Clinical Nutrition 41 (2022) 1667–1675

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

A high periconceptional maternal ultra-processed food consumption impairs embryonic growth: The Rotterdam periconceptional cohort

Ashley J.P. Smit [a], Batoul Hojeij [a], Melek Rousian [a], Sam Schoenmakers [a], Sten P. Willemsen [b], Régine P.M. Steegers-Theunissen [a, *], Lenie van Rossem [a]

[a] Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center, 3015 GD Rotterdam, the Netherlands
[b] Department of Biostatistics, Erasmus MC, University Medical Centre, 3015 GD Rotterdam, the Netherlands

ARTICLE INFO

Article history:
Received 30 December 2021
Accepted 3 June 2022

Keywords:
Embryonic growth
Ultra-processed food
Maternal diet
Crown-rump length
Embryonic volume

SUMMARY

Background & aims: Periconceptional maternal dietary patterns contribute to embryonic growth and development. No knowledge is available about the impact of periconceptional maternal ultra-processed food consumption on embryonic growth. Therefore, the aim of the present study is to investigate the impact of periconceptional maternal ultra-processed food consumption on embryonic growth using repeated crown-rump length (CRL) and embryonic volume (EV) measurements.

Methods: This study is embedded in the ongoing prospective observational Rotterdam periconceptional cohort (Predict Study). A total of 701 pregnancies, of which 446 were conceived after natural conception and 255 after IVF or ICSI treatment were included. Women were at least 18 years of age and were recruited at the outpatient clinic before 13^{+0} weeks of gestation. CRL and EV were measured using three-dimensional ultrasound datasets and virtual reality techniques at the 7th, 9th and 11th week of gestation. The food frequency questionnaire of each participant was used to calculate the percentage of maternal energy consumed from ultra-processed foods (PEI-UPF) for each participant. The association between PEI-UPF and the first trimester CRL and EV measurements was studied with linear mixed models and adjusted for potential confounders including maternal factors, gestational age, foetal sex, and total energy intake.

Results: PEI-UPF ranged from 16% to 88%. In fully adjusted linear mixed models, a 10% increase in maternal PEI-UPF was significantly associated with smaller growth trajectories of CRL and EV (b −0.041 $\sqrt{}$mm (95% confidence interval (CI) −0.074 to −0.008), P = 0.02 and b −0.016 $\sqrt[3]{}$cm (95% CI -0.030 to −0.001), P = 0.04, respectively). When additionally adjusted for micronutrient content of diet (vitamins B1, B2, B6, B11 and B12, and zinc), the associations for the CRL and EV measurements lost significance.

Conclusion: Periconceptional maternal consumption of ultra-processed foods is associated with smaller embryonic growth. Interventions promoting healthy food practices during pregnancy could be beneficial for embryonic growth.

1. Introduction

Embryonic growth trajectories are not identical among pregnancies [1,2]. Reduced embryonic growth during the first trimester is associated with adverse birth outcomes, such as an increased risk of preterm birth, low birth weight, and small for gestational age [3–5]. Neonates born with these conditions often show catch up growth, which is associated with increased risks of obesity and early features of non-communicable diseases in early life [6,7]. To decrease and minimize these risks, it is important to pinpoint and study which modifiable factors have an impact on embryonic growth. Several studies have shown that maternal deficiencies or excesses of nutrients can impair embryonic growth and development, and influence pregnancy outcomes [8]. However, rather than focusing on the quantity of nutritional components alone, addressing the dietary quality as a whole may provide a better

Abbreviations: UPF, Ultra-processed food; EV, Embryonic volume; CRL, Crown-rump length; FFQ, Food frequency questionnaire.

* Corresponding author. Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Centre, PO Box 2040, 3000CA Rotterdam, the Netherlands.
E-mail address: r.steegers@erasmusmc.nl (R.P.M. Steegers-Theunissen).

https://doi.org/10.1016/j.clnu.2022.06.006

insight in the effect of maternal food consumption as proxy of the nutritional status on embryonic growth, as a diet is more complex than the sum of its nutrients. This is supported by our previous studies demonstrating for example that a periconceptional maternal 'high fish and olive oil, low meat' dietary pattern is associated with increased embryonic growth and that an energy-rich dietary pattern is associated with an increased embryonic size in the first trimester [9,10].

Over the years, western diets have shifted towards an increased consumption of packaged, ready-to-consume, processed products, thus replacing traditional dietary patterns based on freshly prepared dishes and meals [11,12]. Between 10% and 50% of household food purchase in Europe is represented by ultra-processed foods (UPF) [13]. UPF are products created mostly or entirely from substances extracted from foods by physical and chemical processes. They often contain additives to extend their durability and make them highly palatable. Examples of UPF are chocolate bars, instant soups, and sweetened breakfast cereals. The share of UPF is negatively related to the overall nutritional quality of diets, as UPF often contain a large amount of added sugars and saturated fat while lacking fibres and vitamins [14,15]. In addition, UPF tend to be consumed in great amounts [11]. High UPF consumption has been associated with an increased risk of non-communicable diseases such as obesity, hypertension and cancer [16–18]. Few studies have investigated the impact of maternal UPF consumption on pregnancy course and outcome. However, one study reported an association between maternal percentage of energy intake from ultra-processed foods (PEI-UPF) during pregnancy and increased gestational weight gain and neonatal body fat [19].

As maternal food consumption serves as the main source of nourishment of the embryo, we hypothesize that the UPF dominated diet could exert a negative effect on embryonic growth. Therefore, this study aimed to investigate whether periconceptional maternal UPF consumption is associated with embryonic growth using repeated crown-rump length (CRL) and embryonic volume (EV) measurements.

2. Materials & methods

2.1. Study population

The data used for this study were collected in the Rotterdam Periconceptional Cohort (Predict) study, a prospective tertiary hospital-based cohort study conducted at the department of Obstetrics and Gynaecology of the Erasmus Medical Centre in Rotterdam, the Netherlands [20]. All participants provided written informed consent. The rationale and design of the Predict study were previously published [20,21]. A total of 2693 pregnancies from women of at least 18 years of age were recruited in the outpatient clinic before 13^{+0} weeks of gestation between November 2010 and December 2019. In the current study, we excluded 66 gemelli pregnancies, as embryonic growth in twin pregnancies differs from singleton pregnancies [22]. An additional 28 pregnancies resulting from oocyte donation were excluded due to the lack of information on general characteristics, periconceptional lifestyle, and food consumption of the maternal donor. We excluded 1306 pregnancies due to missing or unreliable ultrasound measurements. Another 128 pregnancies were excluded due to the absence of a Food Frequency Questionnaire (FFQ). Dietary under-reporters were identified with the Goldberg cut-off method as proposed by Black (Supporting Material 1), and were excluded from analysis (n = 414) [23]. Another 50 pregnancies were excluded because their cut-off value could not be calculated due to missing physical parameters. From the remaining 701 pregnancies, 446 were conceived naturally, and 255 were conceived through in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment (Fig. 1).

2.2. Data collection

2.2.1. Embryonic growth measurements and gestational age

CRL and EV are objective measurements of embryonic growth. CRL is a parameter that is used to estimate the gestational age of the embryo, and can be used to determine growth restriction of the embryo. However, since CRL is one of our outcomes we could not use the CRL to calculate the gestational age as this would introduce bias. Therefore, the gestational age was calculated based on the first day of the last menstrual period. CRL and EV are measured through 3D ultrasound (3D-US) scans. Initially, all women received weekly transvaginal 3D-US scans from enrolment up to 13^{+0} weeks' gestation. However, from December 2012 the number of ultrasound scans was reduced to three, specifically in the 7th, 9th, and 11th week of gestation, as a pilot study revealed that this was enough to accurately model the longitudinal embryonic growth curves [20]. All CRL and EV measurements were performed using virtual reality techniques, by trained research staff. The virtual reality applications allow real depth perception; and semi-automated analyses of volumetric measures like the EV. Interobserver and intraobserver agreement have been reported as excellent, with an inter- and intraclass correlation coefficient of 0.99 [21,24]. Detailed information about the 3D-US scans can be found in "Cohort profile: The Rotterdam Periconceptional Cohort (Predict Study)" [20,21].

2.2.2. Food frequency questionnaire

All participants received an FFQ at enrolment consisting of 190 food and beverage items, which included questions on frequency of consumption, portion size and method of preparation over the previous four weeks. The FFQ was used to estimate habitual food consumption, during the periconceptional period. The periconceptional period was defined as the period of 14 weeks before up to 10 weeks after conception [25]. The FFQ has been developed by the division of Human Nutrition, Wageningen University, the Netherlands, and validated to estimate, among other micro- and macronutrient content of diet, the energy intake [26]. Energy and nutritional intake of each food item was determined with the Dutch food composition table. Energy and macronutrient intakes were validated using three times 24 h recalls (two weekdays and one weekend day over a three weeks period) and dietary history [26,27]. For folate and vitamin B12 intakes, the FFQ was validated using the method of triads [26]. For energy intake, there was difference of 12% between FFQ and 24 h recall and 5% between FFQ and dietary history [26,27].

2.2.3. Percentage of energy intake from ultra-processed foods (PEI-UPF)

Each food and beverage item on the FFQ was categorized according to the NOVA food classification into either 'unprocessed or minimally processed foods', 'processed culinary ingredients', 'processed foods' or 'ultra-processed foods', independently by a master student in clinical research, a dietician, and a nutritional epidemiologist (Supporting Material 2) [11]. The classifications were compared and consensus was reached among the three researchers in case classifications differed. When uncertainty existed about whether an item was mostly consumed as homemade or store bought, nutritional websites and papers about Dutch shopping behaviour and preparation methods were consulted. After classification of each food item according to the NOVA classification, the average nutrient and energy intake by each NOVA group was calculated for each individual participant. This resulted in the calculation of the PEI-UPF for each participant.

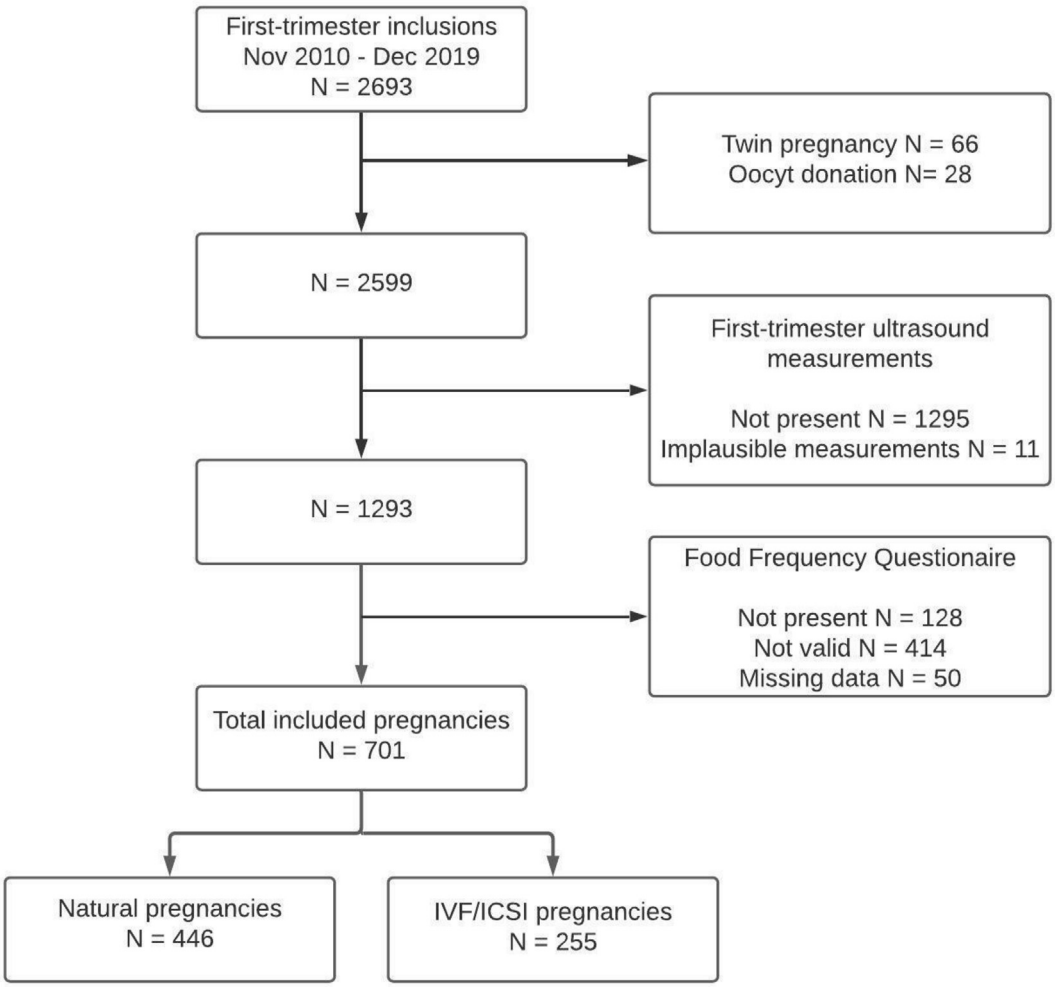

Fig. 1. Selection of study participants. IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

2.2.4. Covariates

Data on maternal characteristics (date of birth, parity, ethnicity, educational level), lifestyle factors (periconceptional smoking and alcohol consumption, physical exercise, folic acid supplement use), and mode of conception were collected through questionnaires. Parity was dichotomised into nulliparous and multiparous. Ethnicity was transformed into a dichotomous variable, differentiating western from non-western women according to the classification of the Dutch central bureau of statistics (CBS) [28]. Educational level, as an indicator of socio-economic status, was categorised as either low, intermediate, or high according to the classification of the CBS [29]. Periconceptional smoking and alcohol consumption were dichotomous variables (yes/no), and a participant was classified as 'smoker' or 'alcohol consumer' when she was smoking or drinking alcohol 8 weeks before till 4 weeks after conception. Physical exercise was a dichotomous variable (yes/no). Folic acid supplement use was a categorised variable with the following categories: 'yes, with vitamin', 'yes, 0.4/0.5 mg', 'yes, 5.0 mg' and 'no'. Mode of conception was either natural or with IVF/ICSI.

Maternal age was calculated by subtracting the maternal date of birth from her due date as a continuous variable. BMI was a continuous variable and has been calculated as weight (kg)/height^2 (m), which were measured during a visit in the first trimester. Information on the sex of the infant (male/female) was collected through requested delivery reports and post-partum questionnaires.

2.3. Statistical analysis

To study whether there are differences in participant characteristics between those who have a high PEI-UPF and those who have a low PEI-UPF, the participants were categorized according to PEI-UPF quartiles. The difference in characteristics among the PEI-UPF groups was tested using chi-square for categorical variables, and Kruskal–Wallis or ANOVA for continuous variables with skewed or normal distribution respectively.

The PEI-UPF was used in mixed model analyses to study its association with EV and CRL trajectories (primary analysis). We used the square root of the CRL measurements and the cube root of the EV measurements, to approach a linear association of the embryonic measurements with gestational age. A Directed Acyclic Graph was used to determine which covariates should be adjusted for in the mixed model analyses (Supporting Material 3). Multivitamin use was excluded for analysis because it turned out to be too heterogeneous. A top-down strategy was used for model selection. For all continuous covariates, we tested the linearity of the association by adding non-linear terms. We have tested interaction terms between the exposure and all the maternal covariates to study potential effect modification, and between the covariates (BMI*age, smoking*alcohol consumption, smoking*age and alcohol*age) to increase model fit. No effect modification was revealed and none of the interactions terms improved our model fit, so we restricted our regression model to a linear model without interaction terms. This

resulted in linear mixed models adjusted for gestational age, foetal sex, maternal age, ethnicity, parity, folic acid use (dichotomous), periconceptional alcohol consumption, periconceptional smoking, periconceptional physical activity, educational level, and BMI. The models included a random intercept and a random slope for gestational age. A nested effect was included to adjust for women who recurrently participated in the Predict study with different pregnancies.

To test whether the association between UPF consumption and embryonic growth could be completely explained by the low nutritional quality of the diet [30,31], we additionally adjusted the model for macro- and micronutrients which can play an important role in this association [8,32–34]. These included saturated fatty acids and vitamins B1, B2, B6, B11 and B12, and zinc. Additionally, to study the potential positive effect of consumption of unprocessed or minimally processed foods (MPF) on embryonic growth (secondary analysis), the PEI-UPF was replaced by the percentage of energy intake from unprocessed or minimally processed foods (PEI-MPF). To adjust for the potential beneficial effect of the consumption of MPF in respect to the potential detrimental effect of UPF on embryonic growth, a ratio between the PEI-MPF and the PEI-UPF, defined as the PEI-MPF divided by the PEI-UPF, was used in another linear mixed model.

Since mode of conception can affect embryonic growth and responses to nutritional exposures [35], a sub-analysis was performed after stratification of the study population into either natural or IVF/ICSI pregnancies.

P values $\leq$ 0.05 were considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM SPSS Statistics) and R version 4.0.3 (R for Windows; R Core Team).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the included and excluded pregnancies are shown in Supporting Material 4. The mothers of the excluded pregnancies had a higher BMI, reported more often periconceptional alcohol use, were more often of non-Dutch ethnicity, conceived naturally more often, exercised less, had a lower total energy intake, age and education level, and used less often folic acid supplement than included pregnancies.

In the included study population, women had a median age of 33.0 years, 52.4% was nulliparous and the majority was of Western origin (89.2%) and highly educated (61.9%). The median BMI was 23.5 kg/m^2 and the median energy intake was 8567.7 kJ/day. Of the participants, 63.6% conceived naturally. Periconceptional alcohol use and smoking was reported by 34.4% and 15.6% of the participants, respectively. Less than half of the women exercised (46.0%) and 1.3% of women reported no use of folic acid supplements (Table 1).

The contribution of ultra-processed foods ranged from 16.3% to 88.3%, with a median contribution of 47.5% (Table 1). Among the four quartiles of PEI-UPF, increased UPF consumption was significantly associated with a lower maternal age, lower educational level, and a lower number of women who practise sport. In addition, increased PEI-UPF was statistically significant associated with a higher daily energy intake, higher BMI, and higher number of women who smoke periconceptionally. Furthermore, there was a statistically significant difference in periconceptional alcohol use among the four PEI-UPF quartiles.

The mean CRL at approximately 11 weeks (range 10^{+1} to 11^{+6}) was 46.55 mm ($\sqrt{}$CRL 6.79 mm). The mean EV at 11 weeks was 9.31 cm^3 ($\sqrt[3]{}$EV 2.05 cm^3).

3.2. Primary analyses: associations between PEI-UPF and embryonic growth

Table 2 shows the associations between PEI-UPF and embryonic growth. Model 1 shows negative associations between PEI-UPF and CRL and EV trajectories (b −0.041 (95% CI -0.074; −0.008), P value 0.02; b −0.016 (95% CI -0.030; −0.001), P value 0.04, respectively), which means that an increase of PEI-UPF by 10% decreases $\sqrt{}$CRL by 0.041 mm and $\sqrt[3]{}$EV by 0.016 cm^3. In essence, these associations mean that in the total study population, at a gestational age of 11 weeks, the difference in CRL between the first and the last quartile of PEI-UPF is 1.34 mm, which is a decrease of 3.0%, and the difference in EV between the first and the last quartile of PEI-UPF is 0.45 cm^3, which is a decrease of 5.6% (Fig. 2). When additionally adjusted for micronutrient content of diet (vitamins B1, B2, B6, B11 and B12, and zinc), the effect size for the association between PEI-UPF with CRL and EV became smaller and non-significant, particularly after addition of vitamin B11 to the model (Table 2, model 3). Adjustment for saturated fatty acids did not change the effect size between PEI-UPF and CRL and EV, and the association remained statistically significant (Table 2, model 2).

Table 3 shows the association between PEI-UPF and embryonic growth in natural and in IVF/ICSI pregnancies. In natural pregnancies, the association between PEI-UPF and embryonic growth remained significant for CRL trajectories (b −0.061 (95% CI -0.116; −0.006), P value 0.034). Moreover, the effect size between PEI-UPF and CRL trajectories was larger in natural pregnancies compared to the effect size in the total study population. In essence, these associations mean that in natural conceived pregnancies, at a gestational age of 11 weeks, the difference in CRL between the first and the last quartile of PEI-UPF is 1.96 mm, which is a decrease of 4.5%. In IVF/ICSI pregnancies group, no association was present between PEI-UPF and embryonic growth trajectories.

3.3. Secondary analyses: associations between PEI-MPF and embryonic growth

The range in PEI-MPF varied from 2.3% to 77.9%. A non-significant positive association was observed between PEI-MPF and embryonic growth, in which a ten percentage increase in PEI-MPF results in a 0.032 mm (95% CI -0.05; 0.068, P value 0.088) increase of $\sqrt{}$CRL and a 0.012 cm^3 increase of $\sqrt[3]{}$EV (95% CI -0.005; 0.028, P value 0.154) (Table 4). Additionally, there was a positive association between the ratio of PEI-MPF and PEI-UPF and embryonic growth measurements, though this association was significant for CRL measurements only (b 0.094 (95% CI 0.013; 0.175), P value 0.025) (Table 4). This model suggests that an increase of this ratio by 1, increases $\sqrt{}$CRL by 0.094 mm.

4. Discussion

The findings of this study show that an increased periconceptional PEI-UPF is negatively associated with embryonic growth. In our study population, at 11 weeks of gestation, CRL and EV were respectively 3.0% and 5.6% significantly smaller in the last PEI-UPF quartile compared to the first, when PEI-UPF has an absolute mean increase of 24.6%. The effects for CRL were even larger in the subgroup of natural conceived pregnancies (4.5%). When adjusted for micronutrient content of the diet, the detrimental effect of PEI-UPF became less strong, and lost significance for CRL and EV.

4.1. Interpretation of findings and comparison with other studies

Two hypotheses could explain the detrimental effect of PEI-UPF on embryonic growth. First of all, the nutritional value of ultra-

Table 1
Baseline characteristics of the study population (n = 701) of women in the periconception period stratified for PEI-UPF quartiles (Q)*.

Characteristics	Total (n = 701)	Q1 16.26–40.22% (n = 175)	Q2 40.23–47.53% (n = 176)	Q3 47.54–54.82% (n = 175)	Q4 54.83–88.31% (n = 175)	P value†
Age, in years						<0.001
Measured	33.0 (30.3–36.1)	33.9 (31.3–36.7)	33.7 (31.0–36.2)	32.2 (29.9–35.6)	31.9 (29.4–35.0)	
Missing data	0	0	0	0	0	
Parity						0.912
Nulliparous	344 (52.4)	84 (52.2)	90 (54.5)	85 (50.6)	85 (52.1)	
Missing data	44	14	11	7	12	
Ethnicity						0.104
Western	606 (89.2)	146 (84.4)	161 (93.1)	152 (89.4)	152 (89.9)	
Missing data	22	4	4	7	7	
Educational level						<0.001
High	420 (61.9)	136 (78.6)	105 (61.4)	98 (57.6)	84 (49.4)	
Intermediate	209 (30.8)	33 (19.1)	56 (32.7)	61 (35.9)	62 (36.5)	
Low	49 (7.2)	4 (2.3)	10 (5.8)	11 (6.5)	24 (14.1)	
Missing data	23	4	6	7	6	
Energy intake (kJ/d)						<0.001
Measured	8567.7 (7578.6–9755.6)	8012.5 (7389.7–9050.2)	8535.1 (7581.4–9673.7)	8573.8 (7672.3–9921.3)	9145.4 (7916.2–10612.1)	
BMI (kg/m^2)						0.001
Measured	23.5 (21.5–26.5)	23.2 (21.2–25.7)	22.9 (21.2–25.3)	24.0 (21.7–27.0)	24.2 (22.0–27.7)	
Missing data	0	0	0	0	0	
Mode of conception						0.376
Natural	446 (63.6)	117 (66.9)	103 (58.5)	115 (65.7)	111 (63.4)	
IVF-ICSI	255 (36.4)	58 (33.1)	73 (41.5)	60 (34.3)	64 (36.6)	
Alcohol						0.040
Any use	233 (34.4)	63 (37.1)	58 (33.7)	68 (40.5)	44 (26.2)	
Missing data	23	5	4	7	7	
Smoking						<0.001
Any use	106 (15.6)	15 (8.8)	19 (11.0)	33 (19.6)	39 (23.1)	
Missing data	22	5	4	7	6	
Physical exercise						0.004
Practises	312 (46.0)	95 (55.6)	83 (48.5)	72 (43.1)	62 (36.7)	
Missing data	23	4	5	8	6	
FA supplement use						0.646
Yes, with vitamin	362 (53.3)	92 (53.8)	90 (52.6)	90 (53.6)	90 (53.3)	
Yes, 0.4/0.5 mg	291 (42.9)	73 (42.7)	78 (45.6)	69 (41.1)	71 (42.0)	
Yes, 5.0 mg	17 (2.5)	5 (2.9)	3 (1.8)	5 (3.0)	4 (2.4)	
No	9 (1.3)	1 (0.6)	0	4 (2.4)	4 (2.4)	
Missing data	22	4	5	7	6	

Data are presented as number of individuals (%) or as median (IQR). BMI = body mass index; FA = folic acid.
*Q1 includes women with the lowest PEI-UPF (16.26–40.22% of their total energy intake), whereas Q4 includes the women with the highest PEI-UPF (54.83–88.31% of their total energy intake).
†P value indicates whether the difference in characteristic among the PEI-UPF quartiles was statistically significant.

Table 2
Associations between PEI-UPF and embryonic growth measurements from linear mixed models, including the number of mothers, pregnancies and measurements.

Model by outcome measurement	Effect size	95% CI	P value	Mothers (n)	Pregnancies (n)	Measurements (n)
PEI-UPF (for each 10% increase)						
√Crown-rump length (mm)						
Model 1	−0.041	−0.074; −0.008	0.017	580	612	1707
Model 2	−0.043	−0.076; −0.009	0.015	580	612	1707
Model 3	−0.038	−0.079; 0.002	0.064	578	610	1701
∛Embryonic volume (cm^3)						
Model 1	−0.016	−0.030; −0.001	0.039	566	597	1552
Model 2	−0.016	−0.031; −0.001	0.034	566	597	1552
Model 3	−0.015	−0.033; 0.003	0.108	564	595	1546

Model 1 is adjusted for gestational age, foetal sex, maternal age, ethnicity, parity, folic acid use, periconceptional alcohol consumption, smoking and physical activity, educational level, total energy intake and BMI.
Model 2 is as model 1, but additionally adjusted for saturated fatty acid intake.
Model 3 is as model 1, but additionally adjusted for vitamins B1, B2, B6, B11 and B12, and zinc.

processed foods is generally poor, as they often contain a large amount of added sugars and saturated fat [14,15]. Therefore, increased consumption of UPF may result in a decreased diet quality and increased energy intake. Previous reports have associated deficiencies or excesses in a range of macro- and micronutrients with significant impairment in foetal development [8,36]. In the current study, the association between UPF and embryonic growth became less strong and non-significant when adjusting for the B vitamins (B1, B2, B6, B11, B12) and zinc, particularly due to vitamin B11, whereas the associations remained after adjustment for saturated fatty acid. Since we did not examine all the relevant aspects of diet in relation to UPF (e.g. other macro- and

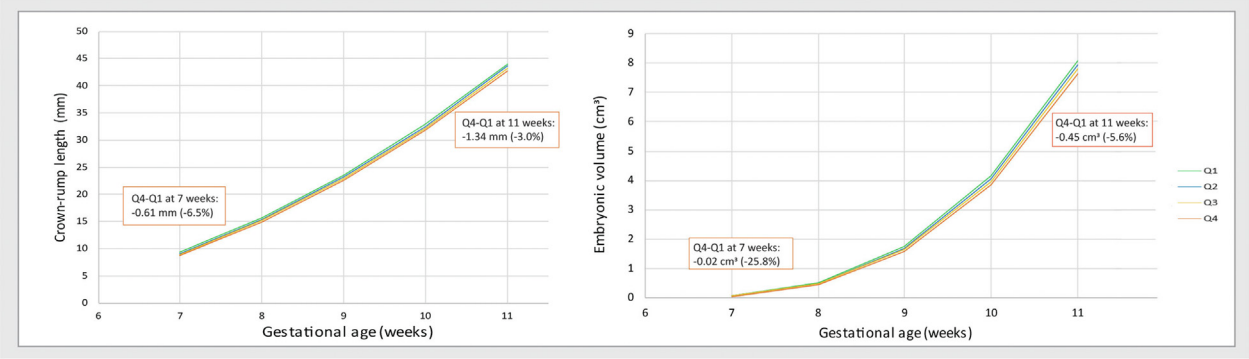

Fig. 2. Graphical representation of model 1 in Table 2: Predicted embryonic growth trajectories (crown-rump length and embryonic volume), stratified for PEI-UPF quartiles (Q), with Q1 35.7%, Q2 44.0%, Q3 50.7% and Q4 60.3%.

Table 3
Associations between PEI-UPF and embryonic growth measurements from linear mixed models, including the number of mothers, pregnancies and measurements, stratified for natural and IVF/ICSI pregnancies.

Model by outcome measurement	Effect size	95% CI	P value	Mothers (n)	Pregnancies (n)	Measurements (n)
PEI-UPF (for each 10% increase)						
√Crown-rump length (mm)						
Natural	−0.061	−0.116; −0.006	0.034	376	395	1116
IVF/ICSI	−0.001	−0.041; 0.039	0.94	212	223	585
∛Embryonic volume (cm^3)						
Natural	−0.023	−0.046; 0.001	0.062	367	386	1014
IVF/ICSI	0.004	−0.016; 0.025	0.562	219	230	641

Models for natural pregnancies are adjusted for gestational age, foetal sex, maternal age, ethnicity, parity, folic acid use, periconceptional alcohol consumption, smoking and physical activity, educational level, total energy intake and BMI.
Models for IVF/ICSI pregnancies are adjusted for gestational age, foetal sex, maternal age, folic acid use, periconceptional alcohol consumption and smoking, educational level, total energy intake and BMI.

Table 4
Associations between PEI-MPF and embryonic growth measurements from linear mixed models, including the number of mothers, pregnancies and measurements.

Model by outcome measurement	Effect size	95% CI	P value	Mothers (n)	Pregnancies (n)	Measurements (n)
PEI-MPF (for each 10% increase)						
√Crown-rump length (mm)						
Model 1	0.032	−0.05; 0.068	0.088	580	612	1707
∛Embryonic volume (cm^3)						
Model 1	0.012	−0.005; 0.028	0.154	566	597	1552
Ratio (PEI MPF/PEI UPF)						
√Crown-rump length (mm)						
Model 1	0.094	0.013; 0.175	0.025	580	612	1707
∛Embryonic volume (cm^3)						
Model 1	0.036	−0.002; 0.072	0.052	566	597	1552

Model 1 is adjusted for gestational age, foetal sex, maternal age, ethnicity, parity, folic acid use, periconceptional alcohol consumption and smoking, physical activity, educational level, total energy intake and BMI.

micronutrients), conclusions on which dietary factors might mediate the effect of PEI-UPF consumption on embryonic growth cannot be established from this study. In addition, the associations between the ratio PEI-MPF/PEI-UPF and embryonic growth measurements (Table 4) were comparable to the association between the results shown for PEI-UPF alone (Table 2). For the PEI-MPF/PEI-UPF ratio, the difference in CRL between Q1 and Q4 at 11 weeks of gestational age was 1.22 mm. For EV this difference was 0.42 cm^3 (data not shown). These outcomes suggest that PEI-UPF is a key player in maternal diet affecting embryonic growth, though the underlying mechanism should be elucidated. A second hypothesis concerns other properties of UPF beside their nutritional quality, such as food additives and the physical structure of UPF [37]. Although the levels of food additives are regulated for each individual food product to protect the consumers against adverse effects, the effect of their long-term cumulative consumption on health are not always completely clear [38]. It has been argued that additives affect the gut microbiota composition, function and bacteria–host interactions [39]. Furthermore, the physical structure of the food matrix can be altered during processing, which can interfere with the nutrient bio-accessibility and absorption kinetics. This subsequently affects the gut microbiota composition, metabolism, and growth [39]. Alterations in the gut microbiome due to dietary changes could result in dysbiosis and microbiota encroachment, leading to intestinal inflammation [40]. Furthermore, differences in the gut microbiome have been associated with gestational weight gain [41] and gestational diabetes [42]. Even more so, studies in rodents show that the loss of microbiota

diversity due to a western diet can be transferred to later generations [43], emphasizing the importance of the maternal diet for the microbiome of their offspring.

Our results show that the association between PEI-UPF and embryonic growth in this study is likely driven by naturally conceived pregnancies. However, there is not sufficient power to stratify each analysis by mode of conception. The absence of an effect of PEI-UPF on embryonic growth in IVF/ICSI pregnancies is in line with our previous findings in the same cohort [9,44]. This might be explained by the underlying subfertility or the procedure of IVF and ICSI itself. There is a considerable amount of evidence that shows the influence of IVF on epigenetic modifications of the embryo [35]. The underlying cause of subfertility or the IVF/ICSI procedure might have a larger effect on embryonic growth, therefore diminishing the association between PEI-UPF and embryonic growth.

In comparison to previous found associations between maternal lifestyle with embryonic growth, the association between periconceptional maternal PEI-UPF and embryonic growth is comparable in effect size to maternal smoking (>10 cigarettes a day) [1,45]. In addition the effect size is larger than with maternal alcohol use (any use) [1,45]. Another paper identified a maternal diet comprising a high consumption of fish and olive oil and a low consumption of meat as beneficial for embryonic growth in natural pregnancies [9]. Both fish and meat could fit in multiple NOVA categories, while olive oil fits in the processed culinary ingredients category. Considering food processing, we expect that the beneficial association between fish and embryonic growth that has been found results mostly from fresh, unprocessed fish consumption, and that the detrimental association between meat and embryonic growth results mostly from processed meats. However, the lack of information about the amount of processing in the study by Parisi et al. [9] makes it difficult to make proper comparisons. Embryonic growth trajectories in the first trimester of pregnancy associate with birth weight and risk of delivering small for gestational age infant [5,46]. Furthermore, decrease in first trimester CRL is associated with growth acceleration in early childhood [3].

4.2. Strengths and limitations

A major strength of this study is that the Predict cohort provides a unique collection of many longitudinal high quality 3D US-scans in the first trimester of pregnancy, which enabled very precise embryonic growth measurements, performed using state-of-the-art virtual reality techniques. Additionally, the extensive collection of participant characteristics reduced the risk of confounding bias. Besides, women with high intake of UPF might be socially disadvantaged. However, we considered education level as a proxy for socio-economic status and adjusted for lifestyle factors highly associated with socio-economic status. Educational level is considered the strongest indicator of socio-economic status as it reflects health literacy and ability to receive and seek for information and act on this. As the estimates between the crude and adjusted model (which included indicators of socio-economic status) were quite similar, we think it is unlikely that residual confounding explained our results. Another important aspect of our study is the variation of PEI-UPF in our population (from 16% to 88%), as it allowed us to properly study the effect of PEI-UPF on embryonic growth throughout the full range of exposure. Though there are no national data available in the Netherlands, a study by Monteiro et al. (2018) estimated the median average household energy availability for UPF in nineteen European countries at 26.4% [13]. Compared to the previous value, the energy contribution of UPF to the diet of our population (median 47.5%) seems high. However, this number is comparable to the UPF household energy availability found in North-West European countries [13].

This study has some limitations as well. Firstly, the external validity of the results might be limited, as participants were recruited in a tertiary referral hospital, resulting in a study population mainly consisting of high-risk pregnancies. Secondly, we observed differences in BMI, lifestyle and socio-economic factors between included and excluded pregnancies. As in most observational cohort studies, included participants are in general healthier, have a healthier lifestyle and are of higher socio-economic status. Although we can only speculate about this, as we do not have the data for the excluded pregnancies, we think it is highly unlikely that this resulted in selection bias, as the association between periconceptional maternal PEI-UPF and embryonic growth likely has the same direction in the excluded pregnancies. Thirdly, 37.1% of the women with a completed FFQ were excluded from analysis for underreporting of their energy intake, even though the FFQ is a validated questionnaire for dietary intake. Moreover, sensitivity analysis using 99% CI for Gold-burg cut-off showed similar outcomes. Reasons for underreporting can be due to the length of the FFQ, as well as participants deliberately altering their answers because they felt embarrassed by their food consumption [47]. In addition, under reporters had a higher BMI than women who did not underreport (data not shown). This is consistent with previous studies that state that underreporting is more common in overweight individuals [47]. Fourthly, though eventual agreement was reached among three researchers, discussions concerning whether certain food products were mostly bought ready-to-consume or were more often freshly prepared arouse during the classification. Therefore some misclassification of food products into NOVA categories could have occurred. This non-differential misclassification most likely underestimated the effect, although the possibility of overestimation cannot be ruled out.

4.3. Implications for research and practice

The high PEI-UPF in our study population shows that there is a great window of opportunity for interventions discouraging the consumption of UPF during the periconceptional period and pregnancy [48]. This can be also achieved through implementing policies that focus on maintaining the affordability of unprocessed foods, while increasing the ultra-processed food costs (e.g. by means of taxes). Future research to study what aspects of UPF influence embryonic growth and whether the detrimental effect of PEI-UPF on embryonic growth observed in our population remain visible after the first trimester of pregnancy is warranted.

5. Conclusion

To our knowledge, this study is the first to show a negative association between a high periconceptional maternal consumption of ultra-processed foods and impaired embryonic growth. Our findings underline the importance of periconceptional maternal diet on embryonic growth. Reducing UPF consumption might be a promising topic to improve pregnancy outcomes and long-term maternal and neonatal health.

Funding

This work was supported by the Department of Obstetrics and Gynaecology of the Erasmus Medical Centre; BH received funding from European Union's Horizon 2020 research and innovation programme (DohART-NET) [grant agreement No 812660].

Author contributions

Ashley JP Smit: conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, writing-review & editing, visualization; Batoul Hojeij: methodology, writing-review & editing; Melek Rousian: writing-review & editing; Sam Schoenmakers: writing-review & editing; Sten P Willemsen: methodology, formal analysis; Régine PM Steegers-Theunissen: conceptualization, methodology, writing-review & editing, funding acquisition; Lenie van Rossem: conceptualization, methodology, investigation, writing-review & editing, supervision.

Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.06.006.

References

[1] van Uitert EM, van der Elst-Otte N, Wilbers JJ, Exalto N, Willemsen SP, Eilers PHC, et al. Periconception maternal characteristics and embryonic growth trajectories: the Rotterdam Predict study. Hum Reprod 2013;28:3188–96.

[2] Bottomley C, Daemen A, Mukri F, Papageorghiou AT, Kirk E, Pexsters A, et al. Assessing first trimester growth: the influence of ethnic background and maternal age. Hum Reprod 2008;24:284–90.

[3] Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, Jaddoe VW. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA 2010;303:527–34.

[4] Smith GC, Smith MF, McNay MB, Fleming JE. First-trimester growth and the risk of low birth weight. N Engl J Med 1998;339:1817–22.

[5] Bukowski R, Smith GC, Malone FD, Ball RH, Nyberg DA, Comstock CH, et al. Fetal growth in early pregnancy and risk of delivering low birth weight infant: prospective cohort study. BMJ 2007;334:836.

[6] Druet C, Stettler N, Sharp S, Simmons RK, Cooper C, Smith GD, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol 2012;26:19–26.

[7] Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. Bmj 2014;348:g14.

[8] Gernand AD, Schulze KJ, Stewart CP, West Jr KP, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nat Rev Endocrinol 2016;12:274–89.

[9] Parisi F, Rousian M, Huijgen NA, Koning AHJ, Willemsen SP, de Vries JHM, et al. Periconceptional maternal 'high fish and olive oil, low meat' dietary pattern is associated with increased embryonic growth: the Rotterdam Periconceptional Cohort (Predict) Study. Ultrasound Obstet Gynecol 2017;50:709–16.

[10] Bouwland-Both MI, Steegers-Theunissen RP, Vujkovic M, Lesaffre EM, Mook-Kanamori DO, Hofman A, et al. A periconceptional energy-rich dietary pattern is associated with early fetal growth: the Generation R study. BJOG: Int J Obstet Gynaecol 2013;120:435–45.

[11] Monteiro CACG, Levy RB, Moubarac J-C, Jaime P, Martins AP, Canella D, et al. NOVA. The star shines bright. [Food classification, Public health]. World Nutr 2016;7:28–38.

[12] Baker P, Machado P, Santos T, Sievert K, Backholer K, Hadjikakou M, et al. Ultra-processed foods and the nutrition transition: global, regional and national trends, food systems transformations and political economy drivers. Obes Rev 2020;21:e13126.

[13] Monteiro CA, Moubarac JC, Levy RB, Canella DS, Louzada M, Cannon G. Household availability of ultra-processed foods and obesity in nineteen European countries. Publ Health Nutr 2018;21:18–26.

[14] Martinez Steele E, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. Popul Health Metrics 2017;15:6.

[15] Louzada M, Ricardo CZ, Steele EM, Levy RB, Cannon G, Monteiro CA. The share of ultra-processed foods determines the overall nutritional quality of diets in Brazil. Publ Health Nutr 2018;21:94–102.

[16] Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Alles B, Mejean C, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. Bmj 2018;360:k322.

[17] Juul F, Hemmingsson E. Trends in consumption of ultra-processed foods and obesity in Sweden between 1960 and 2010. Publ Health Nutr 2015;18:3096–107.

[18] Mendonca RD, Lopes AC, Pimenta AM, Gea A, Martinez-Gonzalez MA, Bes-Rastrollo M. Ultra-processed food consumption and the incidence of hypertension in a mediterranean cohort: the seguimiento universidad de Navarra Project. Am J Hypertens 2017;30:358–66.

[19] Rohatgi KW, Tinius RA, Cade WT, Steele EM, Cahill AG, Parra DC. Relationships between consumption of ultra-processed foods, gestational weight gain and neonatal outcomes in a sample of US pregnant women. PeerJ 2017;5:e4091.

[20] Steegers-Theunissen RP, Verheijden-Paulissen JJ, van Uitert EM, Wildhagen MF, Exalto N, Koning AH, et al. Cohort profile: the Rotterdam periconceptional cohort (Predict study). Int J Epidemiol 2015;45:374–81.

[21] Rousian M, Schoenmakers S, Eggink AJ, Gootjes DV, Koning AHJ, Koster MPH, et al. Cohort Profile Update: the Rotterdam Periconceptional Cohort and embryonic and fetal measurements using 3D ultrasound and virtual reality techniques. Int J Epidemiol 2021;50(5):1426–1427l.

[22] Hiersch L, Okby R, Freeman H, Rosen H, Nevo O, Barrett J, et al. Differences in fetal growth patterns between twins and singletons**. J Matern Fetal Neonatal Med 2020;33:2546–55.

[23] Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord 2000;24:1119–30.

[24] Rousian M, Koning AHJ, van Oppenraaij RHF, Hop WC, Verwoerd-Dikkeboom CM, van der Spek PJ, et al. An innovative virtual reality technique for automated human embryonic volume measurements. Hum Reprod 2010;25:2210–6.

[25] Steegers-Theunissen RP, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Hum Reprod Update 2013;19:640–55.

[26] Verkleij-Hagoort AC, de Vries JH, Stegers MP, Lindemans J, Ursem NT, Steegers-Theunissen RP. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. Eur J Clin Nutr 2007;61:610–5.

[27] Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993;58:489–96.

[28] Alders M. Classification of the population with a foreign background in the Netherlands the measure and mismeasure of population the statistical use of ethnic and racial categories in multicultural societies. Paris: Centraal Bureau Statistiek (CBS); 2001.

[29] Standaard onderwijsindeling, Editie 2020/'21 In: (CBS) CBS, editor. Den Haag 2021.

[30] Falcao R, Lyra CO, Morais CMM, Pinheiro LGB, Pedrosa LFC, Lima S, et al. Processed and ultra-processed foods are associated with high prevalence of inadequate selenium intake and low prevalence of vitamin B1 and zinc inadequacy in adolescents from public schools in an urban area of northeastern Brazil. PLoS One 2019;14:e0224984.

[31] Louzada ML, Martins AP, Canella DS, Baraldi LG, Levy RB, Claro RM, et al. Impact of ultra-processed foods on micronutrient content in the Brazilian diet. Rev Saude Publica 2015;49:45.

[32] Mani I, Dwarkanath P, Thomas T, Thomas A, Kurpad AV. Maternal fat and fatty acid intake and birth outcomes in a South Indian population. Int J Epidemiol 2016;45:523–31.

[33] Boskabadi H, Maamouri G, Akhondian J, Ashrafzadeh F, Boskabadi A, Faramarzi R, et al. Comparison of birth weights of neonates of mothers receiving vs. not receiving zinc supplement at pregnancy. BMC Pregnancy Childbirth 2021;21:187.

[34] McCullough LE, Miller EE, Mendez MA, Murtha AP, Murphy SK, Hoyo C. Maternal B vitamins: effects on offspring weight and DNA methylation at genomically imprinted domains. Clin Epigenet 2016;8:8.

[35] Lonergan P, Fair T, Corcoran D, Evans AC. Effect of culture environment on gene expression and developmental characteristics in IVF-derived embryos. Theriogenology 2006;65:137–52.

[36] Sinclair KD, Watkins AJ. Parental diet, pregnancy outcomes and offspring health: metabolic determinants in developing oocytes and embryos. Reprod Fertil Dev 2013;26:99–114.

[37] Juul F, Vaidean G, Parekh N. Ultra-processed foods and cardiovascular diseases: potential mechanisms of action. Adv Nutr 2021;12:1673–80.

[38] Maffini MV, Neltner TG, Vogel S. We are what we eat: regulatory gaps in the United States that put our health at risk. PLoS Biol 2017;15:e2003578.

[39] Zinocker MK, Lindseth IA. The western diet-microbiome-host interaction and its role in metabolic disease. Nutrients 2018;10.

[40] Lobionda S, Sittipo P, Kwon HY, Lee YK. The role of gut microbiota in intestinal inflammation with respect to diet and extrinsic stressors. Microorganisms 2019;7.

[41] Santacruz A, Collado MC, Garcia-Valdes L, Segura MT, Martin-Lagos JA, Anjos T, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr 2010;104:83–92.

[42] Kuang YS, Lu JH, Li SH, Li JH, Yuan MY, He JR, et al. Connections between human gut microbiome and gestational diabetes mellitus. GigaScience 2017;6.

[43] Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature 2016;529:212–5.

[44] Hoek J, Koster MPH, Schoenmakers S, Willemsen SP, Koning AHJ, Steegers EAP, et al. Does the father matter? The association between the periconceptional paternal folate status and embryonic growth. Fertil Steril 2019;111:270–9.

[45] Van Dijk MR, Borggreven NV, Willemsen SP, Koning AHJ, Steegers-Theunissen RPM, Koster MPH. Maternal lifestyle impairs embryonic growth: the Rotterdam periconception cohort. Reprod Sci 2018;25:916–22.
[46] van Uitert EM, Exalto N, Burton GJ, Willemsen SP, Koning AH, Eilers PH, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod 2013;28:1753–61.
[47] Macdiarmid J, Blundell J. Assessing dietary intake: who, what and why of under-reporting. Nutr Res Rev 1998;11:231–53.
[48] Gomes CB, Malta MB, Louzada M, Benicio MHD, Barros AJD, Carvalhaes M. Ultra-processed food consumption by pregnant women: the effect of an educational intervention with health Professionals. Matern Child Health J 2019;23:692–703.