Dietary patterns and birth outcomes in the ELSPAC Pregnancy Cohort

Authors:

Ondřej Mikeš[1], Anne Lise Brantsæter[2], Helle Katrine Knutsen[2], Liv Elin Torheim[3], Julie Bienertová-Vašků[1], Tomáš Pruša[1,4], Pavel Čupr[1,*], Karel Janák[2], Ladislav Dušek[1,5], Jana Klánová[1]

Affiliations:

[1] RECETOX, Faculty of Science, Masaryk University, Kotlarska 2, Brno, Czech Republic

[2] Division of Climate and Environmental Health, Norwegian Institute of Public Health, PO Box 222 Skoyen, NO-0213 Oslo, Norway

[3] Division of Mental and Physical Health, Norwegian Institute of Public Health, PO Box 222, Skoyen, NO-0213 Oslo, Norway

[4] Department of Public Health, Faculty of Medicine, Masaryk University, Kamenice 753/5, 625 00 Brno, Czech Republic

[5] Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Czech Republic, Kamenice 126/3, 625 00 Brno, Czech Republic

***Corresponding author:** Pavel Čupr[1], RECETOX Centre, Faculty of Science, Masaryk University, Kamenice 753/5, pavilion A29, 625 00 Brno, Czech Republic, Phone number: +420 549 493 511, fax +420 549 492 840, E-mail: pavel.cupr@recetox.muni.cz

Author names for PubMed indexing:

Mikes O, Brantsæter AL, Knutsen HK, Torheim LE, Dobrovolna J, Prusa T, Cupr P, Janak K, Dusek L, Klanova J.

Authorship Declaration:

The work presented here was carried out in collaboration between all authors. OM, ALB, JD, HKK, LET, JK, PČ and JK defined the design and research theme, OM and ALB evaluated the data inputs and analyse the data and co-worked with JD and TP on the results of the analyses, LD. co-evaluated the statistical approaches. All co-authors worked on the discussion and conclusion part of the manuscript. All authors have contributed to, read and approved the final manuscript.

Funding:

This study was supported by Research Infrastructure RECETOX RI (No LM2018121) financed by the Ministry of Education, Youth and Sports of Czech Republic, and Operational Programme Research, Development and Innovation - project CETOCOEN EXCELLENCE (No CZ.02.1.01/0.0/0.0/17_043/0009632) and CETOCOEN Plus (No CZ.02.1.01/0.0/0.0/15_003/0000469). This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 857340. This publication reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains. The authors of this study (ie, not the ELSPAC Scientific Council) are responsible for the content of this publication.

Conflict of Interest: The authors have declared that no competing interests exist.

Running title: Diet in pregnancy and birth outcomes: ELSPAC-CZ

Word count: 3,742

Figures and Tables: Figure 1, Tables 1–3

Keywords: diet, pregnancy, birth weight, longitudinal studies

Abstract

Objectives: The aim of this study was to identify dietary patterns in a Czech pregnancy cohort established in the early post-communist era and investigate associations between dietary patterns, maternal characteristics, and birth outcomes.

Methods: Pregnant women were recruited for the Czech part of the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ). A self-reported questionnaire answered in late pregnancy was used to assess information about the weekly intake of 43 food items. Information about birth outcomes (birth weight, height, ponderal index, head circumference, cephalisation index, gestational length, and Apgar score) was obtained from the National Registry of Newborns. Complete details on diet and birth outcomes were available for 4,320 mother-infant pairs.

Results and Conclusion: The food items were aggregated into 28 variables and used for extraction of two dietary patterns by principal component factor analysis. The patterns were denoted “unhealthy” and “healthy/traditional” based on the food items with the highest factor loadings on each pattern. The “unhealthy” pattern had high positive loadings on meat, processed food, and confectionaries. In contrast, the “healthy/traditional” pattern had high positive loadings on vegetables, dairy, fruits, and wholemeal bread**.** Following adjustment for covariates, we found that high adherence to the unhealthy pattern (expressed as beta for 1 unit increase in pattern score), that is, the higher consumption of less healthy foods, was associated with lower birth weight: -23.8 g (95% CI: -44.4 to -3.2 g) and length: -0.10 cm (95% CI: -0.19 to -0.01 cm) and increased cephalization index: 0.91 µm/g (95% CI: 0.23 to 1.60 µm/g). The “healthy/traditional” pattern was not associated with any birth outcomes. This study supports the recommendation to eat a healthy and balanced diet during pregnancy.

What is already known on this subject

- Maternal diet in pregnancy may affect fetal growth and thus increase the risk of several chronic diseases.
- Dietary pattern analysis is more suitable for describing the overall diet than single nutrient approaches.

What this study adds

- This study is one of few studies of maternal dietary patterns and birth outcomes conducted in a Central European population.
- The study indicated that a dietary pattern reflecting frequent intake of unhealthy foods was associated with reduced birth weight and length.
- To the best of our knowledge, this is the first study to report an association between an unhealthy dietary pattern and higher cephalisation index – a marker of possible negative neurodevelopment.

Introduction

Maternal nutrition is vital for the health, growth, and development of the fetus and the new-born.[1] The regulation of normal human fetal growth involves multiple multidirectional interactions between the mother, fetus and placenta. It should be noted that fetal growth largely depends on endocrine factors, and nutritional deficiency or excess may constitute a basis for significant variations. Among the various hormones involved (thyroid hormones, insulin, multiple variants of growth hormone, leptin, cortisol) a key role is played by Insulin-like growth factor (IGF)-1 and IGF-2, that exert multiple effects in the prenatal as well as postnatal period of growth. For example, placenta secretes IGF-1 throughout gestation and IGF-1 then stimulates the placental transfer of essential nutrients from the mother to the fetus. The importance of IGF-1 is further highlighted by the fact that the fetal circulating IGF-1 increases and cord serum IGF-1 concentrations at term are positively associated with a fetal size and fat mass of the newborn.[2–4] Size at birth is a predictor of children's survival and health later in life.[5] Intrauterine growth restriction is one of the leading risk indicators of childhood neurocognitive development and future cardiovascular disease.[5–7]

The maternal diet can be examined at different levels, e.g. single substances (various nutrients), food items, or dietary patterns. Dietary pattern analysis considers all food consumed and provides insight into dietary behaviour and dietary quality in a population. Contrary to single substances or food item estimates, dietary pattern analysis is less sensitive to inaccuracy and dietary assessment bias and is a more holistic approach for capturing the complex interactions among nutrients and foods.[8–10] Dietary patterns have been identified and examined in relation to fetal growth in many populations.[10–16] Recent reviews of dietary patterns indicate associations of maternal dietary patterns with a variety of birth outcomes[16–18]. However, it has also been suggested that some pregnancy outcomes remain to be investigated[17,18]

Few studies have studied dietary patterns in pregnancy and birth outcomes in a Central European population. The aims of this study were to characterize dietary patterns during pregnancy and examine the associations between these patterns, maternal characteristics, and birth outcomes using data from the Czech Republic ELSPAC birth cohort study in the early post-communist era.

Methods

The ELSPAC-CZ is one of six prospective birth cohort studies initiated by the World Health Organization (WHO) in European countries. In former Czechoslovakia (present-day Czech Republic), all eligible mothers originating from the South Moravian region expected to deliver between 1 March 1991 and 30 June 1992 were selected as the target study population. Mothers were enrolled between the ultrasound examination at the 20 week of pregnancy and the birth. Obstetricians informed eligible mothers about the study and forwarded contact details of women who were interested in the study to the study team. In total, 7,589 mothers were registered. More details and description of the ELSPAC-CZ recruitment and follow-up are summarized in the cohort profile article.[19] Women who consented to participate were asked to answer two questionnaires during pregnancy, one about themselves and one about their pregnancy, including food frequency questions, both answered around gestational week 32.

Ethical approval for the study was obtained from the ELSPAC Law and Ethics committee (Ref. No. ELSPAC/EK/1/2014) and local research ethics committees. Written informed consent was obtained from all study participants.

Mother and child pairs were excluded from this study if they failed to return the questionnaires or if they failed to answer more than five questions (n=2,682). Additional exclusion criteria were still-birth (n=14), multiple birth (n=87), missing birth outcome data (n=239), infant birth weight (n=14), gestational age (n=1) and maternal characteristics (n=74). Participants in the upper and lower percentiles (1^{st} and 99^{th}) of the calculated total energy intake were subsequently excluded to avoid outliers (n=158). The exclusion strategy is shown in Figure 1. Of the 7,589 eligible mothers invited, 4,478 (59.0%) consented to participate and 4,320 (56.9%) mother and child pairs were included in the final study population.

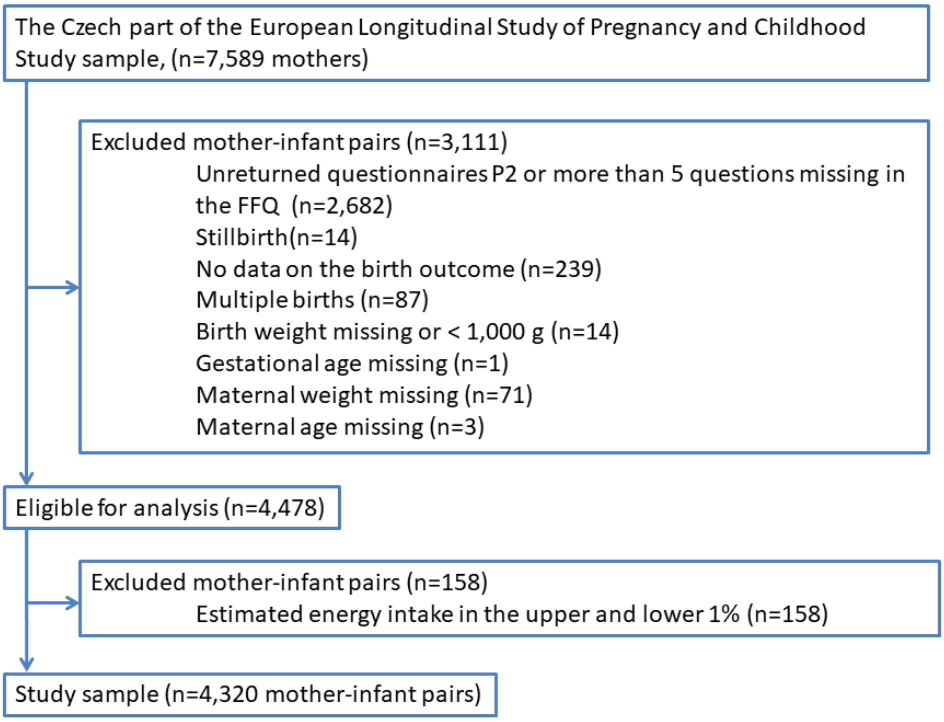

Figure 1 Flow chart illustrating the exclusion criteria of participants in the study.

Information about covariates, including potential confounding variables was obtained from the pregnancy questionnaires. Maternal age was treated as a continuous variable in the analyses except for the descriptive part of the cohort, where five-year age categories were used. Maternal education was divided into three categories according to the highest achieved degree: elementary school, secondary school, and university. Smoking status was categorized as smoker during pregnancy, former smoker (quit smoking before pregnancy), and non-smoker.

Alcohol intake was dichotomized into two groups based on any or no reported consumption of alcohol during pregnancy[20]. Body Mass Index was calculated from self-reported height and weight before pregnancy and categorized as normal for BMI 18.5–24.9 kg/m^2, underweight for BMI <18.5 kg/m^2, overweight for BMI 25–29.9 kg/m^2, and obese for BMI ≥30.0 kg/m^2.[21]

The Food frequency questionnaire (FFQ) part of the questionnaire was sent to participants in the 3rd trimester and included questions about a total of 43 food and drink items. With only minor regional adaptations, the questionnaire was equal to the British Avon Longitudinal Study of Parents and Children (ALSPAC) pregnancy FFQ.[22] The respondents were asked to mark one of five alternative frequency options to describe their habitual intake of each item during pregnancy: never or rarely (calculated as 0.1 times a week), once in 2 weeks (calculated as 0.25 times a week), 1–4 times a week (calculated as 2.5 times a week), 4–7 times a week (calculated as 5.5 times a week), and more than once a day (calculated as ten times a week). This is similar to the calculation done for the ALSPAC FFQ.[23]

At the time of its administration, the FFQ had not been validated in its present form in the population of Czech pregnant women. However, an almost identical FFQ was validated and used in the parallel ALSPAC study.[22] Intake estimates based on the ALSPAC FFQ have been used in a number of studies.[24–27]

We aggregated the 43 food questions into 33 non-overlapping food groups by adding the frequencies for similar food items (eg, three questions about breakfast cereals). For overlapping food items, the highest reported value when merging the responses was used (eg, consumption of eggs and specific question about breakfast egg consumption).

We used principal component factor analysis (PCA) to extract dietary patterns and varimax rotation for interpretation purposes. The reported weekly consumption frequencies of the 33 non-overlapping food groups were used as input variables, and 28 were used in the final analysis, and two dietary patterns extracted. Factor analysis with PCA as the extraction methods reduces the data and constructs new variables as the linear sum of the original variables (called here PCA components or dietary patterns) reflecting the combinations of foods consumed by individual participants. The coefficients defining the PCA components are called factor loadings and represent the correlations between each food variable with the PCA components.[9,10] The factors explains as much of the variation in the original variables as possible. We considered food items with factor loadings with absolute values over 0.3 meaningful for interpreting each dietary pattern.

The number of PCA components retained was based on a scree plot, eigenvalues, and meaningful interpretation of the patterns. The new linear components (dietary patterns) were named according to the nature of the input variables with the highest factor loadings. In this study, the two extracted patterns were those with eigenvalues larger than 2.[10] We used the Bartlett test of sphericity and the Kaiser-Mayer-Olkin (KMO) test to examine the appropriateness of using factor analysis on our data.

Individuals are given factor scores for each of the patterns. Factors scores are standardized and have a mean score of zero and a one unit increase equals one standard deviation (SD). Higher factor scores indicate higher consumption of food items defining that pattern.

Birth outcomes in the study were obtained from the National Registry of Newborns.[28] They included markers of fetal growth (birth weight, birth length, head circumference, ponderal index, cephalization index), gestational length, and Apgar score at 5 min. The mean birth outcomes in the study population were in agreement with those in the general Czech population.[19] The ponderal index was calculated as birth weight (kg) divided by the cubed birth length (m^3). The cephalization index was expressed as head circumference ratio at birth (cm × 10^4) to birth weight (g) and subsequently expressed as µm/g.[29] Birth weight, birth length, head circumference, ponderal, and cephalization indices were used as continuous variables in all analyses except for descriptive statistics, for which they were categorized into quartiles.

Gestational age was calculated using the date of the first day of the last menstrual period since this variable suffered from a minor missing information issue. In case of missing data (n=371), information from the ultrasound examination was used. Gestational age in the current study population ranged from 36 to 44 weeks. It was categorized into five categories of delivery: preterm (before 37 weeks), early term (37–38 weeks), full-term (39–40 weeks), late-term (41–42 weeks), and post-term delivery (over 42 weeks). Small for gestational age (SGA) was calculated below the 10^{th} percentile for each gestational week for both genders. Data for the Apgar score in the 5^{th} minute were divided into five groups as follows; physiological birth (9–10), light asphyxia (7–8), medium asphyxia (4–6), and severe asphyxia (0–3).

All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. The Kolmogorov-Smirnov test and Q-Q plots showed that the dietary patterns scores were not normally distributed. We therefore examined differences between groups for descriptive statistics using the non-parametric Kruskal-Wallis test for continuous variables and the Mann-Whitney test for dichotomous variables, that is, SGA and parity. Crude and adjusted associations between the dietary patterns and the outcomes were estimated using multiple linear regression (betas (β) and 95% confidence intervals (95% CI)) for all birth outcomes except SGA, for which multiple logistic regression was used (odds ratios (OR) and 95% CI). We selected the adjustment variables based on previous knowledge, availability in our study, and bivariate associations. Variables were entered one by one and retained in the final models if their inclusion influenced the associations or if there was a strong theoretical reason for keeping them in the model. Those included in the final models were maternal pre-pregnancy BMI, age, education, smoking status, alcohol consumption, sex of the child, and gestational age. Missing values were excluded pairwise. All independent variables in the regression models were tested for possible multi-collinearity by tolerance, assuming that values >0.60 indicate no collinearity for continuous variables, and >0.35 were acceptable for categorical (dummy) variables. The Durbin-Watson statistic was used to estimate the independence of the data points. For all models, we tested the assumptions of linearity and homoscedasticity by graphically plotting predicted values against standardised residuals. We also applied Cook's distance and delta–beta plots to check the influence of outliers on the models. No outliers were removed. All analyses were carried out using IBM SPSS Statistics for Windows software, Version 27.0.

Results

The mean (SD) age of mothers was 25 (5) years, and the mean pre-pregnancy BMI was 22.0 (3.3) kg/m^2. Most of the mothers were multiparous (61%). 7.5% of mothers had completed elementary school, 75% had completed secondary education, and 17.5% had obtained a university degree. Smoking during pregnancy was reported by 8.5% of the mothers, 33.3% were former smokers, while 56.8% had never smoked. Alcohol consumption during pregnancy was reported by 14.2% of the mothers. The mean infant birth weight was 3,311 (474) g, the mean birth length was 50.3 (2.2) cm, and the mean head circumference was 34.6 (1.4) cm. The prevalence of preterm delivery was 4.1%. Maternal attributes did not differ between participants who provided dietary information and those who did not (p>0.05) while the child characteristics differed between these two groups. Children born to mothers who did not provide dietary information had lower birth weight (mean difference 60 g; 95% CI: 37, 83 g), lower birth length (mean difference 0.27 cm; 95% CI: 0.15, 0.37 cm), and smaller head circumference (mean difference 0.13 cm; 95% CI: 0.06, 0.20 cm) than children born to mothers who provided dietary information.

Two dietary patterns were extracted from the dietary data using principal component factor analysis. The first principal component explained 13.0% (eigenvalue 4.5) and the second one 12.3% (eigenvalue 2.6) of total food intake variation. The frequency of fried food consumption was included in the PCA but was not used in the energy intake calculation, because it reflected the frequency of this culinary treatment but not the consumption of specific food items. Frequencies of alcoholic beverages, coffee, and tea were excluded from the analysis as they had low factor loadings on both of the extracted dietary patterns.[30] Pulses and eggs had similar cross-loadings on both patterns (0.317 and 0.378; 0.308 and 0.377 respectively) and were therefore excluded from the PCA; the final number of variables thus considered in the PCA was 28. Bartlett's test of sphericity was significant ($p<0.001$), and the KMO test returned a value of 0.834. We labelled the two different extracted dietary patterns as “unhealthy” and “healthy/traditional” to reflect the quality of food items with the highest loadings on the respective pattern. The unhealthy pattern had high positive loadings on offal (liver, kidney, heart), fried foods (meat, fish, bacon, ham, eggs), processed foods (eg, pizza, fish products), processed meat (sausages, smoked meat, hamburgers), all meat and confectionary foods (eg, sugary drinks, cakes, chocolate, and sweets). In contrast, the healthy/traditional pattern had the highest positive loadings on for example, vegetables, dairy, fruits, and wholemeal bread (Table 1). The “traditional” label was added to indicate the high loadings of milk and dairy products and moderate loadings of juices and white bread in this pattern perceived by citizens as healthy in the time they have received the questionnaire.

Table 1 Structure of the two dietary patterns extracted by principal components factor analysis in 4,320 pregnant women defined by factor loadings for food items with factor loading higher than 0.3

	Component	
	Unhealthy	**Healthy/Traditional**
Fried potatoes	**0.68**	
Offal	**0.65**	
Fish and products	**0.61**	
Pizza	**0.59**	
Donuts and omelettes	**0.55**	
Fried food	**0.47**	
Poultry	**0.47**	
Cake and pies	**0.42**	
Processed meat	**0.41**	
Pasta	**0.40**	
Cola drinks	**0.38**	
Wafers	**0.37**	
Chocolate and sweets	**0.36**	
Red meat	**0.32**	
Sweet drinks	**0.30**	
Root vegetables		**0.62**
Cheese		**0.57**
Milk		**0.57**
Dairy products		**0.57**
Fresh fruits		**0.56**
Leafy vegetables		**0.56**
Salads		**0.47**
Wholemeal bread		**0.43**
Boiled potatoes		**0.42**
Juice		**0.41**
Herbal tea		**0.37**
Honey		**0.36**
White bread		**0.35**

All factor food items load on both patterns, but for only loadings higher than 0.30 are shown. The two patterns explained 25% of the total variance in the reported food frequency intakes.

Adherence to the unhealthy and healthy/traditional patterns differed with maternal characteristics. Underweight mothers scored highest on the unhealthy pattern while obese mothers had the lowest healthy/traditional pattern scores. Women in the older age groups and mothers who were multiparous had higher scores on the healthy/traditional and lower scores on the unhealthy pattern than young women and first-time mothers. Higher education was associated with higher scores on the healthy/traditional and lower scores on the unhealthy pattern. Similar trends were observed for smoking and alcohol consumption, with smokers and alcohol consumers having higher scores on the unhealthy pattern and vice versa (Table 2).

Table 2 Dietary pattern scores* by participant characteristics (n=4,320)

	All N (%)	Unhealthy pattern score Median (IQR)	Healthy/Traditional pattern score Median (IQR)
Maternal BMI			
<18.5 kg/m^2	334 (7.7)	-0.10 (0.87)	0.02 (1.22)
18.5–24.9 kg/m^2	3,213 (74.4)	-0.17 (0.75)	0.05 (1.22)
25–29.9 kg/m^2	442 (10.2)	-0.24 (0.70)	-0.14 (1.20)
≥30 kg/m^2	129 (3.0)	-0.22 (0.75)	-0.17 (1.16)
Missing information	202 (4.7)	0.05 (0.82)	-0.19 (1.35)
p-trend		<0.001	<0.001
Maternal age			
<20 years	779 (18.0)	-0.03 (0.87)	-0.21 (1.29)
20-24.9 years	1,462 (33.8)	-0.13 (0.77)	-0.07 (1.23)
25-29.9 years	1,345 (31.1)	-0.25 (0.68)	0.13 (1.19)
30-34.9 years	503 (11.6)	-0.26 (0.77)	0.19 (1.16)
≥35 years	231 (5.3)	-0.18 (0.71)	0.10 (1.20)
p-trend		<0.001	<0.001
Parity			
Primiparous	1,675 (38.8)	-0.13 (0.79)	-0.08 (1.22)
Multiparous	2,645 (61.2)	-0.18 (0.74)	0.06 (1.25)
p-trend		0.003	<0.001
Maternal education			
Elementary	323 (7.5)	0.07 (1.00)	-0.23 (1.24)
Secondary school	3,223 (74.6)	-0.15 (0.78)	-0.05 (1.23)
University	752 (17.4)	-0.30 (0.63)	0.29 (1.18)
Missing information	22 (0.5)	-0.23 (0.80)	0.23 (0.95)
p-trend		<0.001	<0.001

Smoking status			
Smoker	369 (8.5)	0.06 (0.87)	-0.34 (1.17)
Former smoker	1,439 (33.3)	-0.11 (0.78)	-0.06 (1.25)
Non-smoker	2,452 (56.8)	-0.22 (0.73)	0.10 (1.21)
Missing information	60 (1.4)	-0.14 (0.92)	0.01 (1.37)
p-trend		<0.001	<0.001
Alcohol in pregnancy			
No	3,468 (80.3)	-0.18 (0.76)	0.03 (1.25)
Yes	612 (14.2)	-0.11 (0.72)	-0.02 (1.14)
Missing information	240 (5.5)	-0.13 (0.92)	-0.15 (1.15)
p-trend		0.029	0.280

p-trend by non-parametric tests Kruskal-Wallis (Mann-Whitney for parity and alcohol consumption).

* Overall mean factor score for each pattern is zero. Positive factor scores indicate higher adherence to a pattern and negative scores indicate lower adherence.

In the unadjusted analyses of dietary patterns and birth outcomes (Table 3) the unhealthy dietary pattern was significantly associated with birth weight, length, cephalization index, and SGA. In the adjusted analysis, associations with the unhealthy pattern remained significant for birth weight, birth length, and cephalisation index. For infant birth weight, a one-unit increase in the unhealthy pattern score resulted in a mean birth weight reduction of -23.8 g (95% CI: -44.4 to -3.3 g, p=0.023). For birth length, a one-unit increase in the unhealthy pattern score was associated with a mean reduction of -0.10 cm (95% CI: -0.19 to -0.01 cm, p=0.040). For the cephalisation index, a one-unit increase in the unhealthy pattern score resulted in a mean increase of 0.91 µm/g (95% CI: 0.23 to 1.60 µm/g, p=0.009). The healthy/traditional pattern was not associated with birth outcomes.

Table 3 Crude and adjusted associations between dietary pattern scores and birth outcomes Beta (95% confidence intervals) is the change in birth outcome by 1 SD increase in the pattern score*

	Unhealthy pattern		Healthy Traditional pattern	
	β (95% CI)	p-value	β (95% CI)	p-value
Birth weight (g)				
Crude	-40 (-60, -20)	<0.001	64 (-92, 22)	0.423
Adjusted	**-24 (-44, -33)**	**0.023**	0.68 (-15, 17)	0.934
Birth length (cm)				
Crude	-0.17 (-0.26, -0.08)	<0.001	0.02 (-0.06, 0.09)	0.654
Adjusted	**-0.10 (-0.19, -0.01)**	**0.040**	-0.01 (-0.09, 0.06)	0.734
Ponderal index (g/cm^3)				
Crude	-0.06 (-0.16, 0.04)	0.225	0.03 (-0.04, 0.11)	0.378
Adjusted	-0.04 (-0.14, 0.07)	0.486	0.03 (-0.05, 0.11)	0.458
Head circumference (cm)				
Crude	-0.02 (-0.08, 0.05)	0.620	-0.02 (-0.07, 0.03)	0.396
Adjusted	0.01 (-0.05, 0.08)	0.693	-0.02 (-0.07, 0.03)	0.334
Cephalization index (μm/g)				
Crude	1.40 (0.79, 2.10)	<0.001	-0.36 (-0.87, 0.15)	0.167
Adjusted	**0.91 (0.23, 1.60)**	**0.009**	-0.14 (-0.67, 0.39)	0.604
Gestational age (weeks)				
Crude	-0.004 (-0.074, 0.066)	0.913	-0.006 (-0.060, 0.049)	0.836
Adjusted	-0.102 (-0.275, 0.071)	0.247	0.338 (-0.189, 0.422)	0.453
Apgar score				
Crude	0.008 (-0.056, 0.073)	0.799	0.021 (-0.029, 0.071)	0.414
Adjusted	0.016 (-0.052, 0.084)	0.650	0.014 (-0.039, 0.066)	0.611
Small for gestational age	OR (95% CI)		OR (95% CI)	
Crude	1.14 (1.01, 1.28)	0.030	0.97 (0.88, 1.07)	0.576
Adjusted	1.04 (0.91, 1.19)	0.590	1.01 (0.90, 1.13)	0.850

*All birth outcomes modelled by linear regression except SGA (logistic regression) for which the effect estimate is OR (95% CI). The dietary patterns modelled together in all models. Adjusted models were additionally adjusted for maternal age, prepregnant BMI, education, gestational age (not for gestational age and SGA), alcohol consumption, sex of the child and smoking status. Significant results ($p<0.05$) in the adjusted analyses are shown in bold.

Discussion

Two major dietary patterns were extracted, one reflecting the regular consumption of items not recommended (eg, fried food, confectionaries) by the Dietary Guidelines in the Czech Republic[31] and the other reflecting conscientious and recommended eating behaviour with high intakes of vegetables, milk, dairy products, fruits, and wholemeal bread. Maternal characteristics, particularly education and smoking, were significantly associated with pattern adherence. This observation is in agreement with several studies linking low educational attainment and smoking to higher scores on processed, energy-dense dietary patterns and lower scores on healthy or prudent patterns.[10,23,32] It is important to note that FFQ collection took place in the time of a transition towards better health in Central and Eastern Europe at the beginning of the 1990s after the end of the communist era. One of the factors influencing this phenomenon was a change in previous dietary behaviour (high fat and low vegetable and fruit intake) as a wider variety of fruits and vegetables became available on the market.[33]

In our study, fish and fish products had high factor loadings on the unhealthy dietary pattern. This finding may seem unexpected; however, at the time of dietary assessment, fish and fish products available on the Czech market were frequently commercially processed items such as canned, smoked, breaded, and marinated fish, that is, items which are not considered to be particularly healthy.

Three birth outcomes remained significant in the adjusted analyses (birth weight, birth length, and cephalisation index), all of which were related to the unhealthy pattern. While this observational study of the quality of maternal food intake and dietary patterns does not allow us to establish causality, food is known to affect the maternal metabolism as well as birth weight.[10] For the unhealthy pattern, a multicentre European study found that intakes of similar foods high in acrylamide during pregnancy was associated with lower birth weight and smaller head circumference.[34] High loading on similar food items (red and white meat, fatty and lean fish, low-fat dairy, but opposite loading for high-fat cheese) was also identified in a "dioxin-diet" score and associated with low birth weight in a five country population study.[35]

A previous dietary pattern study reported that high adherence to a pattern characterized by food items similar to commodities with high factor loadings on our unhealthy pattern resulted in reduced birth weight and increased risk of SGA in the Danish National Birth Cohort.[13] While we found no significant association with SGA in this study, a case-control study of 1,714 mother-infant pairs in New Zealand[14] in the late 1990s found that a high traditional diet score in early pregnancy (though not in late pregnancy) was associated with a lower risk of SGA. The Generation R Study, focused on the Mediterranean diet (MD), concluded that low adherence to MD in early pregnancy seems to be associated with lower birth weight.[36] A recent meta-analysis of dietary patterns and birth outcomes concluded that unhealthy dietary patterns, characterized very similarly to our study (processed meat, refined grains, foods with high saturated fat or sugar) were also associated with lower birth weight.[16]

In the current study, we found a significant association between the unhealthy pattern and reduced birth length, which is in agreement with the results from a retrospective, cross-sectional study of preconceptional dietary patterns and birth outcomes in 309 mother-infant pairs in Australia. That study showed that high adherence to a pattern denoted as "high fat/sugar/takeaway" was associated with reduced birth length.[37] Rodríguez-Bernal et al. also reported a positive association between diet quality and birth length with diet quality assessed using the Alternate Healthy Eating Index. Children born to mothers in the highest quintile were 0.47 cm longer than those in the lowest quintile.[38] However, several studies did not find any associations between maternal diet and birth length.[39,40]

In the current study, we observed that the cephalization index, a possible negative neurodevelopment marker, was positively associated with the unhealthy dietary pattern. Few studies have reported associations between maternal diet and the cephalization index. We are aware of only two studies, which both specifically focused on exposure to polyaromatic hydrocarbons, which are chemicals that originate from grilled or fried food [29,41]; to the best of our knowledge, this is the first study to link the cephalization index with maternal dietary patterns.

The two dietary patterns identified in this study reflect opposing dietary qualities and aspects, typically found in most populations and labelled as ‘prudent’ and ‘western’ patterns.[8,42–44] Patterns with similar overall food composition also likely apply to present-day Czech society, although, to the best of our knowledge, no dietary pattern analysis for the contemporary Czech population has been carried.

The strengths of this study include the prospective cohort study design and a large number of participants. Participants were unaware of the pregnancy outcomes when they completed the questionnaires, and their reporting was not affected by the outcome. The cohort represents a highly homogenous urban population with low genetic diversity, which may be beneficial in terms of “unmasking” possible effects. Furthermore, we were able to adjust for important confounders such as BMI, gestational age, smoking, education, and alcohol consumption.

Limitations of this study are mainly associated with the use of an FFQ and include the possibility of misreporting of food intake and inaccurate assessment of some food frequencies, mainly with respect to seasonally consumed food items. Furthermore, it may be particularly challenging to recall and report the average frequency of intake during pregnancy as most women experience nausea and other pregnancy-related changes affecting food preferences. We could not adjust for some potentially important confounders such as maternal dietary supplement use and pre-pregnancy dietary habits. The FFQ has not been validated in the Czech Republic, but the nearly identical questionnaire was validated in the UK; notwithstanding, some limitations may remain due to regional differences. The participation rate in the current study was close to 60%, but bias due to self-selection is a concern in all observational studies. Likewise, self-reported data and missing information may introduce bias. Several variables related to maternal sociodemographic and lifestyle variables had some missing data, but the highest proportion of missing was 5.5% in alcohol consumption variable. Children born to mothers who did not provide dietary data had slightly lower mean birth weight, length, and head circumference than those included in the current study. This study examined several birth outcomes, and most of the associations would not remain significant if adjusted for multiple comparisons. Therefore, the results should be interpreted with caution. Finally, although we adjusted for available confounders, residual confounding may still exist. This study is observational, and no causal implications can be inferred.

In conclusion, this study indicates that the dietary qualities of the maternal diet may affect birth outcomes. High adherence to a dietary pattern characterized by energy dense, unhealthy food items, which are not in agreement with current dietary recommendations, was associated with reduced birth weight and length and increased cephalization index. To the best of our knowledge, this study is the first to report a significant association between an unhealthy dietary pattern and an increase in the cephalization index. This study supports newer dietary recommendations which suggest higher intakes of healthy foods and restricting the intakes of unhealthy foods and shows that maternal diet in pregnancy is an important modifiable risk factor with respect to several adverse birth outcomes.

Reference List

1. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. *Epidemiol Rev*. 2010;32. doi:10.1093/EPIREV/MXQ001
2. Baumann MU, Schneider H, Malek A, et al. Regulation of human trophoblast GLUT1 glucose transporter by Insulin-Like Growth Factor I (IGF-I). *PLoS One*. 2014;9(8). doi:10.1371/journal.pone.0106037
3. Hiden U, Glitzner E, Hartmann M, Desoye G. Insulin and the IGF system in the human placenta of normal and diabetic pregnancies. In: *Journal of Anatomy*. Vol 215. J Anat; 2009:60-68. doi:10.1111/j.1469-7580.2008.01035.x
4. Street ME, Seghini P, Ziveri MA, et al. Interleukin-6 and insulin-like growth factor system relationships and differences in the human placenta and fetus from the 35th

week of gestation. *Growth Horm IGF Res*. 2006;16(5-6):365-372. doi:10.1016/j.ghir.2006.09.007

5. Leitner Y, Fattal-Valevski A, Geva R, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. *J Child Neurol*. 2007;22(5):580-587. doi:10.1177/0883073807302605
6. Shenkin SD, Starr JM, Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. *Psychol Bull*. 2004;130(6):989-1013. doi:10.1037/0033-2909.130.6.989
7. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG*. 2015;122(8):1062-1072. doi:10.1111/1471-0528.13435
8. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13(1):3-9. http://www.ncbi.nlm.nih.gov/pubmed/11790957
9. Newby PK, Muller D, Tucker KL. Associations of empirically derived eating patterns with plasma lipid biomarkers: A comparison of factor and cluster analysis methods. *Am J Clin Nutr*. 2004;80(3):759-767.
10. Englund-Ögge L, Brantsæter AL, Sengpiel V, et al. Maternal dietary patterns and preterm delivery : results from large prospective cohort study. *BMJ Br Med J*. 2014;1446(March):1-18. doi:10.1136/bmj.g1446
11. Bouwland-Both MI, Steegers-Theunissen RPM, Vujkovic M, et al. A periconceptional energy-rich dietary pattern is associated with early fetal growth: the Generation R study. *BJOG*. 2013;120(4):435-445. doi:10.1111/1471-0528.12086
12. Colon-Ramos U, Racette SB, Ganiban J, et al. Association between dietary patterns during pregnancy and birth size measures in a diverse population in Southern US. *Nutrients*. 2015;7(2):1318-1332. doi:10.3390/nu7021318
13. Knudsen VK, Orozova-Bekkevold IM, Mikkelsen TB, Wolff S, Olsen SF. Major dietary patterns in pregnancy and fetal growth. *Eur J Clin Nutr*. 2008;62(4):463-470. doi:10.1038/sj.ejcn.1602745
14. Thompson JMD, Wall C, Becroft DMO, Robinson E, Wild CJ, Mitchell EA. Maternal dietary patterns in pregnancy and the association with small-for-gestational-age infants. *Br J Nutr*. 2010;103(11):1665-1673. doi:10.1017/S0007114509993606
15. Grulichová M, Zlámal F, Andrýsková L, Švancara J, Pikhart H, Bienertová-Vašků J. Dietary pattern longitudinality during 8 years in children: results from the European Longitudinal Study of Pregnancy and Childhood (ELSPAC-CZ). *Public Health Nutr*. Published online 2020:1-7. doi:10.1017/S1368980020001056
16. Chia AR, Chen LW, Lai JS, et al. Maternal Dietary Patterns and Birth Outcomes: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2019;10(4):685-695. doi:10.1093/advances/nmy123
17. Chen X, Zhao D, Mao X, Xia Y, Baker PN, Zhang H. Maternal dietary patterns and pregnancy outcome. *Nutrients*. 2016;8(6):1-26. doi:10.3390/nu8060351
18. Raghavan R, Dreibelbis C, Kingshipp BL, et al. Dietary patterns before and during pregnancy and birth outcomes: a systematic review. *Am J Clin Nutr*. 2019;109(Supplement_1):729S-756S. doi:10.1093/ajcn/nqy353
19. Piler P, Kandrnal V, Kukla L, et al. Cohort profile: European Longitudinal Study of

Pregnancy and Childhood (ELSPAC) in the Czech Republic. *Int J Epidemiol*. Published online 2016. doi:10.1093/ije/dyw091
20. Lu MS, Chen QZ, He JR, et al. Maternal dietary patterns and fetal growth: A large prospective cohort study in China. *Nutrients*. 2016;8(5). doi:10.3390/nu8050257
21. WHO. Body mass index - BMI. Published January 7, 2016. Accessed January 7, 2016. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi
22. Rogers I, Emmett P, Team AS. Diet during pregnancy in a population of pregnant women in South West England. *Eur J Clin Nutr*. 1998;52:246-250.
23. Northstone K, Emmett PM, Rogers I. Dietary patterns in pregnancy and associations with nutrient intakes. *Br J Nutr*. 2008;99(2):406-415. doi:10.1017/S0007114507803977
24. Emmett P. Dietary assessment in the Avon Longitudinal Study of Parents and Children. *Eur J Clin Nutr*. 2009;63 Suppl 1:S38-S44. doi:10.1038/ejcn.2008.63
25. Smith ADAC, Emmett PM, Newby PK, Northstone K. A comparison of dietary patterns derived by cluster and principal components analysis in a UK cohort of children. *Eur J Clin Nutr*. 2011;65(10):1102-1109. doi:10.1038/ejcn.2011.96
26. Emmett PM, Jones LR, Golding J. Pregnancy diet and associated outcomes in the Avon Longitudinal Study of Parents and Children. *Nutr Rev*. 2015;73 Suppl 3(Suppl 3):154-174. doi:10.1093/nutrit/nuv053
27. Feinstein L, Sabates R, Sorhaindo A, et al. Dietary patterns related to attainment in school: The importance of early eating patterns. *J Epidemiol Community Health*. 2008;62(8):734-739. doi:10.1136/jech.2007.068213
28. IHIS. *National Registry of Newborns (NRNAR)*.; 2016. https://www.uzis.cz/index-en.php
29. Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. *Environ Health Perspect*. 2008;116(5):658-665. doi:10.1289/ehp.10958
30. Smith ADAC, Emmett PM, Newby PK, Northstone K. Dietary patterns obtained through principal components analysis: the effect of input variable quantification. *Br J Nutr*. Published online 2012:1-11. doi:10.1017/S0007114512003868
31. Brázdová Z, Fiala J. *Dietary Guidelines in the Czech Republic*. MU LF; 1998. Accessed January 21, 2016. http://www.muni.cz/research/publications/80-210-1956-5/679
32. Cucó G, Fernández-Ballart J, Sala J, et al. Dietary patterns and associated lifestyles in preconception, pregnancy and postpartum. *Eur J Clin Nutr*. 2006;60(3):364-371. doi:10.1038/sj.ejcn.1602324
33. Safaei J. Post-Communist health transitions in Central and Eastern Europe. *Econ Res Int*. 2012;2012:1-10. doi:10.1155/2012/137412
34. Pedersen M, Von Stedingk H, Botsivali M, et al. Birth weight, head circumference, and prenatal exposure to acrylamide from maternal diet: The European prospective mother-child study (NewGeneris). *Environ Health Perspect*. 2012;120(12):1739-1745. doi:10.1289/ehp.1205327
35. Papadopoulou E, Kogevinas M, Botsivali M, et al. Maternal diet, prenatal exposure to

dioxin-like compounds and birth outcomes in a European prospective mother-child study (NewGeneris). *Sci Total Environ*. 2014;484(1):121-128. doi:10.1016/j.scitotenv.2014.03.047

36. Timmermans S, Steegers-Theunissen RP, Vujkovic M, et al. The Mediterranean diet and fetal size parameters: The Generation R Study. *Br J Nutr*. 2012;108(8):1399-1409. doi:10.1017/S000711451100691X

37. Grieger JA, Grzeskowiak LE, Clifton VL. Preconception Dietary Patterns in Human Pregnancies Are Associated with Preterm. *J Nutr*. 2014;(8):1-6. doi:10.3945/jn.114.190686.The

38. Rodríguez-Bernal CL, Rebagliato M, Iñiguez C, et al. Diet quality in early pregnancy and its effects on fetal growth outcomes: the Infancia y Medio Ambiente (Childhood and Environment) Mother and Child Cohort Study in Spain. *Am J Clin Nutr*. 2010;91(6):1659-1666. doi:10.3945/ajcn.2009.28866

39. Shapiro ALB, Kaar JL, Crume TL, et al. Maternal diet quality in pregnancy and neonatal adiposity: The Healthy Start Study. *Int J Obes*. 2016;40(7):1056-1062. doi:10.1038/ijo.2016.79

40. Okubo H, Miyake Y, Sasaki S, Tanaka K, Murakami K, Hirota Y. Maternal dietary patterns in pregnancy and fetal growth in Japan: the Osaka Maternal and Child Health Study. *Br J Nutr*. 2012;107(10):1526-1533. doi:10.1017/S0007114511004636

41. Polańska K, Dettbarn G, Jurewicz J, et al. Effect of prenatal polycyclic aromatic hydrocarbons exposure on birth outcomes: the Polish mother and child cohort study. *Biomed Res Int*. 2014;2014:408939. doi:10.1155/2014/408939

42. Appel LJ. Dietary Patterns and Longevity: Expanding the Blue Zones. *Circulation*. 2008;118(3):214-215. doi:10.1161/CIRCULATIONAHA.108.788497

43. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary Patterns and Risk for Type 2 Diabetes Mellitus in U.S. Men. *Ann Intern Med*. 2002;136(3):201. doi:10.7326/0003-4819-136-3-200202050-00008

44. Montonen J, Knekt P, Härkänen T, et al. Dietary patterns and the incidence of type 2 diabetes. *Am J Epidemiol*. 2005;161(3):219-227. doi:10.1093/aje/kwi039