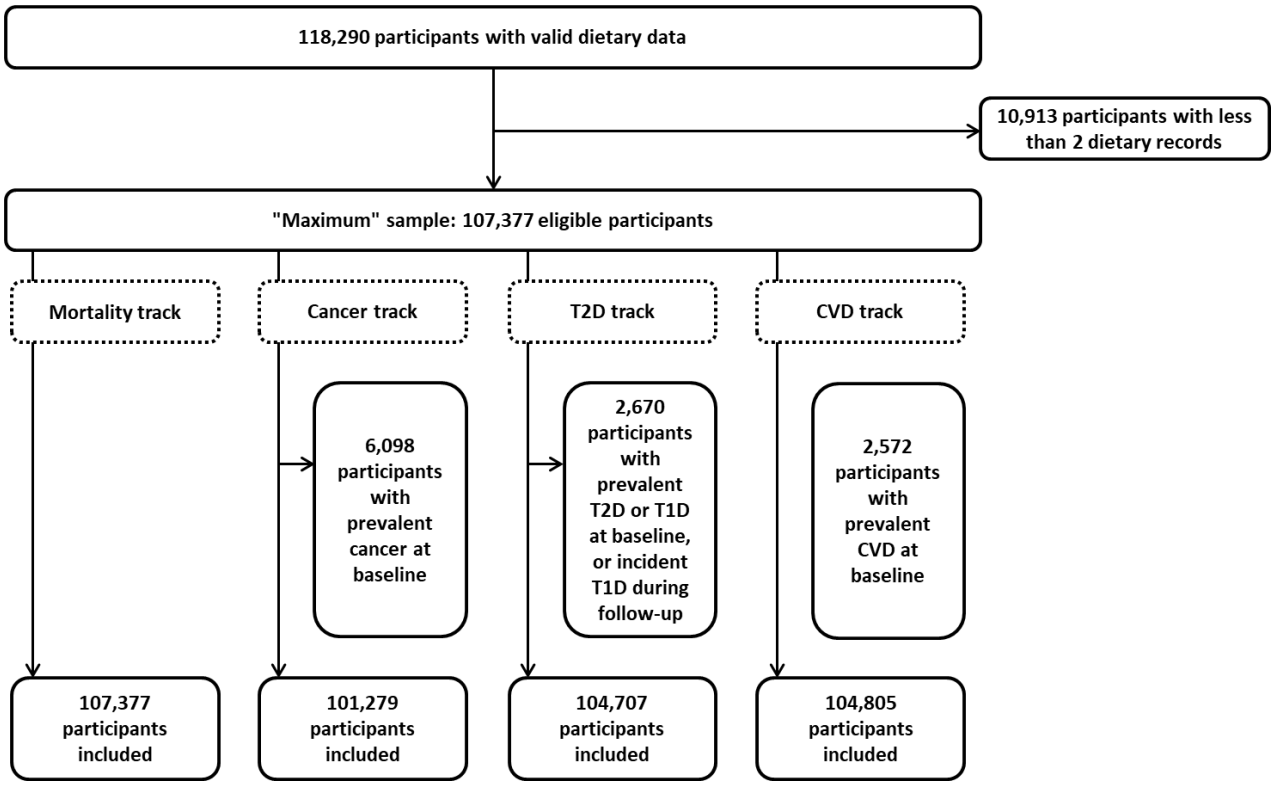
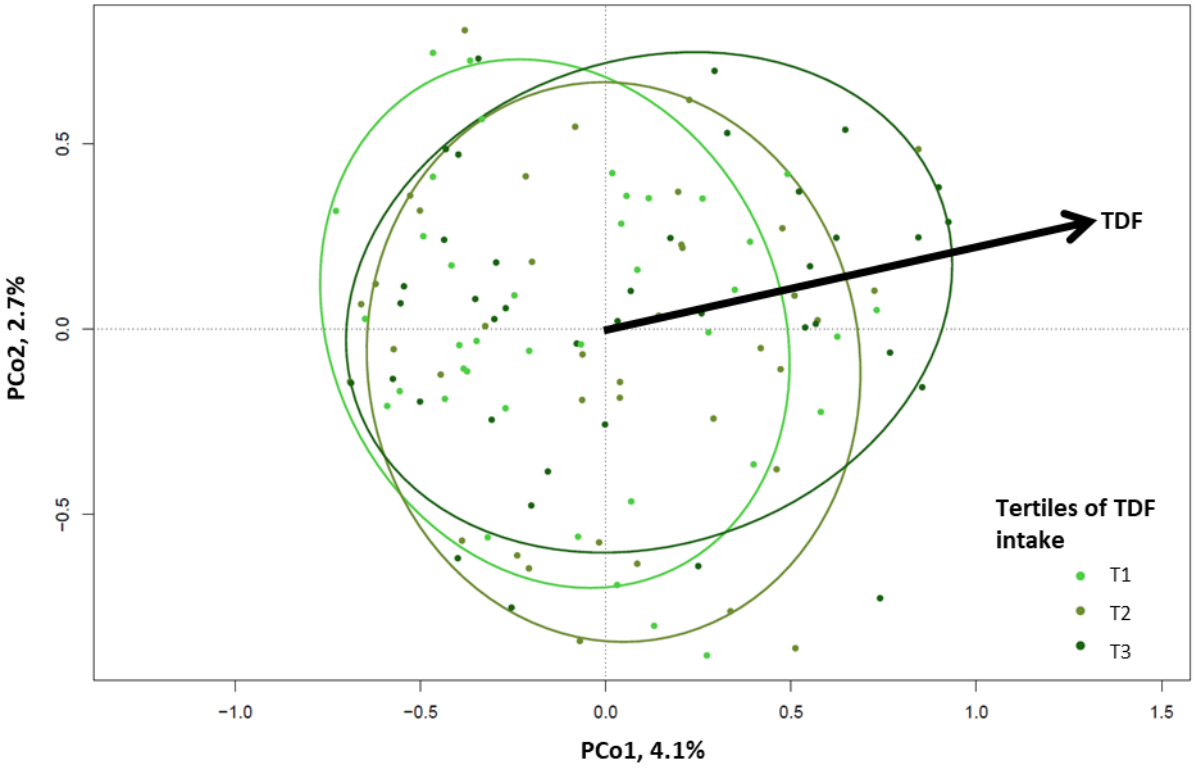


Figure 2. Interindividual variation in gut microbiota composition represented by unconstrained principal coordinate analysis (PCoA) of the weighted Bray-Curtis distance, Milieu Intérieur study, France, 2012 (N=117).



Legend: Each point represents an individual from the study sample. Arrows indicate the direction of TDF consumption gradient and was obtained via the *envfit* function (package vegan). Standard deviational ellipses were obtained via the *ordiellipse* function (package vegan). Percentages on the axes represent the proportion of variation explained by the 2 first components of the PCoA.

TDF, Total dietary fiber

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AUTHORS' CONTRIBUTIONS

The authors' contributions were as follows: VP, BS, MD, 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; SM: performed microbiota sequencing; VP: performed statistical analysis and wrote the original draft; 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.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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The funding bodies had no role in the design of the study, the collection, analysis, and interpretation of data, or in the writing of the manuscript.

APPROVAL AND ETHICS

The NutriNet-Santé protocol is conducted in accordance with the Declaration of Helsinki and was approved by the *Comité d'évaluation éthique de l'INSERM* (CEEI/IRB INSERM n°0000388FWA00005831), the *Commission Nationale Informatique et Libertés* (CNIL n°908450 et n°909216), as well as the *Comité consultatif sur le traitement de l'information en matière de recherche* (CCTIRS n°08.301). The protocol is registered under ClinicalTrials.gov (NCT03335644). Informed consent is obtained from each participant through the signing of an electronic consent form.

The Milieu Intérieur study is sponsored by *Institut Pasteur* (Pasteur ID-RCB Number: 2012-A00238-35). It was conducted as a single center study and without any investigational product, and was approved by the *Comité de Protection des Personnes – Ouest 6* on 06/13/2012 (CPP Ouest 6-728/MS2) and by *Agence Nationale de Sécurité du Médicament* on 06/22/2012 (ID-RCB Number: 2012-A00238-35, ref. ANSM: B120239-70). The protocol, which is registered under ClinicalTrials.gov (NCT01699893), was designed and conducted in accordance with the Declaration of Helsinki and good clinical practice as outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice.

DATA SHARING

Gut microbiota sequencing data including 16S rRNA gene sequences are available on the European Genome-phenome Archive (EGA), under the accession number EGAS00001003419. No additional data is available.