Journal of Affective Disorders 335 (2023) 340–348

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Consumption of ultra-processed foods is associated with depression, mesocorticolimbic volume, and inflammation

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ARTICLE INFO

Keywords:
Ultra-processed foods and drinks
Depressive symptoms
Obesity
Inflammation
Amygdala
Cingulate cortex

ABSTRACT

Background: The consumption of ultra-processed foods and drinks (UPF) has been associated with depression and inflammation and preclinical studies showed that some UPF components disrupt the amygdala-hippocampal complex. We combine diet, clinical and brain imaging data to investigate the relationship between the UPF consumption, depressive symptoms, and brain volumes in humans, considering interactions with obesity, and the mediation effect of inflammation biomarkers.

Methods: One-hundred fifty-two adults underwent diet, depressive symptoms, anatomic magnetic resonance imaging assessments and laboratory tests. Relationships between the % of UPF consumption (in grams) of the total diet, depressive symptoms, and gray matter brain volumes were explored using several adjusted regression models, and in interaction with the presence of obesity. Whether inflammatory biomarkers (i.e., white blood cell count, lipopolysaccharide-binding protein, c-reactive protein) mediate the previous associations was investigated using R mediation package.

Results: High UPF consumption was associated with higher depressive symptoms in all participants ($\beta = 0.178$, CI = 0.008–0.261) and in those with obesity ($\beta = 0.214$, CI = −0.004–0.333). Higher consumption was also associated with lower volumes in the posterior cingulate cortex and the left amygdala, which in the participants with obesity also encompassed the left ventral putamen and the dorsal frontal cortex. White blood count levels mediated the association between UPF consumption and depressive symptoms ($p = 0.022$).

Limitations: The present study precludes any causal conclusions.

Conclusions: UPF consumption is associated with depressive symptoms and lower volumes within the mesocorticolimbic brain network implicated in reward processes and conflict monitoring. Associations were partially dependent on obesity and white blood cell count.

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https://doi.org/10.1016/j.jad.2023.05.009
Received 13 December 2022; Received in revised form 28 April 2023; Accepted 5 May 2023
Available online 18 May 2023

1. Introduction

Depressive disorders are among the most common psychiatric disorders worldwide, with 300 million people in the world estimated to live with depression (Stringaris, 2017). It is projected that they will be the first cause of the disease burden by 2030. It severely limits psychosocial functioning and diminishes the quality of life (Malhi and Mann, 2018). The consumption of ultra-processed foods and drinks (UPF in brief) may contribute to depression according to recent studies (see Lane et al., 2021, 2022 for a meta-analysis). UPF are ingredients formulations, most of exclusive industrial use (Monteiro et al., 2016). They contain no or relatively small amounts of minimally processed foods that conserved their nutritional properties. Most UPF have lower nutrient density, but higher energy density compared to unprocessed foods, being high in saturated and trans fatty acids, added sugars, and salt, and are poor sources of protein, dietary fiber, and micronutrients (Gupta et al., 2019). In addition, UPF usually contain additives to intensify their sensory qualities and imitate the minimally processed foods' appearance, making them edible, palatable, highly attractive, and habit-forming (Monteiro et al., 2019).

Recent studies have started to shed light on the potential adverse effects that UPF consumption may have on mental health and the brain (Contreras-Rodriguez et al., 2022; Pagliai et al., 2021). Higher UPF consumption has been cross-sectionally associated with an increased presence of depressive symptoms, and with increased risk of subsequent depression in prospective studies (Lane et al., 2022). However, the underlying brain mechanisms in humans remain to be understood (Contreras-Rodriguez et al., 2022). Preclinical studies show that UPF components (i.e., nanosized particles contained in additives, trans fatty acids, and bisphenol A) can disrupt the amygdala-hippocampal complex (Medina-Reyes et al., 2020; Patisaul, 2020), a key region within the frontolimbic emotion regulation brain network (Buhle et al., 2014). Also, 6-month consumption of sucralose in drinking water in mice altered tryptophan-derived metabolites (Bian et al., 2017), which is the main precursor of the neurotransmitter serotonin (5-HT) in frontolimbic brain networks, being implicated in mood, cognition, impulse control (Celada et al., 2013), and depressive states (Strasser et al., 2016; Yohn et al., 2017). Potential adverse effects may be more pronounced in individuals with obesity, a condition that has been associated with higher UPF consumption (Beslay et al., 2020; Insausti et al., 2020; Juul et al., 2018), and present a high comorbidity with depressive symptoms (Blasco et al., 2020).

A possible route through which UPF consumption may contribute to the risk to develop depression is because of its role in inflammatory processes. Laboratory evidence has associated the high content of additives in UPF products with inflammation and oxidative stress (Laster and Frame, 2019; Medina-Reyes et al., 2020). Pro-inflammatory biomarkers (e.g., white blood cell count lipopolysaccharide-binding protein and C reactive protein levels) in turn, have been consistently associated with depression (Beurel et al., 2020; Lee and Giuliani, 2019; Sealock et al., 2021). However, no study to our knowledge has explored the interplay between direct estimations of UPF consumption, depression, the structural integrity within the underlying frontolimbic brain networks, as well as the inflammatory markers that may influence these associations in humans.

The present study aims to investigate the relationship between the consumption of UPF and depressive symptoms, as well as providing new data of the association between the consumption of these products and the gray matter brain volumes in 152 adults. We also aimed to explore interaction effects with obesity, as well as assessing whether inflammatory biomarkers mediate these previous associations. As a working hypothesis, we expect that higher UPF consumption will be associated with higher depressive symptoms, and lower volumes in the amygdala and frontal regions, especially in participants with obesity as they are usually characterized by higher levels of UPF consumption (Pagliai et al., 2021) and inflammation (Guillemot-Legris and Muccioli, 2017). Finally, because of the association between UPF consumption and inflammation (Laster and Frame, 2019; Medina-Reyes et al., 2020), we expect that inflammation levels will act as a mediator on the association found between the consumption of these products, depression, and the brain volumes.

2. Methods and materials

2.1. Participants

Two-hundred and thirty-three participants were recruited as eligible participants in this cross-sectional study undertaken in the Endocrinology Department of Dr. Josep Trueta University Hospital from January 2016 to July 2021. Eligible participants could be of both sexes, older than 18 years old, and healthy except for the obesity presence. Exclusion criteria were: (i) current or past medical illness presence (e.g., diabetes mellitus or impaired glucose tolerance, cancer, inflammatory-related illnesses) or incapacitating psychiatric disorders (e.g., major eating or psychiatric disorders, including eating disorders), as evidenced by semi-structured interviews, (ii) magnetic resonance imaging (MRI) contraindications (e.g., claustrophobia, ferromagnetic implants), (iii) excessive acute or chronic alcohol intake (i.e., $\geq$40 g OH/day in females or $\geq$80 g OH/day in males), (iv) clinical symptoms and infection signs in the previous month or antibiotic, antifungal or antiviral treatment in the previous 3 months, and (v) pregnancy and lactation. After discarding subjects with missing or defective MRI scans ($N = 40$) and/or missing the food frequency questionnaire ($N = 71$) we obtained a final sample of 152 participants (63 without and 89 with obesity). In typical scenarios, the group sample sizes are enough to obtain robust between-group differences at the brain level according to previous studies with similar samples (Contreras-Rodríguez et al., 2019; Contreras-Rodríguez et al., 2017a). The study data is available at https://thinkgut.eu/equipo/. The Institutional Review Board-Ethics Committee and the Committee for Clinical Research at the University Hospital of Girona Dr. Josep Trueta (Girona, Spain) approved the study protocol. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided informed written informed consent before the study started.

2.2. Dietary intake and UPF consumption

Diet information during the last year was collected through validated food frequency questionnaires with 133 items (Vioque et al., 2013). We obtained total energy intake and the macronutrient composition based on food composition tables (USDA database). We used the NOVA (name not acronym) food classification system to classify foods and drinks based on their processing degree, rather than in nutrient terms. Particularly, we focused on group NOVA4 which contains ultra-processed industrial formulations with high salt, added sugar, and fatty acids as well as additives. Foods were classified according to the consensus of a nutritionists group with expertise in the research with UPF products (Chang et al., 2021; Romaguera et al., 2021) and based on the literature. Further details and underlying assumptions are described in the Supplemental Annex 1. We calculated the UPF consumption percentage in the total diet ([UPF consumption daily grams / total diet daily grams] * 100).

2.3. Metabolic parameters and inflammatory biomarkers

Body mass index was estimated by using the participants weight (kilograms) and height (meters) (BMI = Weight / (Height)^2). Participants with a BMI $\geq$ 30 were considered as having obesity. Fat mass was assessed using a dual-energy X-ray absorptiometry (DEXA, GE Lunar, Madison, Wisconsin). Fasting plasma glucose, lipid profiles (i.e., cholesterol and triglycerides), and high-sensitivity C reactive protein

(hsCRP) were measured using an analyzer (Cobas 8000 c702, Roche Diagnostics, Basel, Switzerland). Glycated hemoglobin (HbA1c) was determined by performance liquid chromatography (ADAM®A1c HA-8180V, ARKRAY, Inc., Kyoto, Japan). White blood cell count (WBC) were measured using routine laboratory tests (Coulter Electronics, Hialeah, FL) (López-Bermejo et al., 2011). Serum lipopolysaccharide-binding protein (LBP) levels were measured by human-LBP enzyme-linked immuno-sorbent assay (ELISA) (HyCult Biotechnology, Huden, the Netherlands) with intra- and interassay coefficients of variation <8 %.

2.4. Depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire 9 (PHQ-9), a module of the PRIME-D diagnostic instrument for mental disorders that assesses the depressive symptomatology presence in the last two weeks (Spitzer et al., 1999). It encompasses nine items, all based on the depression description in the Diagnostic and Statistical Manual of Mental Disorders (fourth edition), that range from 0 to 27. Scores of 5, 10, 15, and 20 represent cut-points for mild, moderate, moderately severe, and severe depressive symptoms, respectively. The PHQ-9 has shown a Cronbach's alpha between 0.86 and 0.89 in previous studies with primary care patients (Kroenke et al., 2001; Policastro et al., 2023).

2.5. Brain imaging acquisition

All participants were assessed on a 1.5-T Ingenia system (Philips Healthcare, Best, the Netherlands) with fifteen-channel head coils. Participants underwent a T1 anatomical scan (TR = 8.3 ms, TE = 4.1 ms, flip angle = 8°, FOV = 230 × 190 mm, 232 × 229 pixel matrix; slice thickness = 1 mm).

2.6. Preprocessing and structural volumetric analysis

Structural imaging data were processed and analyzed using MATLAB version R2017a (The MathWorks Inc., Natick, MA) and Statistical Parametric Mapping software (SPM12; The Welcome Department of Imaging Neuroscience, London). Firstly, images were examined by an expert neuroradiologist to detect gross and clinically relevant anatomical abnormalities. Next, images were preprocessed using a standard procedure including three main steps: tissue segmentation, normalization to Montreal Neurological Institute (MNI) space, and smoothing. Images were segmented using the "new segment" algorithm, and the rigidly transformed versions of gray matter (GM) images derived from this algorithm were normalized using a Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra algorithm (DARTEL) (Ashburner, 2007). Specifically, using the option "create templates", images were iteratively matched to a template generated from their own average, to generate a series of templates with increasing resolution. Then, native space GM images from participants were registered to the highest resolution GM template within a high-dimensional diffeomorphic framework. Subsequently, spatially normalized tissue maps were modulated by the Jacobian determinants from the corresponding flow fields to restore the volumetric information lost during the high-dimensional spatial registration. Normalized images were registered to the standard SPM template and re-sliced to a 2-mm resolution. Finally, images were smoothed with an 8-mm full-width at a half-maximum isotropic Gaussian kernel.

2.7. Structural covariance analysis

To identifying those frontal regions structurally connected with the amygdala, we first identified as a region of interest (ROI) the amygdala using 3.5-mm radial spheres centered at the left (x = −19, y = −5, z = −15) and right (x = 23, y = −5, z = −13) hemispheres as done in previous research of our group (Cano et al., 2016; Picó-Pérez et al., 2017). To calculate the whole-brain structural covariance pattern of the amygdala, we estimated one SPM model that included those voxels with a probability of being GM >0.2. In addition, the variables of interest and covariables in the model were sequentially orthogonalized following an iterative Gram-Schmidt procedure. Specifically, sex was always the first variable to be entered, followed by age, obesity, total gray matter volumes (GMV) (sum of all modulated voxel values), and finally, the amygdala as a seed of interest. Following such an approach, we aimed to remove from the seed of interest all the variance shared with general confounding factors, therefore avoiding the inclusion of multiple collinear measurements in the design matrix. Then, we generated contrast images (beta values) to create t statistic maps of the within-group voxel-wise correlations (positive and negative) in the patterns of structural covariance of the amygdala seed. The different confounding covariates were also included in this statistical model.

3. Statistical analyses

3.1. Association between UPF consumption, depressive symptoms, and brain volumes

Associations between the consumption of UPF and depressive symptoms were assessed using linear regression analyses (enter method) in all participants adjusting for sex, age, and in interaction with obesity in SPSS (SPSS Inc., Chicago, IL, USA). The same analyses were used to assess the association between UPF consumption and gray matter brain volumes in SPM12. Particularly, the individual voxel-wise gray matter volume images were included in a second-level regression model with the UPF consumption as a unique predictor of interest, and sex, age, presence of obesity and total GMV as covariates of no interest. Two sample *t*-test analyses were used when exploring the effects based on the presence of obesity. When the interaction with obesity was explored, the presence of obesity was not included as a covariate in the analyses.

To assess for specific associations with UPF consumption, the above analyses were repeated further adjusting for education and the associated macronutrients (adjusted by kilocalories/weight of the participant, from now on the term "adjusted" will refer to these adjustments), and total energy intake. Associations between UPF consumption and the diet macronutrient composition (adjusted by kilocalories/weight of the participant) were explored using Pearson correlation analyses.

3.2. Inflammatory biomarkers

Pearson analyses were used to test for associations between UPF consumption and the inflammatory biomarkers (i.e., WBC, LBP, hsCRP) using SPSS (SPSS Inc., Chicago, IL, USA). In addition, to investigate whether the inflammatory biomarkers (the mediator M) could mediate the relationship between UPF consumption (exposure X) and depressive symptoms (outcome variable Y), a mediation analysis was performed using R software (version 4.2.3) with the mediation package (Tingley et al., 2014), with age and sex as covariates. Total (exposure-outcome association, path c), direct (non-inflammatory-mediated, path c′) and indirect (inflammatory-mediated, path a * b) effects between the consumption of UPF and depressive symptoms were estimated by ordinary least square regression. Percentile method nonparametric bootstrapping analyses with 1000 iterations (random sampling with replacement) were conducted to generate a 95 % CI for indirect effect. A 95 % CI for the indirect effect of inflammatory biomarkers that does not include 0 is equivalent to significant mediation. A significant mediation implies that part of the relationship is significantly explained by the level of inflammatory biomarkers, or that they are a critical step in the relationship between the exposure and the outcome. The effect of inflammation on the significant associations between UPF consumption and the brain volumes was assessed by further adjusting for WBC, LBP or hsCRP in the initial SPM12 regression model with all participants.

Table 1
Demographic and health information, UPF consumption, dietary intake, and inflammatory biomarkers of the study participants.

Variable	Total ($N = 152$)	No-obesity ($N = 63$)	Obesity ($N = 89$)	p
Age (years)	50.23 [40.59–57.51]	52.23 [44.78–59.12]	48.01 [36.83–54.5]	**0.008**
Sex				0.875
Female	112, 73.68 %	46, 73.00 %	66, 74.20 %	
Male	40, 26.32 %	17, 27.00 %	23, 25.80 %	
Education (years)[a]	14 [11–17]	15 [12–17]	12 [10–15]	**<0.001**
BMI (kg/m^2)	36.2 [25.23–43.76]	24.56 (2.69)	42.93 (6.32)	**<0.001**
Fasting plasma glucose (mg/dL)[c]	100.89 (11.27)	99.22 (11.33)	102.12 (11.14)	0.131
Glycated haemoglobin (%)	5.5 [5.3–5.7]	5.4 [5.25–5.5]	5.55 (0.33)	**0.007**
Cholesterol (mg/dL)	194.41 (38.93)	199.43 (35.82)	185 [160–214]	**0.045**
Triglycerides (mg/dL)	90 [66.75–135.25]	82 [58–98.5]	107 [75–149]	**<0.001**
Fat mass (g)[d]	41,895 [22,162.5–57,946.5]	21,376.11 (5204.89)	55,612.65 (12,041.22)	**<0.001**
Smoking, yes	2, 13.90 %	9, 14.50 %	12, 13.50 %	**0.033**
Alcohol intake (g/d)[d]	0.86 [0–3.78]	1.95 [0–6.80]	0 [0–2.02]	**<0.001**
Depressive symptoms[b]	5 [3–9]	4 [2–6]	6 [4–10]	**<0.001**
Antidepressant treatment, yes	35, 23.03 %	8, 12.7 %	27, 30.3 %	**0.011**
GM volume (mL)	677.92 ± 68.33	684.31 ± 72.62	673.39 ± 65.17	0.342
Total energy (kcal/day)	2079.4 [1691.5–2515.29]	1971.55 [1652.25–2523.13]	2148.7 [1792.1–2510.58]	0.341
UPF intake of the total diet (g %)	5.65 [3.63–10.64]	5.38 [2.7026–8.39]	5.98 [3.98–11.83]	**0.044**
Proteins (g/day)	98.38 [79.15–115.79]	90.97 (24.04)	105.99 (27.48)	**<0.001**
Total fatty acids (g/day)	92.73 [76.65–113.87]	91.15 [75.85–111.67]	93.09 [76.72–116.85]	0.597
Saturated fatty acids (g/day)	25.51 [19.70–30.96]	23.46 [19.52–30.41]	26.72 [20.01–31.49]	0.354
Cholesterol (mg/day)	325.1 [260.35–442.67]	302.6 [238.7–388.13]	361.59 [275–483.49]	**0.002**
Monounsaturated fatty acids (g/day)	45.18 [38.09–55.12]	46.22 [39.42–55.16]	43.8 [37.65–54.94]	0.556
Polyunsaturated fatty acids (g/day)	12.52 [10.73–16.49]	12.22 [10.72–14.92]	12.90 [10.73–17.26]	0.454
Carbohydrates (g/day)	204.44 [165.49–259.75]	205.17 [159.92–254.49]	216.44 (69.86)	0.954
Complex carbohydrates (g/day)[e]	84.78 [63.03–100.06]	78.2 [56.81–96.88]	88.15 [64.64–116.16]	0.119
Simple carbohydrates (g/day)[e]	77.64 [61.99–104.05]	88.53 (30.37)	73.46 [59.22–100.82]	0.083
Monosaccharides (g/day)[e]	23.70 (9.71)	25.59 (9.55)	22.08 (9.65)	0.063
Disaccharides (g/day)[e]	24.56 [15.78–33.81]	28.49 [19.67–32.8]	21.52 [13.09–34.48]	0.236
Total fiber (g/day)	23.21 [18.20–28.03]	22.18 [18.08–27.48]	23.82 [18.40–28.41]	0.483
Soluble fiber (g/day)[e]	13.70 (3.88)	13.67 (3.63)	13.72 (4.13)	0.945
Insoluble fiber (g/day)[e]	6.28 (1.72)	6.16 (1.56)	6.38 (1.85)	0.494
Total white blood cells (K/μL)	6065 [5047.5–7282.5]	5060 [4575–6495]	6984.49 (1812.19)	**<0.001**
Ultrasensitive CRP (mg/dL)[f]	2.6 [0.78–5.54]	0.66 [0.46–1.63]	3.97 [2.66–7.49]	**<0.001**
LBP (μg/mL)[g]	15.15 [11.49–18.03]	12.03 (3.40)	16.95 [15.17–19.80]	**<0.001**

Results are expressed as frequencies and percentages for categorical variables, mean and standard deviation (SD) for continuous variables and median and interquartile range [IQR] for non-normally distributed continuous variables. Statistically significant p-values are shown in bold ($p < 0.05$). Abbreviations: BMI, body mass index; PHQ-9, Patient Health Questionnaire 9; GM, total gray matter brain volumes; CRP, C-reactive protein; LBP, lipopolysaccharide-binding protein; UPF, ultra-processed foods and drinks. Diet variables are provided for 147 participants (62 without obesity and 85 with obesity).

[a] Provided for $N = 145/152$.
[b] Education level and PHQ-9 provided for $N = 146/152$.
[c] Fasting plasma glucose provided for $N = 142/152$.
[d] Fat mass and alcohol intake provided for $N = 148/152$.
[e] Provided for $N = 106/147$.
[f] Provided for $N = 149/152$.
[g] Provided for $N = 105/152$.

3.3. Significance thresholding

In SPSS and R mediation analyses significance threshold was set at $p < 0.05$. In all SPM imaging analyses statistical (including the structural covariance analysis, and the interaction with obesity) significance was determined by a combination of voxel-level and cluster-extent thresholds, using AlphaSim algorithm as implemented in the SPM REST toolbox (Song et al., 2011). The minimum spatial cluster extent (KE) to satisfy a voxel threshold probability of $p < 0.001$ was 74 voxels. Input parameters included a cluster connection radius of 5 mm, and the respective actual smoothness of imaging data, within a whole-brain gray matter mask volume of 128,190 voxels (2 × 2 × 2 mm). Based on our a priori interest in frontolimbic brain networks, associations were also explored with the amygdala using small-volume corrections from multiple comparisons ($p_{FWE\text{-}SVC} < 0.05$) in 3.5-mm radial spheres centered at the coordinates of the amygdala ROIs used to perform the structural covariance analyses (Cano et al., 2016; Picó-Pérez et al., 2017), as well as in those brain clusters that showed whole-brain significant structural covariance with the amygdala. Statistical differences between the groups with and without obesity were tested using Fisher r-to-z transformations. Finally, in the post hoc models including additional adjustment (i.e., UPF-associated macronutrients, and inflammation levels) significance was determined using $p_{FWE\text{-}SVC} < 0.05$ using a 3.5-mm radial spheres centered at the coordinates of the regions showing a significant association with UPF consumption in the initial regression model.

4. Results

4.1. Participants' characteristics

Demographic and health information are provided in Table 1. Obesity was present in 58.6 % of the participants. The study participants reported mild depressive symptoms, with 20.5 % of them with a score ≥ 10, indicative of moderate depressive symptoms. Participants with obesity showed a higher level of depressive symptoms compared to those without obesity.

Nutritional information and inflammatory levels are shown in Table 1. The median UPF consumption in the study participants was 5.65 % of total food intake. Those with obesity showed higher UPF consumption compared to those without obesity. White blood cell count, hsCRP, and LBP levels were higher in participants with compared to

Table 2
Association between UPF intake and depressive symptoms.

	β	*p*	95 % CI
All participants			
Model 1[a]	0.178	**0.038**	0.008–0.261
Model 2[b]	0.143	0.086	−0.015–0.231
Model 3[c]	0.214	**0.019**	0.027–0.293
Model 4[d]	0.152	0.075	−0.012–0.240
Model 5[e]	0.146	0.087	−0.016–0.234
Model 6[f]	0.153	0.095	−0.020–0.250
Model 7[g]	0.143	0.094	−0.019–0.233
Interaction obesity			
With obesity	0.214	**0.052**	−0.004–0.333
Without obesity	−0.000	0.999	−0.186–0.185

Values are standardized regression coefficients (β). Statistically significant *p*-values are shown in bold ($p < 0.05$).
[a] Adjusted for age, sex.
[b] Adjusted for age, sex, and education.
[c] Adjusted for age, sex, and adjusted fiber intake.
[d] Adjusted for age, sex, and adjusted fatty acids intake.
[e] Adjusted for age, sex, and adjusted carbohydrates intake.
[f] Adjusted for age, sex, and total energy intake.
[g] Adjusted for age, sex, and inflammation levels.

those without obesity.

4.2. UPF consumption, depressive symptoms, and brain volume

Higher consumption of ultra-processed foods and drinks was significantly associated with higher presence of depressive symptomatology, although this association lost significance when education was adjusted (Table 2). At the brain level, higher consumption of UPF was associated with lower volumes of the ventral posterior cingulate cortex and the left amygdala, while a tendency towards association was found with the middle anterior cingulate cortex that was significantly connected with the amygdala in the structural covariance analyses (Fig. 1, Table 3). These results remained virtually unchanged when education was considered in the model. The full pattern of the brain regions showing a significant structural covariance with the amygdala is provided in Fig. S1 and Table S1.

High consumption of UPF was significantly associated with total energy intake, higher fatty acids, and carbohydrates intake, and

Table 3
Brain regions showing volume decreases in association with high UPF consumption.

Brain regions	x	y	z	*t*	CS	*p*-Value
All participants						
Ventral posterior cingulate	−2	−53	23	3.63	121	<0.001
Middle cingulate gyrus	−9	6	42	3.35	–	*0.056*
L amygdala	−20	−2	−14	2.95	–	0.030
Participants with obesity						
L ventral putamen[a]	−26	−2	−8	4.07	143	<0.001
L amygdala[b]	−20	−2	−14	2.84	–	0.039
Dorsomedial frontal cortex[b]	−6	18	53	3.37	–	0.044

Anatomical coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. Tendency towards significance is indicated in italics. Adjustments include age, sex, obesity and total GMV. Presence of obesity was not controlled when assessing interactions with this variable.
[a] Results surpassed a height threshold of $p < 0.001$ and a cluster of 74 voxels.
[b] Results surpassed small-volume corrections $p_{FWE} < 0.05$.

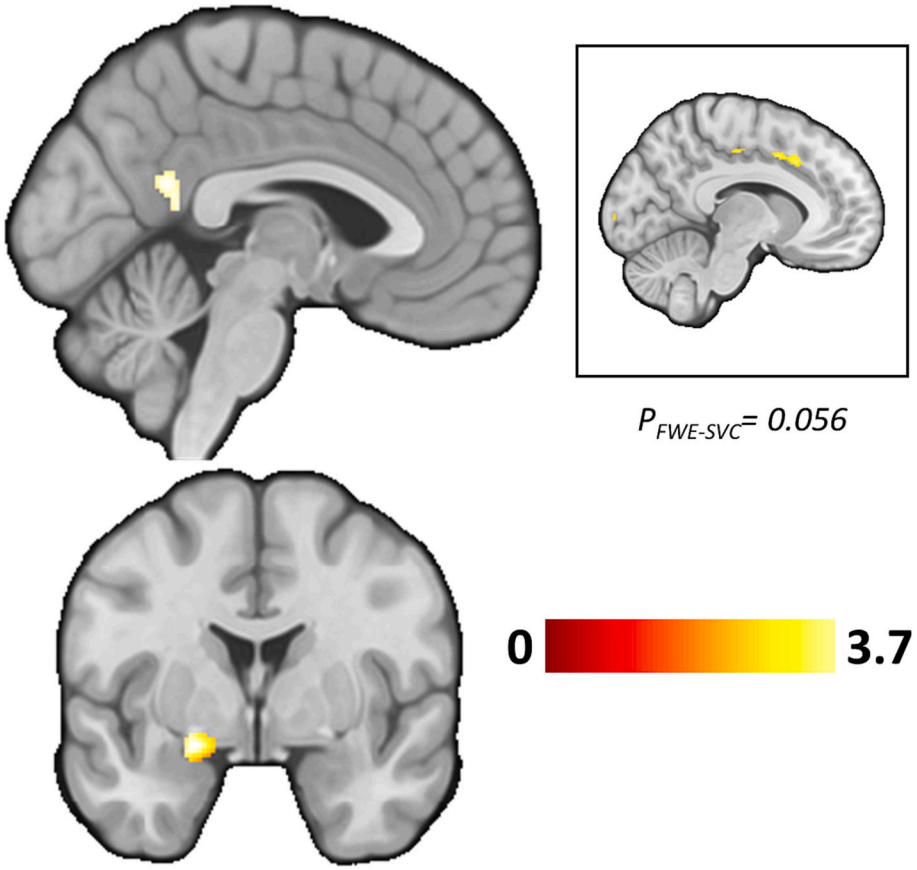

Fig. 1. Negative association between UPF consumption and the volumes of the posterior cingulate cortex, the left amygdala, and the tendency in the middle cingulate gyrus. Analyses are adjusted for age, sex, obesity, and total GMV. The right hemisphere corresponds to the right side of the axial brain view, and the left side of the sagittal lateral view. The color bar indicates *t*-values.

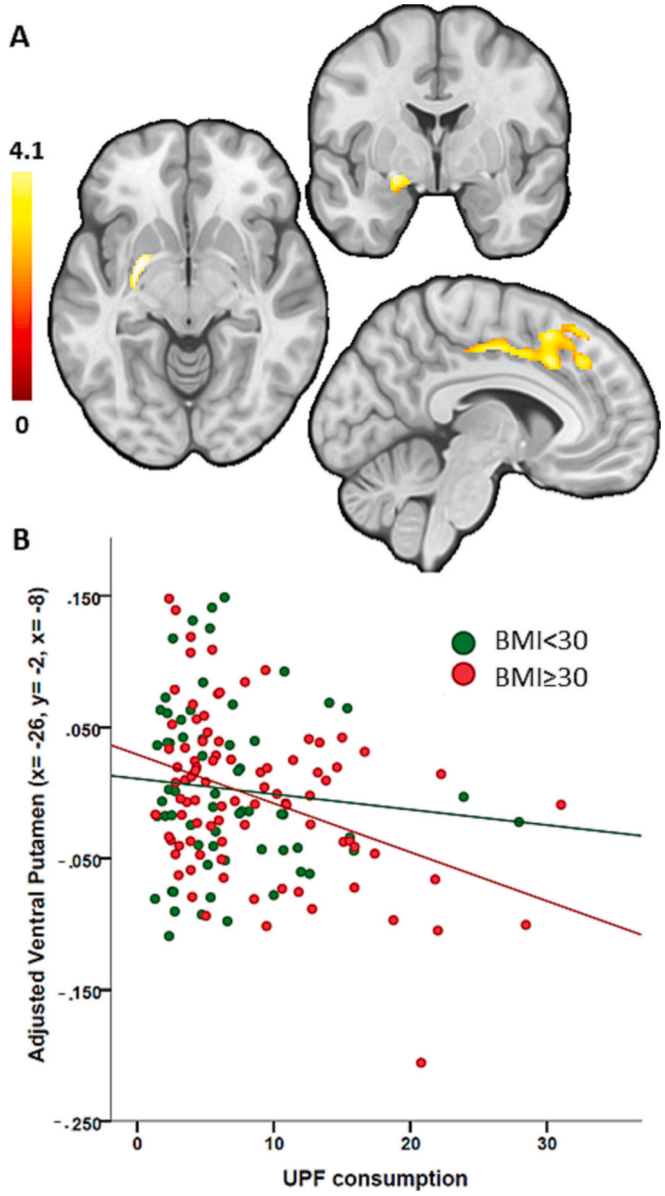

Fig. 2. (A) Negative association between UPF consumption and the volume of the left ventral putamen and amygdala, and the dorsal frontal cortex. Analyses are adjusted for age, sex, and total GMV. The right hemisphere corresponds to the right side of the axial brain view, and the left side of the sagittal lateral view. The color bar indicates t-values. (B) The scatter plot represents the higher positive correlation between the peak coordinate of the adjusted signal of the left ventral putamen and UPF consumption in the participants with (red) compared to those without (green) obesity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

negatively associated with fiber intake (Table S2). The positive relationship between UPF consumption and depressive symptoms remained significant when fiber was further adjusted, but it lost significance after adjustment for fatty acids, carbohydrates, and total energy intake (Table 2). At the brain level all results remained virtually unchanged (all $p_{FWE\text{-}SVC} < 0.05$, data not shown).

4.3. Obesity-interaction effects

Depression symptoms were also positively associated with UPF consumption only in the participants with obesity ($\beta = 0.21$, $p = 0.05$, 95 % CI −0.004–0.333). Higher consumption of UPF in this group was associated with lower volume in the left ventral putamen, the left amygdala, and a cluster in the dorsomedial frontal cortex that extended to the middle cingulate cortex (Fig. 2, Table 3). Fisher *t*-tests of the between-group differences were only significant for the association between UPF consumption and the volume of the ventral putamen ($Z = 1.85$, $p = 0.032$, Fig. 2).

4.4. Mediation analyses: inflammatory mediation assessment

UPF consumption showed a significant positive association with WBC levels ($r = 0.204$, $p = 0.012$), but not with the other inflammation indices (i.e., LBP $r = 0.03$, $p = 0.592$, and hsCRP $r = 0.053$, $p = 0.692$). The effect of the consumption of UPF on depressive symptoms was fully mediated via the WBC count. As Fig. 3 illustrates, the total effect between the consumption of UPF and presence of depressive symptoms was significant (path c). The indirect effect (a * b) was 0.036, while the direct effect was non-significant (path c′). The bootstrapped unstandardized indirect effect was 0.036, and the 95 % confidence interval ranged from 0.004 to 0.09. Thus, the indirect effect was statistically significant ($p = 0.022$). The associations reported between UPF consumption, and the brain volumes remained significant when adjusting for WBC, LBP and hsCRP (all $p_{FWE\text{-}SVC} < 0.05$, data not shown).

5. Discussion

In the present study, we found a positive association between UPF consumption and depressive symptoms, and a negative association with the gray matter volumes of the posterior cingulate cortex and the left amygdala. When obesity interactions were explored, only participants with obesity maintain the association with depressive symptoms, and the volume with the left amygdala, while additional volume reductions were found in the left ventral putamen and the dorsomedial prefrontal cortex. WBC levels influenced the association between UPF consumption and depressive symptoms, but not the association with brain volumes.

The median UPF consumption of 5.65 % in grams of total food consumption in our sample is low compared to that estimated by previous studies in populations with similar ages (Adjibade et al., 2019; Julia et al., 2018; Schnabel et al., 2019; Srour et al., 2019). The presence of obesity in 58.56 % of the participants who were consulting for weight loss in the Endocrinology Department could have influenced dietary habits. Indeed, some research has reported people with obesity to have a higher UPF consumption (Pagliai et al., 2021). Under-reporting of UPF consumption in the participants with obesity herein cannot be discarded (Wehling and Lusher, 2019). However, despite the unexpected low UPF consumption reported by the participants, the positive association with depressive symptoms is consistent with previous research in humans (Lane et al., 2022).

Associations with UPF consumption at the brain level involved the volume of the left amygdala and the posterior cingulate cortex, which have been associated to food reward processes in previous neuroimaging studies in humans (García-García et al., 2013; Litt et al., 2011; Morales and Berridge, 2020). The negative association with the volume of the amygdala herein complement the findings of preclinical studies showing that some UPF components (i.e., nanosized particles of additives, trans fatty acids, BPA) are associated with disruptions in the amygdala-hippocampal complex (Medina-Reyes et al., 2020; Patisaul, 2020). This finding may also be congruent with research in humans that showed that the activation in the amygdala is associated with artificial sweetener use (Rudenga and Small, 2012), or the mere presence of UPF-related food advertisements or logos (Contreras-Rodriguez et al., 2022). The posterior cingulate cortex, in turn, receives information about actions being performed from parietal cortices and whether the actions were rewarded through the information sent from the amygdala via the orbitofrontal cortex. In this way, the posterior cingulate cortex helps to adapt behavior to obtain rewards and avoid punishers through the middle cingulate cortex and its outputs to premotor areas (Rolls, 2019).

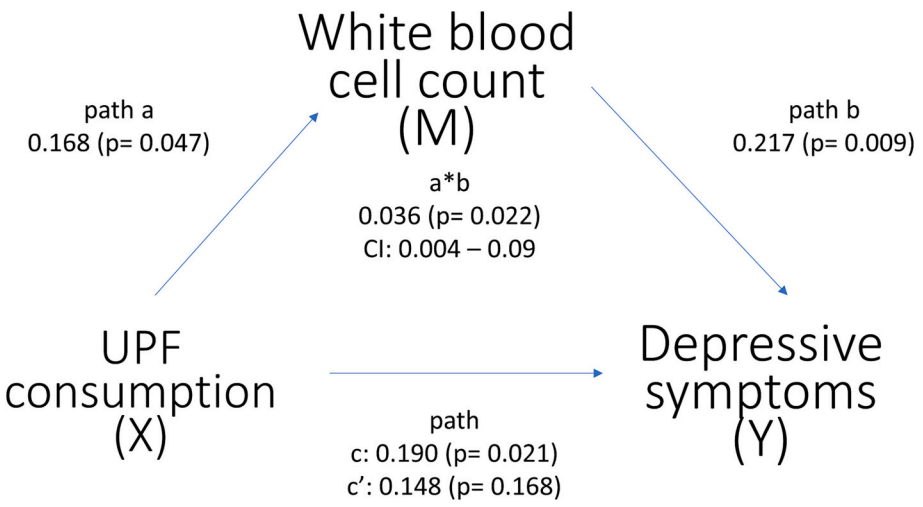

Fig. 3. Mediation model assessing whether white blood cell count (M) mediates the relationship between UPF consumption (X exposure) and depressive symptoms (Y outcome). Path a: effect of one-unit changes in exposure on mediator; path b: effect of one-unit changes in mediator on outcome adjusted on exposure; path c′ (direct effect): effect of one-unit change in exposure on outcome independently of mediator value; path c (total effect): effect of one-unit change in exposure on outcome not adjusted on mediator; a * b (indirect effect): effect of one-unit change in exposure on outcome through mediator change. Standardized estimates are provided. CI: 95 % Confidence intervals.

When the interaction with obesity was explored, only participants with obesity showed the positive association between UPF consumption and depressive symptoms in congruence with previous studies, although the association was not as strong as expected based on the previous studies focused on obesity conditions (Beslay et al., 2020; Insausti et al., 2020; Juul et al., 2018; Milaneschi et al., 2019; Pagliai et al., 2021). These participants also maintained the association between higher UPF consumption and the lower volume in the left amygdala, as well as with additional brain regions part of the mesocorticolimbic network, including the ventral putamen and the dorsomedial prefrontal cortex. Together with the amygdala, the ventral putamen has been associated with food-triggered motivation or "wanting" of foods (Morales and Berridge, 2020). Particularly, the ventral putamen, as part of the limbic striatum, is implicated in reward processing (Hartogsveld et al., 2022; Marche et al., 2017) and habitual behavior (de Wit et al., 2012), and plays a key role in the control of food intake (Contreras-Rodríguez et al., 2017b; Val-Laillet et al., 2015), with its altered connectivity being associated with food craving in individuals with excess weight (Contreras-Rodríguez et al., 2017a). The dorsomedial frontal cortex, in turn, participates in the integration of affective salient signals into cognitive control processes mediated by the prefrontal cortex (Margulies et al., 2007), and in conflict monitoring (Botvinick et al., 2004; Carter et al., 2000), and it has been associated with the ability to resist the urge for an immediate reward (e.g., palatable foods such as UPF) vs maintaining the effort to achieve long-term goals (e.g., positive health). This finding is congruent with recent evidence that high consumption of UPF is associated with a decline in executive functions (Gonçalves et al., 2022).

Overall, the current findings showed that UPF consumption is associated with the volume of brain regions implicated in reward processes and conflict monitoring. The addictive potential of UPF is under current debate (Lustig, 2020; Schulte et al., 2015), with previous studies having reported an association between direct estimation of UPF consumption with food addiction traits (Filgueiras et al., 2019; Pursey et al., 2017). The present study lacks the appropriate reward-based indices to substantiate the association between the UPF-associated brain volumes and these specific behaviors. In addition, the present work cannot conclude if the UPF-associated brain regions contribute to depressive symptoms, and more specifically to those associated with reward processing dysfunction, such as anhedonia. However, the brain regions associated to UPF consumption are part of the brain network altered under depressive states (e.g., see Kerestes et al., 2014 for a systematic review), and there is evidence that major depressive disorder is associated with blunted responses within the reward circuit, including the amygdala and the ventral striatum (Ng et al., 2019).

The mediation analysis showed that the association between UPF consumption and depressive symptoms was explained by the inflammatory status, with effects being restricted to WBC levels. This is consistent with previous laboratory (Medina-Reyes et al., 2020) and clinical (Alonso-Pedrero et al., 2020; Edalati et al., 2021) research showing that consumption of these products induces inflammation. However, contrary to our hypothesis, the inflammation biomarkers did not influence the association between UPF consumption and the brain volumes, although the association of inflammatory biomarkers on other brain properties (e.g., brain functioning) remains to be investigated.

Strengths of the current study include the sample size of cases studied through diet, depression questionnaires, the evaluation of brain structures using MRI, and inflammatory assessments. Foods and drinks in the validated FFQ were carefully classified using NOVA system, according to the degree of processing, by a panel of nutritionists. Indeed, the robustness of the UPF exposure index was supported by the association found with total energy intake, and fatty acids and carbohydrates that makes most of the UPF nutrient profile, but the negative association with fiber consumption (Gupta et al., 2019; Monteiro et al., 2019). Several sensitivity analyses were performed to test the robustness of our results, which overall showed that the association between UPF consumption and depression is dependent upon the total intake of fatty acids, carbohydrates, and total energy intake. The main limitations are inherent to the diet assessment using FFQ. Dietary data might be subject to measurement error; nevertheless, a previously validated FFQ for the Spanish population was used. Also, some studies have cast doubt on whether the FFQ has sufficient precision to allow detection of moderate but important diet-disease associations (Schatzkin et al., 2003). The complementary use of a 24-h recall questionnaire may help to characterize UPF consumption (Reales-Moreno et al., 2022). In addition, although we adjusted for a range of potential confounders, residual confounding cannot be totally ruled out, and the effect of further confounders may be explored by future research. Finally, the cross-sectional design of the present study may be susceptible to reverse causality and, consequently, our analyses cannot shed light on causality between UPF consumption and depression. Further research is needed to understand the potential adverse effects of larger prolonged UPF consumption during late childhood and adolescence, as these key neurodevelopmental periods coincide when the higher UPF consumption is described.

In conclusion, UPF consumption associates with depressive symptoms and the gray matter volume within a brain network involved in reward processing and conflict monitoring. These results seem to be partially dependent on the presence of obesity and inflammation levels, particularly the levels of white blood cells. The behavioral and psychological implications of the results, as well as the causality of the

associations should be explored further in longitudinal studies.

CRediT authorship contribution statement

Conceptualization: OCR, MRM. Data curation: SFB, AC, MAR, CB. Analyzed and interpreted the patient data: OCR, MRM, SFB, AC, MAR, CB, AMA, MC. Funding acquisition: JMFR. Project administration: MAR, AMA, JMFR. Resources: SFB, JB, JMFR. Major contributor in writing the manuscript: OCR, MRM, JMFR. All authors read and approved the final manuscript.

Funding source

This study has been funded by the Project Grant IRONMET (PI15/01934) from the ISCIII, and the Project ThinkGut (EFA345/19) 65 % co-financed by the European Regional Development Fund (ERDF) through the Interreg V-A Spain-France-Andorra program (POCTEFA 2014-2020) (JM Fernández-Real). Partial support was also obtained by the CIBER-SAM – Consorcio Centro de Investigación Biomédica en Red Salud Mental – Proyectos Intramurales, ISCIII, Ministerio de Ciencia e Innovación, Spain (O Contreras-Rodríguez). O Contreras-Rodriguez is funded by a "Miguel Servet" contract (CP20/00165) from the ISCIII. M Cano is funded by a 'Sara Borrell' postdoctoral contract (CD20/00189) from the Carlos III Health Institute (ISCIII).

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

The research team would like to thank the individuals who generously shared their time for the purposes of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.05.009.

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