



Impact of intra-category food substitutions on the risk of type 2 diabetes: a modelling study on the pizza category

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Abstract

Advice on replacing unhealthy foods with healthier alternatives within the same food category may be more acceptable and might ease the transition towards a healthy diet. Here, we studied the potential impact of substitutions within the pizza category on the risk of type 2 diabetes (T2D). The study sample consisted of 2510 adults from the INCA2 French national survey. Based on their nutritional characteristics, the 353 pizzas marketed in France were grouped into 100 clusters that were used to run various scenarios of pizza substitutions, which were either isoenergetic (IE) or non-isoenergetic (NIE). We then used a model structurally similar to the Preventable Risk Integrated ModEl to assess the expected rate of change in risk of T2D. Pizzas characterised by a low energy, high vegetable content and whole grain dough were associated with a greater reduction in the risk of T2D. The rates of change in risk of T2D were markedly stronger in men and for NIE substitutions. When the rates of change were estimated in the subsample of pizza consumers, replacing the observed pizzas with the best pizza resulted in a T2D risk reduction of -6.7% (-8.4% ; -4.9% , IE) and -8.9% (-11.2% ; -6.3% , NIE), assuming that this is their usual diets. The greatest risk reduction induced by an IE substitution of the observed pizza with a mixed dish was similar to that observed with the best pizzas. Overall, this modelling study suggests that healthy swaps within a category can effectively supplement broader dietary changes towards a healthier diet.

Key words: Food substitutions: Pizza categories: Type 2 diabetes: Public health

Diabetes is one of the most challenging public health issues, with a prevalence that is steadily increasing worldwide⁽¹⁾. According to the International Diabetes Federation, the number of people with diabetes is expected to rise from 425 million in 2017 to 629 million in 2045⁽²⁾. Diabetes can lead to long-term complications, including coronary heart disease, kidney disease, stroke, eye disease and neurological damage, Y5 and increase the overall risk of premature death. It has a considerable health-care cost and significantly impacts quality of life^(1,3–5).

Type 2 diabetes (T2D) is the most common type of diabetes. Epidemiological studies suggest that a combination of non-modifiable risk factors (such as age, ethnicity and genetics) and modifiable risk factors (including physical inactivity, unhealthy diet, excess body weight and tobacco use) are contributors to the development of T2D^(6,7). According to current scientific evidence, eating a healthy diet, having a high level of physical

activity and avoiding smoking could prevent up to 80% of type 2 diabetes cases^(8,9). Regarding the T2D risk, several epidemiological studies have shown negative associations for healthy diets (characterised by a high consumption of plant-based foods, whole grain products and fish and olive oil) ensuring an adequate intake of various vitamins and minerals, and positive associations for unhealthy diets (characterised by a high consumption of red and processed meats, refined grains, and foods high in sugars and saturated fats or trans fats)^(10–12). Mediterranean and vegetarian diets have been shown to be particularly beneficial^(13–15).

An overall healthy dietary pattern is the core objective for populations in public health nutrition, but because changing overall dietary patterns is an overwhelming task, guidelines have increasingly focused on making healthy choices within the different food groups as a practical method for implementation⁽¹⁶⁾. More

Abbreviations: IE, isoenergetic; NIE, non-isoenergetic; PRIME, Preventable Risk Integrated ModEl; RR, relative risks; T2D, type 2 diabetes.

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specifically, choosing a healthier alternative within a food category may be more readily achievable than substituting foods between different categories. However, to our knowledge, the efficiency of within-category substitutions on reducing the risk of T2D has not been evaluated to date.

The aim of this study was therefore to evaluate the potential impact of pizza substitutions on the risk of T2D as compared with substitutions by foods from the different category of mixed dishes and to identify the characteristics of pizzas related to a stronger reduction in the risk of T2D. We also wanted to examine whether the impact of tailored substitutions, i.e. implementing a substitution based on an individual dietary risk assessment differed from that of generic substitution, i.e. the same substitution for all individuals. The pizza category (generally classified as unhealthy) was selected for the present study because of the considerable nutritional variability in this category and its relatively high consumption⁽¹⁷⁾.

Materials and methods

Study population

Our analyses were based on the second Individual and National Food consumption survey (INCA2) conducted in 2006–2007 by the French Agency for Food, Environmental and Occupational Health Safety (agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES) to assess dietary intake and associated behaviours in a nationally representative sample of the French population^(18,19). The survey included two home visits by trained investigators. The INCA2 survey has been approved by the French National Commission for Computed Data and Individual Freedom (Commission Nationale de l'Informatique et des Libertés, CNIL)⁽¹⁸⁾.

In the present study, participants aged 3–17 years (n 1455) were excluded from the initial INCA2 sample (n 4079). Under-reporters defined as participants who reported a daily energy intake of < 1000 kcal (n 114) were also excluded. The final sample therefore included 2510 participants (57.1% women) aged 18–79 years (online Supplementary Fig. 1).

Data collection

Socioeconomic, demographic and physical activity data were collected during face-to-face interviews. Regarding physical activity, the short form of the French version of the International Physical Activity Questionnaire⁽²⁰⁾ was used to estimate energy expenditure in metabolic equivalents, expressed in MET-min per week. Trained investigators also collected weight and height data and BMI was calculated as the ratio of weight to squared height (kg/m^2).

Dietary data

Dietary intake was assessed using 7-d food records⁽¹⁸⁾. During the survey week, the participants were asked to report all foods and beverages consumed at each meal. Portion sizes were estimated using validated photographs⁽²¹⁾, household measurements or by specifying the exact amount consumed.

In order to obtain a precise estimate of the consumption of each food group identified as having an impact on the risk of T2D (whole grains, refined grains, fruits, green leafy vegetables, other vegetables, nuts, potatoes, dairy products, red meats, fish, eggs, processed meats, butter, olive oil, tea, coffee, chocolate, sugar-sweetened beverages and alcoholic beverages)^(12,22–29), each item reported by the participants was broken down into its ingredients (expressed as a quantity). The daily intake of energy and certain nutrients (carbohydrates, dietary fibres and Mg) associated with the risk of T2D^(30–32) were also estimated for each participant using CIQUAL (Centre d'Information sur la Qualité des Aliments) food composition tables. Other nutrients associated with the risk of T2D, such as polyphenols⁽³³⁾ were not considered in our study because the data were not available.

Pizza composition and classification

We used the database from the 'Observatoire de la qualité de l'alimentation' (Oqali), which collects labelling information on foods marketed in France, to estimate the nutrient composition and proportions of ingredients in the 353 pizza recipes (data collected in 2011) sold by medium and large supermarkets and frozen food stores. These 353 pizzas presented considerable diversity in terms of their nutritional quality, which was dependent on numerous criteria, such as the pizza family (cheese, vegetarian, ham-cheese, etc.), ratio of animal:plant ingredients or the quantity of dough.

These pizzas were grouped into 100 clusters based on their recipes and nutritional composition using a hierarchical ascending classification. First, a principal component analysis was performed using the quantities of the main ingredients and the nutritional composition of the pizzas as input variables. The hierarchical ascending classification using Ward's step method was then performed for the first four factors resulting from the principal component analysis (54% of the total variance explained). In order to keep a good picture of the large variability in the composition of the pizza category, the number of clusters at the end of the hierarchical ascending classification was set at 100. For each cluster, the mean recipe and nutritional composition were determined, and an 'average' pizza (online Supplementary Table 1) was therefore used for the pizza substitutions.

Statistical analysis

Baseline characteristics are presented separately for pizza consumers (participants who reported pizza consumption at least once during the 7-d food records) and non-consumers using means and standard deviation for continuous variables and percentages for categorical variables. Pizza consumers were compared with non-consumers using χ^2 tests or t tests as appropriate.

Estimation of the rate of change in the risk of type 2 diabetes. The rate of change in the risk of T2D was estimated using a model structurally similar to the Preventable Risk Integrated Model (PRIME). PRIME is a scenario model that estimates the impact of lifestyle changes in the population (diet, alcohol/tobacco consumption, BMI and physical activity) on non-communicable disease mortality^(34,35). Briefly, the PRIME estimates the change in the annual number of non-communicable disease deaths between

the baseline and counterfactual scenarios that depends on changes in the distribution of one or more behavioural risk factors in the study population. The model is parameterised using meta-analyses of epidemiological studies providing estimates of relative risks (RRs) linking diet and lifestyle variables and disease outcomes.

Using comparative risk assessment to estimate the rate of changes in T2D risk consists in estimating $(x'-x)/x$, where x is the observed baseline incidence resulting from the initial distribution of risk factors and x' is the counterfactual situation resulting from changes in risk factors. Here, we set $x = 1$, resulting in a rate of change in risk being equal to $x'-1$, which is thus the relative change (expressed as %) in risk.

If referring to the classical framework of the Comparative Risk Assessment on which the PRIME model is based⁽³⁵⁾, this rate of change in risk for each factor (i.e. nutritional variable) is the final Population Attributable Fraction ascribed to this factor. The Population Attributable Fraction for the different risk factors 1 to n for the same disease are then combined multiplicatively in the PRIME model (PAF_{tot}).

$$PAF = \left[\int RR(q)P(q)dq - RR(q)P'(q)dq \right] / \int RR(q)P(q)dq$$

and

$$PAF_{tot} = 1 - \prod_{i=1}^n (1 - PAF_i)$$

where $RR(q)$ is the relative risk of disease for risk factor level q (i.e. the level of intake for the nutritional variable), $P(q)$ is the number of people in the population with risk factor level q in the baseline scenario and $P'(q)$ is the number of people in the population with risk factor level q in the counterfactual scenario.

With this background, the rate of change in risk as estimated in the present study therefore refer to -PAF_{tot}.

In this study, we estimated the rate of change in the risk of T2D that would result from pizza substitutions (i.e. how much the risk of T2D varies when varying the intake of dietary factors (food groups and nutrients in the diet as affected by the pizza substitution). The model parameterisation does not require data regarding the mortality nor the diabetes incidence in the population, and the latter was anyway not reliably available for France. Model parameterisation was achieved using recently published RR data on the dose–response associations between diet (food groups and nutrients previously mentioned) and the risk of T2D^(12,22–28,30–32) as shown in Supplementary Fig. 2. The macrosimulation model also requires the baseline distributions of the various nutritional variables that are risk factors (sex-specific distributions for each food group and nutrient in the study population before pizza substitution) and the counterfactual distributions (sex-specific distributions for each food group and nutrient after pizza substitution).

Monte Carlo simulations (10 000 iterations) were performed to estimate 95% credible intervals around the estimates (2.5th percentile; 97.5th percentile).

Given the strong association between BMI (and therefore energy intake) and the risk of T2D, both isoenergetic (IE) and non-isoenergetic (NIE) substitutions were considered. The IE substitution consisted in replacing the observed pizza with the same weight of another pizza, while maintaining energy intake constant, by homogeneously adjusting the weight of all the other

solid foods consumed. The NIE substitution only consisted in replacing the observed pizza with the same weight of another pizza without maintaining energy intake.

The macrosimulation model algorithm was implemented in R. All other statistical analyses were conducted using SAS (version 9.4; SAS institute Inc.) with a significance level of 0.05 for two-sided tests.

Pizza substitutions. The substitutions were first performed at the individual level in order to identify for each participant the best/worst pizzas. To do this, each individual was artificially over-represented (so that it represents half of the overall population) so as to achieve sufficient precision in the estimate and thereby enabling easy individual ranking of the pizzas. The rates of change in the risk of T2D attributable to the various pizza substitutions were then ranked in ascending order to identify the pizzas leading to the highest relative increase (worst pizzas) or decrease (best pizzas) in the risk of T2D.

Second, we made three different types of pizza substitutions in pizza consumers in the overall sample. These substitutions consisted in simultaneously replacing the observed pizza by: (1) each of the five best/worst pizzas specific to the individual (tailored substitution); (2) the pizzas most frequently identified as the best or worst by all consumers (generic substitution) and (3) all the sixty-eight mixed dishes identified in the INCA food database (generic substitution; online Supplementary Table 2). Generic substitutions were analysed by considering either the overall sample study (i.e. pizza consumers and non-consumers) or the subsample of pizza consumers (all pizza consumers, as well as consumer sub-groups created according to their observed pizza consumption level), or other subgroups based on age, fruit and vegetable consumption, BMI and the overall diet quality.

Diet quality was measured using three dietary scores, namely the Literature-Based Adherence Score to the Mediterranean Diet (MEDI-LITE), the provegetarian food pattern (FP) and the modified version of the French National Nutrition Health Program (Programme National Nutrition Santé Guideline Score, mPNNS-GS). The mPNNS-GS, MEDI-LITE and provegetarian FP had, respectively, been developed to measure adherence to French nutritional guidelines, adherence to the Mediterranean diet and preferences for plant-derived foods^(36–39). The description and scoring systems for these dietary scores are presented in Supplementary Fig. 3.

Results

The analyses included 1076 men and 1434 women aged 46.6 ± 15.5 and 45.2 ± 15.2 years, respectively. Among the 880 pizza consumers, 78.2% reported pizza consumption once during the food data collection week and 16% twice. Compared with non-consumers, pizza consumers were more likely to be men, younger people, living alone, smokers, students or people in employment. They were also more likely to have a higher level of education (high school diploma or university level), a normal BMI and a low consumption of fruits and vegetables (< 400 g/d) (Table 1).

**Table 1.** Characteristics of the study population, INCA2 study (Mean values and standard deviations; numbers and percentages)

Characteristics	Pizza consumers (n 880)				Non pizza consumers (n 1630)				P*
	Men		Women		Men		Women		
	n	%	n	%	n	%	n	%	
n	426		454		650		980		
Age, years									<0.0001
Mean	41.2		39.2		50.1		48.0		
SD	14.3		14.3		15.2		14.9		
Marital status									<0.0001
Living alone	103	24.2	110	24.2	121	18.6	147	15.0	
Married/Cohabiting	286	67.1	275	60.6	456	70.2	606	61.8	
Divorced/Widowed	37	8.7	69	15.2	73	11.2	225	23.0	
Missing values	0		0		0		2	0.2	
Educational level									0.0002
< High school diploma	210	49.3	200	44.0	356	54.8	517	52.8	
High school diploma	84	19.7	97	21.4	86	13.2	167	17.0	
University level	132	31.0	156	34.4	207	31.9	295	30.1	
Missing values	0		1	0.2	1	0.1	1	0.1	
Employment status									<0.0001
Employed/Self-employed	304	71.4	269	59.3	383	58.9	535	54.6	
Unemployed	33	7.7	90	19.8	43	6.6	205	20.9	
Students	38	8.9	52	11.4	21	3.2	29	3.0	
Retired/Early-retired	51	12.0	43	9.5	203	31.3	211	21.5	
Smoking									0.002
Non smokers	133	31.2	203	44.7	190	29.2	487	49.7	
Former smokers	132	31.0	94	20.7	247	38.0	220	22.5	
Current smokers	158	37.1	146	32.2	202	31.1	247	25.2	
Missing values	3	0.7	11	2.4	11	1.7	26	2.6	
BMI									0.0002
Underweight/Normal weight	243	57.0	321	70.7	290	44.6	608	62.0	
Overweight	132	31.0	88	19.4	282	43.4	228	23.3	
Obesity	51	12.0	43	9.5	75	11.5	127	13.0	
Missing values	0		2	0.4	3	0.5	17	1.7	
Number of recording days									0.02
Mean	6.9		6.9		6.9		6.9		
SD	0.4		0.4		0.6		0.5		
Total energy intake, Kcal/d									0.27
Mean	2347		1830		2382		1834		
SD	613		452		677		466		
Energy intake without alcohol, kcal/d									0.15
Mean	2213		1787		2223		1784		
SD	582		438		640		452		
Carbohydrates, % energy†									0.0003
Mean	44.6		43.5		43.5		42.9		
SD	5.8		5.9		6.6		5.9		
Plant protein, % energy†									0.25
Mean	4.9		4.6		4.9		4.6		
SD	0.8		0.8		1.0		0.9		
Animal protein, % energy†									<0.0001
Mean	11.7		11.2		12.3		11.8		
SD	2.8		2.9		3.4		3.2		
Lipids, % energy†									0.81
Mean	37.6		38.9		38.0		38.6		
SD	5.2		5.5		6.1		5.7		
Fruit and vegetables consumption									<0.0001
< 400 g/d	337	79.1	355	78.2	434	66.8	638	65.1	
≥ 400 g/d	89	20.9	99	21.8	216	33.2	342	34.9	
Diet quality scores									0.001
mPNNs-GS‡									
Mean	7.9		8.2		8.0		8.4		
SD	1.4		1.4		1.5		1.5		
MEDI-LITE									<0.0001
Mean	7.2		7.2		7.7		7.7		
SD	2.4		2.4		2.7		2.6		
Provegetarian FP									0.11
Mean	35.7		35.6		36.1		35.9		
SD	4.8		4.8		5.1		5.0		

Table 1. (Continued)

Characteristics	Pizza consumers (n 880)				Non pizza consumers (n 1630)				P*
	Men		Women		Men		Women		
	n	%	n	%	n	%	n	%	
Pizza consumption§									
1	316	74.2	372	82.0					
2	74	17.4	66	14.5					
≥ 3	36	8.4	16	3.5					
Average pizza portion size, g									
Mean	262.0		187.3						
SD	153.9		132.0						

INCA2 second Individual and National Food consumption survey; *MEDI-LITE* Literature-based adherence score to the Mediterranean diet; *mPNNS-GS* modified Programme National Nutrition Santé Guideline Score; *Provegetarian FP* Provegetarian food pattern.

Values are means and standard deviation or numbers (percentages) as appropriate.

* *P*-values are based on the *t* test or χ^2 test, and refer to the comparison between consumers and non-consumers of pizza.

† Values are percentages of total daily energy intake without alcohol.

‡ Twelve missing data among pizza consumers and thirty-five among non-pizza consumers.

§ Number of times during the food data collection period.

We used the pizza ranking results specific to each individual to identify the best pizzas to be used for generic substitutions. Only four pizzas resulted in the highest risk reduction in at least one consumer. In IE substitutions, pizza clusters #88, #99, #22 and #100 were identified as the best pizzas for 96.6%, 1.6%, 0.9% and 0.9% of pizza consumers, respectively (online Supplementary Table 1). These four clusters were characterised by a high proportion of vegetables (including green leafy vegetables for cluster #100) and a whole grain dough (except the cluster #100). Clusters #88 and #100 were also identified as the best pizzas in NIE substitutions for 99.9% and 0.1% of pizza consumers, respectively (online Supplementary Table 1). Regarding the worst pizzas, the clusters identified (clusters #78 and #84 for both IE substitutions and NIE substitutions) were characterised by a low proportion of vegetables and a high proportion of processed meat (online Supplementary Table 1).

Tailored and generic pizza substitutions in the whole population resulted in rates of change in the risk of T2D in the range of -3.6%; +5.2% (Fig. 1). Overall, the rates of change were stronger in men and for NIE substitutions. For IE substitutions, replacing each consumer's pizza with one of his/her five best pizzas (tailored substitution) led to a population-wide reduction in the risk of T2D that ranged from -2.6% (-3.3%; -1.9%) to -2.0% (-2.5%; -1.4%) in men and -1.4% (-1.8%; -1.0%) to -1.1% (-1.4%; -0.7%) in women. Symmetrically, changing for one of the five worst pizzas led to an increased risk of T2D that ranged from 2.6% (1.8%; 3.4%) to 1.1% (0.7%; 1.5%) among men and 1.3% (0.9%; 1.7%) to 0.6% (0.4%; 0.8%) among women. The beneficial/detrimental estimated impacts of tailored substitutions decreased significantly between the first and third best/worst pizzas and only slightly thereafter.

For generic substitutions (using the pizzas most frequently identified as the best/worst), only pizzas identified as such for both IE and NIE substitutions (clusters #88 and #100 for the best pizzas and clusters #78 and #84 for the worst pizzas) were considered. The IE substitution of the observed pizzas for one of these four pizzas resulted in rates of change in the risk of T2D that ranged from -2.6% (-3.3%; -1.9%) to +2.6% (1.8%; 3.4%) in men (Fig. 1). Overall, the greatest reduction was

achieved with cluster #88 for both IE and NIE substitutions. In addition, generic substitutions (Fig. 1, lower panel) showed similar rates of change in the risk of T2D that were similar to those observed for tailored substitutions (Fig. 1, upper panel).

For both IE and NIE substitutions, the rates of change in the risk of T2D were more pronounced when estimated in the pizza consumers sub-sample, with a rate of change that increased in line with the frequency of pizza consumption (Table 2). Regarding the rates of change in the risk of T2D among other population subgroups, the most important changes were generally observed among younger participants (online Supplementary Table 3).

Inter-category substitutions resulted in rates of change in the risk of T2D for the whole population that ranged from -5.4% to +9.5% (Fig. 2). We identified one best mixed dish (pan bagnat for IE substitutions and spaghetti with tomato sauce for NIE substitutions) and one worst mixed dish (hotdog, for both IE and NIE substitutions). For IE substitutions, no replacement with a mixed dish led to a greater reduction in T2D than that observed when replacing with the best pizza, unlike NIE substitutions where a few mixed dishes allowed greater risk reductions than those observed with the best pizzas. For both IE and NIE substitutions, we found that some mixed dishes had a markedly stronger rates of change in the risk of T2D than the worst pizzas identified in this study. The best/worst mixed dishes were the same in the different population subgroups, except in the case of NIE substitutions where the best mixed dish was spaghetti with tomato sauce for some subgroups and spring rolls for others (online Supplementary Table 4).

Discussion

To our knowledge, this is the first study to have investigated the potential impact of food substitutions within the same category on the risk of T2D. In this modelling study based on food records collected on a large representative sample of the French population, we found that substitutions within the pizza category showed high rates of change in the risk of T2D when the recipe included several ingredients with a documented impact on T2D.

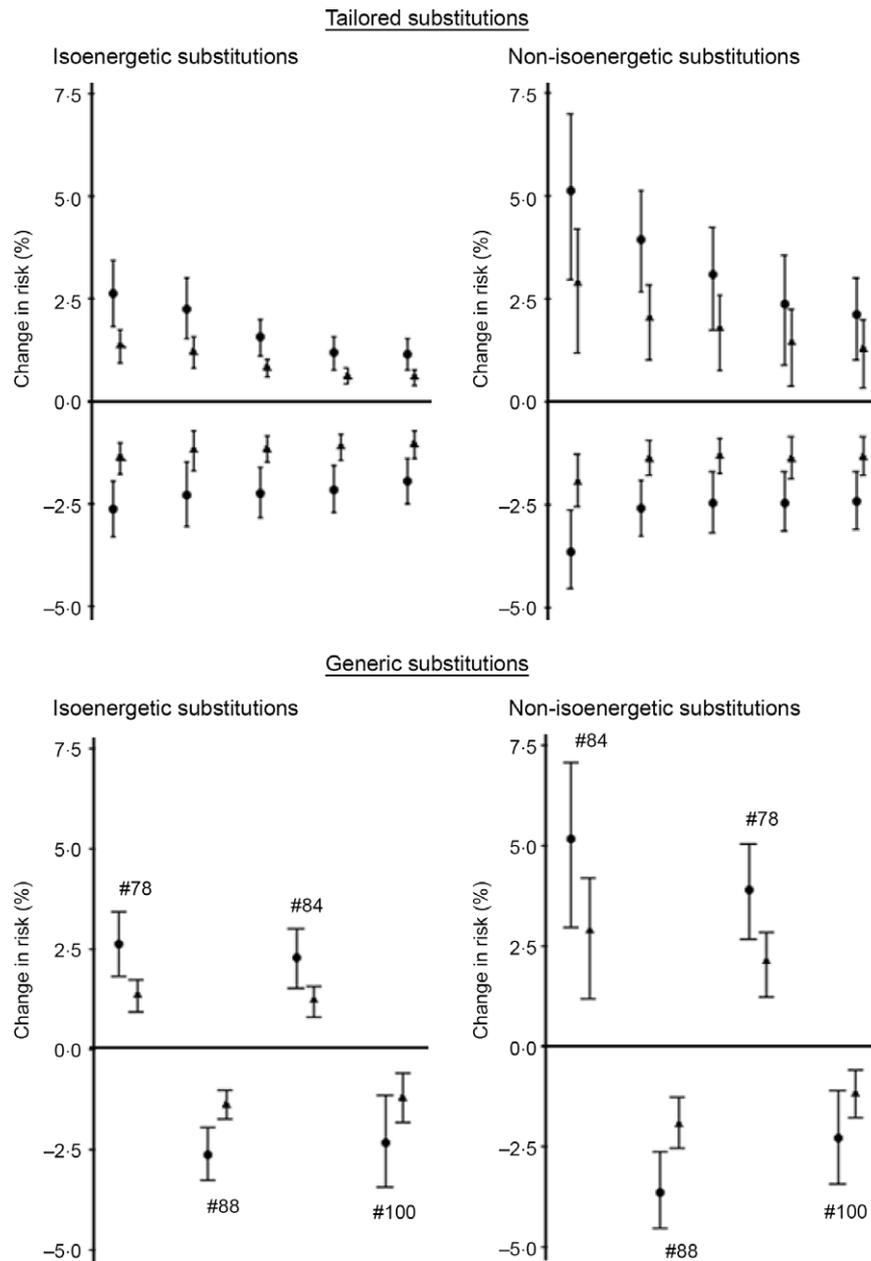


Fig. 1 Rates of change in risk of type 2 diabetes in the overall sample population when simulating substitutions with the five best and five worst pizzas (out of 100) specific to each of 2510 individuals ('tailored substitution'). Upper panels: according to isoenergetic substitutions (upper left) or non-isoenergetic substitutions (upper right); and substitutions with the four pizzas most frequently identified as the best/worst ('generic substitution'), according to isoenergetic substitutions (lower left) or non-isoenergetic substitutions (lower right). The numbers below the estimates are the ID of the pizza. 'Pizza' here stands for a cluster of pizzas (n 100, out of 353 pizzas). ●, Men; ▲, Women

The best pizzas identified in this study contained high levels of plant-based ingredients and had a whole grain dough. Most of them had a low energy density and contain large quantities of fibre and Mg. Despite the large number of pizzas containing a high proportion of vegetables, only four were identified as the first best for IE substitutions. These findings could be explained by the fact that all vegetables have a low and borderline beneficial impact on the risk of T2D (RR = 0.98; 95 % CI = 0.96, 1.00)⁽¹²⁾. Overall, the food groups included in PRIME that are considered to have a strong impact on the risk of T2D are whole

grains (RR = 0.87; 95 % CI = 0.82, 0.93), green leafy vegetables (RR = 0.87; 95 % CI = 0.76, 0.99) and olive oil (RR = 0.91; 95 % CI = 0.87, 0.95)^(12,29). Indeed, whole grains are an important source of phytochemicals and other nutrients such as vitamins B and E, cereal fibre, Zn and Mg^(40–42). The regular consumption of whole grains (particularly high-fibre cereals) has been associated with greater insulin sensitivity and lower fasting insulin levels. Eating plenty of whole grains may also reduce the risk of T2D by lowering levels of inflammatory markers, including C-reactive protein and interleukin-6⁽⁴³⁾. As for green leafy vegetables, their

Table 2. Rates of change in risk of type 2 diabetes for substitutions with the best and worst pizzas* (Odd ratios and 95 % confidence intervals)

Population	Isoenergetic substitution				Non-Isoenergetic substitution				
	Men		Women		Men		Women		
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	
1st Best pizza (#88)									
Whole population	-2.6	-3.3, -1.9	-1.4	-1.7, -1.0	-3.6	-4.5, -2.6	-2.0	-2.5, -1.3	
Pizza consumers	-6.7	-8.4, -4.9	-4.5	-5.6, -3.3	-8.9	-11.2, -6.3	-6.0	-7.9, -3.9	
Participants who consumed pizza once	-5.1	-6.4, -3.8	-3.9	-4.9, -2.8	-6.8	-8.6, -4.91	-5.3	-6.8, -3.5	
Participants who consumed pizza twice	-9.9	-12.4, -7.3	-6.4	-8.0, -4.7	-12.7	-16.1, -8.9	-7.8	-10.7, -4.6	
Participants who consumed pizza more than twice	-13.9	-17.2, -10.4	-10.3	-12.8, -7.6	-18.3	-23.2, -12.6	-14.6	-18.5, -9.7	
2nd Best pizza (#100)									
Whole population	-2.3	-3.4, -1.1	-1.2	-1.8, -0.6	-2.3	-3.4, -1.1	-1.2	-1.8, -0.6	
Pizza consumers	-5.7	-8.5, -2.8	-3.8	-5.6, -1.9	-5.7	-8.5, -2.8	-3.7	-5.6, -1.8	
Participants who consumed pizza once	-4.4	-6.5, -2.2	-3.3	-4.9, -1.6	-4.4	-6.5, -2.1	-3.2	-4.8, -1.5	
Participants who consumed pizza twice	-8.4	-12.3, -4.2	-5.5	-8.1, -2.8	-8.4	-12.3, -4.2	-5.4	-8.1, -2.7	
Participants who consumed pizza more than twice	-11.9	-17.4, -5.8	-8.7	-12.9, -4.2	-12.3	-17.8, -6.2	-8.9	-13.1, -4.5	
1st Worst pizza (#78)									
Whole population	2.6	1.8, 3.4	1.3	0.9, 1.7	3.9	2.7, 5.0	2.1	1.2, 2.8	
Pizza consumers	6.6	4.5, 8.6	4.2	2.9, 5.4	9.7	6.5, 12.8	6.5	3.7, 8.9	
Participants who consumed pizza once	4.8	3.3, 6.2	3.5	2.5, 4.6	7.2	4.8, 9.4	5.6	3.3, 7.6	
Participants who consumed pizza twice	9.8	6.8, 12.8	6.0	4.2, 7.8	14.4	9.5, 19.2	8.3	4.0, 12.4	
Participants who consumed pizza more than twice	16.0	10.7, 21.4	10.8	7.5, 14.2	23.0	15.0, 30.9	17.2	10.7, 23.0	
2nd Worst pizza (#84)									
Whole population	2.3	1.5, 3.0	1.2	0.8, 1.6	5.2	2.9, 7.0	2.8	1.2, 4.2	
Pizza consumers	5.6	3.8, 7.5	3.7	2.6, 4.9	13.1	7.1, 18.3	9.0	3.5, 13.5	
Participants who consumed pizza once	4.1	2.8, 5.4	3.2	2.2, 4.1	9.6	5.2, 13.4	7.8	3.2, 11.6	
Participants who consumed pizza twice	8.4	5.5, 11.2	5.3	3.6, 6.9	19.6	10.8, 27.8	10.7	2.1, 18.7	
Participants who consumed pizza more than twice	14.0	9.1, 19.0	9.7	6.6, 12.9	32.4	17.9, 46.1	25.7	12.3, 36.9	

* Substituted pizzas are those identified as the first best/worst at individual level substitutions. 'Pizza' here stands for a cluster of pizzas (*n* 100, out of 353 pizzas).

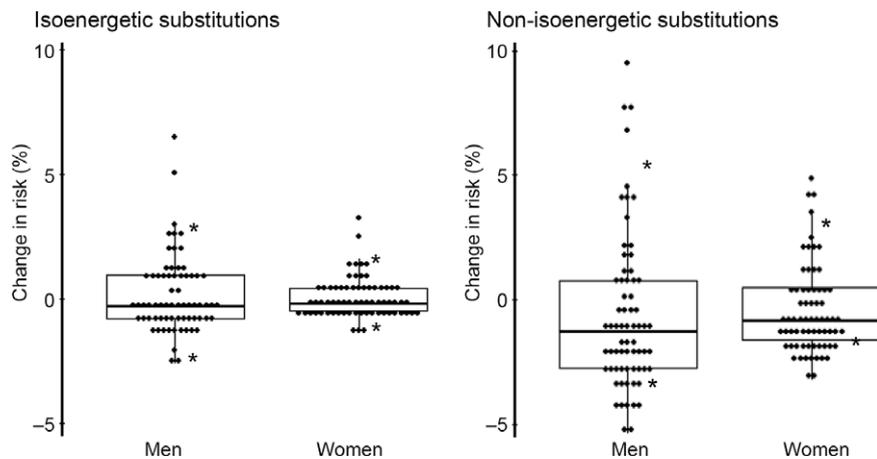


Fig. 2 Rates of change in risk of type 2 diabetes in the overall sample when simulating substitutions in each pizza consumer with the mixed dishes (*n* 68). *reports the estimates found for generic substitutions with the best and worst pizzas (see Fig. 1), for the comparison purposes. 'Pizza' here stands for a cluster of pizzas (*n* 100, out of 353 pizzas).

beneficial impacts have been attributed to their low carbohydrate content and antioxidant and anti-inflammatory properties⁽²⁹⁾. Our modelling study could provide final risk estimates regarding the potential impact of modulating these ingredients in the recipe of a food item found to be consumed by the population.

For both pizzas and the other dishes, NIE substitutions showed higher rates of change in the risk of T2D than IE substitutions. Indeed, based on data from meta-analyses^(12,22-28,30-32), our model was parameterised so that an increase in energy

intake resulted in an increased T2D risk, as a function of the BMI and level of physical activity of the subjects. Under this model, a change in energy intake is an important factor for risk estimates, in line with the importance of energy imbalances in being overweight and of being overweight in the T2D risk, as highlighted in the literature⁽⁴⁴⁾. However, although energy density and portion size are key drivers of a long-term energy imbalance, mechanisms for adjustment to subsequent energy intake should partly buffer the impact of a difference in energy content between two dishes on long-term energy intake. Therefore, the

final impact of a substitution is expected to be somewhere between the impacts of IE and NIE substitutions.

More specifically, we found that the rates of change in the risk for IE and NIE pizza substitutions were more pronounced when the substitution resulted in an increase in risk and very small when it resulted in a decrease. This could be explained by the fact that when pizzas contain a highly adverse pattern of ingredients they are also higher in energy. Conversely, only two of the four best pizzas identified for IE substitutions remained the best when used for NIE substitutions, apparently because their energy content is not particularly high. Differences in energy content could also explain the switch in the order of the two worst pizzas, depending on whether they were used for IE or NIE substitutions.

In this study, the rates of change in the risk of T2D attributable to the various pizza substitutions observed in the whole population may appear to be small. In contrast, rates of change in the risk of T2D were higher for NIE substitutions and when estimated in the pizza consumers sub-sample, with a rate of change that increased in line with the frequency of pizza consumption. The small range observed for the rates of change in the risk of T2D could first be explained by the fact that only one food category was replaced, while a diet consists of several meals and therefore several food categories. Second, not all participants in this study consumed pizza during the food data collection period. In addition, pizza was consumed in relatively small portions (particularly among women, with an average portion size of 187 g for women compared with 262 g for men) and approximately 78% of pizza consumers ate it only once during the food record week. Intra-category substitutions applied simultaneously to several food categories would lead to much greater reductions in the T2D risk. We had previously reported that extended and repeated intra-category substitutions can drive very marked healthy changes in nutrient intakes in the whole population⁽⁴⁵⁾. Here, we once again showed that rates of change in risk for NIE substitutions in the population of men consuming pizzas more than twice per week could reach –18% and +32%.

The findings of this study show that tailored substitutions do not have a greater impact than generic substitutions with pizzas that have been identified as the best. This was explained by the fact that the first best pizza (cluster #88) was the same for almost all pizza consumers (96.5%). Cluster #88 differed from the other clusters by its low energy content and high whole grain content. Interestingly, substitutions at the individual level showed that if cluster #88 were set aside, the second best pizza (cluster #100) was the same for a large majority (76%) of pizza consumers. This second best pizza enabled a reduction in the T2D risk close that obtained with cluster #88, with a different recipe, as it included green leafy vegetables but not whole grains. Taken together, these results of intra-category substitutions showed that the dietary levers for reducing the T2D risk proved to be the same for the vast majority of the population, which makes tailored advice useless. Although pizzas present a broad diversity of composition, we cannot generalise this finding to all food categories.

Quite unexpectedly, we failed to identify a mixed dish that induced a greater reduction in the risk of T2D than the best pizza in IE substitution. This may have been due to the fact that

although we considered a broad range of dishes (n 68), their recipes included no or only a tiny proportion of ingredients from the food groups with the most favorable expected impacts on the risk of diabetes. The best mixed dish identified for IE substitutions had nutritional characteristics similar to those of the best pizza, i.e. high in fibre and Mg. Regarding NIE substitutions, the greatest estimated T2D risk reduction achieved with mixed dishes such as spaghetti or spring rolls compared with the best pizza was not due to their higher proportion of healthy ingredient, but to their lower energy density. Overall, these results showed that substitutions within a category can have a considerable impact on the T2D risk since it was comparable to substitutions between categories.

In this study, our estimates were not translated into numbers of avoided incident cases of T2D because we do not have valid direct estimates of diabetes incidence in France in the entire adult population⁽⁴⁶⁾. However, based on available data, we may consider that T2D incidence might be in the order of 500 per 100 000 persons per year in men and 350 per 100 000 persons in women. If using data from Table 2 showing rates of changes in risk of diabetes in men and women for substitution with the best and worst pizzas, and if considering that the effect would lie in between that of iso-energetic substitution and NIE substitutions, the substitutions might result in between 6700 and 9400 new cases of diabetes avoided each year in France.

This modelling study has some potential limitations that should be mentioned. First, parametrisation of our model is limited by the availability of robust meta-analyses estimating RR values for associations between lifestyle indicators and health outcomes. Indeed, most of the available RR have been estimated for the general population, while for some factors, the estimated risks may vary as a function of socio-demographic and health characteristics. In addition, in the absence of reliable information, we considered that the initial risk of T2D was the same for all the population subgroups examined in our study. Further, some nutritional factors such as polyphenols, cholesterol and Zn, among others, could not be included in the model, either because their relation to T2D risk has not been sufficiently characterised or due to lack of detailed data on their contents in different foods. Another limitation of this study is that it cannot be excluded that the relative risks used in the parameterisation of the model may vary slightly according to the population groups considered, and this may have added some uncertainty on the estimates of risk changes drawn on this population.

In this study, some participants had missing data on some variables, but BMI is the only one that is used in the risk assessment model. The missing values that could have an impact on the model are limited to two missing BMI values among the 878 pizza consumers for whom NIE substitutions were run.

Some important strengths of this study include its large sample size (with approximately 35% of pizza consumers), the quality of the dietary data based on 7-day food records that reflected the actual dietary habits of the participants as well as that of anthropometric data because they were taken by trained investigators. Another strength is the availability of a large database including recipes of more than 300 pizzas marketed in France, which was useful to exploring all possibilities in a realistic way.



In conclusion, the results of this study suggest that substitutions within the pizza category are associated with modest reduction in T2D risk, with a rate of change that increased in line with the frequency of pizza consumption, justifying the promotion of a healthier swap, as it is increasingly advocated in dietary guidelines. Our results also suggest that substitutions within the same category might be particularly effective inasmuch as in principle they are easier to implement than the total exclusion of a food category and could play a role in achieving a generally better dietary pattern. For these theoretical results to work in practice, the messages would of course need to be accompanied by a radical transformation of the food offer that takes account of sensory acceptability. The results of this article remain theoretical and are based on comparative risk assessment on modelled diets. They would need to be corroborated in long-term interventional studies, assessing the effects of limited and well-defined dietary changes on endpoints related to diabetes risk.

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None of the other authors declare any conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114521002130>

References

- World Health Organization (2016) *Global Report on Diabetes*. France: WHO.
- International Diabetes Federation (2017) *IDF Diabetes Atlas*. 8th ed. Brussels: International Diabetes Federation.
- Zhang P, Zhang X, Brown J, *et al.* (2010) Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* **87**, 293–301.
- Chevreur K, Berg Brigham K & Bouché C (2014) The burden and treatment of diabetes in France. *Glob Health* **10**, 6.
- da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, *et al.* (2016) IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. *Diabetes Res Clin Pract* **117**, 48–54.
- Zheng Y, Ley SH & Hu FB (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* **14**, 88–98.
- Sami W, Ansari T, Butt NS, *et al.* (2017) Effect of diet on type 2 diabetes mellitus: a review. *Int J Health Sci* **11**, 65–71.
- World Health Organization (2008) *2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases*. Geneva: WHO.
- Steinbrecher A, Morimoto Y, Heak S, *et al.* (2011) The preventable proportion of type 2 diabetes by ethnicity: the multiethnic cohort. *Ann Epidemiol* **21**, 526–535.
- Jannasch F, Kröger J & Schulze MB (2017) Dietary patterns and type 2 diabetes: a systematic literature review and meta-analysis of prospective studies. *J Nutr* **147**, 1174–1182.
- Qian F, Liu G, Hu FB, *et al.* (2019) Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med* **179**, 1335–1344.
- Schwingshackl L, Hoffmann G, Lampousi A-M, *et al.* (2017) Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* **32**, 363–375.
- Olfert MD & Wattick RA (2018) Vegetarian diets and the risk of diabetes. *Curr Diab Rep* **18**, 101.
- Schwingshackl L, Missbach B, König J, *et al.* (2015) Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. *Public Health Nutr* **18**, 1292–1299.
- Lee Y & Park K (2017) Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. *Nutrients* **9**, 603.
- US Department of Health and Human Services & US Department of Agriculture (2015) 2015–2020 Dietary Guidelines for Americans. <https://health.gov/our-work/food-nutrition/previous-dietary-guidelines/2015> (accessed June, 2018).
- Rhodes DG, Adler ME, Clemens JC, *et al.* (2014) Consumption of Pizza: What We Eat in America, NHANES 2007–2010. Food Surveys Research Group Dietary Data Brief No. 11. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/DBrief/11_consumption_of_pizza_0710.pdf (accessed October, 2019).
- Dubuisson C, Lioret S, Touvier M, *et al.* (2010) Trends in food and nutritional intakes of French adults from 1999 to 2007: results from the INCA surveys. *Br J Nutr* **103**, 1035–1048.
- Agence française de sécurité sanitaire des aliments (AFSSA) (2009) Etude Individuelle Nationale des Consommations Alimentaires 2 (INCA2) 2006–2007 [Individual National Study of Food Consumption 2006–2007]. Maisons-Alfort: AFSSA. <https://www.anses.fr/fr/system/files/PASER-Ra-INCA2.pdf> (accessed February 2019).
- Hagstromer M, Oja P & Sjostrom M (2006) The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutr* **9**, 755–762.
- 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 dietary assessment of the SU.VI.MAX study]. *Cab Nutr Diet* **31**, 158–164.
- Schwingshackl L, Schwedhelm C, Hoffmann G, *et al.* (2019) Potatoes and risk of chronic disease: a systematic review and dose-response meta-analysis. *Eur J Nutr* **58**, 2243–2251.
- Pimpin L, Wu JHY, Haskelberg H, *et al.* (2016) Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. *PLoS One* **11**, e0158118.
- Huang J, Wang X & Zhang Y (2017) Specific types of alcoholic beverage consumption and risk of type 2 diabetes: a systematic review and meta-analysis. *J Diabetes Investig* **8**, 56–68.
- Carlström M & Larsson SC (2018) Coffee consumption and reduced risk of developing type 2 diabetes: a systematic review with meta-analysis. *Nutr Rev* **76**, 395–417.
- Yang W-S, Wang W-Y, Fan W-Y, *et al.* (2014) Tea consumption and risk of type 2 diabetes: a dose-response meta-analysis of cohort studies. *Br J Nutr* **111**, 1329–1339.
- Yuan S, Li X, Jin Y, *et al.* (2017) Chocolate consumption and risk of coronary heart disease, stroke, and diabetes: a meta-analysis of prospective studies. *Nutrients* **9**, 688.



28. Neuenschwander M, Ballon A, Weber KS, *et al.* (2019) Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. *BMJ* **366**, l2368.
29. Li M, Fan Y, Zhang X, *et al.* (2014) Fruit and vegetable intake and risk of type 2 diabetes mellitus: meta-analysis of prospective cohort studies. *BMJ Open* **4**, e005497.
30. InterAct Consortium (2015) Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. *Diabetologia* **58**, 1394–1408.
31. Greenwood DC, Threapleton DE, Evans CEL, *et al.* (2013) Glycemic index, glycemic load, carbohydrates, and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. *Diabetes Care* **36**, 4166–4171.
32. Dong J-Y, Xun P, He K, *et al.* (2011) Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. *Diabetes Care* **34**, 2116–2122.
33. Rienks J, Barbaresco J, Oluwagbemigun K, *et al.* (2018) Polyphenol exposure and risk of type 2 diabetes: dose-response meta-analyses and systematic review of prospective cohort studies. *Am J Clin Nutr* **108**, 49–61.
34. Scarborough P, Morgan RD, Webster P, *et al.* (2011) Differences in coronary heart disease, stroke and cancer mortality rates between England, Wales, Scotland and Northern Ireland: the role of diet and nutrition. *BMJ Open* **1**, e000263.
35. Scarborough P, Harrington RA, Mizdrak A, *et al.* (2014) The preventable risk integrated ModEl and its use to estimate the health impact of public health policy scenarios. *Scientifica* **2014**, 748750.
36. Kesse-Guyot E, Amieva H, Castetbon K, *et al.* (2011) SU.VI.MAX 2 Research Group. Adherence to nutritional recommendations and subsequent cognitive performance: findings from the prospective Supplementation with Antioxidant Vitamins and Minerals 2 (SU.VI.MAX 2) study. *Am J Clin Nutr* **93**, 200–210.
37. Estaquio C, Kesse-Guyot E, Deschamps V, *et al.* (2009) Adherence to the French Programme National Nutrition Sante Guideline Score is associated with better nutrient intake and nutritional status. *JAmDietAssoc* **109**, 1031–1041.
38. Sofi F, Macchi C, Abbate R, *et al.* (2014) Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* **17**, 2769–2782.
39. Martínez-González MA, Sánchez-Tainta A, Corella D, *et al.* (2014) A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr* **100**, 320S–328S.
40. Aune D, Norat T, Romundstad P, *et al.* (2013) Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Eur J Epidemiol* **28**, 845–858.
41. Venn BJ & Mann JI (2004) Cereal grains, legumes and diabetes. *Eur J Clin Nutr* **58**, 1443–1461.
42. Steyn NP, Mann J, Bennett PH, *et al.* (2004) Diet, nutrition and the prevention of type 2 diabetes. *Public Health Nutr* **7**, 147–165.
43. Xu Y, Wan Q, Feng J, *et al.* (2018) Whole grain diet reduces systemic inflammation. *Medicine* **97**, e12995.
44. Toplak H, Leitner DR, Harreiter J, *et al.* (2019) ‘Diabesity’-Obesity and type 2 diabetes (Update 2019). *Wien Klin Wochenschr* **131**, 71–76.
45. Verger EO, Holmes BA, Huneau JF, *et al.* (2014) Simple changes within dietary subgroups can rapidly improve the nutrient adequacy of the diet of French adults. *J Nutr* **144**, 929–936.
46. Fuentes S, Mandereau-Bruno L, Regnault N, *et al.* (2020) Is the type 2 diabetes epidemic plateauing in France? A nationwide population-based study. *Diabetes Metab* **46**, 472–479.