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

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Running title: Pizza substitutions and risk of type 2 diabetes

Abbreviations:

ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health Safety)

BMI: Body mass index

CIQUAL: Centre d'Information sur la Qualité des Aliments (Food Quality Information Center)

CNIL: Commission Nationale de l'Informatique et des Libertés (French National Commission for Computed Data and Individual Freedom)

FP: Food Pattern

HAC: Hierarchical Ascending Classification

IDF: International Diabetes Federation

IE substitution: Isoenergetic substitution

INCA2: Etude Individuelle Nationale des Consommations Alimentaires 2 (second Individual and National Food consumption survey)

MEDI-LITE: Literature-Based Adherence Score to the Mediterranean Diet

mPNNS-GS: version modifiée du Programme National Nutrition Santé Guideline Score (modified version of the French National Nutrition Health Program)

NCD: Non-Communicable Disease

NIE substitution : Non-isoenergetic substitution

Oqali: Observatoire de la qualité de l'alimentation (French food quality observatory)

PCA: Principal Component Analysis

PRIME: Preventable Risk Integrated ModEl

T2D: Type 2 Diabetes

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 2,510 adults from the INCA2 French national survey. Based on their nutritional characteristics, the 353 pizzas marketed in France were grouped in 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 (PRIME) to assess the expected rate of change in risk of T2D. Pizzas characterized 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 toward a healthier diet.

Keywords: Food substitutions: Pizza categories: Type 2 diabetes: Public health

INTRODUCTION

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 (IDF), 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, 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 (characterized by a high consumption of plant-based foods, whole grain products, fish and olive oil) ensuring an adequate intake of various vitamins and minerals, and positive associations for unhealthy diets (characterized by a high consumption of red and processed meats, refined grains, and foods high in sugars, 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 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 to 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 behaviors 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=1,455) were excluded from the initial INCA2 sample (n = 4,079). Under-reporters defined as participants who reported a daily energy intake of less than 1000 Kcal (n=114) were also excluded. The final sample therefore included 2,510 participants (57.1% women) aged 18-79 years (**Supplemental Figure 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 body mass index (BMI) was calculated as the ratio of weight to squared height (kg/m²).

Dietary data

Dietary intake was assessed using 7-day 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, 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 fibers and magnesium) 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 (HAC). First, a principal component analysis (PCA) was performed using the quantities of the main ingredients and the nutritional composition of the pizzas as input variables. The HAC using Ward’s step method was then performed for the first 4 factors resulting from the PCA (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 HAC was set at 100. For each cluster, the mean recipe and nutritional composition were determined and an “average” pizza (**Supplemental 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-day food records) and non-consumers using means and standard deviation for continuous variables and percentages for categorical variables. Pizza consumers were compared to non-consumers using chi2 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 (NCD) mortality (34,35). Briefly, the PRIME estimates the change in the annual number of NCD deaths between the baseline and counterfactual scenarios that depends on changes in the distribution of one or more behavioral risk factors in the study population. The model is parameterized using meta-analyses of epidemiological studies providing estimates of relative risks (RR) 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' 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 (PAF) ascribed to this factor. The PAF for the different risk factors 1 to n for the same disease are then combined multiplicatively in the PRIME model (PAF_{tot}).

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

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 parameterization 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 parameterization 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 **Supplemental figure 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., Cary, NC, USA) 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 68 mixed dishes identified in the INCA food database (generic substitution; **Supplemental Table 2**). Generic substitutions were analyzed 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 **Supplemental Figure 3**.

RESULTS

The analyses included 1,076 men and 1,434 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 to 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 ($<400\text{g/day}$) (**Table 1**).

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 (**Supplemental Table 1**). These four clusters were characterized 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 (**Supplemental Table 1**). Regarding the worst pizzas, the clusters identified (clusters #78 and #84 for both IE substitutions and NIE substitutions) were characterized by a low proportion of vegetables and a high proportion of processed meat (**Supplemental 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% (**Figure 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 (**Figure 1**). Overall, the greatest reduction was achieved with cluster #88 for both IE and NIE substitutions. In addition, generic substitutions (**Figure 1**, lower panel) showed similar rates of change in the risk of T2D that were similar to those observed for tailored substitutions (**Figure 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 (**Supplemental 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% (**Figure 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 (**Supplemental 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 modeling 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.

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 fiber and magnesium. 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 fiber, zinc and magnesium (40–42). The regular consumption of whole grains (particularly high-fiber 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 beneficial impacts have been attributed to their low carbohydrate content and

antioxidant and anti-inflammatory properties (29). Our modeling 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 parameterized 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. Secondly, 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 to 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 generalize 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 fiber and magnesium. Regarding NIE substitutions, the greatest estimated T2D risk reduction achieved with mixed dishes such as spaghetti or spring rolls compared to 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 person year in men and 350 per 100.000 person 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 non-isoenergetic 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, parametrization 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 zinc, among others, could not be included in the model, either because their relation to T2D risk has not been sufficiently characterized 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 parameterization 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 2 missing BMI values among the 878 pizza consumers for whom non-isoenergetic 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.

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Table 1 Characteristics of the study population, INCA2 study †

Characteristics	Pizza consumers (n=880)		Non pizza consumers (n=1,630)		P ‡
	Men	Women	Men	Women	
n	426	454	650	980	
Age, years	41.2 ± 14.3	39.2 ± 14.3	50.1 ± 15.2	48.0 ± 14.9	<0.0001
Marital status, n (%)					<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, n (%)					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, n (%)					<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, n (%)					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)	
Body mass index, n (%)					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	6.9 ± 0.4	6.9 ± 0.4	6.9 ± 0.6	6.9 ± 0.5	0.02
Total energy intake, Kcal/days	2347 ± 613	1830 ± 452	2382 ± 677	1834 ± 466	0.27
Energy intake without alcohol, Kcal/d	2213 ± 582	1787 ± 438	2223 ± 640	1784 ± 452	0.15
Carbohydrates, % energy §	44.6 ± 5.8	43.5 ± 5.9	43.5 ± 6.6	42.9 ± 5.9	0.0003
Plant proteins, % energy §	4.9 ± 0.8	4.6 ± 0.8	4.9 ± 1.0	4.6 ± 0.9	0.25
Animal proteins, % energy §	11.7 ± 2.8	11.2 ± 2.9	12.3 ± 3.4	11.8 ± 3.2	<0.0001
Lipids, % energy §	37.6 ± 5.2	38.9 ± 5.5	38.0 ± 6.1	38.6 ± 5.7	0.81
Fruit and vegetables consumption, n (%)					<0.0001
< 400 g/days	337 (79.1)	355 (78.2)	434 (66.8)	638 (65.1)	
≥ 400 g/days	89 (20.9)	99 (21.8)	216 (33.2)	342 (34.9)	
Diet quality scores					
mPNNS-GS	7.9 ± 1.4	8.2 ± 1.4	8.0 ± 1.5	8.4 ± 1.5	0.001
MEDI-LITE	7.2 ± 2.4	7.2 ± 2.4	7.7 ± 2.7	7.7 ± 2.6	<0.0001
Provegetarian FP	35.7 ± 4.8	35.6 ± 4.8	36.1 ± 5.1	35.9 ± 5.0	0.11
Pizza consumption, n (%) ¶					
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	262.0 ± 153.9	187.3 ± 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 ± standard deviation or numbers (percentages) as appropriate

‡ P-values are based on the T-test or chi-square test, and refer to the comparison between consumers and non-consumers of pizza

§ Values are percentages of total daily energy intake without alcohol

|| 12 missing data among pizza consumers and 35 among non-pizza consumers

¶ Number of times during the food data collection period

Table 2 Rates of change in risk of type 2 diabetes (percentage) for substitutions with the best and worst pizzas †

Population	Isoenergetic substitution		Non-Isoenergetic substitution	
	Men	Women	Men	Women
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; -4.9)	-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).

Figure 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 2,510 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).

Figure 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 Figure 1), for the comparison purposes. “Pizza” here stands for a cluster of pizzas ($n=100$, out of 353 pizzas).

Supplemental Figure 1 Flow chart of participant selection

Supplemental Figure 2 Structure and parameters of the macrosimulation model

*The change in BMI was calculated as indicated by Scarborough et al., but at constant physical activity.

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mPNNS-GS (Kesse-Guyot et al., 2011a ; Estaquio C. et al, 2009) †

Food intake recommendations	Moderation in consumption	Penalty
Fruit and vegetables without potatoes (0-2), starchy foods (0-1), whole grain products (0-1), milk and dairy products (0-1), meat, poultry, fish, eggs, and seafood (0-1), seafood (0-1), vegetable fat (0-1), water vs soda (0-1)	Sweetened foods (-0.5-1), salt (-0.5-1.5), added fats (0-2), alcohol (0-1)	Deduction of points if energy intake exceeded energy needs by 5%
The mPNNS-GS score is the sum of components minus penalty (range: 0-13.5 points)		

MEDI-LITE (Sofi F. et al, 2013) ‡

Desirable components (0-2 points for each component)	Undesirable components (0-2 points for each component)
Fruit, vegetables without potatoes, grains, legumes, fish, olive oil, moderate alcohol consumption	Meat/meat products, dairy products
The MEDI-LITE score is the sum of components (range: 0-18 points)	

Provegetarian food pattern (Martínez-González. et al, 2014) §

Vegetable food groups (1-5 points for each food group)	Animal food groups (1-5 points for each food group)
Fruit, vegetables, legumes, cereals, potatoes, nuts, olive oil	Meats/meat products, eggs, animal fats for cooking or as a spread, Fish and other seafood, dairy products
The Provegetarian FP is the sum of the sex-specific quintile values of the 12 food groups (range: 12-60 points)	

***MEDI-LITE** Literature-Based Adherence Score to the Mediterranean Diet; **mPNNS-GS** modified Programme National Nutrition Santé Guideline Score.*

† Values were assigned by using fixed portion numbers for each food group, with a maximum of points attributed for high consumption of “desirable” components

‡ Values were assigned to food groups by using fixed cut-off points (portion sizes multiplied by the number of servings per day/week) determined from an extensive published review of the literature. A maximum of points is attributed for high consumption of “desirable” components and the scoring was reversed for the “undesirable” components.

§ Consumption (g/d) of each food group was energy-adjusted using the residual method and divided into sex-specific quintiles. A value between 1 and 5 was assigned to each quintile, with a maximum of points attributed for high consumption of “vegetable food groups”. The scoring was reversed for the “animal food groups”.

Supplemental Figure 3 Computation of diet quality scores

Supplemental table 1 Nutritional characteristics of the 100 pizza clusters

Cluster	Number of pizzas	Average composition per 100g										Isoenergetic substitution †		Non-Isoenergetic substitution ‡	
		Energy (Kcal)	Whole grains (g)	Refined grains (g)	Dairy products (g)	Green leafy vegetables (g)	Other vegetables (g)	Fish (g)	Red meat (g)	Processed meat (g)	Olive oil (g)	1 st best or worst (n)	2 nd best or worst (n)	1 st best or worst (n)	2 nd best or worst (n)
#1	4	200.6 ± 6.5	0	28.5 ± 0.3	12.7 ± 4.1	0	4.6 ± 1.9	0	0	11.6 ± 1.5	0	2 ^w			
#2	6	200.5 ± 7.7	0	30.0 ± 0.7	10.7 ± 3.5	0	19.5 ± 3.0	0	0	12.8 ± 0.7	0				
#3	14	241.9 ± 11.6	0	29.8 ± 1.1	24.7 ± 2.2	0	23.0 ± 2.2	0	0	0	0				
#4	8	229.9 ± 12.0	0	28.1 ± 0.6	13.5 ± 2.5	0	24.2 ± 2.3	0	0	13.2 ± 0.5	0				
#5	4	186.8 ± 2.9	0	27.8 ± 0.6	8.5 ± 0.7	0	32.1 ± 2.5	0	0	8.9 ± 0.2	0				
#6	7	243.4 ± 9.7	0	27.1 ± 0.9	19.7 ± 2.3	0	22.7 ± 2.0	0	0	9.8 ± 0.8	0				
#7	7	208.6 ± 6.3	0	27.6 ± 1.3	18.8 ± 1.9	0	33.1 ± 2.5	0	0	0	0				
#8	2	219.3 ± 1.0	0	36.7 ± 0.0	4.5 ± 0.0	0	17.4 ± 0.0	0	0	14.8 ± 0.0	0				
#9	9	213.9 ± 10.6	0	23.1 ± 0.8	16.2 ± 1.4	0	29.4 ± 3.0	0	0	12.3 ± 1.6	0				
#10	12	202.3 ± 7.4	0	24.3 ± 1.3	16.0 ± 1.8	0	21.5 ± 1.4	0	0	18.1 ± 2.3	0				
#11	5	258.0 ± 13.4	0	25.0 ± 0.9	18.4 ± 0.9	0	19.5 ± 2.2	0	0	16.5 ± 1.0	0				
#12	13	198.8 ± 7.7	0	25.2 ± 1.0	12.1 ± 1.3	0	31.3 ± 2.2	0	0	11.2 ± 0.8	0				
#13	8	236.4 ± 12.1	0	22.4 ± 0.6	36.4 ± 2.7	0	23.0 ± 4.8	0	0	0	0				
#14	13	257.6 ± 10.8	0	25.7 ± 0.8	31.6 ± 2.0	0	23.6 ± 3.0	0	0	0	0				
#15	6	209.7 ± 5.0	0	25.8 ± 0.9	11.0 ± 4.1	0	31.1 ± 2.7	0	0	6.9 ± 1.1	0				
#16	6	230.5 ± 8.3	0	32.2 ± 2.6	10.6 ± 2.9	0	22.1 ± 3.1	0	0	9.5 ± 0.9	0				
#17	10	193.3 ± 5.5	0	27.0 ± 0.7	16.8 ± 2.1	0	26.3 ± 1.5	0	0	9.2 ± 1.9	0				
#18	4	186.5 ± 5.4	0	25.4 ± 0.8	4.0 ± 3.3	0	40.9 ± 2.5	0	0	2.2 ± 4.5	0				
#19	12	224.4 ± 6.4	0	27.7 ± 1.2	28.6 ± 3.2	0.04 ± 0.1	20.4 ± 3.2	0	0	0.6 ± 2.0	0				
#20	6	269.2 ± 8.0	0	25.5 ± 1.3	12.2 ± 4.4	0	26.9 ± 2.4	0	0	14.1 ± 1.0	0				
#21	4	227.3 ± 8.4	0	30.8 ± 1.2	15.2 ± 1.0	0	24.6 ± 1.7	0	0	8.2 ± 1.6	0				
#22	3	259.3 ± 3.1	12.5 ± 0.2	12.5 ± 0.2	36.6 ± 1.6	0	19.6 ± 1.1	0	0	0	0	8 ^b	146 ^b		
#23	2	195.0 ± 5.7	0	32.9 ± 0.2	0	0	33.7 ± 0.3	0	0	0	0				

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‡ Number of participants for whom the cluster was identified as the first or second best (b) / worst (w) pizza for non-isoenergetic substitutions

Cluster	Number of pizzas	Average composition per 100g										Isoenergetic substitution †		Non-Isoenergetic substitution ‡	
		Energy (Kcal)	Whole grains (g)	Refined grains (g)	Dairy products (g)	Green leafy vegetables (g)	Other vegetables (g)	Fish (g)	Red meat (g)	Processed meat (g)	Olive oil (g)	1 st best or worst (n)	2 nd best or worst (n)	1 st best or worst (n)	2 nd best or worst (n)
#24	4	258.5 ± 5.3	0	30.0 ± 0.4	31.4 ± 1.4	0	16.9 ± 1.7	0	0	0	0				
#25	7	248.7 ± 8.5	0	25.1 ± 0.3	23.5 ± 4.5	0	21.7 ± 2.7	0	0	4.1 ± 2.0	0				
#26	4	216.1 ± 5.5	0	32.3 ± 0.8	16.6 ± 0.5	0	12.4 ± 4.7	0	0	16.6 ± 3.6	0				
#27	4	239.0 ± 6.6	0	22.5 ± 0.5	28.4 ± 2.1	0	18.0 ± 6.3	0	0	8.2 ± 1.2	0				
#28	5	237.0 ± 4.1	0	22.5 ± 1.0	19.2 ± 2.8	0	22.1 ± 2.2	0	0	17.4 ± 1.4	0				
#29	2	262.0 ± 0.0	0	23.3 ± 1.1	14.0 ± 0.0	0	30.9 ± 0.2	8.9 ± 0.1	0	0	0				
#30	2	238.5 ± 3.5	0	27.0 ± 0.8	27.1 ± 1.2	0	0	0	0	0	0				
#31	4	169.0 ± 1.4	0	24.3 ± 1.8	8.7 ± 3.3	0	34.8 ± 2.7	0	0	14.7 ± 2.2	0				
#32	5	230.0 ± 15.5	0	31.6 ± 3.2	11.8 ± 1.9	0	26.8 ± 2.9	0	0	0	0				
#33	4	191.7 ± 8.0	0	25.2 ± 1.1	8.7 ± 2.2	0	36.1 ± 2.1	0	9.7 ± 0.4	0	0				
#34	2	199.2 ± 7.3	0	33.0 ± 0.0	17.2 ± 0.2	0	26.1 ± 1.9	0	0	0	0				
#35	6	220.3 ± 14.7	0	26.1 ± 0.8	19.4 ± 3.6	0	22.1 ± 1.8	0	0	0	0				
#36	5	268.6 ± 9.7	0	27.2 ± 1.7	27.5 ± 1.5	0	12.4 ± 2.3	0	0	12.8 ± 1.4	0				
#37	4	209.3 ± 7.0	0	29.5 ± 0.6	9.7 ± 2.6	0	29.6 ± 3.3	0	0	7.9 ± 1.5	0				
#38	3	272.0 ± 7.2	0	23.3 ± 2.0	39.2 ± 1.8	0	18.1 ± 2.9	0	0	0	0				
#39	4	196.5 ± 5.1	0	23.6 ± 0.7	11.5 ± 4.0	0	38.2 ± 3.3	0	0	0	0				
#40	3	225.5 ± 12.6	0	27.0 ± 0.0	17.8 ± 2.7	0	20.9 ± 3.3	12.1 ± 1.0	0	0	0				
#41	3	224.0 ± 4.6	0	29.0 ± 0.9	34.8 ± 2.4	0	11.2 ± 2.8	0	0	0	0				
#42	3	226.7 ± 5.8	0	24.6 ± 1.6	9.1 ± 2.9	0	28.4 ± 2.8	0	0	17.7 ± 0.8	0				
#43	4	200.4 ± 14.7	0	26.6 ± 1.0	4.4 ± 3.3	0	26.5 ± 4.2	0	0	14.2 ± 3.2	0				
#44	3	248.0 ± 10.5	0	31.3 ± 0.4	19.3 ± 2.8	0	14.8 ± 2.0	0	0	12.7 ± 2.2	0				
#45	4	204.3 ± 3.4	0	28.6 ± 0.9	9.2 ± 3.6	0	22.0 ± 3.7	0	0	0	0				
#46	4	213.3 ± 5.4	0	26.1 ± 2.4	9.7 ± 0.9	0	32.5 ± 2.2	0	8.0 ± 0.7	0	0				
#47	3	226.7 ± 7.1	0	27.8 ± 1.6	26.6 ± 2.8	0	0	0	0	0	0				
#48	3	201.9 ± 9.1	0	31.0 ± 3.5	9.2 ± 3.0	0	22.8 ± 4.5	0	0	9.8 ± 0.3	0				
#49	4	205.8 ± 14.8	0	28.4 ± 0.9	12.4 ± 0.9	0	2.7 ± 3.1	0	0	11.0 ± 1.1	0				

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‡ Number of participants for whom the cluster was identified as the first or second best (b) / worst (w) pizza for non-isoenergetic substitutions

Cluster	Number of pizzas	Average composition per 100g										Isoenergetic substitution †		Non-Isoenergetic substitution ‡	
		Energy (Kcal)	Whole grains (g)	Refined grains (g)	Dairy products (g)	Green leafy vegetables (g)	Other vegetables (g)	Fish (g)	Red meat (g)	Processed meat (g)	Olive oil (g)	1 st best or worst (n)	2 nd best or worst (n)	1 st best or worst (n)	2 nd best or worst (n)
#50	2	210.5 ± 4.9	0	24.6 ± 1.7	8.2 ± 1.7	0	37.0 ± 0.5	12.4 ± 0.6	0	0	0				
#51	3	284.3 ± 15.8	0	29.0 ± 1.4	37.7 ± 4.7	0	11.9 ± 1.1	0	0	0	0				
#52	3	200.0 ± 11.5	13.1 ± 0.9	13.1 ± 0.9	11.2 ± 1.9	0	26.6 ± 4.5	0	0	15.4 ± 3.5	0				
#53	3	181.3 ± 11.0	0	26.9 ± 1.2	18.9 ± 4.7	0	19.2 ± 0.7	0	0	11.5 ± 2.8	0				
#54	2	202.5 ± 16.3	0	27.3 ± 0.5	15.4 ± 0.1	3.4 ± 0.1	19.7 ± 0.6	0	0	14.2 ± 0.1	0				
#55	6	226.7 ± 11.0	0	25.3 ± 1.2	21.4 ± 2.1	0.2 ± 0.3	15.7 ± 2.8	0	0	14.1 ± 3.4	0				
#56	2	210 ± 0.0	0	27.8 ± 2.2	19.0 ± 0.0	0	16.3 ± 3.2	17.0 ± 0.0	0	0	0				
#57	5	215.2 ± 19.1	0	31.2 ± 2.9	12.8 ± 1.2	0	10.4 ± 5.0	0	0	1.3 ± 1.8	0				
#58	3	229.0 ± 21.2	11.1 ± 0.8	11.1 ± 0.8	13.8 ± 2.6	0	36.8 ± 0.8	0	0	9.1 ± 0.5	0				
#59	3	226.0 ± 13.5	0	25.6 ± 0.3	12.8 ± 6.1	0	38.9 ± 5.3	0	0	0	0				
#60	2	193.0 ± 9.9	0	32.1 ± 0.4	7.4 ± 0.6	0	15.0 ± 2.1	8.3 ± 1.9	0	0	0				
#61	2	184.6 ± 6.5	0	29.1 ± 1.3	9.3 ± 0.3	0	34.3 ± 6.6	0	0	0	0				
#62	4	231.0 ± 12.4	13.9 ± 1.1	13.9 ± 1.1	13.5 ± 1.9	0	24.9 ± 3.0	0	0	12.6 ± 4.1	0				
#63	2	266.1 ± 2.6	0	31.8 ± 5.1	25.7 ± 3.3	0	5.0 ± 7.0	0	0	0	0				
#64	2	259.8 ± 9.5	0	31.2 ± 2.5	10.0 ± 4.4	0	20.8 ± 2.4	0	0	8.6 ± 1.1	0				
#65	2	244.0 ± 0.0	0	37.7 ± 3.3	19.5 ± 2.1	0	15.8 ± 3.2	0	0	0	0				
#66	2	260.5 ± 9.2	0	28.3 ± 0.6	24.7 ± 4.5	0	11.4 ± 0.2	0	11.8 ± 0.8	3.5 ± 4.9	0				
#67	2	245.5 ± 12.0	0	29.1 ± 0.4	24.6 ± 1.2	0	21.4 ± 1.3	0	0	1.5 ± 2.2	1.9 ± 0.2				
#68	2	214.0 ± 2.8	0	28.2 ± 1.7	17.8 ± 0.4	0	12.4 ± 0.4	0	14.5 ± 1.7	0	0				
#69	2	202.0 ± 8.5	0	25.9 ± 3.3	10.4 ± 0.4	0	13.8 ± 10.5	0	10.6 ± 0.0	1.3 ± 1.9	0				
#70	2	235.5 ± 0.7	0	30.3 ± 0.4	18.6 ± 2.0	0	25.4 ± 5.2	0	0	4.9 ± 6.9	0.4 ± 0.1				
#71	2	241.0 ± 15.6	13.8 ± 0.4	13.8 ± 0.4	27.0 ± 2.3	0	19.6 ± 3.3	0	0	5.2 ± 7.4	0				
#72	2	221.0 ± 18.4	7.8 ± 0.4	7.8 ± 0.4	22.5 ± 10.1	0	35.8 ± 1.4	0	0	0	0				
#73	2	227.5 ± 3.5	10.4 ± 0.2	10.4 ± 0.2	21.9 ± 6.7	0	26.1 ± 3.3	0	0	12.0 ± 7.3	0				
#74	1	217.0	0	30.0	4.0.0	0	21.5	15.5	0	0	0				

Cluster	Number of pizzas	Average composition per 100g										Isoenergetic substitution †		Non-Isoenergetic substitution ‡	
		Energy (Kcal)	Whole grains (g)	Refined grains (g)	Dairy products (g)	Green leafy vegetables (g)	Other vegetables (g)	Fish (g)	Red meat (g)	Processed meat (g)	Olive oil (g)	1 st best or worst (n)	2 nd best or worst (n)	1 st best or worst (n)	2 nd best or worst (n)
#75	1	221.0	0	24.6	10.9	0	31.3	16.8	0	0	0	820 ^w	60 ^w	19 ^w	789 ^w
#76	1	201.0	9.0	9.0	14.0	0	37.1	0	0	11.9	0				
#77	1	196.0	0	27.6	25.1	0	11.6	11.3	0	0	0				
#78	1	269.0	0	25.1	32.3	0	0.7	0	0	25.1	0				
#79	1	280.0	0	27.0	16.0	0	0	0	0	18.7	0				
#80	1	220.0	0	22.2	13.9	0	12.0	0	0	0	0	60 ^w	818 ^w	861 ^w	19 ^w
#81	1	231.0	0	30.0	6.5	0	35.5	0	0	7.5	0.5				
#82	1	178.0	0	25.4	13.8	0	25.1	9.2	0	0	0				
#83	1	210.0	0	25.8	9.1	0	17.7	4.6	0	0	0				
#84	1	320.0	0	19.8	29.0	0	12.2	0	0	24.5	0				
#85	1	290.0	0	21.6	27.6	0	20.4	0	0	12.2	0	850 ^b	9 ^b 44 ^b	879 ^b	1 ^b 253 ^b
#86	1	220.0	0	28.2	23.3	0	28.6	0	0	0	1.1				
#87	1	251.0	0	27.0	33.3	0	18.7	0	0	0	1.3				
#88	1	190.0	14.1	14.1	11.7	0	27.6	0	0	0	0				
#89	1	210.0	12.3	12.3	14.2	0	7.1	0	0	0	0				
#90	1	210.0	0	28.8	3.2	0	25.5	0	15.5	0	0	14 ^b 8 ^b	5 ^b 676 ^b	1 ^b	21 ^b 72 ^w 210 ^b
#91	1	252.0	8.4	8.4	40.0	0	28.8	0	0	0	0				
#92	1	211.0	0	25.8	13.1	0	33.2	0	0	6.8	1.7				
#93	1	255.0	0	31.7	17.0	0	22.3	0	6.7	0	0				
#94	1	293.0	12.6	12.6	21.2	0	3.5	0	0	10.7	0				
#95	1	191.0	0	28.2	4.9	2.4	37.1	0	0	0	0	14 ^b 8 ^b	5 ^b 676 ^b	1 ^b	21 ^b 72 ^w 210 ^b
#96	1	235.0	0	27.0	35.2	3.3	6.6	0	0	0	0				
#97	1	250.0	0	29.4	36.2	0	0	10.7	0	0	0				
#98	1	203.0	0	23.4	10.4	5.2	45.4	0	0	0	0				
#99	1	354.0	12.3	12.3	15.9	0	25.7	0	11.5	0	0				
#100	1	227.0	0	31.2	15.0	9.0	24.0	0	0	0	0				

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Supplemental table 2 Nutritional characteristics of mixed dishes used for inter-categories substitutions

Mixed dish name	Proportion per 100 g												
	Energy (Kcal)	Refined grains (g)	Green leafy vegetables (g)	Other vegetables (g)	Fruit (g)	Dairy products (g)	Fish (g)	Eggs (g)	Red meat (g)	Processed meat (g)	Potatoes (g)	Butter (g)	Olive oil (g)
Canned cassoulet	136	1	0	5	0	0	0	0	6	20	0	0	0
Canned sauerkraut	110	0	0	27.5	0	0	0	0	7.5	14	10	0	0
Shepherd's pie	145	2.3	0	19	0	26	0	0	13	0	8	7.5	0
Sausages with lentils	131	0.5	0	4	0	0	0	0	13	13	0	0	0
Pot-au-feu	72.3	0	0	36.3	0	0	0	0	52.5	0	10.6	0	0
Meat ravioli with tomato sauce (canned product)	97.4	54.5	0	26.7	0	0	0	0	10	0	0	0	0.3
Garnished mutton couscous	148	30.5	0	26.5	0	0	0	0	30	0	0	0	1.5
Paella	169	50.5	0	14	0	0	6	0	0	3	0	0	0
Potato gratin	110	0	0	0	0	26.9	0	7.5	0	0	62	3.1	0
Milanese “osso bucco”	102	3.1	0	23.2	0	0	0	0	37	0	0	0	2.8
Hotpot from Auvergne (pork, sausages and vegetable)	88.4	0	0	40	0	0	0	0	20	8	23	0	0
Cannelloni with meat	154	22.8	0	25.3	0	12.7	0	0	25	0	1.5	0.3	0.3
Lasagne with bolognese sauce	140	44.0	0	14.6	0	11.8	0	0	13.5	0	0	0.2	0.1
Pasta bolognese	137	57	0	25.4	0	0	0	0	10	0	0	0	0
Fried rice	141	61	0	15	0	0	0	10	0	9	0	0	0
Basque chicken with rice	101	1	0	28.4	0	0	0	0	0	0	0	0	0
Basque chicken with pasta	96.6	9.4	0	21.6	0	0	0	0	0	0	0	0	0
Spaghetti with tomato sauce	67.4	47.5	0	13	0	0	0	0	0	0	0	0	0
Baked pasta	150	56.2	0	0	0	21.5	0	15	0	7	0	0	0
Moussaka	138	3.4	0	47	0	22.2	0	0	17	0	0	0.5	0
Lamb stew	139	1.5	0	41.4	0	0	0	0	47	0	0	0	0
Royal couscous with meat	149	31	0	28	0	0	0	0	10	5	0	0	1.5
Endive gratin with ham	90.9	1.4	0	31.6	0	41.7	0	0	0	23.5	0	1	0
Pasta carbonara	166	74.9	0	0	0	12	0	5	0	8	0	0	0
Tartiflette	144	0	0	4	0	31	0	0	0	3	61	0	0
Chicken couscous	158	31	0	29	0	0	0	0	0	0	0	0	1.5
Cheese ravioli	209	21.5	0	0	0	32.5	0	9	0	0	2	0	0
Vegetable gratin	107	1.9	0	81.7	0	5.3	0	3.2	0	0	0	1.07	0
Croque-monsieur (toasted ham and cheese sandwich)	290	25.6	0	0	0	28.7	0	0	0	24	0	0.2	0
Hot-dog	318	32.6	0	3	0	0	0	0	0	50	0	0	0
French quiche Lorraine	292	21	0	0	0	48.4	0	10	0	11	0	3	0

Hamburger	216	26.1	3.5	10.5	0	2.1	0	0	39.5	0	0	0	0
Cheeseburger	262	28.8	2.5	4.5	0	22.3	0	0	23	0	0	0	0
Double cheeseburger	297	24.6	5.5	7.5	0	24	0	0	25	0	0	0	0
Vegetable pie	237	22.1	7.5	30	0	28	0	8	0	0	0	4.3	0
Spring rolls	116	20.4	9	41	0	0	0	0	0	0	0	0	0
Kebab and raw vegetable	233	17.7	7	26.2	0	0	0	0	43	0	0	0	0
Tuna and raw vegetable sandwich	274	43.9	2.7	12.6	0	0	19.3	0.9	0	0	0	0	0
Ham panini with mozzarella and tomatoes	243	28.9	5	16	0	20.9	0	0	0	16.5	0	0	0
Cheese pie or quiche	263	22.4	0	0	0	48.5	0	16	0	0	0	8.8	0
Ham sandwich with boiled egg and raw vegetable	222	42.5	4.7	14.2	0	0	0	6.7	0	21	0	4.3	0
Chicken and raw vegetable sandwich	258	41.5	4	13	0	0	0	0.8	0	0	0	0	0
Smoked salmon, and butter sandwich	265	57.2	0	0	5.2	0	19.5	0	0	0	0	3.3	0
Chicken vol-au-vent with fish and seafood	208	7.9	0	17	0	37.2	16	0	0	0	0	2.7	0
Chicken nugget	188	9.2	0	0	0	0	0	19.4	0	0	0	0	0
Pan bagnat	245	32.7	0	30	0	0	8.7	5	0	0	0	0	10.2
Ham and butter sandwich	283	47.7	0	0	0	0	0	0	0	30	0	10	0
Cheese and butter sandwich	339	47.7	0	0	0	30	0	0	0	0	0	10	0
Pâté and pickle sandwich	299	41.3	0	0	0	0	0	0.9	9.4	0	0.4	0	0
Butter and dry sausage sandwich	375	47.7	0	0	0	0	0	0	0	30	0	10	0
Ham sandwich with emmental and butter	309	42.1	0	0	0	13	0	0	0	25	0	9	0
Sandwich with raw vegetable and mayonnaise	221	39.9	0	37	0	0	0	0.9	0	0	0	0	0
Turkey sandwich with raw vegetable	255	43.1	2	11	0	0	0	1.1	0	0	0	0	0
Egg and raw vegetable sandwich	247	43.9	2.7	12.6	0	0	0	20.2	0	0	0	0	0
Pork and raw vegetable sandwich	267	43.1	2	11	0	0	0	1.1	19	0	0	0	0
Sandwich with merguez, ketchup and mustard	282	39.7	0	0	0	0	0	0	0	42	0	0	0
Salami and butter sandwich	379	47.7	0	0	0	0	0	0	0	30	0	10	0
Croque-madame (toasted ham and cheese sandwich topped with a fried egg)	264	20.3	0	0	0	25.3	0	17.9	0	19	0	0.1	0
Flamenkueche (salted pie with bacon)	263	34	0	16	0	18	0	0.6	17	11.2	0	0	0
Stuffed pancake with bechamel, ham, cheese and mushroom	145	14	0	20	0	48.1	0	7.9	0	7	0	0.8	0
Leek pie	258	24.2	0	18.2	0	43.8	0	0	0	0	0	4.1	0
Tomato pie	218	25.2	0	45.5	0	8	0	4	0	0	0	4.9	0.8
Salmon and sorrel pie	230	21.7	14.5	16	0	33.1	17	0	0	0	0	4.5	0
Tuna salad with vegetable (canned product)	123	0.3	0	57.6	0	0	24.92	0	0	0	0	0	1.3
Potato salad	127	0.4	0	22	0	0	2.7	4.7	0	2	54.5	0	0

Supplemental table 3 Rates of change in risk of type 2 diabetes (percentage) in population subgroups for substitutions with the best and worst pizzas

Population	Isoenergetic substitution		Non-isoenergetic substitution	
	Men	Women	Men	Women
1st Best pizza (#88)				
Age < 45 years	-4.2 (-5.2; -3.1)	-1.9 (-2.4; -1.4)	-5.4 (-7.0; -3.7)	-2.4 (-3.3; -1.4)
Age ≥ 45 years	-1.4 (-1.7; -1.0)	-0.9 (-1.1; -0.6)	-2.0 (-2.4; -1.5)	-1.3 (-1.6; -0.9)
Body mass index < 25	-3.2 (-4.0; -2.4)	-1.5 (-1.9; -1.1)	-3.2 (-4.7; -1.7)	-1.5 (-2.3; -0.6)
Body mass index ≥ 25	-2.0 (-2.5; -1.5)	-1.2 (-1.5; -0.8)	-3.3 (-3.8; -2.6)	-2.0 (-2.4; -1.6)
Fruit and vegetables consumption < 400g/day	-3.0 (-3.7; -2.2)	-1.6 (-2.0; -1.2)	-4.1 (-5.1; -2.9)	-2.3 (-3.0; -1.5)
Fruit and vegetables consumption ≥ 400g/day	-1.7 (-2.2; -1.3)	-0.9 (-1.1; -0.6)	-2.4 (-3.0; -1.8)	-1.2 (-1.6; -0.8)
Low adherence to the mPNNS-GS	-3.3 (-4.1; -2.4)	-1.5 (-1.8; -1.1)	-4.5 (-5.7; -3.1)	-2.0 (-2.6; -1.3)
Medium adherence to the mPNNS-GS	-2.1 (-2.6; -1.5)	-1.6 (-2.1; -1.2)	-2.9 (-3.6; -2.2)	-2.3 (-3.0; -1.5)
High adherence to the mPNNS-GS	-2.4 (-3.0; -1.8)	-1.2 (-1.5; -0.9)	-3.3 (-4.2; -2.4)	-1.7 (-2.1; -1.1)
Low adherence to the MEDI-LITE	-3.0 (-3.7; -2.2)	-1.5 (-1.9; -1.1)	-4.1 (-5.2; -2.9)	-2.2 (-2.9; -1.5)
Medium adherence to the MEDI-LITE	-2.9 (-3.6; -2.1)	-1.5 (-1.9; -1.1)	-4.0 (-5.0; -2.9)	-2.0 (-2.7; -1.3)
High adherence to the MEDI-LITE	-2.0 (-2.5; -1.5)	-1.2 (-1.5; -0.9)	-2.8 (-3.5; -2.0)	-1.6 (-2.1; -1.0)
Low adherence to the provegetarian FP	-2.8 (-3.6; -2.1)	-1.4 (-1.8; -1.1)	-4.0 (-5.0; -2.9)	-2.1 (-2.8; -1.4)
Medium adherence to the provegetarian FP	-2.6 (-3.3; -1.9)	-1.3 (-1.6; -1.0)	-3.7 (-4.6; -2.7)	-1.9 (-2.4; -1.3)
High adherence to the provegetarian FP	-2.3 (-2.9; -1.7)	-1.4 (-1.8; -1.1)	-3.2 (-4.0; -2.3)	-1.9 (-2.4; -1.2)
2nd Best pizza (#100)				
Age < 45 years	-3.6 (-5.3; -1.8)	-1.7 (-2.5; -0.8)	-3.6 (-5.3; -1.8)	-1.6 (-2.5; -0.8)
Age ≥ 45 years	-1.2 (-1.8; -0.6)	-0.8 (-1.1; -0.4)	-1.2 (-1.8; -0.6)	-0.7 (-1.1; -0.3)
Body mass index < 25	-2.8 (-4.2; -1.4)	-1.3 (-2.0; -0.7)	-2.8 (-4.2; -1.4)	-1.3 (-2.0; -0.7)
Body mass index ≥ 25	-1.8 (-2.7; -0.9)	-1.0 (-1.5; -0.5)	-1.8 (-2.7; -0.9)	-1.0 (-1.5; -0.5)
Fruit and vegetables consumption < 400g/day	-2.6 (-3.9; -1.3)	-1.4 (-2.2; -0.7)	-2.6 (-3.9; -1.3)	-1.4 (-2.1; -0.7)
Fruit and vegetables consumption ≥ 400g/day	-1.5 (-2.2; -0.7)	-0.7 (-1.1; -0.3)	-1.5 (-2.2; -0.7)	-0.7 (-1.1; -0.3)
Low adherence to the mPNNS-GS	-2.9 (-4.3; -1.4)	-1.3 (-1.9; -0.6)	-2.9 (-4.3; -1.4)	-1.3 (-1.9; -0.6)
Medium adherence to the mPNNS-GS	-1.8 (-2.7; -0.9)	-1.5 (-2.2; -0.7)	-1.8 (-2.7; -0.8)	-1.4 (-2.2; -0.7)
High adherence to the mPNNS-GS	-2.1 (-3.2; -1.0)	-1.0 (-1.5; -0.5)	-2.1 (-3.1; -1.0)	-1.0 (-1.5; -0.5)
Low adherence to the MEDI-LITE	-2.6 (-3.9; -1.3)	-1.4 (-2.0; -0.7)	-2.6 (-3.9; -1.3)	-1.4 (-2.0; -0.7)
Medium adherence to the MEDI-LITE	-2.5 (-3.8; -1.2)	-1.3 (-1.9; -0.6)	-2.5 (-3.7; -1.2)	-1.2 (-1.9; -0.6)
High adherence to the MEDI-LITE	-1.7 (-2.6; -0.8)	-1.0 (-1.5; -0.5)	-1.7 (-2.6; -0.8)	-1.0 (-1.5; -0.5)
Low adherence to the provegetarian FP	-2.5 (-3.8; -1.2)	-1.3 (-2.0; -0.7)	-2.5 (-3.7; -1.2)	-1.3 (-2.0; -0.6)
Medium adherence to the provegetarian FP	-2.3 (-3.5; -1.1)	-1.1 (-1.7; -0.6)	-2.4 (-3.5; -1.2)	-1.1 (-1.7; -0.5)
High adherence to the provegetarian FP	-2.0 (-3.0; -1.0)	-1.2 (-1.8; -0.6)	-2.0 (-3.0; -0.9)	-1.2 (-1.8; -0.6)
1st Worst pizza (#78)				
Age < 45 years	4.1 (2.9; 5.4)	1.9 (1.3; 2.4)	5.7 (3.7; 7.7)	2.6 (1.3; 3.7)
Age ≥ 45 years	1.3 (0.9; 1.7)	0.8 (0.5; 1.0)	2.1 (1.5; 2.7)	1.3 (0.9; 1.7)
Body mass index < 25	3.2 (2.2; 4.2)	1.5 (1.1; 2.0)	3.2 (1.3; 5.0)	1.4 (0.3; 2.5)
Body mass index ≥ 25	2.1 (1.4; 2.7)	1.1 (0.8; 1.4)	3.5 (2.8; 4.3)	2.2 (1.7; 2.6)
Fruit and vegetables consumption < 400g/day	2.9 (2.0; 3.8)	1.5 (1.1; 2.0)	4.3 (2.9; 5.7)	2.4 (1.4; 3.3)
Fruit and vegetables consumption ≥ 400g/day	1.8 (1.2; 2.3)	0.8 (0.6; 1.1)	2.7 (1.9; 3.4)	1.3 (0.8; 1.7)
Low adherence to the mPNNS-GS	3.3 (2.3; 4.2)	1.5 (1.0; 1.9)	4.8 (3.1; 6.3)	2.2 (1.2; 3.0)
Medium adherence to the mPNNS-GS	2.0 (1.4; 2.6)	1.6 (1.1; 2.1)	3.1 (2.2; 3.9)	2.5 (1.5; 3.4)
High adherence to the mPNNS-GS	2.5 (1.7; 3.3)	1.1 (0.8; 1.4)	3.6 (2.5; 4.7)	1.7 (1.1; 2.3)
Low adherence to the MEDI-LITE	2.8 (2.0; 3.7)	1.5 (1.0; 1.9)	4.3 (2.9; 5.6)	2.4 (1.5; 3.2)
Medium adherence to the MEDI-LITE	2.9 (2.0; 3.8)	1.4 (1.0; 1.8)	4.4 (3.0; 5.7)	2.1 (1.2; 2.9)
High adherence to the MEDI-LITE	2.1 (1.5; 2.7)	1.2 (0.8; 1.5)	3.0 (2.1; 3.9)	1.7 (1.0; 2.3)
Low adherence to the provegetarian FP	2.8 (1.9; 3.6)	1.4 (1.0; 1.9)	4.2 (2.9; 5.5)	2.3 (1.4; 3.1)
Medium adherence to the provegetarian FP	2.6 (1.8; 3.5)	1.3 (0.9; 1.6)	4.0 (2.7; 5.1)	2.0 (1.2; 2.6)
High adherence to the provegetarian FP	2.4 (1.6; 3.1)	1.3 (0.9; 1.7)	3.4 (2.3; 4.4)	1.9 (1.1; 2.7)

2nd Worst pizza (#84)

Age < 45 years	3.5 (2.4; 4.7)	1.6 (1.1; 2.2)	7.3 (3.4; 10.6)	3.2 (0.8; 5.4)
Age ≥ 45 years	1.2 (0.8; 1.5)	0.7 (0.5; 0.9)	2.9 (1.9; 3.8)	1.9 (1.0; 2.6)
Body mass index < 25	2.7 (1.8; 3.6)	1.3 (0.9; 1.8)	2.8 (-0.7; 6.4)	1.2 (-1.0; 3.4)
Body mass index ≥ 25	1.8 (1.2; 2.4)	0.9 (0.6; 1.2)	5.1 (4.0; 6.1)	3.3 (2.6; 4.0)
Fruit and vegetables consumption < 400g/day	2.5 (1.7; 3.3)	1.3 (0.9; 1.8)	5.7 (3.1; 7.9)	3.3 (1.3; 4.9)
Fruit and vegetables consumption ≥ 400g/day	1.6 (1.1; 2.1)	0.8 (0.6; 1.0)	3.6 (2.3; 4.8)	1.8 (0.8; 2.6)
Low adherence to the mPNNS-GS	2.7 (1.8; 3.6)	1.3 (0.8; 1.7)	6.2 (3.2; 8.8)	2.8 (1.0; 4.4)
Medium adherence to the mPNNS-GS	1.7 (1.2; 2.3)	1.4 (0.9; 1.8)	4.2 (2.5; 5.6)	3.4 (1.4; 5.0)
High adherence to the mPNNS-GS	2.2 (1.5; 2.9)	1.0 (0.7; 1.3)	4.8 (2.9; 6.5)	2.4 (1.1; 3.4)
Low adherence to the MEDI-LITE	2.4 (1.6; 3.1)	1.2 (0.8; 1.6)	5.7 (3.1; 7.9)	3.3 (1.6; 4.7)
Medium adherence to the MEDI-LITE	2.5 (1.7; 3.4)	1.2 (0.8; 1.6)	5.9 (3.4; 7.9)	2.9 (1.0; 4.4)
High adherence to the MEDI-LITE	1.9 (1.3; 2.5)	1.1 (0.7; 1.4)	4.0 (2.4; 5.5)	2.3 (0.9; 3.4)
Low adherence to the provegetarian FP	2.3 (1.5; 3.1)	1.2 (0.8; 1.6)	5.6 (3.2; 7.7)	3.2 (1.4; 4.6)
Medium adherence to the provegetarian FP	2.3 (1.5; 3.0)	1.1 (0.8; 1.5)	5.3 (3.1; 7.1)	2.7 (1.2; 3.9)
High adherence to the provegetarian FP	2.1 (1.5; 2.8)	1.2 (0.8; 1.6)	4.5 (2.5; 6.2)	2.6 (0.8; 4.0)

MEDI-LITE, Literature-based adherence score to the Mediterranean diet; ***mPNNS-GS***, modified Programme National Nutrition Santé Guideline Score; ***NIE substitution***, Non-isoenergetic substitution; ***Provegetarian FP***, Provegetarian food pattern. “Pizza” here stands for cluster of pizzas (*n*=100, out of 353 pizzas).

Supplemental table 4 Rates of change in risk of type 2 diabetes (in percentage) for inter-categories substitutions in the whole population and in population subgroups †

Population	Isoenergetic substitution		Non-isoeenergetic substitution	
	Men	Women	Men	Women
Pan bagnat				
Whole population	-2.6 (-3.7; -1.5)	-1.4 (-1.9; -0.8)	-2.1 (-3.2; -1.0)	-1.1 (-1.7; -0.4)
Pizza consumers	-6.5 (-9.1; -3.9)	-4.3 (-6.0; -2.5)	-5.4 (-8.1; -2.6)	-3.4 (-5.3; -1.4)
Participants who consumed pizza once	-5.0 (-7.0; -3.0)	-3.7 (-5.2; -2.2)	-4.1 (-6.2; -1.9)	-2.9 (-4.6; -1.2)
Participants who consumed pizza twice	-9.6 (-13.3; -5.7)	-6.2 (-8.6; -3.7)	-8.0 (-12.0; -3.9)	-5.3 (-8.2; -2.4)
Participants who consumed pizza more than twice	-13.5 (-18.6; -8.0)	-9.7 (-13.4; -5.8)	-11.6 (-17.0; -5.8)	-7.7 (-11.9; -3.4)
Age < 45 years	-4.1 (-5.7; -2.4)	-1.9 (-2.6; -1.1)	-3.5 (-5.2; -1.7)	-1.6 (-2.5; -0.7)
Age ≥ 45 years	-1.4 (-1.9; -0.8)	-0.9 (-1.2; -0.5)	-1.0 (-1.6; -0.4)	-0.6 (-1.0; -0.2)
Body mass index < 25	-3.2 (-4.5; -1.9)	-1.5 (-2.1; -0.9)	-3.2 (-4.6; -1.7)	-1.6 (-2.3; -0.8)
Body mass index ≥ 25	-2.1 (-2.9; -1.2)	-1.2 (-1.6; -0.7)	-1.5 (-2.3; -0.6)	-0.7 (-1.1; -0.2)
Fruit and vegetables consumption < 400g/day	-3.0 (-4.2; -1.8)	-1.6 (-2.3; -1.0)	-2.4 (-3.7; -1.1)	-1.3 (-2.0; -0.5)
Fruit and vegetables consumption ≥ 400g/day	-1.7 (-2.4; -1.0)	-0.8 (-1.1; -0.5)	-1.3 (-2.0; -0.5)	-0.6 (-1.0; -0.2)
Low adherence to the mPNNS-GS	-3.3 (-4.6; -2.0)	-1.5 (-2.1; -0.9)	-2.7 (-4.1; -1.3)	-1.2 (-1.8; -0.5)
Medium adherence to the mPNNS-GS	-2.0 (-2.9; -1.2)	-1.7 (-2.3; -1.0)	-1.6 (-2.5; -0.7)	-1.3 (-2.0; -0.5)
High adherence to the mPNNS-GS	-2.4 (-3.3; -1.4)	-1.1 (-1.5; -0.7)	-1.9 (-2.9; -0.9)	-0.8 (-1.3; -0.3)
Low adherence to the MEDI-LITE	-3.0 (-4.2; -1.8)	-1.5 (-2.2; -0.9)	-2.4 (-3.7; -1.2)	-1.2 (-1.9; -0.5)
Medium adherence to the MEDI-LITE	-2.9 (-4.0; -1.7)	-1.4 (-2.0; -0.9)	-2.3 (-3.5; -1.0)	-1.1 (-1.8; -0.4)
High adherence to the MEDI-LITE	-1.9 (-2.8; -1.1)	-1.1 (-1.6; -0.6)	-1.6 (-2.4; -0.7)	-0.9 (-1.4; -0.4)
Low adherence to the provegetarian FP	-2.9 (-4.0; -1.7)	-1.5 (-2.1; -0.9)	-2.3 (-3.5; -1.1)	-1.1 (-1.8; -0.5)
Medium adherence to the provegetarian FP	-2.6 (-3.7; -1.6)	-1.3 (-1.8; -0.7)	-2.1 (-3.2; -1.0)	-1.0 (-1.6; -0.4)
High adherence to the provegetarian FP	-2.3 (-3.2; -1.3)	-1.4 (-1.9; -0.8)	-1.8 (-2.8; -0.8)	-1.1 (-1.7; -0.4)
Spring rolls				
Whole population	-2.1 (-3.3; -0.8)	-1.2 (-1.8; -0.5)	-5.1 (-7.3; -2.4)	-2.9 (-4.5; -1.0)
Pizza consumers	-5.2 (-8.1; -2.1)	-3.6 (-5.6; -1.6)	-11.4 (-16.9; -4.6)	-8.3 (-12.9; -2.4)
Participants who consumed pizza once	-4.0 (-6.2; -1.6)	-3.1 (-4.8; -1.4)	-8.9 (-13.1; -3.9)	-7.4 (-11.3; -2.4)
Participants who consumed pizza twice	-7.6 (-11.7; -3.1)	-5.1 (-7.9; -2.2)	-15.0 (-23.1; -4.8)	-8.9 (-16.6; 0.2)
Participants who consumed pizza more than twice	-11.0 (-16.8; -4.5)	-8.4 (-12.9; -3.7)	-21.6 (-32.9; -6.0)	-19.5 (-29.0; -6.3)
Age < 45 years	-3.2 (-5.0; -1.3)	-1.6 (-2.4; -0.7)	-6.8 (-10.6; -2.2)	-3.1 (-5.6; -0.3)
Age ≥ 45 years	-1.1 (-1.8; -0.5)	-0.7 (-1.1; -0.3)	-3.0 (-4.0; -1.7)	-2.0 (-2.8; -1.0)
Body mass index < 25	-2.6 (-4.0; -1.0)	-1.3 (-2.0; -0.6)	-2.4 (-6.4; 1.9)	-1.1 (-3.5; 1.5)
Body mass index ≥ 25	-1.7 (-2.6; -0.7)	-0.9 (-1.5; -0.4)	-5.2 (-6.5; -3.9)	-3.6 (-4.3; -2.7)
Fruit and vegetables consumption < 400g/day	-2.3 (-3.7; -0.9)	-1.3 (-2.1; -0.6)	-5.6 (-8.2; -2.5)	-3.4 (-5.2; -1.1)
Fruit and vegetables consumption ≥ 400g/day	-1.5 (-2.3; -0.6)	-0.8 (-1.1; -0.3)	-3.6 (-5.0; -2.0)	-1.8 (-2.8; -0.7)
Low adherence to the mPNNS-GS	-2.6 (-4.0; -1.0)	-1.2 (-1.8; -0.5)	-6.0 (-8.9; -2.4)	-2.8 (-4.5; -0.7)
Medium adherence to the mPNNS-GS	-1.7 (-2.6; -0.7)	-1.4 (-2.1; -0.6)	-4.2 (-5.9; -2.2)	-3.4 (-5.3; -1.1)
High adherence to the mPNNS-GS	-2.0 (-3.1; -0.8)	-1.0 (-1.6; -0.5)	-4.7 (-6.7; -2.3)	-2.6 (-3.7; -1.1)
Low adherence to the MEDI-LITE	-2.3 (-3.6; -0.9)	-1.2 (-1.9; -0.5)	-5.6 (-8.2; -2.5)	-3.5 (-5.0; -1.4)
Medium adherence to the MEDI-LITE	-2.4 (-3.7; -1.0)	-1.3 (-2.0; -0.6)	-5.7 (-8.1; -2.9)	-2.9 (-4.6; -0.9)
High adherence to the MEDI-LITE	-1.7 (-2.6; -0.7)	-1.1 (-1.6; -0.5)	-4.0 (-5.7; -2.0)	-2.3 (-3.6; -0.7)
Low adherence to the provegetarian FP	-2.2 (-3.5; -0.8)	-1.2 (-1.9; -0.5)	-5.5 (-8.0; -2.6)	-3.2 (-4.9; -1.1)
Medium adherence to the provegetarian FP	-2.1 (-3.3; -0.8)	-1.1 (-1.7; -0.5)	-5.3 (-7.5; -2.6)	-2.8 (-4.2; -1.1)
High adherence to the provegetarian FP	-2.0 (-3.1; -0.9)	-1.3 (-1.9; -0.6)	-4.4 (-6.4; -2.1)	-2.6 (-4.2; -0.7)
Spaghetti with tomato sauce				
Whole population	-1.1 (-1.5; -0.6)	-0.7 (-0.9; -0.4)	-5.4 (-8.1; -1.8)	-3.2 (-5.3; -0.6)
Pizza consumers	-2.7 (-3.9; -1.4)	-2.2 (-2.9; -1.4)	-11.4 (-18.4; -2.0)	-8.7 (-15.0; -0.6)
Participants who consumed pizza once	-2.1 (-3.0; -1.1)	-1.9 (-2.5; -1.2)	-9.1 (-14.3; -2.2)	-7.9 (-13.1; -1.0)
Participants who consumed pizza twice	-3.9 (-5.7; -2.0)	-2.9 (-4.0; -1.8)	-13.9 (-24.6; 0.6)	-8.1 (-18.6; 4.7)
Participants who consumed pizza more than twice	-5.7 (-8.2; -3.1)	-4.9 (-6.8; -3.0)	-19.7 (-34.9; 2.4)	-20.0 (-32.4; -1.7)
Age < 45 years	-1.6 (-2.3; -0.8)	-0.9 (-1.2; -0.6)	-6.7 (-11.6; -0.5)	-3.2 (-6.5; 0.8)
Age ≥ 45 years	-0.6 (-0.9; -0.4)	-0.5 (-0.7; -0.3)	-3.3 (-4.6; -1.7)	-2.3 (-3.3; -0.9)
Body mass index < 25	-1.3 (-1.9; -0.7)	-0.8 (-1.1; -0.5)	-1.0 (-6.5; 5.0)	-0.5 (-3.9; 3.2)

Body mass index ≥ 25	-0.9 (-1.4; -0.5)	-0.6 (-0.8; -0.4)	-6.0 (-7.4; -4.5)	-4.3 (-5.2; -3.3)
Fruit and vegetables consumption < 400g/day	-1.2 (-1.7; -0.6)	-0.8 (-1.0; -0.5)	-5.8 (-9.0; -1.7)	-3.7 (-6.1; -0.5)
Fruit and vegetables consumption ≥ 400g/day	-0.9 (-1.2; -0.5)	-0.5 (-0.7; -0.4)	-4.0 (-5.6; -1.9)	-2.1 (-3.3; -0.5)
Low adherence to the mPNNS-GS	-1.2 (-1.8; -0.6)	-0.6 (-0.9; -0.4)	-6.1 (-9.9; -1.2)	-3.0 (-5.3; -0.1)
Medium adherence to the mPNNS-GS	-0.9 (-1.2; -0.5)	-0.8 (-1.1; -0.5)	-4.6 (-6.6; -1.9)	-3.8 (-6.2; -0.6)
High adherence to the mPNNS-GS	-1.1 (-1.6; -0.7)	-0.7 (-0.9; -0.5)	-5.0 (-7.5; -1.9)	-2.9 (-4.5; -0.8)
Low adherence to the MEDI-LITE	-1.1 (-1.5; -0.6)	-0.6 (-0.9; -0.4)	-5.9 (-9.1; -1.7)	-3.9 (-5.9; -1.1)
Medium adherence to the MEDI-LITE	-1.3 (-1.8; -0.7)	-0.8 (-1.0; -0.5)	-6.1 (-9.0; -2.3)	-3.2 (-5.5; -0.3)
High adherence to the MEDI-LITE	-1.0 (-1.4; -0.6)	-0.7 (-0.9; -0.5)	-4.2 (-6.4; -1.6)	-2.5 (-4.3; -0.3)
Low adherence to the provegetarian FP	-1.0 (-1.5; -0.5)	-0.6 (-0.9; -0.4)	-5.8 (-8.9; -1.9)	-3.6 (-5.8; -0.7)
Medium adherence to the provegetarian FP	-1.1 (-1.5; -0.6)	-0.6 (-0.9; -0.4)	-5.6 (-8.3; -2.1)	-3.2 (-5.0; -0.8)
High adherence to the provegetarian FP	-1.2 (-1.6; -0.7)	-0.9 (-1.1; -0.6)	-4.6 (-7.1; -1.5)	-2.8 (-5.0; -0.1)
Hot-dog				
Whole population	6.5 (4.2; 9.1)	3.2 (2.1; 4.4)	9.5 (6.3; 12.8)	4.9 (2.9; 6.7)
Pizza consumers	16.2 (10.5; 22.4)	10.1 (6.7; 13.6)	24.2 (15.6; 32.9)	15.5 (9.0; 21.6)
Participants who consumed pizza once	11.6 (7.6; 15.7)	8.5 (5.7; 11.5)	17.3 (11.3; 23.2)	13.2 (7.81; 18.2)
Participants who consumed pizza twice	24.5 (15.7; 34.2)	14.7 (9.6; 20.0)	37.1 (23.8; 51.3)	20.5 (10.2; 30.8)
Participants who consumed pizza more than twice	42.1 (25.8; 61.8)	26.9 (17.3; 37.4)	64.5 (39.9; 93.0)	44.8 (27.1; 62.5)
Age < 45 years	10.4 (6.6; 14.6)	4.5 (2.9; 6.1)	14.3 (8.9; 19.9)	6.1 (3.2; 8.8)
Age ≥ 45 years	3.3 (2.1; 4.5)	1.9 (1.2; 2.6)	5.0 (3.5; 6.6)	3.1 (2.0; 4.1)
Body mass index < 25	7.9 (5.1; 11.1)	3.6 (2.4; 4.9)	8.1 (3.5; 12.9)	3.5 (1.0; 6.0)
Body mass index ≥ 25	5.1 (3.3; 7.2)	2.6 (1.7; 3.6)	8.5 (6.3; 10.9)	5.0 (3.9; 6.3)
Fruit and vegetables consumption < 400g/day	7.3 (4.7; 10.2)	3.7 (2.5; 5.2)	10.6 (6.9; 14.4)	5.7 (3.4; 7.9)
Fruit and vegetables consumption ≥ 400g/day	4.4 (2.8; 6.2)	2.0 (1.3; 2.7)	6.5 (4.4; 8.7)	3.0 (1.8; 4.0)
Low adherence to the mPNNS-GS	8.3 (5.3; 11.6)	3.5 (2.3; 4.8)	11.8 (7.6; 16.3)	5.1 (2.9; 7.2)
Medium adherence to the mPNNS-GS	4.9 (3.2; 6.7)	3.8 (2.5; 5.2)	7.4 (5.0; 9.6)	5.8 (3.4; 8.0)
High adherence to the mPNNS-GS	6.1 (3.9; 8.5)	2.6 (1.7; 3.6)	8.7 (5.8; 11.8)	4.0 (2.5; 5.4)
Low adherence to the MEDI-LITE	7.2 (4.6; 10.0)	3.5 (2.3; 4.8)	10.6 (6.9; 14.4)	5.6 (3.5; 7.6)
Medium adherence to the MEDI-LITE	7.3 (4.7; 10.3)	3.3 (2.2; 4.5)	10.7 (7.1; 14.5)	5.0 (2.9; 7.0)
High adherence to the MEDI-LITE	5.1 (3.3; 7.0)	2.8 (1.8; 3.9)	7.2 (4.9; 9.7)	4.0 (2.3; 5.6)
Low adherence to the provegetarian FP	7.0 (4.5; 9.7)	3.5 (2.3; 4.8)	10.4 (6.8; 13.9)	5.4 (3.3; 7.4)
Medium adherence to the provegetarian FP	6.6 (4.2; 9.4)	3.0 (2.0; 4.1)	9.7 (6.4; 13.2)	4.6 (2.8; 6.3)
High adherence to the provegetarian FP	5.8 (3.8; 8.0)	3.2 (2.1; 4.4)	8.2 (5.4; 11.0)	4.6 (2.6; 6.4)

MEDI-LITE, Literature-based adherence score to the Mediterranean diet; **mPNNS-GS**, modified Programme National Nutrition Santé Guideline Score; **NIE substitution**, Non-isoenergetic substitution; **Provegetarian FP**, Provegetarian food pattern

† Results are the observed risk variations for the best and worst mixed dishes identified for isoenergetic and non-isoenergetic substitutions.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1, 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9; eFigures 3, eTables 1-2
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5-6; eFigures 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5-9; eFigures 2
		(b) Describe any methods used to examine subgroups and interactions	6-9
		(c) Explain how missing data were addressed	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	eFigures 1
		(e) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5; eFigures 1
		(b) Give reasons for non-participation at each stage	5; eFigures 1
		(c) Consider use of a flow diagram	eFigures 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10; Table 2; Figure 1
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11; Table 2; eTables 3-4; Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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