The periconceptional maternal intake of ultra-processed foods and the impact on imaging markers of early utero-placental vascular development: a hospital-based prospective observational cohort study

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Abstract

Objective: To investigate whether periconceptional maternal intake of ultra-processed foods (UPF) impairs first-trimester utero-placental vascular development, and whether macronutrients and dietary patterns substantiate the associations. Design: Prospective observational cohort. Setting: Academic hospital. Population or Sample: Ongoing pregnancies. Methods: 93 women completed a food frequency questionnaire from which we calculated percentage of energy intake from UPF, intake of energy and macronutrients and adherence to dietary patterns. We performed sequential three-dimensional power Doppler ultrasounds of the first-trimester utero-placental vasculature. VOCAL software, Virtual Reality segmentation and a skeletonization algorithm were applied to measure placental volume (PV), utero-placental vascular volume (uPVV) and generate the utero-placental vascular skeleton (uPVS). Absolute vascular morphology was quantified by assigning a morphologic characteristic to each voxel in the uPVS (end-, bifurcation-, crossing- or vessel point) and used to calculate density of vascular branching. Main Outcome Measures: PV, uPVV, uPVS characteristics and density of vascular branching. Results: Fully adjusted linear mixed models showed a 10%/day higher UPF intake was associated with increased first-trimester density of vascular branching (bifurcation points: β=0.465[?]n, 95%CI=0.148;0.782). Higher carbohydrate intake of 10g/day was associated with increased trajectories of uPVV (β=0.017, 95%CI=0.001;0.032) and uPVS (end points (β=0.286, 95%CI=0.062;0.511), bifurcation points (β=0.004, 95%CI=0.003;0.006), vessel points (β=0.772, 95%CI=0.137;1.408). The associations were substantiated by the adherence to the "Snack" dietary pattern. Conclusions: Periconceptional maternal intake of UPF is associated with impaired first-trimester utero-placental vascular development, whereas the intake of carbohydrates and strong adherence to a 'Snack' dietary pattern, is positively associated with first-trimester utero-placental vascular development.

TITLE PAGE

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ABSTRACT

Objective: To investigate whether periconceptional maternal intake of ultra-processed foods (UPF) impairs first-trimester utero-placental vascular development, and whether macronutrients and dietary patterns substantiate the associations.

Design: Prospective observational cohort.

Setting: Academic hospital.

Population or Sample: Ongoing pregnancies.

Methods: 93 women completed a food frequency questionnaire from which we calculated percentage of energy intake from UPF, intake of energy and macronutrients and adherence to dietary patterns. We performed sequential three-dimensional power Doppler ultrasounds of the first-trimester utero-placental vasculature. VOCAL software, Virtual Reality segmentation and a skeletonization algorithm were applied to measure placental volume (PV), utero-placental vascular volume (uPVV) and generate the utero-placental vascular skeleton (uPVS). Absolute vascular morphology was quantified by assigning a morphologic characteristic to each voxel in the uPVS (end-, bifurcation-, crossing- or vessel point) and used to calculate density of vascular branching.

Main Outcome Measures: PV, uPVV, uPVS characteristics and density of vascular branching.

Results: Fully adjusted linear mixed models showed a 10%/day higher UPF intake was associated with increased first-trimester density of vascular branching (bifurcation points: β =0.465[?]n, 95%CI=0.148;0.782). Higher carbohydrate intake of 10g/day was associated with increased trajectories of uPVV (β=0.017, 95%CI=0.001;0.032) and uPVS (end points (β=0.286, 95%CI=0.062;0.511), bifurcation points (β=0.004, 95%CI=0.003;0.006), vessel points (β=0.772, 95%CI=0.137;1.408). The associations were substantiated by the adherence to the "Snack" dietary pattern.

Conclusions: Periconceptional maternal intake of UPF is associated with impaired first-trimester utero-placental vascular development, whereas the intake of carbohydrates and strong adherence to a 'Snack' dietary pattern, is positively associated with first-trimester utero-placental vascular development.

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Keywords :

- Early pregnancy
- Periconceptional nutritional intake
- Ultra-processed foods
- Placental (vascular) development
- 3D power Doppler Ultrasound

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INTRODUCTION

Maternal dietary intake in the periconception period affects fertility, prenatal development and pregnancy outcome with long-lasting consequences for offspring health [1-4]. In the typical Western diet, the intake of fruits, vegetables and whole grains is generally below recommended levels and the proportion of sodium, fats and carbohydrates is relatively high [5]. With the global exponential increase of ultra-processed food (UPF) consumption in the last decade, the nutritional status of women has worsened[4, 6, 7]. Therefore, there is an urgent need to investigate how UPF consumption impacts prenatal development.

UPF, such as soft drinks, instant meals and confectionery, are produced by various processing techniques, and additives are used to produce durable, appetizing, ready-to-eat packaged foods [8]. UPF differ in composition compared to less processed foods as they are generally high in energy and contain higher levels of sodium, sugars and saturated fat [9, 10]. Foods rich in simple carbohydrates and saturated fatty acids are typically associated with a negative impact on overall health and promote obesity[11]. Indeed, several studies have shown a negative effect of high UPF consumption on multiple health domains, including an increased risk of obesity, cardiovascular disease and certain type of cancers [12, 13].

High consumption of UPF in the periconception period is associated with impaired embryonic growth, increased gestational weight gain and higher neonatal body fat [14, 15]. Yet research on associations between maternal UPF consumption and obstetric outcomes are scarce and the underlying mechanisms are not fully understood. As the placenta forms the crucial link between the mother and the growing conceptus and is essential for the delivery of oxygen, energy and nutrients[16, 17], we hypothesize high UPF consumption impairs the utero-placental vascular development with consequences for pregnancy outcomes and prenatal growth[18].

In the present study, our primary aim is to investigate whether periconceptional maternal consumption of UPF impairs first-trimester utero-placental vascular development using recently developed imaging markers [19, 20]. We further explore whether the associations can be substantiated by macronutrient intake and the adherence to specific dietary patterns.

METHODS

2.1 Study design

The VIRTUAL Placenta cohort was embedded in the ongoing prospective Rotterdam Periconception Cohort [21, 22]. Between January 2017 and March 2018, women who were at least 18 years old, carried a singleton pregnancy <10 weeks gestational age (GA), and gave written informed consent were recruited from an

academic hospital. Both naturally conceived pregnancies and pregnancies achieved via in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) were eligible for inclusion. Pregnancies achieved via oocyte donation and miscarriages were excluded from analyses. At enrolment, participants filled out a questionnaire on general characteristics, medical and obstetrical history and lifestyle behaviours, and a Food Frequency Questionnaire (FFQ).

For all participants, two or more study visits were scheduled in the first trimester at 7, 9 and 11 weeks GA during which 3D PD transvaginal ultrasound scans of the whole gestational sac including the placenta and utero-placental vasculature were obtained using the GE Voluson E8 (GE, Zipf, Austria). Standardized ultrasound settings were previously described (quality: max; pulse repetition frequency (PRF): 0.6; wall motion filter (WMF): low1; compound resolution imaging (CRI): off; power Doppler (PD) gain: -8.0) [19]. Ultrasound examinations were performed according to international guidelines on safe use of Doppler ultrasound in the first trimester of pregnancy (ALARA-principle)[23].

At the first study visit, height and weight were measured according to protocol to calculate the body-mass index (BMI). Pregnancy outcomes were collected through a questionnaire filled out by the participant within 1 month after giving birth and complemented with medical delivery records.

2.2 Pregnancy dating

For naturally conceived pregnancies in regular cycles (25-35 days), GA was calculated from the first day of last menstrual period (LMP). In case of unknown LMP or irregular cycle, GA was calculated from Crown-Rump-Length (CRL). If the two methods varied >6 days, the CRL-based GA was assumed the true GA. For fresh IVF/ICSI pregnancies, GA was calculated from oocyte pick-up day +14 days. In case of cryopreserved embryo transfer, GA was calculated from transfer date +19 days.

2.3 Periconceptional maternal dietary intake

We used a standardized semi-quantitative food frequency questionnaire (FFQ) validated for women in the reproductive age [24]. The FFQ consists of 191 food and beverage items and collects detailed information about dietary intake, the frequency of consumption, portion size and method of preparation over the previous four weeks. Energy and nutritional intake of each food item was determined with the Dutch food composition table by Wageningen University.

First, we extracted total daily energy intake (kcal/day) from the FFQ. Using the Goldberg cut-off, designed for an average population as described by Black [25], participants reporting an unrealistically low value of energy-intake were excluded from analysis.

Next, we calculated the percentage energy intake (PEI) of each food item. Then, using the NOVA classification, each food item in the FFQ was categorized as 'unprocessed or minimally processed food', 'processed culinary ingredient', 'processed food' or 'ultra-processed food'[9]. The classification of all items was performed by three researchers independently. In case of discrepancies, items were discussed with a nutritional epidemiologist until consensus was reached. Hereafter, we calculated the percentage of energy intake from ultra-processed food consumption (PEI-UPF, %) for each participant.

To assess the intake of macronutrients, we used the FFQ to calculate the total daily intake of carbohydrates, proteins and fats (g/day). In addition, we calculated the total daily intake of macronutrient compounds, for which we distinguished between mono-/disaccharides and polysaccharides, animal proteins and plant-based proteins, and saturated fatty acids and unsaturated fatty acids (g/day).

To identify distinct dietary patterns, we first reduced all 191 food items into 25 food groups based on similarities in origin and nutrient content, which we adapted from the European Prospective Investigation into Cancer and Nutrition (EPIC) project [26], see Table S1. All food groups were entered in a principal component analysis (PCA) to identify dietary patterns (principal components) based on the degree of reciprocal

correlation between specific food groups. We extracted dietary patterns with eigenvalues >1.0 and used a scree plot to only select dietary patterns that explain a large proportion of the variance in the food groups and exclude the residual components[27]. We provided a nutritional summary per dietary pattern. The PCA automatically calculated a factor loading for each food group, showing the extent to which that specific food group is correlated with each dietary pattern. Finally, participants received a factor score representing their adherence to each dietary pattern.

2.4 Imaging markers of first-trimester utero-placental vascular development

Image quality was scored on a four-point scale ranging between zero (optimal) and three (unusable) based on the presence of artefacts, the ability to distinguish between myometrium and trophoblastic tissue, and completeness of the placenta. Images with a quality score of three were excluded from the analyses.

The placental volume (PV) was measured using VOCAL software according to the previously published validation study [28]. In short, the placental outline and gestational sac contours were repeatedly traced in rotational steps of 15 degrees to calculate total pregnancy volume and gestational sac volume respectively. The gestational sac volume was subtracted from the total pregnancy volume to calculate PV (cm^3) [28].

The utero-placental vascular volume (uPVV) was measured using a virtual reality (VR) desktop system with the V-Scope volume rendering application. First, the threshold for 8-bit Doppler magnitude data was set at a value of 100 and PD artefacts were removed with a virtual eraser. Then, VR segmentation was used to erase the Doppler signal in the embryo, the umbilical cord and the uterine tissue surrounding the placenta (Figure S1A-B). The V-Scope application automatically calculated the volume of all remaining PD voxels to measure the uPVV (cm^3), a volumetric vascular characteristic, as published previously [19] (Figure S1C).

The utero-placental vascular skeleton (uPVS) was generated by applying a skeletonization algorithm to the uPVV segmentations[20]. The skeletonization algorithm repeatedly peels off the outermost layer of voxels from the uPVV, reducing the diameter of the PD signal at each point in the vascular network until one central voxel remains, thereby creating a network-like structure representing the vascular morphology (Figure S1D) [(18)]. Following the construction of the network, the skeletonization algorithm classifies each 26-connected voxel based on the number of neighbouring voxels as endpoint (n) (1 neighbour), bifurcation point (n) (3 neighbours), crossing point (n) (4 neighbours) or as normal vessel point (n) (2 neighbours). Voxels with >4 neighbours are considered an anomaly and excluded from analyses. Further, the algorithm measures total network length and average vascular thickness (mm) (Figure S1E). The 6 uPVS characteristics represent absolute morphologic development of the first-trimester utero-placental vasculature. Also, we calculated ratios of the uPVS end-, bifurcation- and crossing points to the uPVV (n/cm^3) to identify 3 imaging markers to represent the density of vascular branching in the utero-placental vascular volume. Women who had no PV, uPVV or uPVS measurement available were excluded from analysis.

2.5 Statistical analysis

Baseline characteristics were presented as mean with standard deviation. If needed, non-volumetric parameters were transformed using a square root transformation to approximate a normal distribution. For volumetric parameters and ratios a cubic root and natural log transformation were used, respectively.

We used linear mixed models to estimate the association between maternal intake of PEI-UPF, total energy, macronutrients and their compounds and dietary patterns, and imaging markers of utero-placental vascular development, assessed with PV, uPVV and uPVS morphologic and density characteristics. We constructed three different models to explore the potential effects of confounding: model 1 (adjusted for gestational age only); model 2 (model 1 additionally adjusted for maternal age, BMI, parity, conception mode, foetal sex and periconceptional alcohol consumption, smoking and folic acid supplement use); and model 3 (model 2 additionally adjusted for total energy intake). Possible confounders were selected based on literature and discussion amongst authors using a directed acyclic graph.

All analyses were performed using SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) and R (version 4.2.2, R Core Team, Vienna, Austria, 2022). P-values <0.05 were considered statistically significant.

RESULTS

3.1 Study population

The flowchart of participant selection is depicted in Figure S2. A total of 93 women were included in the analyses. Table S2 shows participant characteristics at baseline and periconceptional maternal dietary intake of total energy, PEI-UPF, macronutrients and its compounds.

3.2 Ultra-processed foods and total energy

First, we investigated associations between periconceptional maternal intake of UPF and first-trimester imaging markers of utero-placental vascular development. All models showed higher PEI-UPF is associated with increased density of vascular branching for bifurcation points and crossing points in the uPVS but not with absolute morphologic development, see Table 2. Model 3 shows a statistically significant association between PEI-UPF and density of bifurcation points [β=0.465, 95%CI=0.148;0.782, p-value=0.006].

Next, we investigated associations between the periconceptional maternal intake of total energy (kcal/day) and first-trimester imaging markers of utero-placental vascular development. Total energy intake was negatively associated with density of bifurcation points in the uPVS [β=-0.053, 95%CI=-0.101;-0.004, p-value=0.039], see Table S3. We found no associations with the imaging markers of absolute morphologic utero-placental vascular development.

3.3 Macronutrients

We investigated the intake of separate macronutrients and observed positive associations between the intake of carbohydrates (g/day) and first-trimester development of uPVV [β=0.017, 95%CI=0.001;0.032] and imaging markers of absolute morphologic development: uPVS end points [β=0.286, 95%CI=0.062;0.511], bifurcation points [β=0.004, 95%CI=0.003;0.006], vessel points [β=0.772, 95%CI=0.137;1.408] and total length [β=0.700, 95%CI=0.106;1.295], all p-values<0.05, see Table 3 (only model 3 is shown). No associations were found between carbohydrate intake and imaging markers representing density of vascular branching. Further, we observed positive associations between the periconceptional maternal intake of mono-/disaccharides and first-trimester development of uPVV [β=0.021, 95%CI=0.003;0.039] and imaging markers of absolute morphologic development: uPVS end points [β=0.336, 95%CI=0.072;0.603], bifurcation points [β=0.380, 95%CI=0.057;0.703], crossing points [β=0.257, 95%CI=0.011;0.502], vessel points [β=0.916, 95%CI=0.170;1.662] and total length [β=0.856, 95%CI=0.158;1.554], all p-values<0.05, but not for the intake of polysaccharides, see Table 3. We found no associations between carbohydrate intake and imaging markers representing density of vascular branching.

These analyses were repeated for the total intake of fats and proteins and their respective compounds, see Table S4 (only model 3 shown). We observed no associations between the periconceptional maternal intake of fats, proteins and their compounds and first-trimester imaging markers of utero-placental vascular development in any of our models.

3.4 Dietary patterns

Using the PCA analysis we identified three distinct dietary patterns. The first dietary pattern is associated with higher intake of fresh and processed meats, cereal products, potatoes, eggs, cakes and sauces, and is therefore referred to as a Western dietary pattern, which explains 16.2% of the variance. The second dietary

pattern is associated with higher intake of vegetables, fruits, fish and shellfish, nuts and seeds, vegetable oils and soy- and other plant-based meat-/dairy substitutes. Accordingly, this dietary pattern is referred to as a Mediterranean dietary pattern, which explains 11.7% of the variance. The third dietary pattern is associated with higher intake of sugar and confectionary, savoury snacks, milk and dairy products, soft drinks, fruit/vegetable juices and butter. We refer to this last dietary pattern as a Snack dietary pattern, which explains 8.4% of the variance. A nutritional overview of the dietary patterns is depicted in Table S5.

We investigated associations between periconceptional maternal adherence to the three dietary patterns and imaging markers of utero-placental vascular development. There are no associations between adherence to the Western or Mediterranean dietary patterns and imaging markers of utero-placental vascular development in all three models, see Table 4. Model 2 shows (borderline-) statistically significant positive associations between adherence to the Snack dietary pattern and first-trimester development of uPVV and imaging markers of absolute morphologic development: uPVS end points, bifurcation points, crossing points, vessel points and total length. Model 3 shows similar effect estimates with wide confidence intervals and no statistically significant associations, see Table 4.

DISCUSSION

4.1 Main findings

This study shows a 10%/day higher maternal UPF intake is positively associated with first-trimester density of vascular branching (bifurcation points: $\beta = 0.465$ [?]n, $p = 0.006$). The intake of carbohydrates, in particular of mono-and di-saccharides, is associated with increased absolute morphologic development of the first-trimester utero-placental vasculature, but not with density of vascular branching. We established positive associations between adherence to a Snack dietary pattern and absolute morphologic development of the utero-placental vasculature in model 2, but no clear associations in model 3. A graphic summary of the results is depicted in Figure 4.

4.2 Strengths and Limitations

Strengths of our study are the use of validated FFQ's to study periconceptional nutritional intake, application of the validated Goldberg cut-off to exclude cases with unreliable nutritional intake and the use of EPIC project-based food groups to categorize food items for the identification of the dietary patterns [24-26].

The prospective observational study design allowed us to collect a comprehensive set of patient characteristics, which we used as covariates in advanced statistical models to minimize the effect of confounding bias. Although we cannot exclude the possibility of residual bias from any unknown factors, the direction of the effect estimates is similar in all three models. Therefore we consider it unlikely our findings result from residual confounding.

We used a unique longitudinal data collection of power Doppler ultrasounds in the first trimester of pregnancy to perform validated uPVV measurements (ICC above 0.80 and relative differences of less than 20%) [19] and subsequently generate the uPVS, our imaging markers of utero-placental vascular development[20].

Recruitment from an academic hospital might affect the generalizability of our results. Although our study population contains a relatively high number of IVF-ICSI pregnancies and participants have a higher risk of developing pregnancy complications [21], we believe it is unlikely the direction of the associations will be different in the general population.

We performed multiple statistical analysis, which raises some concern about multiple testing. However, previously uPVV and uPVS characteristics were highly correlated and are inversely correlated with the density of vascular branching[20]. Therefore, the positive correlations between the effect estimates of uPVV

and uPVS characteristics and the inverse correlation with density of vascular branching found in the present study can be interpreted as internal validation.

4.3 Interpretation (in light of other evidence)

4.3.1 Ultra-processed foods

So far, no studies have investigated associations between the consumption of UPF and placental development. High UPF intake is associated with increased total energy intake, an overall unhealthy dietary pattern and an increased risk of obesity [15, 29-31]. UPF intake is negatively associated with embryonic growth and most studies on the effect of UPF-rich diets on birthweight suggests high UPF intake is associated with lower birth weight[14, 32-35]. In the present study, UPF is positively associated with first-trimester density of vascular branching, which has previously been associated with decreased embryonic and foetal growth and lower birth weight percentiles[36, 37]. Associations with UPF persist in model 3, which implies our findings are not solely mediated by higher energy content in UPF. We propose a high UPF exposure induces oxidative stress resulting in aberrant first-trimester vascular development and a compensatory increased density of vascular branching. This way the first-trimester utero-placental vascular development might act as a mediator in the relation between periconceptional maternal intake and pregnancy outcomes. This mechanism is substantiated by previous research on associations between UPF intake, oxidative stress, first-trimester placental development and prenatal growth[21, 22, 38-42].

4.3.2 Carbohydrates

In our study, periconceptional maternal carbohydrate intake, more specifically of mono-and disaccharides, is positively associated with volumetric and absolute morphologic utero-placental vascular development in the first trimester. Carbohydrates seem to affect a different aspect of the utero-placental vascular development than UPF, which likely results from the high heterogeneity of the type and amounts of carbohydrates in UPF-rich foods.

During the first trimester, the placental microenvironment is hypoxic[43]. Rather than on oxidative phosphorylation, the placenta relies on glycolysis for energy production, supported by the rich supply of glucose from the endometrial glands [44]. With increased carbohydrate intake maternal serum glucose concentration rises and subsequently the expression of glucose transporter 1 (GLUT1) increases. GLUT1 is an important cargo molecule of extracellular vesicles that augment decidualization, stimulate angiogenesis, and modulate trophoblast differentiation in the endometrial stroma[45]. The physiological interplay between serum glucose and placental development is substantiated by previous research indicating an insufficient glucose metabolism during gestation results in placental aberrations and foetal growth restriction (FGR)[46-50].

4.3.3 Fats and Proteins

Multiple studies suggest fatty acids to play a regulatory role in the angiogenesis in tumours and in various organs, including the placenta[51-55]. The contradictory pro- and antiangiogenic effects of individual PUFAs might explain why we did not find any associations between the periconceptional intake of fatty acids and utero-placental vascular development [51, 52].

Not much is known about dietary intake of proteins and placental development. Recent studies suggest low-protein diet is associated with placental morphologic disruption and foetal growth restriction and found maternal protein intake positively associated with prenatal growth[56, 57]. Our findings suggest it is unlikely associations between protein intake and prenatal growth are mediated by utero-placental vascular development.

4.3.5 Dietary patterns

The Snack dietary pattern in this study is characterized by excessive consumption of food items with high carbohydrate content. This might explain why we found a (borderline-) statistically significant positive associations between adherence to the high snack pattern and first-trimester density of vascular branching in model 2 similar to the associations with carbohydrates. However, the snack dietary pattern also includes food items with high energetic value but relatively low carbohydrate content, like butter. The heterogeneity in the Snack dietary pattern and the small sample size might explain why the positive associations in model 3 were not statistically significant.

4.4 Implications

The intake of UPF seems to impair first-trimester utero-placental vascular development. These findings are not substantiated by associations with related macronutrients and dietary patterns as increased maternal intake of carbohydrates, within healthy quantities, seems to promote first-trimester utero-placental vascular development. Associations between UPF intake and placental vascular development could reflect the effects of 'ultra-processing' techniques in the food industry, but likely result from a coinciding lack of micronutrients in these food items.[58, 59] UPF-rich diets are associated with deficiencies in folate and vitamin B12, important micronutrients involved in the 1-carbon metabolism. Derangements in the 1-carbon metabolism are associated with hyperhomocysteinemia and oxidative stress, which causes aberrant development of the utero-placental vasculature, associated with placenta-related complications.[60]

CONCLUSION

This study demonstrates associations between periconceptional maternal intake of UPF, carbohydrates and utero-placental vascular development in the first trimester. Interestingly, the periconceptional maternal intake of UPF and carbohydrates and the adherence to the Snack dietary pattern are associated with different aspects of first-trimester development of the utero-placental vasculature. Associations between UPF intake and placental vascular development likely result from a coinciding lack of nutrients in these food items, which induces oxidative stress and causes aberrant development of the utero-placental vasculature. This study's findings substantiate the need of healthy diets and nutritional and lifestyle coaching in periconception and obstetric care. Future research should focus on the impact of periconceptional dietary interventions on first-trimester utero-placental vascular development.

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None.

CONTRIBUTION TO AUTHORSHIP:

E.d.V., A.M., A.K., H.S., R.S.T and L.v.R. were involved with conceptualization and the study design. E.d.V. performed statistical analysis and wrote the first draft of the manuscript. A.M., A.K., R.S.T., and L.v.R. were responsible for reviewing and editing of the manuscript. L.v.R. and R.S.T. had primary responsibility for final content. All authors have read and approved the final manuscript.

DETAILS OF ETHICS APPROVAL:

This study was conducted in accordance with the ethical principles for medical research set out in the Declaration of Helsinki and was approved by the Institutional Review Board of the Erasmus Medical Centre on 2 June 2015 (MEC 2015-494).

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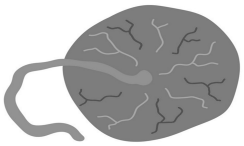

	PV	uPVV	uPVS	Density
Ultra-processed food	✗	✗	✗	+
Total Energy	✗	✗	✗	✗
Carbohydrates	✗	+	+	✗
Fats	✗	✗	✗	✗
Proteins	✗	✗	✗	✗
Western diet	✗	✗	✗	✗
Mediterranean diet	✗	✗	✗	✗
Snack diet	✗	+	+	✗

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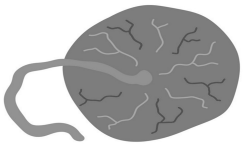

	PV	uPVV	uPVS	Density
Ultra-processed food	×	×	×	+
Total Energy	×	×	×	×
Carbohydrates	×	+	+	×
Fats	×	×	×	×
Proteins	×	×	×	×
Western diet	×	×	×	×
Mediterranean diet	×	×	×	×
Snack diet	×	+	+	×