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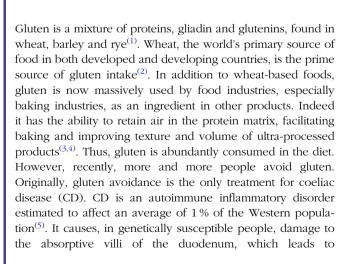
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### **Abstract**

The number of people avoiding gluten is growing in many Western countries. However, little information is available on their sociodemographic and dietary profiles. We aimed to describe sociodemographic, behavioural and dietary profiles of participants avoiding gluten in the NutriNet-Santé cohort. Participants of the NutriNet-Santé cohort – excluding coeliac patients – who completed a questionnaire about food exclusions, with complete data on sociodemographic characteristics and dietary intake were included (n 20 456). Food group consumptions and nutrient intakes according to self-reported avoidance of gluten were estimated using ANCOVA adjusted for age, sex and daily energy intake. Based on principal component analysis, three dietary patterns (DP) were identified. Association between DP and avoidance of gluten was investigated using multivariate logistic regression. All data were weighted on the French census. A total of 10·31 (95 % CI 9·90, 10·73) % of the participants declared avoiding gluten, of which 1.65 % totally. They were more likely to be women, older persons, non-smokers, to have a lower educational level and declared more food intolerances. They had higher consumption of fruit, vegetables and lower consumption of dairy products, salty/sweet and fatty foods and alcohol. After adjustments on confounders, a healthy dietary pattern was positively associated with total gluten avoidance (ORquintile5vsQuintile1 = 14·44, 95 % CI 8·62, 24·19). Our study highlighted that, in this population, individuals who avoid gluten from their diet tend to have a diet more favourable to health. These results can serve as a basis for future studies investigating the potential consequences of a gluten-free diet in non-coeliac population.

Key words: Gluten-free diet: Non-coeliac gluten sensitivity: Sociodemographic characteristics: Dietary patterns: Motives



malabsorption of important nutrients<sup>(6)</sup>. However, in the past decade, avoidance of gluten has occurred outside the diagnosis of CD<sup>(7,8)</sup>. For example, in New Zealand, a study has reported that 5% of children avoided gluten whereas 1% had a CD<sup>(9)</sup>. Besides, a US study showed that among the people following a glutenfree diet (GFD), only 18% had been diagnosed with CD, and 6 % with non-coeliac gluten sensitivity (NCGS)<sup>(10)</sup>. NCGS is a disorder characterised by intestinal and extra-intestinal symptoms occurring after the ingestion of gluten<sup>(1)</sup>. Contrary to CD, no sensitive and specific biomarkers have been identified for this disorder, and a lot of people self-reported NCGS without medical diagnosis.

The majority of people following a GFD are therefore likely healthy people leading to the explosion of the gluten-free market (1,11-13). Indeed, market of gluten-free products showed

Abbreviations: CD, coeliac disease; CU, consumption unit; DP, dietary pattern; GFD, gluten-free diet; NCGS, non-coeliac gluten sensitivity.

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an annual growth rate of 34% between 2009 and 2014 and 10.4% between 2014 and 2019 in the USA and Europe, respectively<sup>(1,11)</sup>. The number of people who avoid gluten is very large and varies, according to the studies and the geographic locations, between 3.7% and 17.2%<sup>(7,14–18)</sup>. Of the few studies that examined gluten avoidance in the general population, most of them focused on the motives and the symptoms related to gluten ingestion. These studies reported that people avoiding gluten were more likely to be women, with other food intolerances like lactose<sup>(14–18)</sup>. Regarding the motives underlying gluten avoidance, the most common reported were weight control, perception that it is healthier and symptoms triggered after gluten ingestion<sup>(16–18)</sup>. These studies<sup>(16–18)</sup> reported that people without CD who avoid gluten included healthy persons and persons that considered themselves to be suffering from NCGS.

The majority of consumers who avoid gluten perceived gluten-free products more healthful than their gluten-containing counterparts<sup>(13,19)</sup>. However, no medical evidence suggests that the general population would be better off by excluding gluten from their diet<sup>(12,20)</sup>. In addition, this diet may result in nutritional consequences because gluten-free foods contain more energy, carbohydrates, Na and lipids and less protein than their gluten-containing equivalents<sup>(21)</sup>. However, very few studies examined the nutritional characteristics of people without CD avoiding gluten and these provided inconsistent findings<sup>(22–25)</sup>.

As many other countries worldwide, French dietary integrate mainly wheat-based products. Thus, our aim was to estimate the prevalence of gluten avoidance in French non-coeliac adults, as well as the motives for avoidance. Furthermore, we sought to compare demographic and nutritional characteristics between people who avoid gluten and those who do not avoid it.

#### Materials and methods

## Study population

Participants were selected from the NutriNet-Santé study, a web-based observational prospective open cohort study launched in France in May 2009, including internet-using adult volunteers aged 18 years and older (26). The NutriNet-Santé study aims to investigate the relationship between nutrition and health, as well as the determinants of dietary behaviours and nutritional status. At baseline, participants completed a set of self-administered questionnaires about socio-economic conditions and lifestyle, health status, diet, physical activity and anthropometrics characteristics. These data are yearly updated. Moreover, during follow-up, additional and optional questionnaires are regularly proposed on various aspects of dietary behaviours and health.

### **Ethics**

The NutriNet-Santé study is conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the French Institute for Health and Medical Research (Inserm institutional review board no. 0000388FWA00005831) and the National Commission on Informatics and Liberty (CNIL nos. 908450 and 909216). All subjects provided their

informed consent with an electronic signature. This study is registered in EudraCT (no. 2013-000929-31) and in Clinical Trials.gov (NCT03335644).

#### Data collection

Definition of participants avoiding gluten. An optional questionnaire was sent to 121 266 participants of the cohort on 9 September 2016 and was available for completion over a 4-month period. Information on food exclusions and their motives were asked. The questionnaire included three parts: self-reported exclusion of eighty-three types of foods, specific diets with their motivations and allergies. Participants were asked the following question: 'Do you exclude products containing wheat/barley/rye/oats (gluten) from your diet?' and the responses were 'yes totally/yes partially/no'. Thus, participants were classified into three groups: total avoiders, partial avoiders or non-avoiders.

Participants reported a CD as they answered 'yes' to the question 'Do you have a coeliac disease?' and that they reported a medical diagnosis or other type of 'diagnosis' answering the following question 'Was it diagnosed by a general practitioner, a specialist, a dietitian?'

Sociodemographic and lifestyle data. Demographic, socioeconomic and lifestyle characteristics were collected upon enrollment and each year thereafter. The baseline questionnaires were compared against traditional assessment methods<sup>(27)</sup>. These characteristics included sex, age, marital status, household composition, number of children, geographical region, education level, occupational category, income, smoking status and physical activity. Monthly household income was divided by consumption unit (CU), where one CU was attributed for the first adult in the household, 0.5 CU for other individuals aged 14 years or older, and 0.3 CU for children under 14 years, following national statistics methodology and guidelines<sup>(28)</sup>. Physical activity was assessed using a short form of the French version of the International Physical Activity Questionnaire<sup>(29)</sup>. BMI (in kg/m<sup>2</sup>) was calculated as the ratio of weight to squared height and then classified following the WHO guidelines<sup>(30)</sup>.

Dietary data. At baseline and every 6 months, participants were invited to complete web-based, self-administered 24-h dietary records using validated tools(31,32). These records were randomly assigned over a 2-week period, on three non-consecutive days (two weekdays and one weekend day). Participants reported all foods and beverages consumed at each eating occasion, as well as portion sizes according to photographs from a validated picture booklet(33). The values for energy, macro- and micronutrients were estimated using a published nutrient database, completed for recent market foods and recipes. The modified Programme National Nutrition Santé Guidelines Score (mPNNS-GS), that reflects adherence to the French dietary recommendations<sup>(34)</sup> (maximum value = 13.5, reflecting the highest level of adherence to the French dietary guidelines), was calculated. Reported foods and beverage items have been reduced to eighteen food/beverage groups: fruits, vegetables, legumes, potatoes and other tubers, meat, fish and seafood,





processed meat (and fish), whole starchy foods, refined starchy foods, breakfast cereals, dairy products, eggs, added fats (including butter, margarine, sauces), oils, salty/sweet and fatty foods, sugary drinks, sugar-free drinks and alcoholic beverages.

Statistical analysis. For the present analysis, we selected participants who had completed at least three 24-h dietary records during the 2-year period preceding the food exclusions questionnaire. Thus, the analysis included all the records made in the 2 years preceding the questionnaire (mean 7.65, sp 3.69). People reporting a CD were excluded as well as those with missing data on the covariates and living overseas.

To adjust our sample to the actual percentage in the French population, weighting was calculated for each sex via the SAS CALMAR (CALage sur MARges) macro developed by the Institut National de la Statistique et des Etudes Economiques (INSEE)(35) based on the following information: sex, age, educational level, occupational categories, marital status and geographical area of residence. All analyses were weighted according to this CALMAR macro.

First, description of sociodemographic characteristics between total avoiders, partial avoiders or non-avoiders was performed and P values referred to  $\chi^2$  tests or ANOVA. Comparison of the eighteen food group consumptions and nutrients intake between the three groups was also realised. Macronutrients were considered as the percentage of energy intake. Micronutrient intakes were adjusted for energy intake using the residual method<sup>(36)</sup>. Then, adjusted mean for age and sex and 95 % CI from ANCOVA were reported. Food group consumptions were also adjusted for daily energy intake.

A factor analysis, using principal component analysis, was performed to extract dietary patterns (DP) that are independent linear combinations of the eighteen food groups, thereby maximising the explained variance in dietary intake. The number of retained patterns was determined using eigenvalues of each factor, Cattel's scree test (plot of the total variance related to each pattern) and interpretability of the factors. For each participant, the individual pattern score was calculated by summing the intake of the eighteen food groups that were weighted by their factor loading. Then, the dietary pattern scores were categorised into quintiles to allow better interpretation of the food intake associated with each one the DP obtained.

To assess the association between the exclusion of gluten and each DP (in quintiles), multivariable polytomic logistic regression models were performed. Adjusted OR with their 95 % CI are presented. A first model was minimally adjusted for age (continuous) and sex. The multivariable model was adjusted for age, sex, educational level (no diploma or primary studies/secondary studies/higher educational level), occupational category (nine classes), income level (<1200 € per CU/ 1200-2300 € per CU/>2300 € per CU), smoking status (never smoker/former smoker/occasional smoker/regular smoker), physical activity (low, moderate, high), number of 24-h dietary records, alcohol and total daily energy intake without alcohol.

All tests of significance were two-sided and a P value <0.0001was considered significant, given the high number of statistical

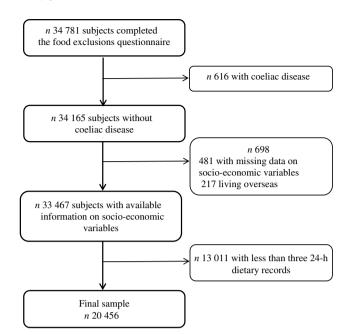


Fig. 1. Flowchart of the study.

tests performed and the large sample size. Statistical analyses were conducted with SAS (version 9.4, SAS Institute, Inc.).

### **Results**

### Sample selection

From the initial 121 266 subjects who received the questionnaire on food exclusions, a total of 34 781 answered the questionnaire. Within this sample, we excluded participants that reported a diagnosed CD, with missing data regarding the socioeconomic characteristics, living overseas and those with missing data on food intake. The final sample available for analysis included n 20 456 individuals (Fig. 1), of whom 375 declared to be total gluten avoiders, 1661 partial avoiders, and 18 420 non-avoiders. The weighted prevalence rate of respondents who were gluten avoiders was 10.31 %, of which 1.65 % were total gluten avoiders.

### Sociodemographic and individual characteristics

Sample weighted characteristics are presented according to the gluten avoidance, as well as for the whole sample (Table 1). Compared with non-avoiders, total and partial gluten avoiders were more likely to be women, older people, non-smokers, to have children and lower educational level.

Total avoiders are distinguished from partial avoiders: they were more likely to be retired, non-employed or managerial staff than manual worker or self-employed, had lower income and a moderate physical activity. Partial gluten avoiders were more often manual worker, with an intermediate profession or self-employed than employee or managerial staff. They were also more likely to have higher income and to present obesity.



**Table 1.** Sociodemographic and lifestyle characteristics according to the gluten avoidance after weighting

(Percentages; mean values and standard deviations)								
	Non- avoiders	Partial avoiders	Total avoiders		Total sample			
	(n 18 420)	(n 1661)	(n 375)	P*	(n 20 456)			
Sex (%) Men Women Age (years)	28·73 71·27	16·07 83·93	12·71 87·29	<0.0001 <0.0001	27·37 72·63			
Mean  SD  Marital status (%)	46·74 16·81	49·60 14·24	55·49 15·31	<0.0001	47·13 16·64			
Single Couple Presence of child	32·99 67·01	30·66 69·34	31·00 69·00	0.1076	32·76 67·24			
Yes No Educational level		66·05 33·95	74·07 25·93	<0.0001	61.80 38.20			
No diploma or primary school	27.38	40.79	40.09		28.75			
Secondary school	46-47	43-22	40-24	<0.0001	46.09			
High education level	26-15	15.99	19-67		25.16			
Occupational cate Farmer Craftsman,	egories (%) 0·78 2·59	1·29 4·71	0·42 1·91	<0.0001	0·82 2·77			
shopkeeper Employee Manual worker Intermediate	21·05 9·75 14·40	17·18 16·78 16·29	19·33 0·99 9·50		20.68 10.22 14.48			
profession Managerial staff	8-30	5.54	10-42		8-10			
Non- employed	10-46	9.61	14-98		10.46			
Student Retired	4.83 27.83	1.93 26.65	2·39 40·06		4·54 27·93			
Income per const <1200 €	20.00	(%) 20.75	27.84	<0.0001	20.19			
1200–2300 €	42.33	38-66	44.64		42.05			
>2300 €	23.97	26.04	20.08		24.09			
Refuse to declare	13.70	14.54	7.45		13-67			
Smoking status (	,	50.40	00.47	0.0004	50.00			
Never smoker Former	51·09 38·73	59·40 33·14	66·17 23·57	<0.0001	52·06 38·00			
smoker Occasional smoker	4.00	3.13	3.83		3.92			
Regular smoker	6.17	4.33	6.44		6.02			
Physical activity I	evel (%)							
Low	22.70	23.17	18.05	<0.0001	22.66			
Medium	36.90	34.20	50.72		36.89			
High BMI (kg/m²)	40.40	42.63	31.23	<0.0001	40.44			
Mean SD PML (%/)	23·98 4·69	25·42 5·79	23·48 4·37		24·10 4·80			
BMI (%) Normal, <25 kg/m <sup>2</sup>	67.58	55-64	68-10	<0.0001	66.55			
Overweight, 25–30 kg/m <sup>2</sup>	22.98	16.28	20.88		22.37			
Obese, ≥30 kg/m²	9.44	28.08	11.02		11.08			

 $<sup>^{\</sup>star}$  P values are based on the  $\chi^{2}$  test or the one-way ANOVA test as appropriate.

Table 2. Motives (%) for avoiding gluten

	Partial avoiders	Total avoiders	
	(n 1661)	(n 375)	P*
Physical comfort and well-being	38-94	25.58	<0.0001
Belief in a long-term health impact	27.79	22.06	
Taste	20.72	26.05	
Allergy, intolerance	8.24	20.77	
Price	2.18	0.03	
Environmental reasons	1.69	0.01	
Convenience	0.24	5.49	
Ethics reasons	0.21	0.01	

<sup>\*</sup> P values are based on the  $\chi^2$  test.

#### Food choice motives

People avoiding gluten reported more frequently health (physical well-being and belief of a long-term health impact) and taste as their main motive (Table 2). The main motive for participants who were total gluten avoiders was suffering from allergy and/or intolerance. Gluten avoiders were also more likely to follow a lactose-free diet, to exclude other foods and report higher number of allergies (online Supplementary Table S1).

## Food consumptions

Gluten avoiders had a higher consumption of vegetables, fruits, whole starchy food, fish and seafood, eggs and oils, and a lower consumption of refined starchy food, dairy products, salty/sweet and fatty foods and alcohol. A trend was observed from non-avoiders to total avoiders. Potatoes were largely consumed by total avoiders, and legumes and added fats were largely consumed by partial avoiders. Partial gluten avoiders had a lower consumption of meat and sugary drinks, whereas non-avoiders had a higher consumption. Partial and non-avoiders had also higher consumption of processed meat. Regarding the adherence to nutritional guidelines, partial gluten avoiders had the highest mean mPNNS-GS compared with total and non-gluten avoiders (Table 3).

## Energy and nutrient intake

Total energy intake was lower in participants with total avoidance, whereas it is higher in participants with partial avoidance (Table 4). Gluten avoiders had a lower percent energy from proteins (total avoiders > partial avoiders > non-avoiders) and higher percent energy from fat. They had the lowest mean contribution of SFA to energy intake and the highest for PUFA and MUFA. They (partial and total) also had lower daily intake of alcohol and cholesterol and higher intake of fibres, *n*-3 and *n*-6 PUFA. Total avoiders had lower intake of complex carbohydrates and higher intake of simple carbohydrates compared with partial avoiders. Regarding micronutrients and minerals intake, gluten avoiders exhibited higher intake except for Ca, retinol, Zn and Na (total avoiders > partial avoiders > non-avoiders).





Table 3. Comparisons of mean intakes of eighteen food groups (in g/d) included in the principal component analysis between total, partial and non-gluten avoiders

(Mean values and 95 % confidence intervals)

Food groups	Non-avoiders (n 18 420)		Pa	rtial avoiders (n 1661)	Total avoiders (n 375)		
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	P*
Fruits	218-29	215.58, 221.00	242.38	235.00, 249.77	310-65	294-22, 327-09	<0.0001
Vegetables	215.05	212.95, 217.15	269.88	264.17, 275.60	301.00	288.28, 313.73	<0.0001
Legumes	13-14	12.69, 13.58	22.80	21.59, 24.02	16.54	13.84, 19.24	<0.0001
Potatoes and other tubers	49.71	49.02, 50.40	47.44	45.57, 49.32	56.52	52.34, 60.70	0.0003
Refined starchy food	144.05	142.85, 145.25	141.93	138-65, 145-20	121.26	113.98, 128.55	<0.0001
Whole starchy food	38-36	37.53, 39.20	43.91	41.64, 46.18	46.59	41.54, 51.65	<0.0001
Meat	72.44	71.49, 73.38	59.77	57 20, 62 34	62.76	57.03, 68.49	<0.0001
Fish and seafood	35.46	34.94, 35.99	41.52	40.08, 42.96	42.30	39.10, 45.50	<0.0001
Eggs	15.29	14.94, 15.64	19.65	18.70, 20.60	23.67	21.56, 25.78	<0.0001
Processed meat	34.66	34.15, 35.17	34.51	33.12, 35.89	27.62	24.54, 30.71	<0.0001
Dairy products	217.66	215.23, 220.10	161.43	154.78, 168.07	137-14	122.35, 151.93	<0.0001
Breakfast cereals	6.11	5.82, 6.39	7.97	7.19, 8.74	10.32	8.60, 12.05	<0.0001
Salty/sweet and fatty foods	98.38	97.46, 99.30	95.29	92.79, 97.80	80.34	74.75, 85.92	<0.0001
Added fats	71.22	70.39, 72.05	84.47	82.21, 86.73	66.42	61.40, 71.45	<0.0001
Oils	8.83	8.68, 8.98	11.19	10.79, 11.59	18.04	17.14, 18.94	<0.0001
Sugary drinks	71.85	69.81, 73.88	53.01	47.47, 58.56	58.22	45.88, 70.57	<0.0001
Sugar-free drinks	1031-82	1022.77, 1040.87	1061-56	1036-89, 1086-22	1013-82	958-91, 1068-73	0.0505
Alcoholic beverages	122.50	120.07, 124.94	112.90	106 28, 119 53	83.29	68 54, 98 04	<0.0001
mPNNS-GS (SD)	7.39	7.37, 7.42	7.79	7.70, 7.87	7.39	7.20, 7.59	<0.0001

mPNNS-GS, modified Programme National Nutrition Santé Guideline Score.

## Dietary pattern

Three DP explaining 27.57 % of the total variance were identified (online Supplementary Table S2). The first DP was labelled 'healthy', it was characterised by a high consumption of fruits, vegetables, legumes, whole starchy foods, oils, sugar-free drinks and a low consumption of meat, processed meat, refined starchy foods, salty/sweet and fatty foods, sugary drinks, alcoholic beverages. The second DP was labelled 'traditional', it was characterised by a high consumption of potatoes and other tubers, added fats, meat, legumes, refined starchy foods, processed meat, alcoholic beverages and a low consumption of breakfast cereals. The third DP was labelled 'unhealthy snack', characterised by a high consumption of dairy products, salty/sweet and fatty foods, breakfast cereals and a low consumption of fish, eggs, alcoholic beverages and oils.

The multinomial logistic regression analysis linking the three groups of gluten avoidance and DP is presented in Table 5. Based on the first model, individuals with higher adherence to the 'healthy' DP were more likely gluten avoiders (O5 v. O1: OR 3.30 (95 % CI 2.82, 3.86) for partial gluten avoiders, and OR 14.38 (95 % CI 8.82, 23.43) for total gluten avoiders). For the 'traditional' DP, an association was only observed among partial gluten avoiders (Q5 v. Q1 only). The 'unhealthy snack' DP was negatively associated with gluten avoiding. Results were quite similar after accounting for confounders except for the 'traditional' DP showing a positive association with total gluten avoiding (Q5 v. Q1: OR 2.46 (95 % CI 1.65, 3.66) for total avoiders).

## Discussion

In this study based on participants from a large nutritional cohort study, investigating for the first time the sociodemographic and dietary characteristics of people avoiding gluten, we found that the percentage of people who avoid gluten was 10.31 %. This prevalence was higher than those reported in the UK, Argentina, Salvador and Mexico but lower than those reported in Australia and Colombia<sup>(7,14-18)</sup>.

Similar to our findings, all previous studies found a greater proportion of women in gluten avoiders(7,14,16-18,22,24,37,38). Concerning age and level of education, gluten avoiders in our study were more likely to be older people and with a lower educational level. Some studies are in line with our results<sup>(14,16,18,22,24)</sup>, whereas others are not<sup>(17,38)</sup>. The other studied characteristics were not reported in previous studies. However, we observed that gluten avoiders were more likely to have children in the household but an opposite association was reported in a previous study<sup>(24)</sup>. In our study, occupational category, income level and the BMI were also different between people who totally or partially avoiding gluten. Regarding the BMI, total avoiders were not different to non-avoiders, whereas partial avoiders presented more often obesity. While our study is cross-sectional limiting causal inference, some studies reported a large increase in BMI after adopting a GFD, but they focused only on patients with CD<sup>(39,40)</sup>. However to the best of our knowledge, no published data support a weight loss or a weight gain among people without CD following a GFD. Beside the fact that gluten avoiders exhibited higher energy intake, several hypothesis can explain this finding: first, many studies reported that people who avoid gluten often declared weight control as motives (12,13,17,18). It is possible that these participants who avoid gluten to lose weight are therefore overweight (41). A second hypothesis would be the consumption of gluten-free substitutes, known to contain more energy, carbohydrates, Na and lipids<sup>(21)</sup>.



P values are based on the ANCOVA test adjusted for total energy intake, age and sex.



**Table 4.** Energy intake, contribution of macronutrients to energy intake and mean micronutrient intake among total, partial and non-gluten avoiders (Mean values and 95 % confidence intervals)

	Non-avoiders (n 18 420)		Partial avoiders (n 1661)		Total avoiders (n 375)			
Energy/nutrients	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI	P*	
Total energy intake including alcohol (kcal/d)†	2052-68	2045-44, 2059-91	2094-27	2074-15, 2114-39	1969-11	1924-02, 2014-20	<0.0001	
Total energy intake excluding alcohol (kcal/d)†	1984-43	1977.34, 1991.52	2032-93	2013-21, 2052-64	1922-27	1878.08, 1966.47	<0.0001	
% of total energy intake excluding alcohol from:								
Total carbohydrates	42.37	42.26, 42.48	42.19	41.88, 42.50	42.01	41.31, 42.71	0.3400	
Simple sugars	19.56	19.47, 19.65	19.09	18.85, 19.34	20.28	19.72, 20.83	<0.0001	
Complex carbohydrates	22.69	22.60, 22.79	22.99	22.72, 23.25	21.62	21.02, 22.21	0.0001	
Total lipids	40.46	40.35, 40.56	41.32	41.03, 41.61	42.02	41.37, 42.68	<0.0001	
PUFA	5.78	5.75, 5.81	6.42	6.33, 6.51	7.19	6.99, 7.39	<0.0001	
MUFA	15.24	15.18, 15.29	16.18	16.02, 16.33	17.57	17.23, 17.92	<0.0001	
SFA	16.46	16.39, 16.52	15.89	15.71, 16.07	14.44	14.04, 14.84	<0.0001	
Total proteins	16.90	16.84, 16.95	16.24	16.08, 16.39	15.71	15.37, 16.05	<0.0001	
PUFA <i>n</i> -3 (g/d)‡	1.46	1.45, 1.47	1.78	1.75, 1.82	2.01	1.93, 2.09	<0.0001	
PUFA n-6 (g/d)‡	10.37	10.30, 10.43	11.46	11.27, 11.64	12-61	12.20, 13.02	<0.0001	
Alcohol (g/d)	9.75	9.57, 9.93	8.76	8.27, 9.26	6.69	5.59, 7.80	<0.0001	
Cholesterol (mg/d)‡	338.31	336.30, 340.32	333.28	327.69, 338.87	316-51	303.98, 329.04	0.0009	
Fibres (g/d)‡	20.79	20.67, 20.91	23.80	23.47, 24.14	24.56	23.81, 25.30	<0.0001	
Micronutients‡								
Vitamin B <sub>6</sub> (mg/d)	1.78	1.78, 1.79	1.86	1.84, 1.88	2.08	2.03, 2.12	<0.0001	
Vitamin B <sub>12</sub> (μg/d)	5.47	5.41, 5.53	5.28	5.11, 5.45	5.47	5.10, 5.84	0.0777	
Vitamin C (mg/d)	108-96	106.73, 111.18	153-61	147.43, 159.79	129.68	115.83, 143.53	<0.0001	
Vitamin D (μg/d)	2.85	2.82, 2.88	2.91	2.82, 3.00	3.04	2.85, 3.24	0.0783	
Vitamin E (mg/d)	12.52	12.45, 12.60	13.51	13.31, 13.72	15.68	15.22, 16.13	<0.0001	
β-Carotene (μg/d)	3502.40	3460 10, 3544 69	4339.05	4221-44, 4456-66	5814.71	5551 10, 6078 33	<0.0001	
Retinol (µg/d)	546.36	536 12, 556 61	494.65	466 16, 523 13	380.94	317.09, 444.79	<0.0001	
Folate (µg/d)	324.15	322.52, 25.78	343.97	339 44, 348 50	368-96	358-81, 379-11	<0.0001	
Minerals‡		,		•		,	<0.0001	
Ca (mg/d)	932-22	928-24, 936-20	850.76	839-69, 861-82	844-11	819.31, 868.92	<0.0001	
K (mg/d)	3141.16	3130.66, 3151.66	3261.47	3232.27, 3290.66	3515-69	3450-26, 3581-13	<0.0001	
Mg (mg/d)	360-40	358 44, 362 37	397-64	392.17, 403.10	445.19	432.93, 457.45	<0.0001	
Na (mg/d)	3439-24	3424.85, 3453.63	3309.92	3269.90, 3349.93	3266-61	3176-93, 3356-30	<0.0001	
Fe (mg/d)	14.46	14.39, 14.52	15.41	15.23, 15.59	17.04	16.64, 17.45	<0.0001	
P (mg/d)	1334-34	1329.42, 1339.26	1336-56	1322.88, 1350.23	1450-36	1419.71, 1481.01	<0.0001	
Zn (mg/d)	11.26	11.22, 11.30	10.87	10.76, 10.99	10.45	10.19, 10.71	<0.0001	

<sup>\*</sup> P values are based on the ANCOVA test, adjusted for age and sex.

Concerning the reasons to avoid gluten, our results are in line with previous studies reporting that a GFD is perceived healthier, but also for personal taste or preference (15-19,42). Our results showed that participants avoiding gluten were also more prone to exclude foods not containing gluten, to have allergies and also to adhere to a lactose-free diet. This is in accordance with previous studies that reported multiple food sensitivities and allergies<sup>(7,15–17,43,44)</sup>, particularly lactose intolerance(15-17,43,45). In 2015, an Australian study, using data obtained through the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Food and Health Survey and including adults aged 18 years and older reported that more than half of people avoiding gluten also avoided dairy products<sup>(15)</sup>. In New Zealand, a study showed that medical diagnosis of lactose intolerance was a strong predictor of gluten avoidance in children<sup>(9)</sup>.

Studies that reported nutritional intake in GFD have mainly focused on people with CD<sup>(46–48)</sup>. The few studies conducted in healthy people provided inconsistent results and involved small samples<sup>(22–25,44)</sup>. Unlike our study, the study conducted by Delvin<sup>(25)</sup>, including fifty-eight participants (twenty-five

persons with GFD) reporting their food consumption over a 5-d period, found inadequate intake such as lower intake of carbohydrates, fibres, folate, Ca and vitamin B, but higher intake of lipids and Na in those with GFD. Several studies did not detect any difference in energy and macronutrients intakes comparing people who avoid or not gluten (22,23,44). Similar to a previous study conducted in 2018 in the USA<sup>(24)</sup>, our results suggested that individuals avoiding gluten have an overall better nutritional profile. However, information about the consumption of gluten-free substitutes was limited in our sample, which may have affected the estimation of nutrient intakes related to these foods. Nevertheless, participants avoiding gluten reported greater consumption of fruits and vegetables and fewer sugary drinks. Their diet is also characterised by a low consumption of processed foods (salty/sweet and fatty foods including cakes, fatty foods), which generally contain more gluten, and by increasing the consumption of unprocessed foods such as fruits and vegetables. People avoiding gluten exhibited a healthier diet as shown by the analysis of DP. This result was is in line with the study conducted by Christoph et al. (24) that reported a healthy behaviour among people avoiding gluten.



<sup>†</sup> To convert energy in kcal to kJ, multiply by 4·184

<sup>‡</sup> Adjusted for total energy intake (without alcohol) using the residual method.



Table 5. Multinomial logistic regression analysis showing the association between dietary pattern and gluten avoidance (Odds ratios and 95 % confidence intervals)

	Non-avoiders ( <i>n</i> 18 420)		Partial avoiders (n 1661)			Total avoiders (n 375)	
	OR (reference)	OR	95 % CI	P	OR	95 % CI	P
Model 1*							
Healthy di	etary pattern						
Q1	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	1.88	1.60, 2.21	<0.0001	3.63	2.13, 6.19	<0.0001
Q3	1	2.05	1.74, 2.42	<0.0001	3.58	2.09, 6.14	<0.0001
Q4	1	1.32	1.10, 1.58	0.0025	3.31	1.92, 5.69	<0.0001
Q4	1	3.30	2.82, 3.86	<0.0001	14.38	8.82, 23.43	<0.0001
Traditiona	l dietary pattern						
Q1	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	0.79	0.67, 0.94	0.0060	1.018	0.71, 1.46	0.9232
Q3	1	1.57	1.35, 1.83	<0.0001	1.17	0.82, 1.69	0.3904
Q4	1	1.09	0.92, 1.29	0.3120	1.39	0.98, 1.98	0.0659
Q4	1	1.67	1.43, 1.95	<0.0001	1.43	0.997, 2.05	0.0522
Unhealthy	snack dietary pattern						
Q1	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	0.74	0.63, 0.86	<0.0001	0.68	0.51, 0.92	0.0107
Q3	1	0.72	0.62, 0.83	<0.0001	0.32	0.23, 0.46	<0.0001
Q4	1	0.38	0.31, 0.45	<0.0001	0.32	0.23, 0.46	<0.0001
Q4	1	0.89	0.78, 1.03	0.1154	0.48	0.34, 0.66	<0.0001
Model 2†							
Healthy di	etary pattern						
Q1 Î	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	1.92	1.62, 2.28	<0.0001	3.76	2.18, 6.48	<0.0001
Q3	1	2.12	1.79, 2.52	<0.0001	3.60	2.06, 6.28	<0.0001
Q4	1	1.39	1.16, 1.68	0.0005	2.87	1.63, 5.04	0.0002
Q5	1	3.73	3.16, 4.40	<0.0001	14.44	8.62, 24.19	<0.0001
Traditiona	I dietary pattern		,			, ,	
Q1	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	0.79	0.66, 0.93	0.0047	1.14	0.79, 1.64	0.5014
Q3	1	1.59	1.361, 1.85	<0.0001	1.42	0.98, 2.05	0.0653
Q4	1	1.06	0.89, 1.27	0.4981	2.00	1.38, 2.88	0.0002
Q4	1	1.46	1.22, 1.75	<0.0001	2.46	1.65, 3.66	<0.0001
	snack dietary pattern	* **	,		=	,	
Q1	1	Reference	Reference	Reference	Reference	Reference	
Q2	1	0.69	0.59, 0.81	<0.0001	0.61	0.45, 0.84	0.0022
Q3	1	0.63	0.54, 0.74	<0.0001	0.24	0.17, 0.35	<0.0001
Q4	1	0;30	0.24, 0.37	<0.0001	0.21	0.14, 0.31	<0.0001
Q4	1	0.58	0.48, 0.69	<0.0001	0.24	0.17, 0.35	<0.0001



Model 1 adjusted for age and sex.

In this study, people avoiding gluten-valued unprocessed foods and had a higher consumption of fruit and vegetables. This point is also in accordance with the health-related motives advanced by the participants.

Our study was subject to some limitations. First, participants enrolled in our study were volunteers in a nutrition cohort and had probably higher health consciousness and interest in nutritional issues than the general population. This may lead to particular characteristics, in particular, a healthier food profile, when compared with the general French population  $^{(49,50)}$ . In addition, the optional nature of the questionnaire on food exclusions may have exacerbated this selection bias, and this can result in an overestimated prevalence of individuals excluding foods. To counteract this issue, all analyses were weighted on the national census data. Second, data collection was based on self-reported questionnaires which are prone to measurement errors. A third limit concerns the list of motives in the questionnaire which were the same for different types of selective diet and were not specific to gluten. In particular, different gastro- and extra-intestinal symptoms related to gluten consumption were not assessed. Fourth, food exclusion questionnaires did not collect information about the date of beginning a gluten-free avoidance and dietary records did not take into account gluten-free products. Hence, it was not possible to know when a person declared eating a product (i.e. bread) if it was gluten-free or not. Taking dietary records into account over a 2-year period preceding the questionnaire may seem inappropriate and a shorter period could have been chosen, because we have no information on their date of beginning of avoidance. However, it would not be representative of a person's dietary habits. As food consumption presented large differences between people avoiding gluten and those do not avoid it, this limitation should have low impact on our results, and if it was the case, the differences would probably be even underestimated. Finally,



<sup>†</sup> Model 2 adjusted for age, sex, education level, occupational category, income, physical activity, smoking status, alcohol, total energy intake without alcohol and number of 24-h



our study was cross-sectional, and because of a potential reverse-causality, participants who adopted a healthy diet may be more likely to avoid gluten.

Our study had also important strengths. First, to the best of our knowledge, this was the first study evaluating the sociodemographic characteristics and dietary profile of people who avoid gluten within such a large sample from the general population, and especially in a French sample. Second, given the large sample size of the NutriNet-Santé cohort, and because participants are interested in nutritional issues, we had an access to a large population of gluten avoiders. This led to a high statistical power and to have a variety of DP. Third, the variety of available data allowed to control for confounding factors. Fourth, all analyses were weighted on national data to be more representative of the French population. Then, we used validated tools to assess dietary data, using repeated and detailed dietary records(31,32). All these data allowed us to describe the sociodemographic and nutritional characteristics, as well as the lifestyle of people who avoid gluten. Indeed, previous studies were generally limited to sociodemographic characteristics and motives. Finally, we used a questionnaire including a very large number of food exclusions, not specific to gluten, unlike some studies(14,16-18) allowing a comprehensive depicting.

# Conclusion

The present study is the first to provide a comprehensive description of dietary pattern related to gluten avoiding among persons without CD. More research is needed to confirm the association between healthy dietary pattern and gluten avoidance taking into account accurate data about nutrient composition of gluten-free foods as well as intake of non-nutritional components. Finally, further longitudinal studies are required to assess the long-term health effects of avoiding gluten among people without CD.

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## Supplementary material

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#### References

- Elli L, Branchi F, Tomba C, et al. (2015) Diagnosis of gluten related disorders: celiac disease, wheat allergy and non-celiac gluten sensitivity. World J Gastroenterol 21, 7110.
- Tovoli F, Masi C, Guidetti E, et al. (2015) Clinical and diagnostic aspects of gluten related disorders. World J Clin Cases 3, 275–284.
- 3. Parada A & Araya M (2010) History of gluten and its effects on celiac disease. *Rev Med Chil* **138**, 1319–1325.
- San Mauro Martín I, Garicano Vilar E, Collado Yurrutia L, et al. (2014) Is gluten the great etiopathogenic agent of disease in the XXI century? Nutr Hosp 30, 1203–1210.
- Fasano A, Berti I, Gerarduzzi T, et al. (2003) Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 163, 286–292.
- Lebwohl B, Sanders DS & Green PHR (2018) Coeliac disease. Lancet 391, 70–81.
- Aziz I, Lewis NR, Hadjivassiliou M, et al. (2014) A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. Eur J Gastroenterol Hepatol 26, 33–39.
- Rubio-Tapia A, Ludvigsson JF, Brantner TL, et al. (2012) The prevalence of celiac disease in the United States. Am J Gastroenterol 107, 1538–1544; quiz 1537, 1545.
- Tanpowpong P, Ingham TR, Lampshire PK, et al. (2012) Coeliac disease and gluten avoidance in New Zealand children. Arch Dis Child 97, 12–16.
- Sapone A, Bai JC, Ciacci C, et al. (2012) Spectrum of glutenrelated disorders: consensus on new nomenclature and classification. BMC Med 10, 13.
- Igbinedion SO, Ansari J, Vasikaran A, et al. (2017) Non-celiac gluten sensitivity: all wheat attack is not celiac. World J Gastroenterol 23, 7201–7210.
- Gaesser GA & Angadi SS (2012) Gluten-free diet: imprudent dietary advice for the general population? *J Acad Nutr Diet* 112, 1330–1333.
- Gaesser GA & Angadi SS (2015) Navigating the gluten-free boom. JAAPA 28, 1–7.



- 14. Ontiveros N, López-Gallardo JA, Vergara-Jiménez MJ, et al. (2015) Self-reported prevalence of symptomatic adverse reactions to gluten and adherence to gluten-free diet in an adult Mexican population. Nutrients 7, 6000-6015.
- 15. Golley S, Corsini N, Topping D, et al. (2015) Motivations for avoiding wheat consumption in Australia: results from a population survey. Public Health Nutr 18, 490-499.
- Cabrera-Chávez F, Granda-Restrepo DM, Arámburo-Gálvez JG, et al. (2016) Self-reported prevalence of gluten-related disorders and adherence to gluten-free diet in Colombian adult population. Gastroenterol Res Pract 2016, 4704309.
- Cabrera-Chávez F, Dezar GV, Islas-Zamorano AP, et al. (2017) Prevalence of self-reported gluten sensitivity and adherence to a gluten-free diet in argentinian adult population. Nutrients 9, 81.
- Ontiveros N, Rodríguez-Bellegarrigue CI, Galicia-Rodríguez G, et al. (2018) Prevalence of self-reported gluten-related disorders and adherence to a gluten-free diet in salvadoran adult population. Int J Environ Res Public Health 15, 786.
- 19. Dunn C, House L & Shelnutt KP (2014) Consumer perceptions of gluten-free products and the healthfulness of gluten-free diets. J Nutr Educ Behav 46, Suppl., S184-S185.
- Marcason W (2011) Is there evidence to support the claim that a gluten-free diet should be used for weight loss? J Am Diet Assoc **111**, 1786.
- 21. Miranda J, Lasa A, Bustamante MA, et al. (2014) Nutritional differences between a gluten-free diet and a diet containing equivalent products with gluten. Plant Foods Hum Nutr 69, 182-187.
- DiGiacomo DV, Tennyson CA, Green PH, et al. (2013) Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. Scand J Gastroenterol 48, 921-925.
- De Palma G, Nadal I, Collado MC, et al. (2009) Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. Br J Nutr 102, 1154–1160.
- Christoph MJ, Larson N, Hootman KC, et al. (2018) Who values gluten-free? dietary intake, behaviors, and sociodemographic characteristics of young adults who value gluten-free food. J Acad Nutr Diet 118, 1389-1398.
- Devlin J (2013) Nutrient intakes of healthy adults on a glutenfree diet. Master's Thesis, Ypsilanti, MI: The School of Health Sciences Dietetics and Human Nutrition, Eastern Michigan University.
- 26. Hercberg S, Castetbon K, Czernichow S, et al. (2010) The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. BMC Public Health 10, 242.
- Touvier M, Méjean C, Kesse-Guyot E, et al. (2010) Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. Eur J Epidemiol 25, 287-296.
- Institut National de la Statistique et des Etudes Economiques (INSEE) (2016) Définition – Unité de consommation. https:// www.insee.fr/fr/metadonnees/definition/c1802 August 2018).
- Hagströmer M, Oja P & Sjöström M (2006) The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. Public Health Nutr 9, 755-762.
- World Health Organization (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000. 894, i-xii, 1-253.
- Touvier M, Kesse-Guyot E, Méjean C, et al. (2011) Comparison between an interactive web-based self-administered 24 h dietary record and an interview by a dietitian for large-scale epidemiological studies. Br J Nutr 105, 1055-1064.

- 32. Lassale C, Castetbon K, Laporte F, et al. (2015) Validation of a web-based, self-administered, non-consecutive-day dietary record tool against urinary biomarkers. Br J Nutr 113,
- 33. Le Moullec N, Deheeger M, Preziosi P, et al. (1996) Validation du manuel-photos utilisé pour l'enquête alimentaire de l'étude SU.VI. MAX (Validation of the photo-manual used for the food survey of the study SU.VI.MAX). Cab Nutr Diététique 31, 158-164.
- 34. Estaquio C, Kesse-Guyot E, Deschamps V, et al. (2009) Adherence to the French Programme National Nutrition Santé Guideline Score is associated with better nutrient intake and nutritional status. J Am Diet Assoc 109, 1031-1041.
- 35. Institut National de la Statistique et des Etudes Economiques (INSEE) (2018) La macro SAS CALMAR Insee. https://www. insee.fr/fr/information/2021902 (accessed August 2018).
- Willett W & Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 124, 17-27.
- Reilly NR (2016) The gluten-free diet: recognizing fact, fiction, and fad. J Pediatr 175, 206-210.
- van Gils T, Nijeboer P, IJssennagger CE, et al. (2016) Prevalence and characterization of self-reported gluten sensitivity in the Netherlands. Nutrients 8, 714.
- Dickey W & Kearney N (2006) Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. Am I Gastroenterol 101, 2356-2359.
- 40. Kabbani TA, Goldberg A, Kelly CP, et al. (2012) Body mass index and the risk of obesity in coeliac disease treated with the gluten-free diet. Aliment Pharmacol Ther 35, 723-729.
- 41. Julia C, Péneau S, Andreeva VA, et al. (2014) Weight-loss strategies used by the general population: how are they perceived?. PLOS ONE 9, e97834.
- 42. Lu Z, Zhang H, Luoto S, et al. (2018) Gluten-free living in China: the characteristics, food choices and difficulties in following a gluten-free diet - an online survey. Appetite 127, 242-248.
- 43. Volta U, Bardella MT, Calabrò A, et al. (2014) An Italian prospective multicenter survey on patients suspected of having non-celiac gluten sensitivity. BMC Med 12, 85.
- Tavakkoli A, Lewis SK, Tennyson CA, et al. (2014) Characteristics of patients who avoid wheat and/or gluten in the absence of celiac disease. Dig Dis Sci 59, 1255-1261.
- 45. Gaillard LA (2016) Navigating gluten-related health disorders and nutritional considerations of gluten-free diets. N C Med J
- 46. Vici G, Belli L, Biondi M & Polzonetti V (2016) Gluten free diet and nutrient deficiencies: a review. Clin Nutr Edinb Scotl 35, 1236-1241.
- 47. Hallert C, Svensson M, Tholstrup J, et al. (2009) Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. Aliment Pharmacol Ther 29, 811-816
- Wild D, Robins GG, Burley VJ, et al. (2010) Evidence of high sugar intake, and low fibre and mineral intake, in the glutenfree diet. Aliment Pharmacol Ther 32, 573-581.
- 49. Andreeva VA, Salanave B, Castetbon K, et al. (2015) Comparison of the sociodemographic characteristics of the large NutriNet-Santé e-cohort with French Census data: the issue of volunteer bias revisited. J Epidemiol Community Health 69, 893-898.
- 50. Andreeva VA, Deschamps V, Salanave B, et al. (2016) Comparison of dietary intakes between a large online cohort study (Etude NutriNet-Santé) and a nationally representative cross-sectional study (Etude Nationale Nutrition Santé) in France: addressing the issue of generalizability in E-Epidemiology. Am J Epidemiol **184**, 660-669.

