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Original article

The association between maternal ultra-processed food consumption during pregnancy and child neuropsychological development: A population-based birth cohort study

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SUMMARY

Background & aims: Maternal ultra-processed food (UPF) consumption during pregnancy may adversely affect child development. Pregnancy sugar-sweetened beverage consumption (as a part of UPF) has been associated with child cognitive dysfunction in the general population, but the role of total UPF consumption during pregnancy in later child neuropsychological development has not been studied. We aimed to analyse the association between maternal pregnancy UPF consumption and child neurodevelopment.

Methods: This study involved 2377 pairs of pregnant women and their offspring from a Spanish birth cohort (recruitment period: 2004–2008, INMA project). Dietary intake was estimated using a 101-item food frequency questionnaire in the third trimester of pregnancy. The NOVA classification was used to identify UPFs, and their consumption was calculated as the daily percentage of total food consumption and categorized into tertiles. Child neuropsychological development was assessed with the Bayley Scales of Infant and Toddler Development (1-year-old, n = 1929) and the McCarthy Scales of Children's Abilities (4-5 years-old, n = 1679). Potential associations were analysed using multivariate linear regression models adjusted for a range of family and child characteristics.

Results: UPF consumption among pregnant women represented an average of 17% of the total diet, with sugar-sweetened beverages being the most commonly consumed type of UPF (40%). Children born to mothers in the highest tertile of UPF consumption (28.9% or more of the total diet) vs the lowest tertile

Abbreviations: Food Frequency Questionnaire (FFQ), Infancia y Medio Ambiente project (INMA); Mediterranean Diet Score (MDS), Ultra-processed food (UPF).

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(7.2% or less), showed a lower score (B = −2.29 [95% Confidence Interval (CI), −4.13; −0.46]) in the Verbal Scale of the McCarthy Scales (p-for-trend = 0.02). No associations were observed with the McCarthy Scales assessing other cognitive domains or with the Bayley Scales.

Conclusion: Of the seven cognitive domains studied, we observed an adverse association between maternal consumption of UPF during pregnancy and verbal functioning in early childhood, which is an important cognitive domain of neurodevelopment.

1. Introduction

In recent decades, there has been an increase in the consumption of ultra-processed foods (UPF) [1–4]. According to the NOVA classification [5,6] proposed by Monteiro et al., UPFs are industrial formulations typically with five or more ingredients, and some of them food-derived substances or additives. Following multiple biological, physical or chemical processes, the final products are conceived to be safe, palatable and affordable. However, they may also have other less desirable properties [7,8], including poor nutritional composition with high amounts of saturated fats, refined starches, palatable additives, such as flavor enhancers, emulsifying salts, sweeteners, thickeners, anti-foaming, bulking, carbonating, gelling and glazing agents, and, the potential presence of components derived from food processing and packaging, such as, heterocyclic amines, acrylamide, polycyclic aromatic hydrocarbons, or plastic additives such as bisphenols or phthalates, which have all been shown to have deleterious effects on human health [7–9].

The period from 24 to 42 weeks of gestation is an important pregnancy time window for child neurodevelopment. It is when synapses and myelination are in full construction [10,11]. The fetal brain is particularly plastic and can suffer adverse changes in structure and function due to maternal health characteristics during pregnancy, with the potential for long-term cognitive implications. The fetus' brain requires nutrients, such as long-chain polyunsaturated fatty acids, choline, protein-energy, iron, zinc and cooper for synaptic efficacy, and if the maternal diet during pregnancy is not adequate, child cognitive dysfunction may occur [10–17]. Furthermore, in experimental studies, exposure to excess saturated fats, which produce oxidative stress, has been shown to lead to neuroinflammation and affect cognitive functioning of the offspring [18,19]. Prenatal life is a period of particular vulnerability to neuroinflammation [20].

One recent prospective study in pregnant women observed an adverse association between maternal sugary drink consumption and child cognitive functioning [21]. However, this previous study assessed only one product type of total UPF consumption. Presently, there is a need to conduct epidemiological studies assessing total UPF consumption during pregnancy and child neurodevelopment outcomes.

The aim of this prospective study is to assess the association between maternal UPF consumption during pregnancy and child neuropsychological development at the ages of 1 and 4–5 years old.

2. METHODS

2.1. Study participants and design

The study sample was based on a large population-based birth cohort of the Spanish Childhood and Environment study (Infancia y Medio Ambiente, shortened to INMA) [22]. The INMA study includes data from four sub-cohorts located in different regions of Spain (Asturias, Gipuzkoa, Sabadell, and Valencia). Participants were recruited between the years 2004 and 2008. A total of 2644 eligible women were recruited during prenatal visits in the first trimester of pregnancy (mean = 13.8 weeks). Women were included if they agreed to participate and met the inclusion criteria. The inclusion criteria were women being 16 years or older, with a single pregnancy and without major previous chronic diseases such as chronic hypertension, arteriosclerosis, chronic kidney disease, vasculitis, cancer, alcoholism, or drug addiction. The women lived in the corresponding hospital area where the INMA study was based. The exclusion criteria were an inability to communicate, a fetus with malformations, or assisted conception. Women were followed-up during pregnancy and their children were enrolled at birth and followed-up until the age of 4–5 years for the work presented here. Further information about the design of the INMA study is published elsewhere [22]. After excluding women who withdrew, were lost to follow-up, had a miscarriage or foetal death, as well as new-borns weighing less than 2000 g or a gestational age less than 32 weeks, a total of 2377 pregnant women and their children were followed-up through delivery. Afterwards, the offspring were assessed with different neuropsychological scales at the ages of 1 year (n = 1929) and 4–5 years (n = 1679), see Fig. 1. The final analytic dataset included 1611 pre-schoolers and their mothers with available data on UPF consumption and other relevant sociodemographic and lifestyle characteristics captured over time.

The study was carried out according to existing ethical guidelines as indicated in the Helsinki Declaration (2013). All participants provided written informed consent, and the study was approved by the hospital and institutional ethics committees in each INMA project site.

2.2. Maternal ultra-processed food consumption (UPF)

The primary explanatory variable was maternal consumption of UPFs. Mothers completed a validated semi-quantitative 101-item food frequency questionnaire (FFQ) during weeks 12 and 32 of gestation [23] to assess the usual daily intake of foods and nutrients. The FFQ was a modified version of the Harvard FFQ questionnaire; adapted for the Spanish population, and validated to evaluate diet during pregnancy [24,25]. The U.S. Department of Agriculture food composition table was used to obtain energy and nutrient values; with information on Spanish food and portion sizes obtained from the "Centre d'Ensenyament Superior de Nutrició i Dietètica (CESNID)" [26,27].

Participants were asked to complete the FFQ, reporting their usual consumption of foods from the last menstruation to the first prenatal visit (11–13 weeks) and from the first prenatal visit to the third trimester visit (28–32 weeks), using reference portions and nine frequency categories capturing how often they had normally eaten these types of foods ranging from "never or less than once per month" to "six or more times per day". In this study, we used UPF consumption data derived from third trimester FFQ as the *a priori* primary exposure of interest, due to the importance of the third

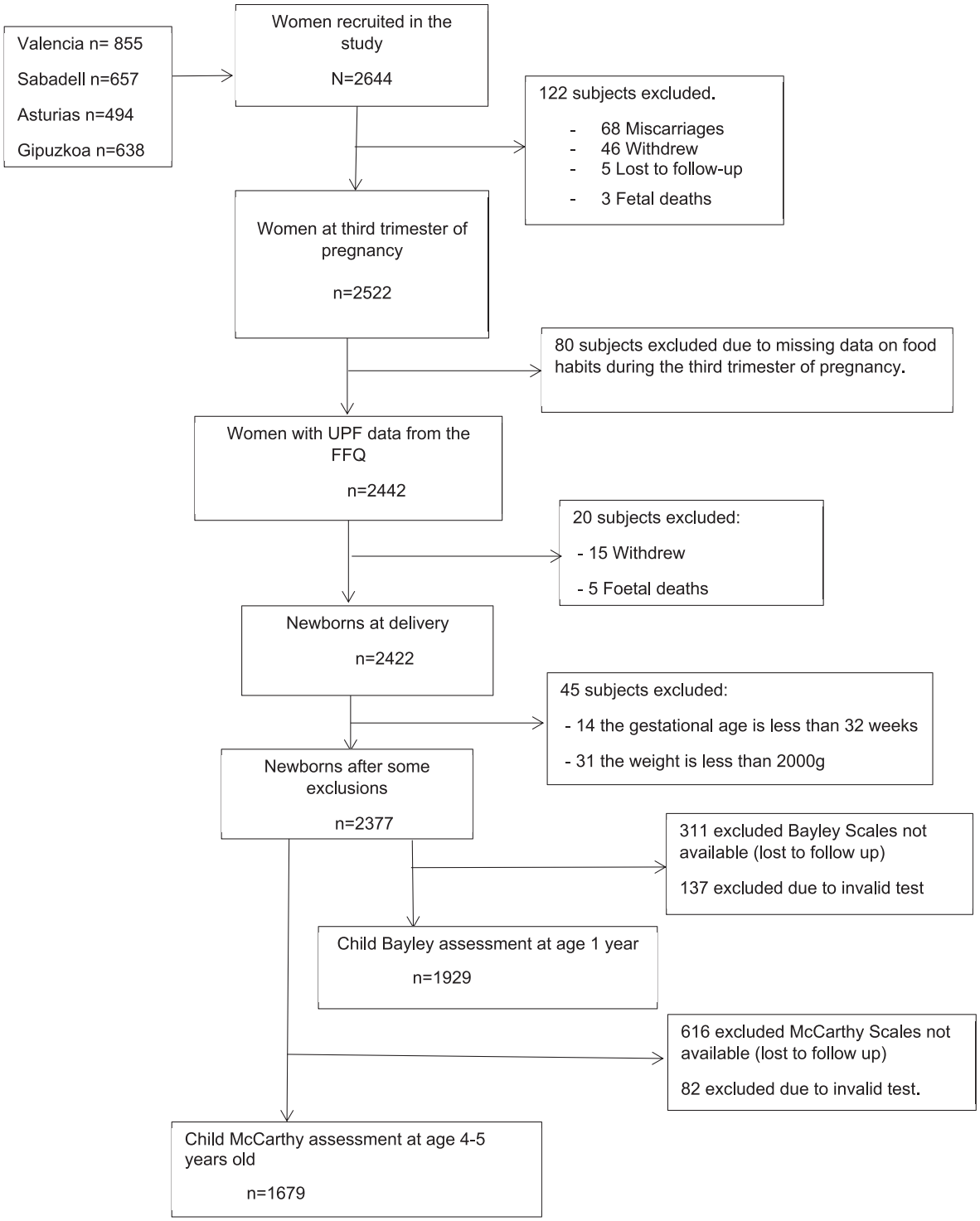

Fig. 1. Main phases of the study and flowchart of the population sample. Spanish Childhood and Environment (INMA) Project, 2004–2008.

trimester in child brain development [11]; however, we also performed secondary sensitivity analyses using first trimester dietary information.

We classified the FFQ items according to the NOVA classification of UPFs [5,6]. The NOVA classification includes four groups, from the least processed to the most processed. The first group includes unprocessed or minimally processed foods such as plants (fruits, leaves and roots), animal products (meat, eggs and milk), fungi and water. For this group, processing of foods includes chilling, freezing, and pasteurising, for preservation, with no added ingredients (such as salt, sugar, oils, or fats). In the second group, culinary ingredients were included, such as salt, sugar, honey or vegetables oils. Processed foods were classified in the third group, formed by combining foods in the previous first and second groups. These foods had two or three added ingredients. They could be canned or bottled vegetables, fruit or legumes, or salted or sugared nuts.

Finally, the fourth group was the UPF group. These foods were industrial formulations and had five or more ingredients added, and usually included substances commonly used in culinary preparations to disguise undesirable sensory qualities of the final product such as casein, lactose, soy protein isolate, maltodextrin, or fructose. Further details of the food classification are included in Supplemental Table 1.

Each FFQ item was categorized into one of the four NOVA groups and their usual consumption expressed in daily grams. The percentage of total daily consumption was calculated for each of the four NOVA groups (daily grams within each group/total daily grams, multiplied by 100). In the present study, we focused on group 4 of the NOVA classification representing UPFs. We divided this variable into tertiles representing categories of low, medium or high consumption of UPF, based on the UPF consumption distribution of included mothers.

In order to check the contribution of each UPF subgroup to total UPF consumption, we further divided the UPF items into the following subgroups: sugary products, sweet drinks, fried food, dairy products, breakfast cereals, processed meat and other (pizza, ketchup among others) (Supplemental Table 1). Then, each subgroup was divided by the total consumption of UPFs and multiplied by 100 to obtain the proportion of UPF consumption for each subgroup.

2.3. Neuropsychological outcomes

Children were assessed by internationally validated and standardized psychometric scales. The main outcome of the study was scores from the McCarthy Scales of Children's Abilities, assessing the following main cognitive domains including global cognitive function, memory function, verbal function, perceptive-performance function and motor function (administrated at 4–5 years of child age) [28]. We further included an additional new cognitive domain, executive function, created by a re-organization of the McCarthy Scale subtests [29]. As a secondary outcome, the Bayley Scales of Infant and Toddler Development were used to assess mental and motor development (administrated at 1 year of child age) [30]. Both psychometric scales were administrated by trained psychologists following a quality control assessment, further outcome quality descriptions and psychometric validity analyses are published elsewhere [31]. Both scales were

Table 1
Sociodemographic characteristics of pregnant women and their children according to categories of UPF consumption, assessed during the third trimester of pregnancy.

	Tertiles of UPF consumption			*p-value*
	Low (n = 814)	Medium (n = 814)	High (n = 814)	
Maternal characteristics				
UPF intake percentage, Mean (SD)[a]	7.2 (2.6)	15.2 (2.3)	28.9 (8.9)	
Relative Mediterranean Diet Score, Mean (SD)[a]	9 (2.4)	8 (2.4)	7 (2.5)	<0.001
Energy intake in kcal, Mean (SD)[a]	2014.5 (827.5)	2090 (717.4)	2226.4 (666.7)	<0.001
Cohort location, n (%)[b]				<0.001
Asturias	223 (27.4)	133 (16.3)	89 (10.9)	
Gipuzkoa	277 (34.0)	202 (24.8)	117 (14.3)	
Sabadell	147 (18.0)	214 (26.2)	253 (31.0)	
Valencia	167 (20.5)	265 (32.5)	355 (43.6)	
Country of origin, n (%)[b]				0.001
Spain	761 (93.6)	752 (92.6)	723 (88.8)	
Others	52 (6.4)	60 (7.3)	91 (11.1)	
Maternal education level (%)[b]				<0.001
Primary school or less	134 (16.4)	178 (21.8)	280 (34.4)	
Secondary school	292 (35.8)	362 (44.5)	359 (44.2)	
University or more	388 (47.6)	273 (33.5)	173 (21.3)	
Maternal smoking during pregnancy, n (%)[b]				<0.001
No	627 (77.0)	552 (67.8)	484 (59.5)	
Yes	187 (23.0)	262 (33.2)	330 (40.5)	
Family Vulnerability Index, Mean (SD)[a]	0.50 (0.14)	0.52 (0.14)	0.54 (0.14)	<0.001
Maternal social class, (%)[b]				<0.001
High Social Class	241 (46.3)	176 (33.8)	103 (19.8)	
Medium Social Class	228 (35.9)	221 (34.8)	186 (29.3)	
Low Social Class	340 (26.8)	409 (32.3)	518 (40.9)	
SCL-90-R Severity global index, Mean (SD)[a]	48.9 (9.4)	50.1 (9.9)	50.7 (10.3)	0.011
Maternal IQ proxy, Mean (SD)[a]	99.8 (14.7)	100.4 (14.4)	98.6 (15.4)	0.13
Child characteristics				
Sex, n (%)[b]				0.65
Female	382 (47.3)	398 (49.4)	396 (49.1)	
Male	426 (52.7)	408 (50.6)	411 (50.9)	
Gestational age in weeks, Mean (SD)[a]	39.6 (1.4)	39.7 (1.5)	39.6 (1.4)	0.39
Predominant breastfeeding in weeks, Mean (SD)[c]	12.6 (9.9)	12.4 (9.5)	11.5 (9.3)	0.03
Paternal characteristics				
Paternal education· n (%)[b]				<0.001
Primary school or less	225 (27.7)	298 (37.1)	335 (41.4)	
Secondary school	365 (45.2)	363 (45.1)	342 (42.3)	
University or more	220 (27.1)	144 (17.8)	131 (16.2)	
Paternal social class, (%)[b]				<0.001
High Social Class	204 (43.5)	137 (29.2)	128 (27.3)	
Medium Social Class	152 (37.1)	143 (34.9)	115 (28.0)	
Low Social Class	439 (29.6)	507 (34.1)	539 (36.3)	

UPF consumption rank tertiles: Lowest tertile (0-11.2), Medium tertile (11.2-19.5), Highest tertile (19.5-87).
[a] ANOVA test for continuous variables.
[b] Chi-square test for categorical variables.
[c] Kruskal–Wallis test for non- normal continuous variables.

standardized to mean 100 and standard deviation 15. Psychologists identified children whose Bayley and McCarthy tests were of poor quality due to basic pathologies (Down syndrome, autism) or a lack of cooperation of the child (owing to fatigue, poor mood, illness, etc.): these tests were excluded from the main analyses and considered as invalid.

2.4. Covariates

All of the included covariates were assessed by questionnaires during pregnancy and childhood. Variables included were maternal and paternal education level (primary education; secondary education; University education), maternal smoking during pregnancy (yes; no), adherence to the Mediterranean diet (relative Mediterranean Diet Score [rMED]) and total energy intake (kcal/d) during the third trimester of pregnancy [27]. Furthermore, we included weeks of gestational age at delivery, cohort location, family vulnerability index, which is an indicator of area-level socioeconomic status based on a relative deprivation index at birth (ISVURSE) [32], maternal and paternal social class (using the UK Registrar General's 1990 classification according to current International Standard Classification of Occupations) recoded into three categories (high (I + II); medium (III); low (IV + V)), maternal mental health at child age of 4 and 5 years (SCL-90-R global severity index) [33], maternal verbal intelligence quotient (IQ) proxy based on the Similarities subtest of the Weschler Adult Intelligence Scale (WAIS-III) [34], and maternal country of origin (Spain/other countries). Finally, as child variables, we included age (in years), sex (male, female) and length of predominant breastfeeding including water, infusions and juices (continuous variable in weeks). The FFQ was also used to estimate consumption of fruit, vegetables, sugar, saturated fatty acids, and fiber, as well as soft drinks separately from total UPFs.

2.5. Statistical analysis

We performed descriptive analyses of socio-demographic and lifestyle characteristics across tertiles of maternal UPF consumption, and used ANOVA, chi-squared and Kruskal–Wallis tests where appropriate. We also explored socio-demographic differences between the included study participants (with complete exposure and outcome data) versus excluded study participants.

Associations between maternal UPF consumption during pregnancy and child neuropsychological outcomes were evaluated by multivariate linear regression analyses. The minimally- and the fully-adjusted models included covariates previously selected based on a literature review and using a Directed Acyclic Graph (DAG) (Supplemental Fig. 1). The minimally-adjusted model included child sex and age, and cohort location. In the fully-adjusted model, we additionally included maternal and paternal education level, maternal smoking during pregnancy, child gestational age, breastfeeding duration and family vulnerability index.

In secondary analyses, we stratified the final models by cohort location to assess associations of UPF consumption and child neurodevelopment outcomes in different regions of Spain. We also included additional covariates, such as, parental social class (instead of parental education), the mother's country of origin, maternal verbal IQ proxy (Similarities, WAIS-III) and maternal psychopathological symptoms (SCL-90-R), the last two variables were assessed at child age of 4–5 years, however, we expect relative stability of these maternal psychological domains during adulthood. We also assessed associations between pregnancy first trimester UPF intake and the study outcomes, as well as associations of UPF consumption and Bayley Scales' outcomes (child age 1-year). We aimed to apply a mixed-model regression for repeated exposure measurements (UPF in both trimesters), however due to low variability between the two measurements, the model did not fit well. We then, created a full pregnancy UPF variable, in tertiles, based on the UPF average intake in both trimesters, and a variable of the difference between the two measurements (trimester 3 − trimester 1). We conducted additional sensitivity analysis to explore the impact of adjustment for several other nutritional factors during pregnancy: Intake of fruits and vegetables, Mediterranean diet score (rMED) [27], total energy intake, saturated fat intake, sugar intake and fiber intake. Finally, we separated the soft drink component from total UPFs and analysed associations with outcomes.

All analyses were conducted using STATA 15 with statistical significance defined as having a p-value <0.05.

3. RESULTS

A total of 2442 women completed the FFQ questionnaire. Mean maternal UPF consumption expressed as a percentage of total food intake during the third trimester of pregnancy was 17.2% of total food intake. Similar results were observed for UPF consumption during the first trimester, with a daily average consumption of 17.9%. The correlation between the two UPF measurements was moderate, r = 0.57.

Sweet drinks and fruit juice were the subgroup contributing most (40%) to total UPF consumption during the third trimester of pregnancy (Fig. 2) followed by processed meat (14%), sugary products (13%), other (12%), dairy products (9%), fried products (8%), and finally, breakfast cereals (4%), see Fig. 2.

Table 1 shows the distribution of demographic and lifestyle variables by tertile of UPF consumption. Women from the north of Spain (Asturias and Gipuzkoa) reported lower consumption of UPF, while women from the Mediterranean regions (Sabadell and Valencia) reported higher UPF consumption. Moreover, mothers with a higher family vulnerability index, lower educational level and lower social class reported higher UPF consumption levels. Women reporting higher UPF consumption also reported higher total energy intakes and a lower adherence to the Mediterranean diet. Finally, lower reports of maternal UPF consumption was related with longer duration of breastfeeding of their offspring.

Data stratified per cohort region showed that there were a greater proportion of women with a university degree in Gipuzkoa (50%) and Asturias (37%) than in Valencia (23%) or Sabadell (28%). Furthermore, participants included in this study were of higher socio-demographic status that those who did not participate (Supplemental Table 2).

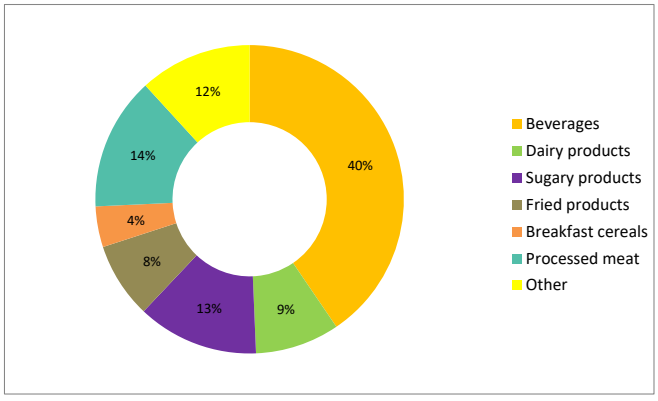

Fig. 2. Maternal consumption of UPF subgroups during the third trimester of pregnancy (%).

Crude Child McCarthy Scale scores by maternal UPF consumption groups during the third pregnancy trimester are shown in Table 2. Global Cognitive, Memory, and Verbal Scales showed statistically significant reductions as UPF consumption increased.

Minimally- and fully-adjusted associations of maternal UPF consumption during the third trimester of pregnancy with child neuropsychological outcomes at age 4–5 years old are shown in Table 3. Higher UPF consumption was significantly associated with lower McCarthy Verbal Scale score in both minimally and fully adjusted models. In the fully adjusted model, children in the highest tertile of maternal UPF consumption had a lower Verbal score with a B = −2.29 (95% CI -4.13; −0.46) compared to those in the lowest tertile (p-for-trend of 0.02). Similar but weaker association patterns were observed for McCarthy General Cognition, Perceptive-Performance, Numeric, Memory, Motor and Executive Function scores in minimally-adjusted models, which weakened in fully-adjusted models and were no longer significant (Table 3). In analysis stratifying by cohort location, results were similar across all sub-cohorts with the exception of Gipuzkoa where null associations with Verbal function scores were observed (Supplemental Table 3). In secondary analyses overall, we substituted parental education level for parental social class in the fully-adjusted models, and we observed similar findings (Supplemental Table 4). When maternal psychometric (WAIS-III similarities and SCL-R-90) and country of origin variables were additionally added to the final models, the results were also similar (Supplemental Table 5).

No significant associations between pregnancy third trimester UPF consumption and Bayley Scales were observed (child age 1-year) (Supplemental Table 6).

Supplemental Table 7 shows the results of sensitivity analyses of UPF consumption during the third trimester and McCarthy Verbal scores. We observed no significant changes after adjusting the models for maternal intake of fruits, vegetables, rMED, total energy intake, saturated fatty acids, sugar or fiber. Furthermore, separating soft drink consumption from total UPF, indicated similar adverse associations, but with the latter being somewhat stronger and statistically significant.

Finally, we analysed the associations between maternal UPF consumption during the first pregnancy trimester and all child neuropsychological outcomes, the B coefficients were weaker and not statistically significant (see Supplemental Table 8). However, the B coefficient for the average of the two trimester measurements (full pregnancy UPF variable in tertiles) and McCarthy Verbal Scale was statistically significant, third tertile versus first tertile = −1.92, 95 CI% (−3.78; −0.07); P-for-trend = 0.046. Despite that, the B coefficient for the difference between the two trimester measurements and McCarthy Verbal Scale was not statistically significant, third tertile versus first tertile = −1.22, 95 CI% (−3.05 to 0.61); P-for-trend = 0.189.

4. Discussion

In this population-based birth cohort study, we found that higher maternal UPF consumption during the third trimester of pregnancy was adversely associated with pre-schooler verbal function. There were no associations observed with other child cognitive functions assessed. Child ability to understand and process verbal stimuli, verbally express thoughts and verbal concept reasoning, may be at risk to fully develop due to exposure to higher levels of UPF consumption during pregnancy. Indeed, this is an important cognitive function, and many milestones during child neurodevelopment require an optimal performance of such function.

This is the first study to explore the association between total maternal UPF consumption in pregnancy and child neuropsychological development. Previous studies observed adverse associations between UPF consumption during pregnancy and obesity and metabolic syndrome among pregnant women [35]. These health problems can additionally adversely affect the general health of the infant in the long-term, including the cognitive development [13–15,36,37]. In relation to this connection described between maternal metabolic syndrome and child neurodevelopment, a recent study observed that children born to mothers with gestational diabetes had worse visuomotor function [38].

We observed that mothers in northern Spanish regions had lower UPF consumption compared with mothers from more Mediterranean regions, which was converse to that expected. Findings in the Gipuzkoa region showed null associations of UPF with child verbal scores. This is likely due to regional differences in maternal education levels, with higher education levels among mothers from northern Spain.

Some previous investigations examined specific types of UPF, such as sugary drinks during pregnancy periods, which account for an important proportion of total food consumption, particularly in western countries [2,16,17]. In the present study, it represented over 40% of the total UPF consumed by pregnant women. In relation to sugary drinks and child neurodevelopment, the study conducted by Cohen et al., concluded that sugary drinks during pregnancy may adversely affect child cognition (21). They observed that sugary drink consumption during the first and second trimesters of pregnancy was associated with poorer global intelligence including verbal and non-verbal functions. The magnitude of the associations were about 1.5-point differences, similar to that observed in our study. Indeed, they reported similar associations when they were analyzing child sugary drink consumption and cognitive outcomes [21]. However, as mentioned before, as far as it is known, no previous human studies have explored neurodevelopmental associations with FFQ estimations of total UPF consumed during pregnancy. Our study supports the adverse findings with child

Table 2
Mean scores of the McCarthy Scales in 4-5-year-old children, according to maternal UPF consumption frequency during the third trimester of pregnancy.

Neuropsychological outcomes	Tertiles of maternal UPF intake				
	All (n)	Low	Medium	High	P-value[a]
McCarthy Scales	1677	(n = 593)	(n = 594)	(n = 490)	
Global cognitive score, Mean (SD)		101.6 (14.5)	100.6 (14.1)	99.3 (15.0)	0.04
Verbal score, Mean (SD)		101.8 (14.8)	100.8 (14)	98.8 (15.1)	0.003
Perceptive-performance score, Mean (SD)		100.8 (14.1)	100.2 (14.5)	100.2 (15.3)	0.70
Memory score, Mean (SD)		101.5 (14.7)	100.3 (14.2)	99.3 (15.2)	0.04
Numeric score, Mean (SD)		101.3 (14.7)	100.2 (14.7)	99.7 (14.8)	0.21
Motor score, Mean (SD)		99.5 (15.1)	101.1 (14.6)	99.6 (14.9)	0.12
Executive function score, Mean (SD)		101.3 (14.4)	100.6 (14.4)	99.5 (15.3)	0.13

[a] ANOVA test p-value.

Table 3
Multivariable regression analyses. Association between maternal UPF consumption in the third trimester of pregnancy and child neuropsychological scores at 4–5 years.

Neuropsychological outcomes	Maternal UPF consumption tertile 3rd trimester (n)	Minimally-adjusted[a]			Fully-adjusted[b]		
		B	95% CI	P for trend	B	95% CI	P for trend
McCarthy Scales	1611						
Global cognitive score	Lowest	Ref	–	<0.001	Ref	–	0.13
	Medium	−1.66	(-3.28; −0.03)		−0.80	(-2.40; 0.78)	
	Highest	−3.13	(-4.89; −1.38)		−1.33	(-3.07; 0.39)	
Verbal score	Lowest	Ref	–	<0.001	Ref	–	0.02
	Medium	−1.42	(-3.11; 0.25)		−0.83	(-2.52; 0.84)	
	Highest	−3.65	(-5.47; −1.84)		−2.29	(-4.13; −0.46)	
Perceptive-performance score	Lowest	Ref	–	0.101	Ref	–	0.97
	Medium	−1.31	(-2.97; 0.30)		−0.64	(-2.25; 0.97)	
	Highest	−1.42	(-3.17; 0.31)		−0.06	(-1.75; 1.75)	
Memory score	Lowest	Ref	–	0.002	Ref	–	0.13
	Medium	−1.64	(-3.32; 0.03)		−0.84	(-2.53; 0.83)	
	Highest	−2.91	(-4.72; −1.01)		−1.41	(-3.24; 0.41)	
Numeric score	Lowest	Ref	–	0.018	Ref	–	0.57
	Medium	−1.47	(-3.11; 0.24)		−0.53	(-2.20; 1.13)	
	Highest	−2.16	(-3.97; −0.34)		−0.51	(-2.33; 1.29)	
Motor score	Lowest	Ref	–	0.250	Ref	–	0.71
	Medium	0.32	(-1.32; 1.98)		0.73	(-0.95; 2.41)	
	Highest	−1.09	(-2.87; 0.68)		−0.38	(-2.21; 1.45)	
Executive function score	Lowest	Ref	–	0.004	Ref	–	0.30
	Medium	−1.20	(-2.86; 0.45)		−0.33	(-1.97; 1.30)	
	Highest	−2.61	(-4.41; −0.82)		−0.95	(-2.74; 0.82)	

[a] B coefficients and 95% CI estimated using linear regression models adjusted for sex of the child, child's age at testing, cohort location.
[b] B coefficients and 95% CI estimated using linear regression models additionally adjusted for maternal and paternal education level, maternal smoking during pregnancy, gestational age, predominant breastfeeding and family vulnerability index.

verbal function, but extends the work by examining total UPF consumption. Moreover, in our separate analyses of sugary drink consumption compared with that of other UPF product type consumption, the association with verbal function was somewhat stronger, and significant in the latter.

The third trimester of pregnancy is recognized as a vulnerable period for child brain development (24–42 weeks of gestation). As far as it is known, environmental exposures such as healthy lifestyles are important determinants of child neurodevelopment during this fetal period. This also includes the need for nutrients, and, if the maternal diet is not adequate, may result in adverse impacts on child mental health [12–14, 39]. This could explain why there were no significant associations observed for maternal UPF consumption in the first pregnancy term in our study, compared with the findings in the third term. Though UPF consumption in the two trimesters was correlated and findings remained significant when we created a new variable representing the average UPF intake average of the two measurement periods.

We hypothesize that the ingredients and substances contained in UPF, such as salt, sugar, acrylamide and saturated fatty acids, may adversely impact the function of the brain, based on the activation of systemic oxidative stress. Indeed, the consumption of UPFs may result in mitochondrial dysfunction and oxidative stress that generate the production and release of pro-inflammatory cytokines affecting DNA, and chronic inflammation affecting the blood–brain barrier and the brain itself. These biological processes may induce neuronal cellular death, which can be particularly harmful during vulnerable intra-uterine life and as a consequence may affect child brain function in the long-term [40–45]. In short, UPFs may induce the systemic release of cytokines in maternal circulation which reach the fetus and result in neuronal death, which may impact child cognition in the long-term. Disruption of the gut microbiota–brain axis by high UPF consumption [40,45], may also affect fetal neurodevelopment.

The main strength of this study is its prospective design with a large range of covariate data. Furthermore, the multicentre structure of this cohort study including different geographical regions of Spain, makes these findings relevant to a more diverse population with different levels of UPF consumption. We used important internationally validated cognitive scales and trained psychologist examiners. These extensive scales allowed us to assess different domains of child cognitive functioning, and with particular attention to the verbal function domain. Additionally, when we explored the potential confounding effect of several other nutritional factors during pregnancy, we observed no changes in our findings. Adverse findings were observed with UPF product types, but were somewhat weaker for soft or sweetened drinks. Furthermore, this study, with additional follow-up, may be informative regarding the persistence of associations among older children in future assessments.

However, this study also faced some limitations. The potential role of postnatal UPF consumption was not analyzed due to the young ages of children included here. The fact that we did not observe an association with early neurodevelopment could suggest that preschooler UPF consumption may play a role as well. Future follow-ups should include the assessment of child UPF consumption, in addition to maternal UPF consumption during pregnancy. Indeed, a more completed picture of this study, would have been including UPF maternal consumption reports prior to conception. The FFQ is not focused on measuring UPFs specifically. However, expert nutrition researchers derived UPF consumption estimations based on grouping the primary FFQ items. Measurement error in the estimation of dietary intake is also possible, although we used a previously validated FFQ for Spanish populations. In addition, several food items could not be unequivocally classified into one of the four NOVA groups, given that our FFQ collected limited information regarding food processing because this questionnaire didn't ask for a wide variety of UPFs. In such cases, we used information on food composition in Spain to classify such food items and, thus, a degree of misclassification is expected. Furthermore, residual confounding cannot be completely ruled out in this observational work, since we lack information on other potential confounders such as home environment stimulation assessed by the HOME scale [46] for example, however we were able to adjust for a number of important variables. Findings may also not be fully generalized to

other global populations. There were also some sociodemographic differences between included vs excluded study participants. Further work in other population based-birth cohort studies in different countries is needed. Finally, multiple test comparisons were performed, so it cannot be ruled out that findings were due to chance.

The present findings suggest the potential risk of exposure to UPFs during pregnancy for developmental neurotoxicity. Although the magnitude of the adverse effect observed was modest, and the clinical relevance unknown at the individual level, the public health consequences are of importance when viewed across the entire population and should be considered for planning future preventive health policies.

In conclusion, this is one of the first studies at a-population level, that investigated the association between the consumption of UPF among pregnant women and the neuropsychological development of their children. We observed an adverse association between the consumption of UPF during the third trimester of pregnancy and child verbal function at age 4–5 years, which is an important cognitive domain related with verbal expression and verbal concept reasoning.

Author contributions

JP-V, DR, SF-B and JJ were involved in the design study, JI, LS-M, SLL, MV and JJ coordinated practical performance of the study and the required fieldwork supervision, JV was involved in nutrition data preparation, JP-V performed the data analyses, JP-V, DR, SF-B and JJ contributed to the preparation of the manuscript, all the authors made critical review of the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.08.005.

References

[1] Cucó G, Fernández-Ballart J, Sala J, Viladrich C, Iranzo R, Vila J, et al. Dietary patterns and associated lifestyles in preconception, pregnancy and postpartum. Eur J Clin Nutr 2006 Mar;60(3):364–71.
[2] Jardí C, Aparicio E, Bedmar C, Aranda N, Abajo S, March G, et al. Food consumption during pregnancy and post-partum: ECLIPSES study. Nutrients. 2019 Oct 14;11(10):2447.
[3] Chen YC, Huang YC, Lo YC, Wu HJ, Wahlqvist ML, Lee MS. Secular trend towards ultra-processed food consumption and expenditure compromises dietary quality among Taiwanese adolescents. Food Nutr Res 2018;62:10.
[4] Marino M, Puppo F, Del Bo C, Vinelli V, Riso P, Porrini M, et al. A systematic review of worldwide consumption of ultra-processed foods: findings and criticisms. Nutrients 2021;13(8):2778. Published 2021 Aug 13.
[5] Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Publ Health Nutr 2018 Jan;21(1):5–17.
[6] Monteiro CA, Cannon G, Levy RB, Moubarac J-C, Jaime P, Martins AP, et al. The star shines bright. World Nutrition 2016;7(1–3):28–38.
[7] Kelly B, Jacoby E. Public Health Nutrition special issue on ultra-processed foods. Publ Health Nutr 2017;21:1–4.
[8] Lawrence M, Baker P. Ultra-processed food and adverse health outcomes. BMJ 2019;365:l2289.
[9] Bielemann Renata M, Motta Janaína V, Gicele C, Horta Bernardo, Denise P. Consumo de alimentos ultraprocesados y su impacto en la dieta de los adultos jóvenes. Rev Saude Publica 2015;49:28. Epub 26 de mayo de 2015.
[10] Arija V, Hernández-Martínez C, Tous M, Canals J, Guxens M, Fernández-Barrés S, et al. Association of iron status and intake during pregnancy with neuropsychological outcomes in children aged 7 Years: the prospective birth cohort Infancia y Medio Ambiente (INMA) study. Nutrients 2019 Dec 7;11(12):2999.
[11] Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 2007 Feb;85(2):614S–20S.
[12] Gomes CB, Malta MB, Louzada MLDC, Benício MHD, Barros AJD, Carvalhaes MABL. Ultra-processed food consumption by pregnant women: the effect of an educational intervention with health professionals. Matern Child Health J 2019 May;23(5):692–703.
[13] Lindsay KL, Buss C, Wadhwa PD, Entringer S. The interplay between nutrition and stress in pregnancy: implications for fetal programming of brain development. Biol Psychiatr 2019 Jan 15;85(2):135–49.
[14] Monk C, Georgieff MK, Osterholm EA. Research review: maternal prenatal distress and poor nutrition - mutually influencing risk factors affecting infant neurocognitive development. JCPP (J Child Psychol Psychiatry) 2013 Feb;54(2):115–30. https://doi.org/10.1111/jcpp.12000.
[15] Ramel SE, Georgieff MK. Preterm nutrition and the brain. World Rev Nutr Diet 2014;110:190–200. https://doi.org/10.1159/000358467. Epub 2014 Apr 11.
[16] Gamba RJ, Leung CW, Petito L, Abrams B, Laraia BA. Sugar sweetened beverage consumption during pregnancy is associated with lower diet quality and greater total energy intake. PLoS One 2019 Apr 25;14(4):e0215686.
[17] Block Gladys. Foods contributing to energy intake in the US: data from NHANES III and NHANES 1999–2000. J Food Compos Anal 2004;17(Issues 3–4):439–47.

[18] Martínez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. Nutrition 2020 Mar;71:110609.
[19] Huang TT, Leu D, Zou Y. Oxidative stress and redox regulation on hippocampal-dependent cognitive functions. Arch Biochem Biophys 2015 Jun 15;576:2–7.
[20] Morris RH, Counsell SJ, McGonnell IM, Thornton C. Early life exposure to air pollution impacts neuronal and glial cell function leading to impaired neurodevelopment. Bioessays 2021 Sep;43(9):e2000288. https://doi.org/10.1002/bies.202000288.
[21] Cohen JFW, Rifas-Shiman SL, Young J, Oken E. Associations of prenatal and child sugar intake with child cognition. Am J Prev Med 2018 Jun;54(6):727–35.
[22] Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J. Cohort profile: the INMA–INfancia y Medio Ambiente–(environment and childhood) project. Int J Epidemiol [Internet] 2012 Aug;41(4):930–40 [cited 2014 Jul 22];.
[23] Vioque J, Navarrete-Muñoz EM, Gimenez-Monzó D. Reproducibility and validity of a food frequency questionnaire among pregnant women in a Mediterranean area. Nutr J 2013;12:26. Published 2013 Feb 19.
[24] Willett W, Sampson L, Stampfer M, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
[25] U.S. Department of Agriculture. Agricultural Research Service, http://www.ars.usda.gov/Main/site_main.htm?modecode=12-35-45- 00.
[26] Palma I, Farran P, Cervera P. Tablas de composición de Alimentos por medidas caseras de consumo habitual en España. Madrid: Mc Graw Hill Interamericana: CESNID.; 2008.
[27] Fernández-Barrés S, Romaguera D, Valvi D, Martínez D, Vioque J, Navarrete-Muñoz EM, et al., INMA Project. Mediterranean dietary pattern in pregnant women and offspring risk of overweight and abdominal obesity in early childhood: the INMA birth cohort study. Pediatr Obes 2016 Dec;11(6):491–9.
[28] McCarthy D. Escalas McCarthy de Aptitudes y Psicomotricidad para Niños. S. A.: TEA Ediciones; 1977.
[29] Julvez J, Forns M, Ribas-Fitó N, Torrent M, Sunyer J. Attention behavior and hyperactivity and concurrent neurocognitive and social competence functioning in 4-year-olds from two population-based birth cohorts. Eur Psychiatr 2011 Sep;26(6):381–9. https://doi.org/10.1016/j.eurpsy.2010.03.013.
[30] Walder DJ, Sherman JC, Pulsifer MB. Neurodevelopmental assessment. In: Evidence-based practice in infant and early childhood psychology. Hoboken,NJ: John Wiley & Sons; 2009. p. 167–205.
[31] Julvez J, Mendez M, Fernandez-Barres S. Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels. Am J Epidemiol 2016;183:169–82.
[32] Spanish Ministry of Public Works. Atlas de La Vulnerabilidad Urbana En España 2001 Y 2011: Metodologia, Contenidos Y Créditos. Edicion de Diciembre de 2015); 2012.
[33] González de Rivera JL, Derogatis L, de las Cuevas C. The Spanish version of the SCL-90-R: normative data in general population. Baltimore: Towson; 1989.
[34] Weschler D, Kaufman A. WAIS-III. Escala de Inteligencia de Wechsler Para Adultos (III). Madrid: TEA Ediciones; 2001.
[35] Graciliano NG, Silveira JACD, Oliveira ACM. The consumption of ultra-processed foods reduces overall quality of diet in pregnant women. Cad Saúde Pública 2021 Mar 12;37(2):e00030120. English, Portuguese.
[36] Monteiro CA, Cannon G, Lawrence M, Louzada MLC, Machado PP. Ultra-processed foods, diet quality, and health using the NOVA classification system. Rome: Food and Agriculture Organization; 2019.
[37] Das JK, Lassi ZS, Hoodbhoy Z, Salam RA. Nutrition for the next generation: older children and adolescents. Ann Nutr Metab 2018;72(Suppl 3):56–64.
[38] Xu T, Faleschini S, Rifas-Shiman SL, Monthé-Drèze C, Oken E, Hivert M, et al. Maternal glucose tolerance in pregnancy and child cognitive and behavioural problems in early and mid-childhood. Paediatr Perinat Epidemiol 2021;35:109–19.
[39] Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology 2010 Jan;35(1):147–68.
[40] Martínez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. Nutrition 2020 Mar;71:110609.
[41] Stephan BC, Wells JC, Brayne C, Albanese E, Siervo M. Increased fructose intake as a risk factor for dementia. J Gerontol A Biol Sci Med Sci 2010 Aug;65(8):809–14.
[42] Attoff K, Johansson Y, Cediel-Ulloa A, Lundqvist J, Gupta R, Caiment F, et al. Acrylamide alters CREB and retinoic acid signalling pathways during differentiation of the human neuroblastoma SH-SY5Y cell line. Sci Rep 2020 Oct 7;10(1):16714.
[43] Stocher D, Klein C, Saccomori A, August P, Martins N, Couto P, Matté C. Maternal high-salt diet alters redox state and mitochondrial function in newborn rat offspring's brain. Br J Nutr 2018;119(9):1003–11.
[44] Monaco AP. An epigenetic, transgenerational model of increased mental health disorders in children, adolescents and young adults. Eur J Hum Genet 2020 Sep 18;29(3):387–95. https://doi.org/10.1038/s41431-020-00726-4.
[45] Hantsoo L, Jašarević E, Criniti S, McGeehan B, Tanes C, Sammel MD, et al. Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy. Brain Behav Immun 2019;75:240–50.
[46] Jones PC, Pendergast LL, Schaefer BA, Rasheed M, Svensen E, Scharf R, et al., MAL-ED Network Investigators. Measuring home environments across cultures: invariance of the HOME scale across eight international sites from the MAL-ED study. J Sch Psychol 2017 Oct;64:109–27.