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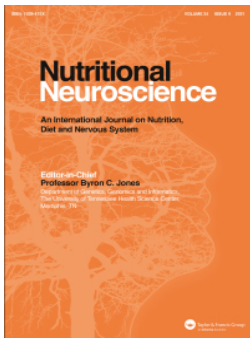
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Association between ultra-processed foods and recurrence of depressive symptoms: the Whitehall II cohort study

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ABSTRACT

Objectives: To examine the association between high intakes of ultra-processed foods (UPF) and recurrence of depressive symptoms (DepS) in a Western non-Mediterranean country and its contribution to the overall diet-depression relationship.

Methods: Analyses were carried out on British participants from the Whitehall II cohort. Present analyses were restricted to white participants $N = 4554$ (74% men, mean age = 61; SD = 5.9). UPF consumption was estimated from a 127-item food frequency questionnaire using the NOVA classification, and cumulative average of UPF intakes (g/day) over 11 years of exposure (1991/1994–2002/2004) was computed. Recurrent DepS after measurement of UPF was defined as having two or more episodes of DepS (the Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 or antidepressants use) during four phases of follow-up (2002/2004–2015/2016).

Results: Over the follow-up, 588 (12.9%) cases of recurrent DepS were observed. After adjusting for socio-demographic factors, health behaviours and health status, participants in top quintile of UPF intakes [mean 33% of total daily intakes in grams] had 31% higher odds of recurrent DepS (odds ratio 1.31; 95% CI 1.04–1.64) compared to participants in the four lowest quintiles of UPF [mean 18.1% of total daily intakes in grams]. Additional analyses showed that associations between adherence to several diet quality measures and recurrent DepS were partially attenuated (17–27%) by UPF intakes.

Conclusion: In this British population, high intakes of ultra-processed foods were associated with increased odds of recurrent depressive symptoms and contributed to the overall diet quality-depressive symptoms association.

KEYWORDS

Depressive symptoms; ultra-processed foods; NOVA classification; diet quality; prospective cohort; nutritional psychiatry; nutritional epidemiology



1. Introduction


There is evidence from observational studies linking overall diet quality and risk of depressive disorders [1,2]. Meta-analyses of prospective cohort studies have shown that higher adherence to healthy dietary guidelines such as Mediterranean diet, is associated with an approximate reduction in risk for depression by 30%, with lower consumption of Western-style diets being associated with a reduced risk of depression [1].

Amongst the numerous potential underlying mechanisms, the role of inflammation has raised particular interest. The anti-inflammatory and antioxidant properties of plant foods including fruits and vegetables, mono and poly-unsaturated fatty acids from foods such as nuts, oily fish and olive oil, have been put

forward to explain the beneficial effect of healthy diets such as the Mediterranean diet on depression. By contrast, the Western-type diet, characterized by high intakes of sugary foods and foods rich in saturated and trans fatty acids, exerts a deleterious effect on the pathophysiological pathways related to depression, including inflammation, oxidative stress, the gut microbiome, epigenetic alterations and neuroplasticity [3].

However, Western type diets are also characterized by intakes of foods that have undergone industrial processing to enhance their texture, taste and shelf-life. A few classification systems have been proposed to classify these food items according to the nature, extent and purpose of processing [4]. Among these, the NOVA food classification system [5] has been the most widely

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used tool in epidemiological studies and consists of categorizing foods and beverages into four progressive groups: namely, (1) unprocessed or minimally processed foods, (2) processed culinary ingredients, (3) processed foods, and (4) ultra-processed foods. Recent systematic reviews and meta-analyses have reported that higher intakes of NOVA classified ultra-processed foods (UPF) increased the risk of several common non-communicable diseases, morbidity and mortality [6].

In terms of mental health and depression, two studies carried out in Mediterranean countries reported that higher intakes of UPF were associated with an increased risk of depressive symptoms (DepS) [7] and depression [8] over 5 and 10 years of follow-up respectively. In non-Mediterranean countries where higher adherence to the Western type diet is generally observed [9], literature on the association between UPF and depression outcomes is scarce.

To our knowledge, only one study carried out in the American population, reported a cross-sectional association between higher UPF intakes and increased odds of DepS [10]. However, no study has yet explored whether long-term exposure to high intakes of UPF is associated with later DepS in a non-Mediterranean environment and whether UPF intakes might partly explain the observed associations between overall diet quality and depressive outcomes.

Using data from the Whitehall II study of British civil servants, we first investigated whether long-term intake of UPF over adult life was associated with subsequent recurrent episodes of DepS assessed over 13 years of follow-up. Secondly, we assessed the extent to which associations between overall diet quality and recurrence of DepS previously observed in the Whitehall II study were attributable to UPF intakes.

2. Methods

2.1 . Study population

The Whitehall II study is an ongoing prospective cohort of 10,308 participants (6895 men, 3413 women) recruited from twenty different civil service departments in London [11]. At phase 1, in 1985/1988 all persons aged 35–55 years were invited to participate by letter, and 73% agreed. Since inclusion, follow-up clinical examinations have taken place approximately every five years: phase 3 (1991/1994, $n = 8815$), phase 5 (1997/1999, $n = 7870$), phase 7 (2002/2004, $n = 6967$), phase 9 (2007/2009, $n = 6761$), phase 11 (2012/2013, $n = 6308$) and phase 12 (2015/2016, $n = 5632$) [11]. Written informed consent was obtained after a thorough

explanation of the study to each participant; the University College London ethics committee approved the study.

The present analyses were restricted to 4554 participants with data available on dietary assessment (assessed dietary intakes over previous 12 months), covariates at phase 7 and measures of recurrence of DepS defined by having at least two episodes of DepS since baseline follow-up (as detailed in flowchart diagram, Figure 1).

2.2. Assessment of exposure

Dietary assessment and NOVA classification. Food frequency questionnaires (FFQ) were administered at phases 3, 5 and 7 to assess participants' dietary intakes. The FFQ has been validated in Whitehall II cohort and details regarding validation has been provided elsewhere [12]. Participants were asked how often, on average, they had consumed a common unit or portion size of each food item during the previous year. A nine-point scale was used to assess the frequency at which food items were consumed. The scale ranges from 'never or less than once per month' to 'six or more times per day'. Daily food consumption was computed for each participant based on the FFQ response. Nutrient intakes were calculated by multiplying the consumption frequency for each food item by its nutrient content (for specified portions) and then summing nutrient contributions from all foods as detailed elsewhere [12]. To account for under or over-reporting participants, women who reported total energy intakes lower than 500 kCal or higher than 3500 kCal were excluded. The same was done for men who reported total energy intakes lower than 800 kCal or higher than 4000 kCal. Participants who had 10% or more FFQ items were also excluded from the main analyses. Participants who had 10% or more items missing out of the 127 food items included in the FFQ were also excluded from the main analyses. We implemented the NOVA classification proposed by Monteiro et al. [13] by categorizing FFQ items into four classes according to the level of processing with group 1 including raw or minimally altered food items to group 4 consisting of UPF that correspond to food items which have undergone industrial processing including the addition of artificial flavours, preservatives, emulsifiers and other additives. Detailed information regarding the classification of the 127 items of the FFQ is given in Appendix-Supplementary Table 1. As dietary intakes were also assessed at phase 3 (1991/1994) and phase 5 (1997/1999) using similar FFQ, the NOVA classification was also implemented at these phases.

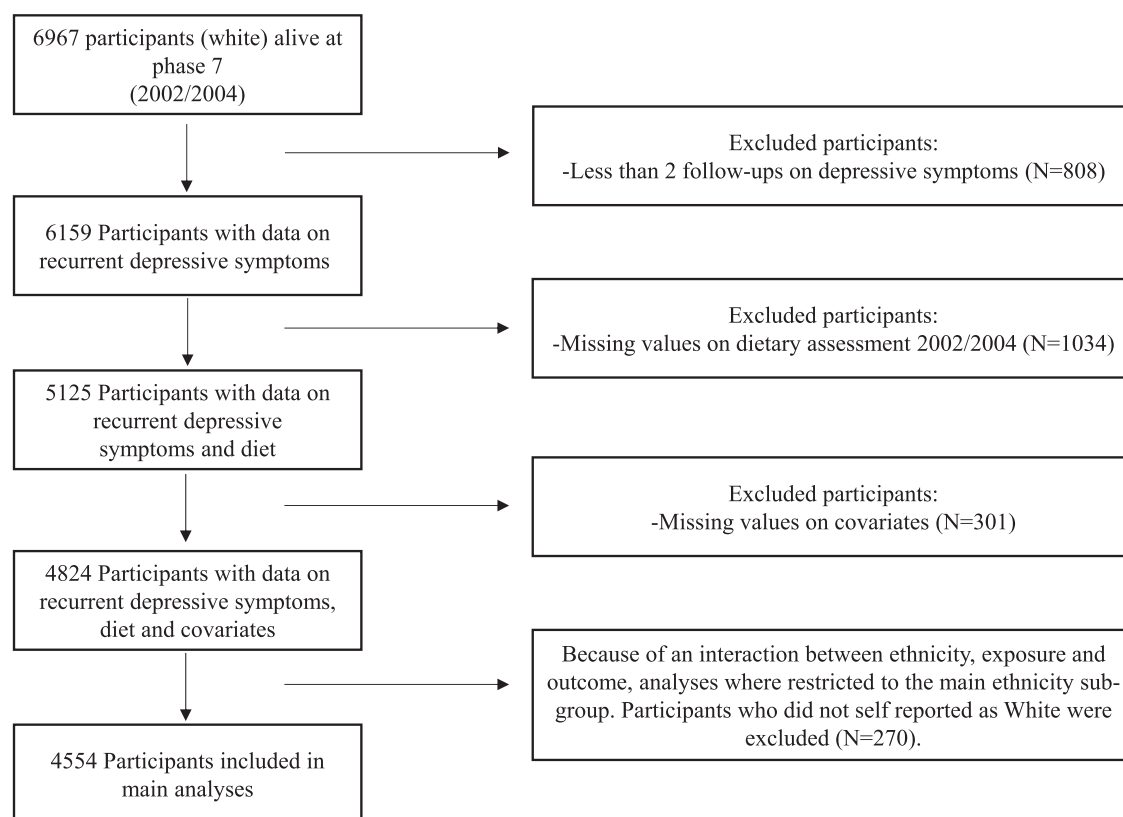


Figure 1. Flowchart mapping the sample selection of participants included in main analyses.

Estimation of Ultra-Processed Food Intakes. To estimate total intakes of UPF, all items belonging to group 4 of the NOVA classification were converted to daily intakes in grams (by multiplying frequency of intakes of each item by relevant portion size) and then summed. The intakes of UPF/day was then calculated as a percentage of total daily intake of food in grams.

$$\frac{\text{Total UPF intakes in grams/day}}{\text{Total food intakes in grams/day}} \times 100$$

As some UPF may carry zero or low calories, this method of calculating UPF intakes was preferred over calculating UPF intakes as percentage of total energy intakes [14]. This has been done at phase 7 (2002/2004) – the baseline of the present study, however when data on dietary exposure prior to phase 7 was available ($n = 4470$ of 4554), the cumulative average of total intakes of UPF was calculated using the repeated measures of dietary intakes in 1991/1994, 1997/1999 and 2002/2004 allowing to represent long-term dietary intakes (11 years of exposure period) and to reduce the possibility of measurement error.

Diet quality scores. Three dietary scores were derived from FFQs to assess overall diet quality.

First, the alternative healthy eating index (AHEI-2010) [15] was scored on the basis of the intake levels

of 11 dietary components: vegetables, fruits, whole grains, nuts and legumes, long chain omega-3 fats (DHA and EPA), polyunsaturated fatty acid, sugar-sweetened drinks and fruit juice, red and processed meat, trans fat, sodium and alcohol intake. Each component is given a maximal score of 10 (when recommendations were fully met) and a minimal score of 0 (representing the least healthy dietary behaviour), with intermediate intakes scored proportionately between 0 and 10. All the component scores are summed to obtain a total AHEI-2010 score, which ranges from 0 to 110, with a higher score representing a healthier diet [15]. The details of AHEI-2010 scoring criteria are provided in Appendix-Supplementary Table 2.

Second, transformed Mediterranean diet scores [16] were derived based on median intake of nine dietary components: vegetables, fruits, whole grains, fish, legumes, higher mono-unsaturated fatty acid/saturated fatty acid ratio, meat (processed, red meat and chicken), dairy and ethanol. Each component is given a minimal score of 0 and a maximal score of 1 according to population's median components' consumption. All component scores are summed to obtain a total Mediterranean diet scores that ranges from 0 to 9, with a higher score representing a

healthier diet [16]. The details regarding scoring of transformed Mediterranean are provided in Appendix-Supplementary Table 3.

Third, the dietary inflammatory index score reflecting the inflammatory potential of the diet is computed using data for 27 of 45 food parameters (energy, carbohydrate, protein, total fat, alcohol, fibre, cholesterol, saturated fat, monounsaturated fatty acid, polyunsaturated fatty acid, omega-3, omega-6, trans fat, niacin, thiamin, riboflavin, vitamin B12, vitamin B6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, and folic acid). The inflammatory potential for each food parameter was scored according to whether it increased, decreased, or had no effect on six inflammatory biomarkers [17]. All of the food parameter-specific dietary inflammatory index scores were then summed to create the overall dietary inflammatory index score for each participant in the study. Details regarding the construction and validation of dietary inflammatory index in Whitehall II have been presented elsewhere [17]. The greater the dietary inflammatory index score, the more pro-inflammatory the diet whereas negative values are related to anti-inflammatory diets.

For these three dietary indices, cumulative averages were calculated using FFQ data at phases 3, 5 and 7.

2.3. Assessment of outcome over a 13-year period (2002/2004–2015/2016)

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess DepS in Whitehall participants at phase 7 (2002/2004), phase 9 (2007/2009), phase 11 (2012/2013) and phase 12 (2015/2016). This self-report scale is composed of 20 items covering symptoms of depression. Participants rated the frequency of having each symptom over the past week using a four-point scale, ranging from 'less than once a week' to '5–7 days a week'. Participants with a CES-D score ≥ 16 or treated by anti-depressants between 2002/2004 and 2015/2016 were defined as DepS cases. Current medications use (generic name, brand name, or both) was self-reported by participants and subsequently coded using the British National Formulary to determine anti-depressant use. As previously reported [18], given the reversible condition of the self-reported DepS via CES-D, considering recurrence of DepS might better reflect long-term DepS than considering a single measure of DepS. Recurrence of DepS was defined as presenting DepS at two, three or all the four phases of follow-up (2002/2004, 2007/2009, 2012/2013 and 2015/2016), while non-recurrent cases were defined as participants

reporting one or no DepS episode over the 13 years of follow-up.

2.4. Assessment of covariates

Three types of covariates were considered, socio-demographic factors, health behaviours and health related factors, all measured in 2002/2004 by questionnaires completed by the participants and measures assessed during physical examination (measures of systolic and diastolic blood pressure, weight, height, fasting glucose, triglycerides assessed from fasting blood samples taken from participants) [11].

Socio-demographic variables include sex, age (continuous), marital status (widowed, divorced/separated, single, married/cohabiting), education levels (< secondary, secondary, university level) and socio-economic status (SES) categorized into three groups: low (clerical or support), intermediate (professional or executive) and high (administrative) [11].

Behavioural covariates consisted of smoking status (ex or non-smokers and current smokers), physical activity: inactive (<1 hour/week of moderate physical activity and <1 hour/week of vigorous physical activity) versus moderate or active (>1 hour/week of moderate or vigorous physical activity) [19] and AHEI-2010 score as measure of overall diet quality (continuous).

Health-related data included prevalent coronary heart disease (CHD) (denoted by clinically verified non-fatal myocardial infarction or definite angina), hypertension (systolic/diastolic blood pressure $\geq 140/90$ mm Hg, respectively, or use of antihypertensive drugs), type 2 diabetes (fasting glucose of ≥ 7.0 mmol/l or 2-hour post-load glucose ≥ 11.1 mmol/L or reported doctor diagnosed diabetes or use of diabetic medication), dyslipidemia (triglycerides >1.7 mmol/L or reported use of lipid lowering drugs), measure of body mass index (BMI) in kg/m^2 and cognitive deficit (a score ≤ 27 in the Mini Mental State Examination). Details about the collection of these data are provided elsewhere [18]. We also considered antecedent DepS, assessed by the general health questionnaire (GHQ) [20] as CES-D was not administered in Whitehall II study prior to phase 7 (2002/2004). GHQ captures common mental disorder symptoms and included the four-item depression subscale. All items were scored from 0 to 3 and then summed; cut-off points of 4 out of 12 were used to identify DepS cases. Participants who reported DepS assessed by GHQ at phase 3 (1991/1994), phase 5 (1997/1999) or phase 7 (2002/2004) or treated by anti-depressants at phase 3 (1991/1994) or phase 5 (1997/1999) were defined as having DepS antecedents. All health status factors added to the statistical models

were used as binary categorical variables (yes/no) except for the BMI (kg/m^2) which was analysed as continuous variable.

2.5. Statistical analyses

The characteristics of participants eligible for inclusion in the present study were compared to those of participants excluded using Chi^2 and Student *t*-tests. Similar tests were used to assess participants' characteristics associated with subsequent recurrence of DepS symptoms over the 13-year follow-up period (2002/2004–2015/2016).

Cumulative average of UPF intakes of the 11 years of exposure period (1991/1994–2002/2004) were categorized using sex-specific quintiles. We compared cumulative average of diet quality scores, food groups, and specific nutrients according to UPF quintiles using Anova or Kruskal–Wallis tests according to their normal or non-normal distributions. Similar tests were used to assess participant characteristics associated with UPF intakes.

The main analyses consisted of estimating the association between high amounts of UPF intakes over 11 years of exposure and subsequent recurrent DepS over the 13 years of follow-up, using logistic regression models. Our initial analyses found a lack of a dose–response association with DepS across the four lower quintiles of UPF intakes. Thus, for the main analyses, UPF intakes was modelled as a binary variable where participants in the top quintile group were compared to participants in the four lower quintiles.

Initial bivariate analyses including an interaction between each covariate and exposure in regard to recurrent DepS showed an interaction between ethnicity and UPF intakes (OR of recurrent DepS associated with high UPF intakes in participants self-reported as white = 1.37; 95% CI 1.12–1.67 versus OR 0.44; 95% CI 0.15–1.29 in non-white participants). Given the small number of non-white participants ($n = 270$), we excluded them from the analyses (detailed in flowchart diagram, Figure 1). No other significant interaction between covariates and UPF exposure was found.

Three levels of adjustment were considered for multivariable regression models. Model 1 was adjusted for sex, age, marital status, education level and socio-economic status. Model 2 was further adjusted for health behaviours including smoking status, physical activity and measure of overall diet quality assessed by AHEI-2010. Finally, health related covariates including CHD, hypertension, type 2 diabetes, dyslipidemia, BMI, cognitive impairment and antecedent DepS, were added in model 3.

For sensitivity analyses, first, we ran fully adjusted logistic models by considering UPF intakes in quintiles and assessed the linearity of associations between UPF intakes and DepS. Second, to isolate the direction of associations, models assessing associations between high amounts of UPF intakes over 11 years of exposure and recurrent DepS were repeated excluding participants with DepS or treated by antidepressants at phase 3 (1991/1994) or phase 5 (1997/1999). Third, as antidepressants can be prescribed for conditions other than depression, we repeated the main analyses with an alternative measure of depressive symptoms based on CES-D score (>16) only.

Finally, we carried out an additional analysis to assess whether change in UPF intakes over the 11 years of exposure were associated with recurrent DepS using logistic regression models.

The second objective of our study was to assess the contribution of UPF in previously reported associations between overall diet quality (AHEI-2010, transformed Mediterranean diet and dietary inflammatory index) and subsequent recurrence of DepS. For these analyses, first, *z*-scores (mean = 0, standard deviation = 1) were computed for the cumulative average (1991/1994–2002/2004) of dietary scores. Logistic regression models were then conducted to estimate associations between *z*-scores of dietary scores and DepS. These models were subsequently adjusted for exposure to high amounts of UPF intakes (top quintile versus four lower quintiles) and percentage attenuation of each overall diet measure–recurrent DepS association by UPF was computed using the following formula:

$$[(\beta_{\text{DepS}} - \beta_{\text{DepS adjusted for UPF}}) / \beta_{\text{DepS}}] \times 100$$

where the β_s are the beta coefficients estimated from the logistic models.

All statistical analyses were conducted using SAS 9.4 software.

3. Results

3.1. Characteristics of population study

The analyses were conducted in 4554 participants (3371 men, 1183 women) self-reported as white. Compared to participants excluded, the included were more likely to be men, younger, and with higher SES (Appendix-Supplementary Table 4). They were less likely to have DepS (antecedents and recurrent DepS over 13 years of follow-up) compared to excluded participants, while no significant difference was observed regarding exposure to high amounts of UPF intakes.

Over the 13 years of follow-up (2002/2004–2015/2016), recurrent DepS occurred for 588 participants (12.9%). Participants with recurrent DepS were more likely to be women (17.7% in women versus 11.2% in men), single or divorced, with lower educational achievement / SES compared to participants with no recurrent DepS (Appendix-Supplementary Table 5). Recurrence of DepS was also associated with being current smokers, physically inactive, dyslipidemia and cognitive deficit. As expected, the participants with antecedent DepS were significantly more likely to have subsequent recurrent DepS (17.9% vs 62.2%).

3.2. Participants' characteristics associated with UPF intakes

Univariate analyses comparing participants' characteristics according to quintiles of UPF intakes assessed over the 11-year exposure period are shown in Table 1. Participants in the top quintile of UPF were more likely to have low SES and low educational attainment. Those in the highest quintile were also more likely to be younger compared to those in the four lower quintiles. Regarding health behaviour and health status, low physical activity, higher total energy intakes and higher

BMI were associated with high intakes of UPF, whereas no association between antecedent DepS and UPF intakes was observed.

Mean of UPF intake over 11 years of exposure was 21.0 (SD = 7.9 expressed as % total daily intakes) with men having higher intakes, on average, compared to women (mean = 21.6; SD = 7.8; versus mean = 19.3; SD = 7.9). In Table 2, we compared diet quality scores, intakes of several food groups and nutrients according to sex-specific quintiles of UPF intakes. As expected, 'being exposed to high amounts of UPF was associated with i) lower scores in AHEI-2010 and transformed Mediterranean diet (whose higher scores indicate healthier diet) and ii) higher score in dietary inflammatory index (reflecting the pro-inflammatory property). Accordingly, higher intakes of UPF coincided with higher the intakes of meat, sugar, sodium, saturated fat and trans-fat intakes. Results of Table 2 also showed that participants in the top quintile of UPF intakes differ significantly regarding certain food groups and nutrients intakes compared to participants in the other four groups. They consumed less vegetables, fruits and fish but consumed more soda and foods rich in fat compared to those in the four lowest quintiles of UPF intakes.

Table 1. Characteristics of participants by sex specific quintiles of cumulative average of UPF intakes over 11 years of exposure.

N = 4554		Quintile 1	Quintile2	Quintile3	Quintile4	Quintile 5	P
Socio-demographics							
Age	(years)	61.4 ± 5.7	61.2 ± 5.9	61.1 ± 5.9	61.1 ± 6.2	60.0 ± 5.9	<0.001
Marital status	(Widowed%)	4.1	4.4	3.7	3.5	3.8	0.54
	(divorced/separated%)	6.7	6.3	6.0	6.8	7.2	
	(single%)	11.9	10.6	12.8	11.3	14.6	
	(married/cohabiting%)	77.4	78.7	77.4	78.4	74.3	
Education level	(<secondary%)	6.8	7.8	8.2	8.9	10.2	<0.001
	(secondary%)	46.6	47.3	49.1	51.5	54.3	
	(university%)	46.6	44.9	42.6	39.6	35.5	
Socio-economic status	(low%)	5.9	7.2	7.6	8.6	9.1	0.008
	(intermediate%)	39.9	39.7	40.2	41.6	45.4	
	(high%)	54.2	53.0	52.2	49.8	45.5	
Health behaviour factors							
Smoking status	(current-smoker%)	7.6	6.4	7.0	6.4	7.5	0.75
	(non/ex-smokers)	92.4	93.6	93.0	93.4	95.5	
Physical activity	(inactive%)	20.4	20.7	25.3	21.1	26.8	0.002
	(moderately active%)	14.7	16.8	17.11	15.8	16.9	
	(active%)	64.8	62.5	57.6	63.1	56.3	
Total energy intake	(kcal/d)	1962 ± 515	2120 ± 561	2191 ± 549	2281 ± 590	2313 ± 610	<0.001
Health status factors							
Coronary heart disease	(yes%)	9.4	7.2	8.3	8.9	7.8	0.46
Hypertension	(yes%)	39.2	37.3	36.9	37.5	34.6	0.37
Type 2 diabetes	(yes%)	7.9	7.1	8.5	7.7	9.3	0.47
Dyslipidemia	(yes%)	30.8	31.2	31.9	30.6	34.2	0.47
Body Mass Index	(kg/m ²)	26.2 ± 3.9	26.4 ± 3.9	26.3 ± 4.0	26.6 ± 4.1	26.9 ± 4.7	0.002
Cognitive deficit	(yes%)	11.8	10.1	9.4	12.9	12.4	0.08
Antecedent DepS	(yes%)	24.3	23.8	23.9	21.2	25.2	0.35
Outcome							
Recurrent DepS ^b	(yes%)	13.8	12.2	9.8	12.7	16.0	0.002

Data presented as Mean ± standard deviation or percentage.

Sex specific quintile of cumulative average of UPF intakes over 11 years of exposure period (1991/1994–2002/2004).

UPF intakes were expressed as % of total food intake/day.

^aObtained from chi² or Anova, as appropriate.

^bRecurrence of DepS assessed from 2002/2004 to 2015/2016.

Table 2. Distribution of diet scores and food groups according to sex specific of cumulative average of UPF intakes over 11 years of exposure.

N = 4554	Quintile 1	Quintile2	Quintile3	Quintile4	Quintile 5	<i>P</i> ^a
UPF (mean % intake of total food/day)	11.4 ± 2.5	16.4 ± 1.5	20.1 ± 1.5	24.3 ± 1.8	33.0 ± 5.6	<0.001
UPF Median (% intake/day)	11.8	16.4	20.1	24.3	31.3	
UPF (intake in g/day)	312.0 ± 98.6	438.2 ± 114.1	521.4 ± 125.7	630.4 ± 165.0	790.5 ± 235.6	
Range UPF men (% intake/day)	2%–15%	15%–19%	19%–23%	23%–28%	28%–61%	
Range UPF women (% intake/day)	2%–13%	13%–17%	16%–20%	20%–25%	25%–64%	
AHEI-2010 score ^b	56.8 ± 8.8	56.9 ± 8.7	56.1 ± 7.9	55.0 ± 7.8	51.6 ± 8.0	<0.001
Transformed Mediterranean diet score ^b	4.7 ± 1.3	4.7 ± 1.3	4.6 ± 1.3	4.4 ± 1.3	4.1 ± 1.3	<0.001
Dietary inflammatory index score ^b	0.07 ± 1.2	0.03 ± 1.1	0.08 ± 1.1	0.1 ± 1.1	0.4 ± 1.2	<0.001
Meat (red, processed meat) (g/day) ^c	93.0 ± 46.1	98.3 ± 46.2	99.4 ± 43.8	103.7 ± 46.9	106.2 ± 46.5	<0.001
Total sugar (g/day) ^c	117.8 ± 37.0	124.5 ± 35.7	128.1 ± 36.8	134.6 ± 38.1	137.6 ± 42.1	<0.001
Total sodium (mg) ^c	2290.7 ± 653.4	2583.9 ± 715.8	2731.9 ± 702.3	2848.6 ± 753.0	2968.8 ± 816.0	<0.001
Total saturated fatty acids (g/100 g fa) ^c	25.4 ± 9.4	29.2 ± 9.8	31.2 ± 9.9	33.3 ± 10.4	34.9 ± 10.9	<0.001
Total trans-fatty acids (g/100 g fa) ^c	1.1 ± 0.5	1.2 ± 0.6	1.3 ± 0.6	1.4 ± 0.6	1.5 ± 0.6	<0.001
Soda (g/day) ^c	150.8 ± 118.4	166.6 ± 120.3	177.2 ± 122.0	207.6 ± 142.9	291.0 ± 214.8	<0.001
Total fat (g) ^c	76.5 ± 27.5	76.5 ± 27.5	76.5 ± 27.5	76.5 ± 27.5	84.0 ± 27.3	<0.001
Vegetable (g/day) ^c	252.7 ± 113.8	244.8 ± 103.1	227.9 ± 92.0	220.0 ± 94.1	191.2 ± 80.7	<0.001
Fruits (g/day) ^c	339.7 ± 228.6	308.9 ± 180.7	288.3 ± 163.1	275.3 ± 161.6	225.3 ± 142.8	<0.001
Fish (g/day) ^c	51.8 ± 27.3	51.6 ± 25.9	50.0 ± 24.1	47.0 ± 23.3	44.2 ± 23.6	<0.001
Total fibre (g/day) ^c	24.8 ± 8.2	26.4 ± 8.1	26.7 ± 7.5	27.0 ± 7.7	26.0 ± 7.7	<0.001

Data presented as Mean ± standard deviation.

Sex specific quintile of cumulative average of UPF intakes over 11 years of exposure period (1991/1994–2002/2004).

UPF intakes were expressed as % of total food intake/day.

^aObtained from Anova or Kruskal-Wallis according to normal or non-normal distributions of variables.

^bMeasures of overall diet. Cumulative average of scores (1991/1994–2002/2004).

^cCumulative average of intake of food groups (1991/1994–2002/2004).

Dietary inflammatory index measures the inflammatory potential of individual's diets. The greater the dietary inflammatory index score the more pro-inflammatory the diet whereas negative values are related to anti-inflammatory diets. AHEI-2010 and transformed Mediterranean diet scores indicate adherence to dietary recommendations of the Alternative Healthy Eating Index and Mediterranean diet respectively. Higher the scores represent better diet quality.

3.3. Results of the association between UPF intakes and recurrent DepS

Regarding distribution of subsequent recurrent DepS, results (Table 1) showed that the rate of DepS did not linearly increase across the UPF quintile groups. Only participants in the top quintile of UPF intakes showed higher rates of recurrent DepS compared to participants in the four lowest quintiles of UPF. Given this description, we further explored associations between UPF intakes (1991/1994–2002/2004) and recurrent DepS by comparing participants in the top sex specific quintile (33% of total daily intake in average, SD = 5.1) to those in the four lower quintile groups of UPF intakes (18.1% of total daily intakes in average, SD = 5.6).

Results of logistic regression model adjusted for socio-demographic variables showed that participants in the top quintile of UPF had a 34% increased likelihood of recurrent DepS (OR 1.34; 95% CI 1.09–1.65) compared to participants in the four lowest quintiles (Figure 2, Model 1). No substantial attenuation was observed when analyses were further adjusted for health behaviours including smoking habits, physical activity (OR = 1.33; 95% CI 1.08–1.64), overall diet quality score of AHEI-2010 (OR 1.29; 95% CI 1.04–1.59, Figure 2, Model 2), health-related factors including BMI and antecedent DepS (OR 1.31; 95% CI 1.04–1.64, Figure 2, Model 3).

3.4. Sensitivity analysis

Three sets of analyses have been conducted. First, to confirm the non-linear association between UPF intakes and rates of recurrent DepS initially reported in Table 1, we repeated the fully adjusted logistic models by considering UPF intakes quintiles (with the lowest quintile as reference) instead of dichotomous variable (highest quintile versus four lowest quintile). Results did not show linear association between UPF quintiles and odds of recurrent DepS (*p* linearity = 0.38). Second, to assess the possibility of reverse causation of the observed association between UPF intakes and recurrence of DepS, we repeated the main analyses by excluding participants who had DepS or were treated for depression (*N* = 883) prior to 2002/2004. Results showed that the association between long term high intakes of UPF remained significantly associated with recurrent DepS (OR 1.41, 95% CI 1.05–1.89) after adjusting for socio-demographic, health behaviours and health related factors. Finally, as anti-depressants can be prescribed for conditions other than depression, we repeated the main analyses with depressive symptoms defined using CES-D only (*N* = 4553; Cases = 445). In the model adjusted for socio-demographic, health behaviours and health related covariates, we observed significant association between high intakes of UPF and recurrent DepS (OR 1.34, 95% CI 1.04–1.72) as shown in Appendix-Supplementary Table 6.

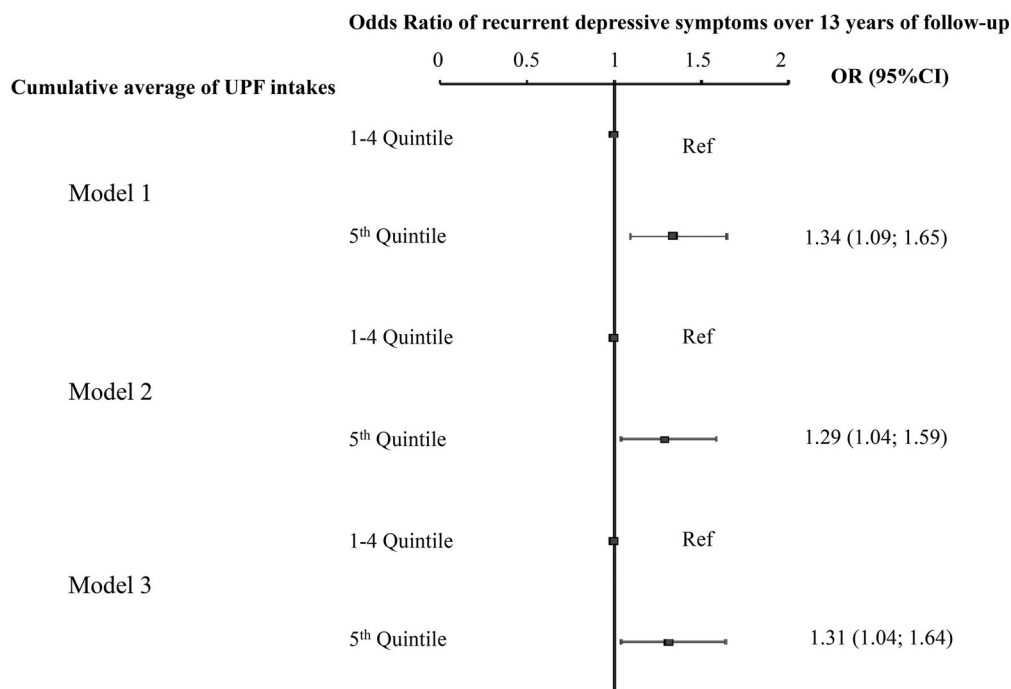


Figure 2. Association between cumulative average of ultra-processed food intakes and subsequent recurrent depressive symptoms ($N = 4554$). Logistic regression models were conducted to estimate odds ratio of recurrent DepS associated with exposure to high UPF intake [cumulative average assessed over 11 years, top sex-specific quintile versus four lower sex specific quintile]. Model 1 adjusted for : sex, age, marital status, education level, social status. Model 2 adjusted for M1 + smoking status, physical activity, overall diet quality (AHEI-2010). Model 3 adjusted for M2 + CHD, hypertension, diabetes, dyslipidimia, BMI, cognitive deficit, antecedent of DepS.

In addition to these sensitivity analyses, we examined whether participants who increased (or decreased) their UPF intakes over the 11-year of follow-up showed a higher (or lower) odd of recurrent DepS. Results detailed in Appendix-Supplementary Table 7 failed to show any significant association between the 11-year change in UPF intakes and recurrent DepS.

3.5. Contribution of UPF in overall diet-DepS association

As our secondary objective, we assessed the extent to which exposure to high amounts of UPF intakes explain the association between overall diet and recurrence of DepS observed in several cohorts including Whitehall II. Estimates of logistic regression models assessing the association of dietary inflammatory index, transformed Mediterranean diet score and AHEI-2010 with recurrence of DepS were compared before and after accounting for UPF intakes. As illustrated in Figure 3, accounting for exposure to high amounts of UPF intakes partially attenuated the associations between measures of overall diet scores and recurrent DepS (percentage of attenuation equals to 17% for AHEI-2010, 27% for transformed Mediterranean diet score and 25% for dietary inflammatory index). After adjustment

for UPF intakes, associations between overall dietary indices and recurrent DepS were attenuated suggesting the substantial contribution of UPF in diet-depression association.

4. Discussion

We found that participants in the top quintile of long-term UPF intakes (33% of total daily intakes in grams) had 31% increased likelihood of recurrent DepS over 13 years of follow-up compared to participants in four lower quintiles of UPF intakes (18.1% of total daily intakes). This association was independent of socio-demographic factors, health behaviours including overall diet quality, health factors and antecedent DepS.

In addition, by investigating the extent to which UPF intakes attenuated the association between overall diet quality and DepS association, our results bring novel findings. After accounting for UPF intakes, the association between dietary scores assessing adherence to dietary guidelines (AHEI-2010, Mediterranean diet and dietary inflammatory index) and DepS were attenuated, with percentages of attenuation by UPF estimated between 17% and 27%.

Despite the similarities among different dietary classification system, wide discrepancies between the

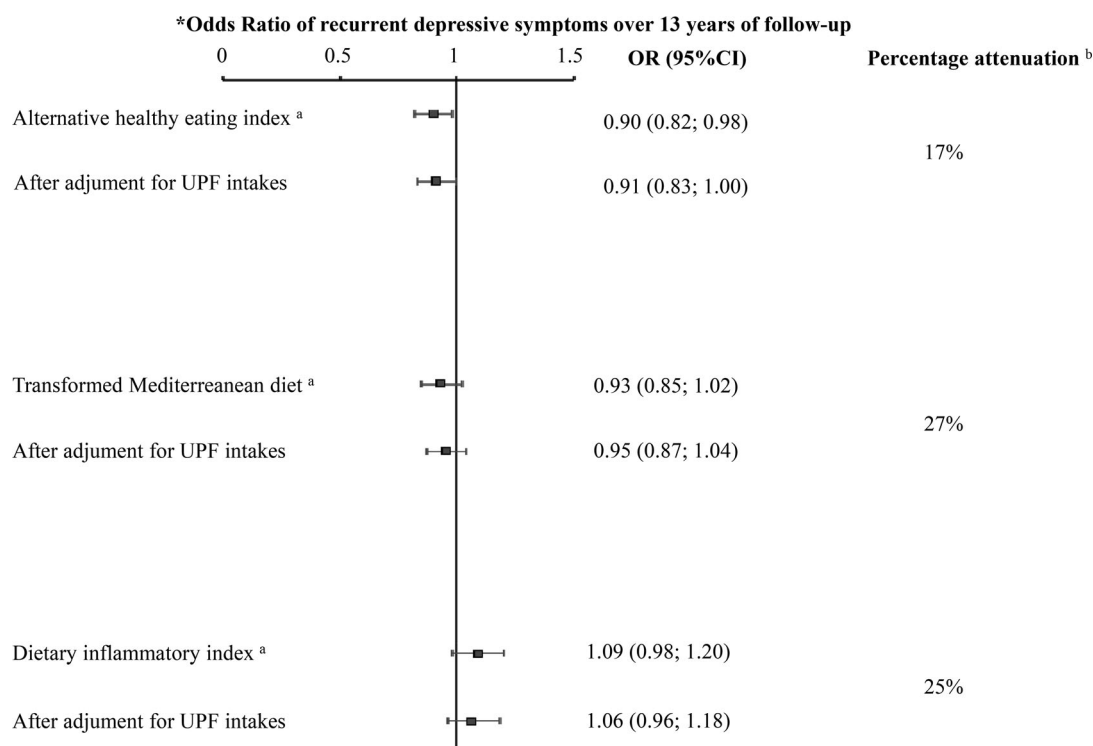


Figure 3. Effect of adjustment for ultra-processed foods intakes on association between overall diet quality measures and subsequent recurrence of depressive symptoms ($N = 4554$). Logistic regression models adjusted for: sex, age, total energy intake, marital status, education level, social status, smoking status, physical activity CHD, hypertension, diabetes, dyslipidimia, BMI, cognitive deficit. ^aZ-scores of cumulative average of diet scores over 11 years of exposure (1991/1994–2015/2016) UPF intake [top sex-specific quintile versus four lower sex specific quintile]. ^b $[(\beta_{\text{DepS}} - \beta_{\text{DepS}} \text{ adjusted for UPF}) / \beta_{\text{DepS}}] \times 100$.

classification systems have been reported and NOVA classification has been suggested to be the most ideal tool for identification of food items based on their nutritional characteristics [21]. These nutritional characteristics linked with industrial processing, could be the significant contributing factor in chronic health conditions including depression [6,13].

4.1. Comparison of the UPF-DepS relationship with other studies

In the present study, the average consumption of UPF was estimated to be 538 g/day; this constituted 21% of total foods consumed in g/day. This estimation is concordant with recently reported UPF consumption (22% of total food intakes) in a large British cohort of similar age [14]. Our results regarding the association between UPF and DepS are in line with those reported by the two prospective studies that investigated this association. In the French Nutri-Net Study, participants in the top quartile of UPF intakes (in which median value of UPF intakes constituted 23% of total food intakes) was associated with 31% (CI: 1.16–1.48) higher risk of incident DepS assessed by CES-D compared to those in the lowest quartile (median value of UPF

intakes = 7%) [7]. In the Seguimiento Universidad de Navarra cohort study carried out in Spain [8], risk of incident depression was 33% (CI: 1.07–1.64) higher in participants in the highest quartile of UPF intakes (mean = 489 g/day) compared to those in the lowest (mean = 109 g/day). Indeed, our results are consistent with a recent systematic review and meta-analysis that combined the effect estimates of these two studies and reported higher versus lower UPF consumption increased the risk of depression or DepS by 22% (CI: 1.16–1.28) [6].

In French and Spanish cohorts, dose–response associations were reported such that increasing UPF intakes from low to moderate increased the risk of depressive outcomes. By contrast, our results suggested a threshold effect where only participants exposed to very high amounts of UPF intakes (median 31.3% of total food intakes in g/day, corresponding to a mean intake of 790.5 g/day) showed significantly increased odds of recurrent DepS compared to participants with a median intake of 18.2% of total food intakes in g/day corresponding to mean intake of 475.6 g/day. We do not have any clear explanation for this discrepancy regarding the shape of the association. However, one reason for this difference might be related to the

differences in distribution of UPF intakes reported in non-Mediterranean Western countries compared to Mediterranean countries [9]. In the Spanish Seguimiento Universidad de Navarra cohort, mean intake of UPF (estimated to 276 g/day) was half of the mean UPF intake observed in Whitehall II participants, and in the French Nutri-net Study average percentage of UPF intakes of total food intake was 30% lower than the one reported in present study. To date, our study was the first to explore the longitudinal UPF-depression association in a Western non-Mediterranean cohort and additional studies are needed to further understand the shape of the relationship. Additional studies are also needed to further examine whether substantial change of UPF intakes over adult life may increase risk of DepS or depression. With only 14.3% of the total participants ($N = 620$) who increased their intakes of UPF over 11 years of follow-up (from UPF intakes < the 33% of total food intake in 1991/93 to $\geq 33\%$ in 2002/04) and amongst them very few recurrent DepS cases ($N = 78$), our analyses assessing change in UPF intakes-recurrent DepS were statistical underpowered to draw any conclusion.

4.2. Possible explanation underlying the UPF-DepS relationship

In the analysis of nutritional characteristics associated with UPF intakes, we observed that participants consuming very high amounts of UPF were consuming higher amounts of soda and food rich in sugar, sodium, saturated and trans-fatty acids. These dietary components, described as having pro-inflammatory properties, are also major contributors to Western type diets, which have previously been shown to be associated with DepS in several cohort studies including ours [22]. Furthermore, consuming higher amount of UPF may also compete with intake of healthier food items and this notion was also supported in our analyses where participants consuming higher amounts of UPF were consuming less fruits, vegetables and fish which are major components of the AHEI-2010 and Mediterranean diet. Therefore, the partial attenuation of the diet-quality - DepS association by UPF intakes reported for the first time in our study was not unexpected.

In addition, properties of UPF other than their nutritional quality might underlie the association with DepS. Amongst those, food processing agents such as additives, emulsifiers or preservatives might be potential drivers of the UPF-DepS association. One such example is titanium dioxide (widely used as an additive in industrial food processing and labelled as E171 in Europe). Titanium dioxide has been shown to induce

inflammation and oxidative stress and is no longer considered safe for consumption [23]. Exposure to low doses of common food emulsifiers carboxymethylcellulose and polysorbate-80 has also been shown to induce inflammation by disrupting intestinal microbiota [24]. Another study reported high levels of phthalate and bisphenol compounds, used in industrial packaging, in urine samples of individuals consuming high levels of UPF [25]. Similarly, there are hundreds of other compounds and additives that are used in industrial food processing with very little knowledge regarding their impact on human health [26]. These compounds might partly explain the UPF-DepS association through inflammatory pathways or by affecting the gut microbiome, resulting in disturbance of the microbiota-gut-brain axis; this is believed to contribute to depression risk [27].

4.3. Strengths and limitations

Our study has limitations. First, we used a semi-quantitative FFQ that covers only specific foods (127 specific food items) to assess the dietary intakes. The FFQ is open to measurement errors common to all self-reported dietary assessments and has been considered to be less precise than other dietary assessment methods such as dietary records. Specifically, in regard to the application of NOVA food classification system, the degree of food processing varies widely according to the brand and category of food, which could possibly lead to misclassification of food items and estimation errors of UPF intakes. However, estimates of UPF intakes observed in current study are in line with those reported in another British cohort [14], and while there are currently no tools designed to classify food items according to their level of processing, FFQs have been used by most published studies to date to assess ultra-processed foods intake [6]. Nonetheless, future studies are needed with more reliable methods like diet records that allow for greater precision regarding classification and data analysis according to the extent and purpose of food processing.

Second, even if the CES-D scale has been shown to be a reliable and valid measurement tool indicating the presence of DepS, the repeated measurements of CES-D may not capture the severity or the chronicity of DepS. We sought to take into account this limitation by considering recurrent DepS defined as participants with a CES-D DepS episode at two out of four follow-up phases. Nevertheless, our results cannot be extended to major depression. Furthermore, the use of anti-depressants as a proxy for DepS may also be questioned as a recent report suggests frequent prescriptions of

anti-depressants for off-label use [28]. To overcome this limitation, we repeated the main analyses on participants with recurrent DepS reported only by CES-D scale and observed similar results.

Another limitation is the bidirectional aspect of the diet-depression association. Despite the prospective design allowing us to assess associations between long-term exposure UPF intakes (assessed over 11 years of exposure period) and an increased risk of subsequent recurrent DepS over 13 years of follow-up, the direction of the association still can be challenged. However, we did not observe any significant association between quintiles of UPF intakes and antecedent DepS in univariate analyses and the association between high intakes of UPF and DepS remained statistically significant even after adjustment for antecedent DepS in our main analysis. Furthermore, similar estimates were also observed in sensitivity analyses conducted after excluding participants with antecedent DepS, reinforcing assumption of a role of UPF on depressive outcomes.

Finally, the generalizability of our results constitutes another drawback. The present analysis was restricted to white office-based civil servants, which is not fully representative of the British general population. In fact, we observed an interaction between ethnicity, diet and DepS, where no association between high intakes of UPF and DepS was observed in non-white participants. It is possible that the NOVA classification failed to capture the dietary exposure in non-white ethnic group. On the other hand, the diet behaviours of non-white ethnic groups, who could be migrants as well, could be significantly different from the natives. It has been reported that migrants in the UK may follow their traditional or cultural diets that differ from the common foods consumed in the UK [29]. However, our small sample of 270 non-white ethnic participants does not allow us to draw any further conclusions.

In addition, some bias owing to selective retention of participants is possible; however, it is unlikely that this could contribute to an overestimation of the association reported as we found higher socioeconomic status, fewer episodes of DepS and better health conditions to be associated with the likelihood of being included in the analyses, while no significant difference was observed for intake of UPF.

Despite these limitations, the findings of our study provide new evidence linking long-term exposure of UPF intakes (assessed over 11 years of exposure period) to an increased risk of recurrent DepS over 13 years of follow-up in British population. This study is apparently the first to confirm the prospective UPF intakes-

depression outcomes association in a Western non-Mediterranean country where larger amounts of UPF intakes are evident compared to Mediterranean countries and lends support to strategies to limit the consumption of UPF. UPF are generally described as a major contributor to low food quality and Western type diet. By showing that in fact UPF intakes were associated with DepS independent of overall diet quality, the present study invites further exploration of the adverse role of specific components of UPF themselves (additives, emulsifiers or preservatives) on depression physiopathology.

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Disclosure statement

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Ethical approval

Written informed consent was obtained after a thorough explanation of the study to each of the participants; the University College London ethics committee approved the study.

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Data availability statement

The data associated with the present paper are only available for Nutritional Neuroscience Journal upon request.

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