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

Ashley J.P. Smit a, Batoul Hojeija a, Melek Rousiana, 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 history:
Received 30 December 2021
Accepted 3 June 2022

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

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 ± 0.074 to 0.008), P = 0.02 and b = -0.016 ± 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.

© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
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 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. 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 dietitian, and a nutritional epidemiologist [20]. 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.
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)/height² (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.

Fig. 1. Selection of study participants. IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.
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 \( 10^{-3} \) to \( 11^{-6} \)) was 46.55 mm (\( \sqrt[3]{\text{CRL}} \) 6.79 mm). The mean EV at 11 weeks was 9.31 cm\(^3\) (\( \sqrt[3]{\text{EV}} \) 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 \( \sqrt[3]{\text{CRL}} \) by 0.041 mm and \( \sqrt[3]{\text{EV}} \) 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 \( \sqrt[3]{\text{CRL}} \) and a 0.012 cm\(^3\) increase of \( \sqrt[3]{\text{EV}} \) (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 \( \sqrt[3]{\text{CRL}} \) 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-
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 micro-nutrients 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
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 cm³ (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

### 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 (cm³) | | | | | | |
| 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 |
| ᵃEmbryonic volume (cm³) | | | | | | |
| 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 |
| ᵃEmbryonic volume (cm³) | | | | | | |
| 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.

**Fig. 2.** Graphical representation of model I 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%.
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. Educational level is considered the strongest indicator of socio-economic status 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].
Monteiro CACG, Levy RB, Moubarac J-C, Jaime P, Martins AP, Canella D, et al.

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

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, de Jonge LL, Hofman A, et al. Ultra-processed foods and cardiovascular disease: the Rotterdam cross-sectional Study. Ultrasound Obstet Gynecol 2017;50:709–16.
[2] Bukowski R, Smith GC, Malone FD, Ball RH, Nyberg DA, Comstock CH, et al. Prediction of aneuploidy and trisomy after early embryonic loss: the Rotterdam Periconceptional cohort Study. Hum Reprod 2010;25:2210–6.
[3] Verkleij-Hagoort AC, de Vries JH, Steegers MP, Lindemans J, Ursem NT, Steegers-Teijlingen RP. Validation of the assessment of folic acid and vitamin B12 intake in women of reproductive age: the method of triads. Eur J Clin Nutr 2007;61:610–5.
[4] Verkleij-Hagoort AC, de Vries JH, Steegers-Teijlingen RP, Twigt J, Pestingervinger, 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.
[5] Alders M. Classification of the population with a foreign background in the Netherlands the measure and misclassification of population the statistical use of ethnic and racial categories in multicultural societies. Paris: Centraal Bureau Statistiek (CBS); 2001.

Standaard onderwijsinleiding, Editie 2020/21 In: (CBS) CBS, editor. Den Haag 2021.

Falcono R, Lyra CO, Morais CMM, Pinheiro LBG, 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 in-adequacy in adolescents from public schools in an urban area of northeastern Brazil. PLoS One 2019;14:e0224984.

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

Manni L, Dwarkanath P, Thomas T, Thomas A, Kupard AP. Maternal fat and fatty acid intake and birth outcomes in a South Indian population. Int J Epidemiol 2016;45:523–31.

Boiskabadi H, Maamouri G, Akhdondian J, Ashrafzadeh F, Boiskabadi A, Faramarzi R, et al. Comparison of birth weights of neonates of mothers receiving vs. not receiving zinc supplement at pregnancy. BMC Pregnancy Childbirth 2012;11:187.

McCullough LE, Miller EE, Mendez MA, Murtha AP, Murphy SK, Hoyo C. Maternal B vitamins: effects on offspring weight and DNA methylation at imprinting sites. Int J Epidemiol 2012;41:129–39.

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

Sinclair KD, Watkins AJ. Parental diet, pregnancy outcomes and offspring health: metabolic determinants in developing oocytes and embryos. Reprod Fertil Dev 2013;25:99–114.

Juul J, Vaidean C, Parekh N. Ultra-processed foods and cardiovascular diseases: potential mechanisms of action. Adv Nutr 2021;12:1673–80.

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 2015:e2003578.

Zinc in the western diet-microbiome-host interaction and its role in metabolic disease. Nutrients 2018;10.

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.

Antucarcu A, Collado MC, Garcia-Valdes L, Segura MT, Martin-Lagos JA, Anjos T, et al. Gut microbiota composition is associated with body weight, body fat and biochemical parameters in pregnant women. Br J Nutr 2015;113:904–9.

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

Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced reductions in the gut microbiota compound over generations. Nature 2015;529:212–7.

Hoek J, Koster MPJ, Schoenmakers S, Willemsen SP, Konig AHJ, Steegers EAP, et al. Does the father matter? The association between the periconceptional paternal folate status and embryonic growth. Fertil Steril 2010;91:723–7.
[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 CJ, 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 CR, 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.