Association between a pro-inflammatory dietary pattern during pregnancy and type 1 diabetes risk in offspring: prospective cohort study

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ABSTRACT

Background Immune-mediated processes leading to childhood type 1 diabetes may begin in fetal life. We hypothesised that a maternal inflammatory diet during pregnancy increases offspring risk of type 1 diabetes.

Methods The Danish National Birth Cohort (DNBC) was recruited during 1996–2002. Maternal Empirical Dietary Inflammatory Index score (EDII-score) was calculated from a comprehensive 360-item self-administered food frequency questionnaire (FFQ) completed around gestation week 25. Information on covariates was derived from maternal interviews. Information on type 1 diabetes diagnosis in the offspring was obtained through registry linkage to the Danish Registry of Childhood and Adolescent Diabetes. The association between the EDII score during pregnancy and the child's subsequent type 1 diabetes risk was examined by Cox regression.

Results We included singleton live births and excluded confirmed maternal type 1 diabetes or type 2 diabetes diagnoses prior to pregnancy, and implausibly high/low energy intake. In 67 701 mother-child pairs eligible for analyses, 281 children were diagnosed with type 1 diabetes. Mean EDII score was −0.1 with a range from −5.3 (anti-inflammatory) to 4.1 (pro-inflammatory) with a standard deviation (SD) of 0.98. Maternal EDII score was significantly associated with type 1 diabetes risk in offspring in both unadjusted and covariate-adjusted analyses. After adjustment for covariates, the incidence rate of type 1 diabetes in offspring increased with increasing EDII score by 16% (95% confidence interval (CI) 2% to 32%) per one unit increase in the EDII score.

Conclusion A maternal diet high in pro-inflammatory foods during pregnancy is associated with increased risk of developing type 1 diabetes in the offspring.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type 1 diabetes is an autoimmune disease resulting from an immune-mediated destruction of insulin-producing β-cells in the pancreas.

⇒ Diet is a modifiable factor influencing low-grade inflammation, with dietary inflammatory scores being linked to an increased risk of cardiometabolic diseases.

⇒ Immune-mediated destruction of insulin-producing β-cells in the pancreas may begin in fetal life and could be affected by the inflammatory properties of the maternal diet during pregnancy.

WHAT THIS STUDY ADDS

⇒ In our prospective population-based study involving 67 701 mother-child pairs, we observed that 1 SD increase in an index reflecting the pro-inflammatory potential of the diet during pregnancy was associated with a 16% (95% CI 2% to 32%) increase in the incidence rate of type 1 diabetes in the children.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We found that three specific lifestyle factors in mid-pregnancy independently predicted the child's risk of type 1 diabetes. Our data suggest that type 1 diabetes might be one of those diseases, the susceptibility of which can be affected by maternal external exposures – we may call it 'fetal programming.'

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INTRODUCTION

Type 1 diabetes is an autoimmune disease characterised by the immune-mediated destruction of insulin-producing β-cells in the pancreas, necessitating lifelong insulin treatment.[1] The disease results from both genetic and environmental factors, with its incidence being highest in countries with a Western lifestyle.[2] Notably, the incidence of type 1 diabetes has been increasing by an average of 3–4% annually, strongly suggesting the significant role of environmental factors.[3] Given that an autoimmune response targeting insulin-producing β-cells is central to type one diabetes (2) external factors influencing the immune system and inflammatory responses are critical areas for research. Since the immune system develops and establishes in early life and to a certain degree antenatally, there is a strong rationale for exploring the aetiological role of maternal diet during pregnancy with specific focus on dietary components with inflammation- and immuno-regulatory

properties. These components may alter the immune cell reactivity and inflammatory state of the mother during pregnancy influencing the progression of the pregnancy and the child's development.

While inflammation typically arises as an acute response to stressors such as trauma or infection, low-grade inflammation is increasingly recognised as a risk factor for several chronic diseases. Furthermore, low-grade inflammation emerges as a potential target for disease prevention due to its association with lifestyle factors. A growing body of evidence suggests that diet is a modifiable determinant of low-grade systemic inflammation, as measured by inflammatory markers:[4–6] for example, processed meats have been linked to higher levels of pro-inflammatory markers.[7] Conversely, certain fruits and vegetables have been associated with lower levels of inflammation and associated diseases.[8]

Several validated indexes have been developed to quantify and reflect the overall inflammatory potential of diet by correlating the frequency of consumption of food groups with the concentration of inflammatory markers in the blood.[9 10] These inflammatory diet scores have been associated with increased risk of chronic diseases[11] such as cardiometabolic diseases[12 13] and colorectal cancer.[14 15] The aim of our study was to develop an empirical dietary inflammatory index (EDII) using the methodology described by Tabung *et al*[9] and to investigate whether this inflammatory diet score during pregnancy is associated with the risk of type 1 diabetes in offspring.

METHODS

Population and study design

Our study was based on data from the Danish National Birth Cohort (DNBC)[16] including pregnant women in Denmark, between January 1996 to October 2002, who were able to fill in questionnaires and to participate in interviews in Danish. There were 91 745 mothers enrolled and they contributed 101 033 pregnancies as they were allowed to enter the study more than once. The recruitment took place through general practitioners (GPs) who consulted the women for the first antenatal visit – typically during gestational week (GW) 6–10. The DNBC data were collected through two self-administered questionnaires (the recruitment form at the beginning and the Food Frequency Questionnaire (FFQ)[17] in mid-pregnancy about GW 25), four telephone interviews (two during pregnancy GWs 12 and 30, and two after delivery 6 and 18 months), and three blood samples (two maternal blood samples during pregnancy and one umbilical cord blood at delivery).

All women who answered the FFQ[17] were included in this study (n=73 010). Participants with missing linkage to the FFQ were excluded (n=158). Mothers with multiple births, stillbirths, abortion/emigration/missing for unknown reason, confirmed type 1 diabetes or type 2 diabetes diagnosis before pregnancy, and with either implausibly low (< 2 500 kJ/day) or high (> 25 000 kJ/day) energy intake were excluded (n=5 151), leaving a total of 67 701 mother-child pairs for analysis (figure 1).

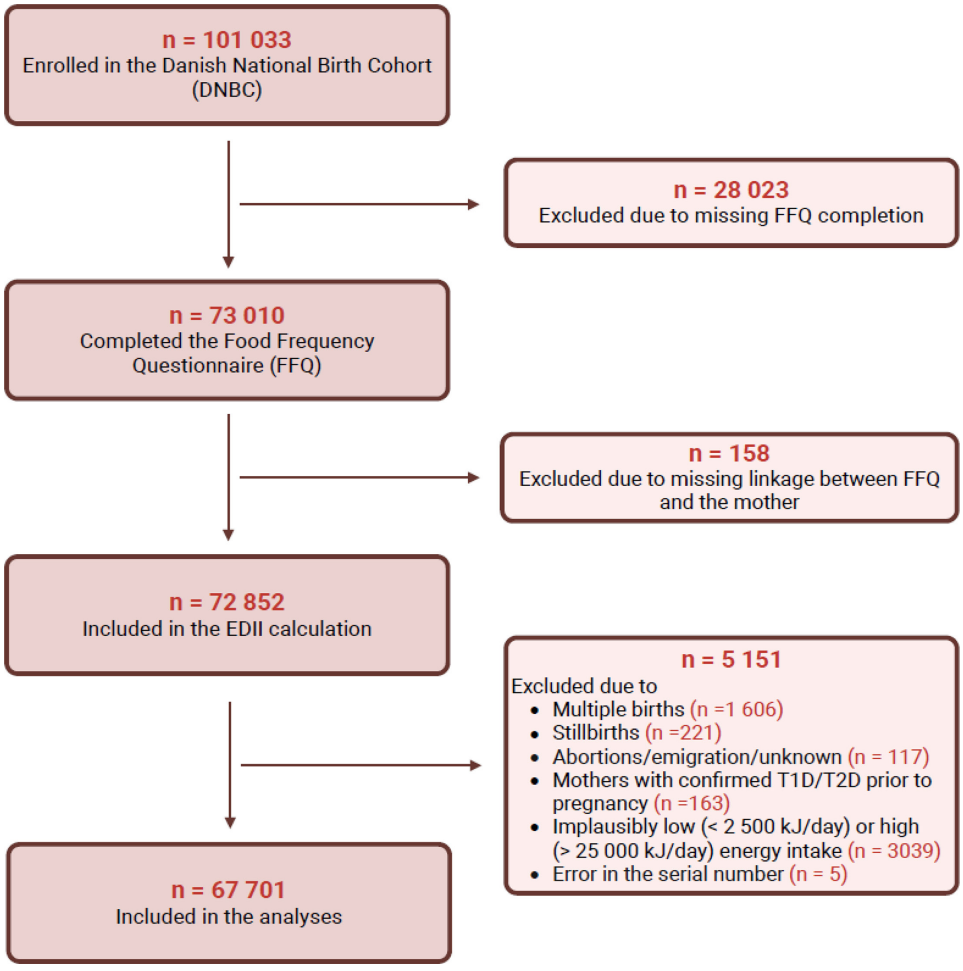

Figure 1 Flowchart of study participants included in the main analyses.

Table 1 The distribution of maternal characteristics across quintiles of the Empirical Dietary Inflammatory Index (EDII) scores

	Quintile 1 n = 13 482 (Most Anti-inflammatory)	Quintile 2 n = 13 711	Quintile 3 n = 13 364	Quintile 4 n = 13 520	Quintile 5 n = 13 624 (Most Pro-inflammatory)
EDII scores range:	−5.29 to −0.83	−0.82 to −0.25	−0.24 to 0.20	0.21 to 0.71	0.72 to 4.05
Maternal age (years)*	31.00 (4.25)	30.88 (4.18)	30.61 (4.18)	30.05 (4.18)	29.49 (4.24)
Pre-pregnancy BMI (kg/m^2)	22.36 (3.50)	22.92 (3.74)	23.37 (3.90)	24.01 (4.35)	25.02 (4.88)
< 18.5	6.7%	4.8%	3.8%	3.3%	3.0%
18.5–24.9	70.9%	69.0%	66.6%	61.0%	52.3%
25–29.9	12.4%	15.3%	17.9%	9.0%	13.9%
≥ 30	3.6%	5.1%	6.2%	9.0%	13.9%
Missing	6.4%	5.9%	5.5%	5.3%	6.9%
Smoking during pregnancy (only first 12 gestational weeks)					
Yes	7.8%	7.6%	7.5%	7.5%	7.3%
No	81.5%	82.3%	82.8%	83.1%	83.0%
Missing	10.7%	10.1%	9.8%	9.4%	9.7%
Smoking during pregnancy (also after 12 gestational weeks)					
Yes	13.0%	12.5%	13.4%	14.1%	17.3%
No	76.3%	77.4%	76.9%	76.5%	73.0%
Missing	10.7%	10.1%	9.8%	9.4%	9.7%
Confirmed GDM					
Yes	0.5%	0.6%	0.7%	0.9%	1.6%
No	99.5%	99.4%	99.3%	99.1%	98.5%
Missing	0	0	0	0	0
Parity					
0	46.9%	45.4%	46.5%	47.3%	47.6%
1	34.9%	35.7%	34.1%	33.9%	33.6%
2	11.1%	12.1%	12.4%	11.7%	11.9%
3+	2.1%	2.4%	2.8%	3.0%	2.8%
Missing	5.0%	4.4%	4.2%	4.1%	4.1%
Parental socioeconomic position†					
Leaders with ≥10 employees	27.7%	27.2%	24.6%	19.9%	14.9%
Leaders with <10 employees	30.1%	31.7%	31.7%	30.4%	26.5%
Skilled	21.4%	21.9%	24.6%	28.6%	33.4%
In education	6.1%	5.1%	4.6%	4.6%	4.8%
Unskilled	8.0%	8.1%	8.6%	10.7%	14.2%
Unemployed	1.5%	1.4%	1.4%	1.7%	1.9%
Missing	5.3%	4.7%	4.5%	4.3%	4.3%

Data are mean (SD) for continuous variables and % for categorical variables. Values presented are before imputation of missing values.
*missing values were<0.1%
†Highest of the parents
BMI, body mass index; EDII, Empirical Dietary Inflammatory Index; GDM, gestational diabetes mellitus.

Patient and public involvement statement

There was no involvement from patients or members of the public in the design, or conduct, or reporting, or dissemination plans of the research related to the present study.

Outcome measures

Children were followed from the date of birth until type 1 diabetes diagnosis or the end of follow-up – 1 June 2018. Date of type 1 diabetes diagnosis during childhood was obtained by linking the personal specific identification number from the Danish Civil Registrations System (CPR)[18] to the Danish Registry of Childhood and Adolescent Diabetes (DanDiabKids),[19] which is validated annually, covering all children aged 0–18 with a type 1 diabetes diagnosis.

Empirical Dietary Inflammatory Index – EDII

The mother's diet during pregnancy was assessed using a comprehensive >360 item self-administered food frequency questionnaire (FFQ)[17] that was validated against 7 day weighted food diaries and blood biomarkers.[20 21] The detailed content of the FFQ and data processing methodologies are outlined elsewhere.[17] An inflammatory diet score for pregnancy diet was developed in the Norwegian Mother, Father and Child Cohort Study (MoBa),[22] which is a similar, but slightly younger cohort. The MoBa FFQ was adapted from the FFQ used in DNBC, and it was distributed to the pregnant women at approximately gestational week 22.[23] The inflammatory diet score was based on methods previously described by Tabung *et al*.[9] EDII weights were derived in a subsample of 2517 MoBa participants with available biomarker measurement, who had a plasma concentration of C-reactive protein (CRP) <10 mg/L. The MoBa subsample and biomarker assessment have been described in detail elsewhere.[24 25] In brief, blood samples were collected from MoBa mothers in mid-pregnancy (mean 18.5 gestational weeks, SD 1.4). The gestational week of blood sampling was

Table 2 Distribution of offspring characteristics across quintiles of the Empirical Dietary Inflammatory Index (EDII) scores

	Quintile 1 n = 13 482 (Most Anti-inflammatory)	Quintile 2 n = 13 711	Quintile 3 n = 13 364	Quintile 4 n = 13 520	Quintile 5 n = 13 624 (Most Pro-inflammatory)
Type 1 diabetes					
Yes	0.4	0.4	0.4	0.4	0.6
No	99.7	99.6	99.6	99.6	99.5
Missing	0	0	0	0	0
Sex					
Male	51.2	50.6	51.3	51.8	51.6
Female	48.8	49.4	48.7	48.2	48.4
Birth weight (kg)	3.56 (056)	3.58 (0.56)	3.59 (0.56)	3.60 (0.58)	3.60 (0.59)
Duration of breastfeeding (months)					
0–1	6.1%	5.8%	7.5%	8.9%	11.4%
2–3	5.7%	6.1%	6.6%	8.0%	9.5%
4–6	11.5%	12.3%	13.3%	13.6%	15.8%
7–9	19.8%	20.7%	20.7%	20.1%	17.4%
≥ 10	28.0%	27.7%	24.6%	22.6%	18.3%
Missing	29.0%	27.5%	27.2%	26.9%	27.5%
Timing of introduction of solid food (age in months)					
1	1.7%	1.7%	1.3%	1.3%	1.3%
2	19.9%	21.0%	21.4%	19.8%	20.2%
3	1.9%	2.10%	1.9%	1.9%	1.8%
4	<0.1%	<0.1%	<0.1%	<0.1%	0.1%
5	0.1%	<0.1%	0.1%	0.1%	0.1%
Not started at 6	50.9%	51.7%	52.5%	53.9%	54.3%
Missing	25.5%	23.5%	22.7%	23.1%	22.3%
Deliver by caesarean section					
Yes	14.4%	14.5%	15.0%	15.6%	16.3%
No	85.6%	85.5%	85.0%	84.4%	83.7%
Missing	0%	0%	0%	0%	0%

Data are mean (SD) for continuous variables and % for categorical variables. Values presented are before imputation of missing values.
EDII, Empirical Dietary Inflammatory Index.

not associated with CRP value (test for linear trend, p-value 0.4).

The mean daily intake of 38 food groups from the FFQs was calculated and Reduced Rank Regression (RRR) was applied to derive a dietary pattern associated with the inflammatory biomarker, CRP. R package PCovR with no rotation and alpha=0.001 was used to extract the first RRR component. RRR identified linear functions of the predictors (food groups) that simultaneously explain as much variation in the response of interest (CRP) as possible. To identify the most important food groups contributing to the first RRR component (RRR dietary pattern), stepwise linear regression analysis was performed using CRP response scores (individual scores in the RRR dietary pattern) as dependent variables, and food groups as independent variables, with a significance level set at $p<0.05$ for entry into the model. The food groups, with unit grams/day transformed with natural log, identified in the stepwise linear regression analyses were weighted by the regression coefficients from the final stepwise linear regression model (online supplemental table S1) and summed to calculate the EDII score.

The EDII score assessed the inflammatory potential of the pregnant woman's diet on a continuum from maximally anti-inflammatory to maximally proinflammatory, with higher scores (more positive) indicating more proinflammatory diets and lower scores (more negative) indicating anti-inflammatory diets. The correlation between the EDII score and measured CRP in MoBa was examined (Pearson's correlation coefficient was 0.20), and the accuracy was assessed using the mean squared prediction error estimated from cross-validation (MSPE=0.04). The last step in the calculation of EDII, which combines regression weights (from MoBa) and estimated intake, can be applied in both cohorts – MoBa and DNBC – due to use of near-identical FFQs to assess the pregnancy diet.[23]

Statistical analysis

Summary statistics and comprehensive visual examination were employed to scrutinise all variables for coding errors and values that appeared implausible. Maternal EDII score was then categorised by quintiles. We examined maternal and offspring characteristics across EDII score percentiles using mean and SD for continuous variables and percentages for dichotomous variables. To estimate the association of EDII score with childhood-onset type 1 diabetes we used Cox proportional hazards regression, reporting hazard ratios (HR) and 95% confidence intervals (CI). Missing covariate values were imputed (n=5) using multiple imputation as implemented in PROC MI in SAS. To test for deviations from linearity, we used a likelihood ratio test (P curvature, F test) to compare the linear model with a model fit that was based on restricted cubic splines.[26]

The statistical analyses were performed in accordance with the statistical analysis plan[27] developed prior to data analyses, with two deviations: for all analyses, we excluded all women

Table 3 Maternal diet and the distribution of food groups included in the EDII calculation across the quintiles of EDII scores. Data are shown as mean (SD)

	EDII score Quintile 1 (Most Anti-inflammatory Group) n = 13 482 Median score = -1.3	EDII score Quintile 2 n = 13 711 Median score = -0.5	EDII score Quintile 3 n = 13 364 Median score = -0.02	EDII score Quintile 4 n = 13 520 Median score = 0.4	EDII score Quintile 5 (Most Pro-inflammatory Group) n = 13 324 Median score = 1.2
Energy and nutrient intake					
Total energy intake (MJ/day)	10.0 (2.7)	10.1 (2.6)	10.1 (2.7)	10.1 (2.7)	10.0 (2.8)
Protein (E%)	14.5 (2.3)	15.1 (2.3)	15.4 (2.3)	15.5 (2.4)	15.8 (2.5)
Carbohydrate (E%)	54.9 (6.4)	54.9 (5.8)	54.5 (5.7)	54.1 (5.7)	53.4 (5.8)
Fibre (E%)	28.4 (9.9)	28.1 (9.4)	27.3 (9.4)	26.6 (9.3)	25.1 (9.4)
Sugar (E%)	8.1 (4.7)	8.0 (4.5)	8.0 (4.4)	7.9 (4.5)	7.9 (4.9)
Fat (E%)	30.7 (6.5)	30.1 (6.1)	30.2 (5.9)	30.4 (5.9)	30.8 (6.0)
Saturated fatty acids (E%)	12.6 (3.7)	12.3 (3.4)	12.3 (3.3)	12.4 (3.2)	12.7 (3.3)
Monounsaturated fatty acids (E%)	9.6 (2.3)	9.5 (2.1)	9.5 (2.1)	9.6 (2.1)	9.8 (2.1)
Polyunsaturated fatty acids (E%)	4.6 (1.0)	4.5 (0.8)	4.5 (0.8)	4.5 (0.9)	4.5 (0.9)
Gluten (g/day)	15.3 (6.5)	15.4 (6.3)	15.1 (6.2)	14.9 (6.3)	14.5 (6.4)
Food group intake* (g/day)					
Red meats	22.2 (17.3)	25.5 (16.4)	27.5 (16.6)	29.1 (16.9)	32.2 (18.3)
Dairy low fat	130.5 (255.1)	258.1 (328.8)	320.2 (352.0)	362.7 (376.0)	434.5 (420.9)
Pizza	12.5 (13.0)	15.7 (12.5)	17.4 (12.8)	18.6 (13.8)	19.9 (14.5)
Margarine	0.2 (0.9)	0.3 (0.9)	0.4 (1.1)	0.5 (1.1)	0.7 (1.4)
Potatoes	110.8 (81.2)	115.5 (76.5)	120.3 (80.3)	126.5 (84.3)	137.3 (92.9)
Low energy drink	38.2 (154.2)	56.8 (184.6)	95.3 (221.8)	154.3 (279.0)	241.1 (356.2)
French fries	14.0 (15.7)	16.4 (15.8)	18.0 (15.4)	19.8 (16.8)	22.2 (17.7)
Savoury snacks	3.3 (4.4)	3.6 (3.9)	4.0 (4.4)	4.4 (4.6)	5.0 (5.0)
Alliums	9.6 (11.3)	9.4 (10.2)	9.1 (9.9)	8.6 (9.8)	8.0 (9.6)
Tomato	14.3 (17.7)	13.5 (15.6)	12.6 (14.7)	11.3 (14.0)	9.5 (12.8)
Whole grain	180.6 (100.0)	180.3 (96.6)	173.4 (95.6)	168.7 (95.0)	158.2 (97.8)
Coffee	161.9 (219.4)	155.5 (217.7)	150.7 (220.3)	134.2 (224.5)	113.9 (228.5)
Green leafy vegetables	9.4 (12.1)	8.5 (10.6)	7.4 (9.6)	6.3 (8.7)	4.8 (7.2)
Fruit juice	193.4 (239.2)	191.3 (246.2)	180.4 (225.6)	166.1 (225.1)	134.9 (228.1)
Dark meat fish	8.3 (9.1)	7.7 (8.3)	7.0 (7.5)	6.1 (7.2)	4.7 (7.0)
Tea	204.6 (230.6)	180.7 (214.4)	158.9 (204.7)	129.4 (190.6)	78.2 (166.6)
Fruits natural	169.8 (107.5)	163.9 (104.6)	155.6 (102.7)	142.6 (102.6)	118.2 (97.9)

*Food groups presented in the table are included in calculation of the EDII-scores.
E%, Percentage of total energy intake; EDII, Empirical Dietary Inflammatory Index; MJ, megajoules.

with a type 1 diabetes/type 2 diabetes diagnosis before pregnancy, and, in model 3, additional adjustment was done for "maternal confirmed gestational diabetes mellitus (GDM)".[28]

Accordingly, the associations were first examined by one unadjusted model (model 1) and two adjusted models (model 2 and model 3). Characteristics potentially influencing the risk of type 1 diabetes were identified a priori and incorporated as potential confounders in our adjusted analyses in a similar way as an earlier study focusing on gluten in pregnancy and child's risk of type 1 diabetes.[29] Thus, in model 2 we adjusted for: Maternal age at childbirth (<25, 25–35, ≥35 years); offspring sex (male, female); maternal pre-pregnancy body mass index (BMI) (underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obese (≥30.0)); parity (primiparous, 1, 2+); maternal smoking during pregnancy (no, only first 12 gestational weeks, also after 12 gestational weeks, modelled as indicator variables); breastfeeding duration (0–1, 2–3, 4–6, 7–9 and ≥10 months); parental socioeconomic status (high/intermediate level proficiency, skilled worker, in education, unskilled worker/unemployed); Caesarean section (yes, no); total energy intake (by quintiles). In model 3, additional adjustment was made for confirmed gestational diabetes.[28]

In our robustness analyses we performed, also according to the *a priori* statistical analysis plan,[27] complete case analyses, and also evaluated, in model 3 with all covariates imputed, the influence of further adjusting for gluten intake during pregnancy and birth weight.

RESULTS

The mean maternal EDII score was −0.1 with a minimum score of −5.3 and a maximum score of 4.1 and SD of 0.98. Among the 67 701 observations, 281 (0.42%) children were diagnosed with type 1 diabetes during a mean follow-up time of 17.58 (SD 1.46) years. Median age at type 1 diabetes diagnosis was 10.2 years, whereas the 10th, 25th, 75th and 90th percentiles were 4.1, 7.0, 13.5, and 15.1 years, respectively.

Maternal, pregnancy and offspring characteristics related to EDII score are detailed in tables 1 and 2 and online supplemental table S2. Higher EDII scores were associated with younger maternal age, lower alcohol consumption, shorter breastfeeding duration, and lower parental socioeconomic position. Conversely, higher EDII scores correlated with increased maternal BMI and greater proportions who smoked beyond

Table 4 Association of maternal Empirical Dietary Inflammatory Index (EDII) and covariates with offspring type 1 diabetes risk

	Hazards ratio (95% CI) of type 1 diabetes in offspring		
	Model 1 (Unadjusted)	**Model 2 (adjusted)***	**Model 3 (adjusted)†**
Empirical Dietary Inflammatory Index (EDII)‡	1.19 (1.05 to 1.36)	1.16 (1.02 to 1.32)	1.16 (1.02 to 1.32)
Maternal age at childbirth (<25 years as reference)			
25–35		0.96 (0.64 to 1.45)	0.96 (0.64 to 1.44)
≥35		0.66 (0.37 to 1.17)	0.65 (0.37 to 1.16)
Offspring sex (Boy as reference)			
Girl		0.96 (0.76 to 1.22)	0.96 (0.76 to 1.22)
BMI before pregnancy (18.5–24.9 as reference)			
< 18.5		1.76 (1.09 to 2.83)	1.76 (1.09 to 2.83)
25–29.9		1.13 (0.82 to 1.55)	1.12 (0.81 to 1.55)
≥ 30		1.29 (0.85 to 1.94)	1.25 (0.82 to 1.89)
Parity (0 as reference)			
= 1		1.11 (0.85 to 1.44)	1.11 (0.85 to 1.44)
> 1		0.77 (0.50 to 1.17)	0.77 (0.50 to 1.17)
Smoking during pregnancy (Only first 12 gestational weeks)		0.95 (0.60 to 1.49)	0.95 (0.60 to 1.49)
Smoking during pregnancy (Also, after 12 gestational weeks)		0.47 (0.31 to 0.72)	0.47 (0.31 to 0.72)
Breastfeeding (≥10 months as reference)			
0–1		1.26 (0.78 to 2.03)	1.26 (0.78 to 2.02)
2–3		1.31 (0.90 to 1.92)	1.31 (0.89 to 1.92)
4–6		0.91 (0.63 to 1.31)	0.91 (0.63 to 1.31)
7–9		0.86 (0.59 to 1.24)	0.86 (0.59 to 1.24)
Parental socioeconomic status (unskilled worker/unemployed as reference)			
High/intermediate level proficiency		1.26 (0.57 to 1.13)	0.80 (0.57 to 1.13)
Skilled worker		0.94 (0.66 to 1.34)	0.94 (0.66 to 1.34)
In education		1.02 (0.40 to 2.58)	1.02 (0.40 to 2.59)
Caesarean section		1.06 (0.77 to 1.46)	1.05 (0.76 to 1.45)
Total energy intake (the lowest quintile as reference)			
Q2		0.97 (0.80 to 1.18)	0.97 (0.80 to 1.18)
Q3		1.07 (0.89 to 1.29)	1.08 (0.89 to 1.29)
Q4		0.99 (0.82 to 1.20)	1.00 (0.82 to 1.21)
Q5		1.18 (0.99 to 1.41)	1.18 (0.99 to 1.41)
Maternal diabetes – confirmed GDM			1.95 (0.79 to 4.83)

*Model 2=adjusted for maternal age at childbirth, offspring sex, maternal body mass index before pregnancy, parity, smoking during pregnancy, breastfeeding duration, parental socioeconomic status, caesarean section, and total energy intake.
†Model 3=Same as model two with additional adjustment for maternal confirmed gestational diabetes mellitus (GDM).
‡Hazards ratio (95% CI) of type 1 diabetes in offspring per one unit increase in the EDII score.
BMI, body mass index; GDM, gestational diabetes mellitus.

12 gestational weeks. Only minor or inconsistent associations were observed between EDII scores and other characteristics, including maternal parity, physical activity, and timing of introduction of solid food.

There was no significant difference in the total energy intake between women with the highest vs lowest EDII scores (table 3). The energy contribution from dietary sources was relatively consistent across the EDII quintiles, except fibre intake which was slightly lower in women with the highest vs the lowest EDII scores (25% v 28%).

The daily intake of *red meats, dairy low fat, pizza, margarine, potatoes, low energy drink, French fries, and savoury snacks* were increasing with higher EDII scores. Whereas the daily intake of *alliums, tomato, whole grain, coffee, green leafy vegetables, fruit juice, dark meat fish, tea, and natural fruits* fell with higher EDII scores (table 3).

The risk of type 1 diabetes in offspring was positively associated with the maternal EDII score with a HR of 1.19 (95% CI 1.05 to 1.36) per 1 unit increase, which approximately corresponds to 1 SD in the EDII score in the unadjusted model and a HR of 1.16 (95% CI 1.02 to 1.32) in both adjusted models 2 and 3 (table 4).

We found no strong indication of deviation from linearity when comparing the fit of restricted cubic splines with that of linear function using the likelihood ratio test (p=0.63).

There were no indications of interaction with sex, with almost the same HR in both sexes (all 1.16 (95% CI 1.02 to 1.32), girls 1.16 (95% CI 0.97 to 1.39), and boys 1.17 (95% CI 0.98 to 1.40)).

Robustness analyses with complete case and additional adjustment for maternal gluten intake or birth weight gave similar results (online supplemental table S3).

The risk was significantly lower in women who smoked throughout their entire pregnancy (HR=0.47 (95% CI 0.31 to 0.72)) (fully adjusted model, table 4) and increased in women reporting a diet with high gluten content (data not shown) (HR per 10 gram increase in gluten intake=1.36 (95% CI 1.09 to 1.71); also fully adjusted model).

DISCUSSION

Statement of principal findings

Our analyses of data from this large national prospective cohort revealed a statistically significant association between the pro-inflammatory index of the maternal diet during mid-pregnancy and subsequent risk of developing type 1 diabetes in the child. After adjusting for potential confounding factors, we found that a 1 SD increase in the maternal EDII score was associated with a 16% (95% CI 2% to 32%) increase in the child's risk of developing type 1 diabetes during the first 18 years of life.

Strengths and weaknesses of the study

DNBC is the first large prospective cohort of its kind, with approximately 70 000 pregnant women who during 1996 to 2003 reported on their dietary intake in mid-pregnancy. Diet was assessed by a comprehensive, general 360-item food frequency questionnaire covering a 1 month time window prior to gestation week 25. The FFQ methodology is recognised for its reproducibility and validity,[30 31] and our FFQ had been validated against 7 day weighed food diaries and biomarkers.[20 21] The use of unique ID numbers for all citizens in Denmark enabled a near 100% follow-up for identifying incident cases of type 1 diabetes; the DanDianKids register, which we used to identify children with type 1 diabetes undergoes annual validation, ensuring the integrity of our data.[19] The comprehensive interview data during pregnancy and postpartum in the DNBC, combined with data extractions from the Medical Birth Register and other registers, enabled us to account for an extensive array of variables. Despite identical principles for calculating the EDII score, the set of foods selected for the calculation may differ across populations due to variations in overall dietary characteristics at population level, but also if the dietary assessment methods vary (eg, how many food items were assessed with an FFQ). It may therefore be regarded as a strength that we based the EDII-score calculations on regression weights obtained from pregnant women in the MoBa cohort,[24 25] given the near identical pregnancy FFQs used in DNBC and MoBa and the general similarities between these two cohorts,[23] as compared with an alternative strategy where one would use regression weights obtained from a totally different setting, for instance that reported by Tabung *et al*, which was based on non-pregnant cohorts in the USA.[9]

The observed association between mid-pregnancy EDII score and subsequent offspring type 1 diabetes risk remained stable after adjustment for a number of potential confounding factors and various robustness challenges including birth weight as an explanatory variable in the analysis and performing complete case analyses. Nevertheless, influence of unmeasured or unidentified potential confounders, such as the inflammatory properties of the child's own diet, cannot be ruled out.[32] Replicating our findings in comparable, independent datasets may provide new insights.

Strengths and weaknesses in relation to other studies in the field

To our knowledge, this is the first prospective study to examine the relationship between inflammatory dietary patterns in pregnancy and the child's subsequent risk of developing type 1 diabetes.

Meaning of the study: possible explanations and implications for clinicians and policymakers

The impact of a high-inflammatory diet during pregnancy on the risk of type 1 diabetes in the offspring might be explained by effects on immune system maturation and inflammatory responses in the child. A low-grade inflammatory state secondary to an altered immune cell profile, which triggers pro-inflammatory pathways, is increasingly acknowledged as a critical early-life factor influencing offspring health. However, the precise mechanisms by which diet modulates the immune response remains elusive, although some clues can be offered for specific dietary components. For example, long-chain n-3 fatty acids, of which fish is the most important food source, have well-documented anti-inflammatory properties.[33] Yet, a recent observational study, based on DNBC and MoBa data did not find an inverse association between the estimated intake of these fatty acids during pregnancy and the child's risk of type 1 diabetes.[34] In our study low fat dairy was a contributor to the overall inflammatory index. Although low fat dairy has not been identified as pro-inflammatory in some previous studies the consumption of low fat dairy in the Nordic countries is relatively high (~500 mL/day in our cohort)[23], which may explain its contribution in this setting. As such, dairy is a major contributor to intake of animal protein, and in a study of Danish pregnant women protein has been identified as being pro-inflammatory.[35] At the same time short-term interventions with dairy have not observed pro-inflammatory effects but weak pro-inflammatory effects have been observed in trials of longer duration.[36] Overall, the contribution of different foods to the pro-inflammatory index do not depend only on the type of food but also the amount of food consumed, which in the case of dairy was relatively high in our cohort.

Previous studies, based on DNBC and MoBa data,[37] have reported an inverse association between smoking during mid-pregnancy and the risk of type 1 diabetes in offspring, a finding which is in line with other studies.[38] We also previously reported[29] a direct association between estimated intake of gluten in pregnancy and the risk of type 1 diabetes in the offspring. A similar study from Norway provides some additional support to this latter finding, although the association in that study was observed for gluten intake during early infancy, with no clear association for maternal intake.[39]

Of particular note is the fact that three factors during mid-pregnancy, pro-inflammatory diet, gluten, and smoking, seemed to independently predict the child's risk of type 1 diabetes. Thus, in the full model including all three variables, and thus with mutual adjustments (results not shown in the tables), a 1-unit increase in the EDII was associated with a 15% (95% CI 1.02% to 31.2%) increase in risk, whereas a 10 gram increase in estimated intake of gluten was associated with a 36% (95% CI 8.6% to 70.8%) increase in risk, while smoking during early and mid-pregnancy was associated with a 50.8% (95% CI 25.0% to 67.0%) reduction in the child's risk of developing type 1 diabetes. Notably, as regards the latter finding, there was no indication that smoking limited to early pregnancy (before gestation week 12) without continuation later in pregnancy, was associated with type 1 diabetes risk in the child (HR=0.94 (95% CI 0.61 to 1.45), fully adjusted model). This suggests that mid-pregnancy may be a critical period during which the fetus is particularly susceptible to maternal lifestyle influences.

Collectively, these findings add to the growing body of evidence suggesting that paediatric type 1 diabetes may be influenced by prenatal or early postnatal modifiable factors.[3]

Further research is needed to clarify the underlying pathways connecting these phenomena. Alternative strategies, such as direct measuring CRP or other inflammatory biomarkers[40] during pregnancy and linking them to the child's subsequent risk of type 1 diabetes, may offer new insights. If strong evidence is

found, then potential intervention studies with for example anti-inflammatory drugs could be the next step.

CONCLUSION

Our study suggests that a high pro-inflammatory diet during pregnancy, as indicated by a high EDII score, may be a risk factor for developing type 1 diabetes with a 1.16-fold increase in risk per 1 SD increase in the EDII score. This finding supports the growing evidence that childhood type 1 diabetes may be influenced by early modifiable factors, including the mother's diet.

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Contributors SFO: Conceptualised the study. RN and SFO: Prepared the first draft of the report. All authors: Critical revision of the manuscript for important intellectual content. IHC, TB, ALB, AAB, RH, and TIH: Developed the RRR weights from the MoBa sub-cohort. CG, RN, TIH, and AAB: Calculated the EDII scores in DNBC. TIH, RN, AAB, CG, and SFO: Developed the statistical analysis plan. TIH: Performed the statistical analyses. CG: Managed the data. Supervision: SFO. SFO is the guarantor.

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Disclaimer The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The DNBC was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human participants were approved by the National Committee on Health Research Ethics in Denmark (H-KF 01-471/94).

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Data availability statement Data may be obtained from a third party and are not publicly available. Data from the Danish National Birth Cohort (DNBC) used in this study is managed by the DNBC Secretariat at Statens Serum Institut in Copenhagen, Denmark, and can be made available to researchers, provided approval from the DNBC organisation, compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owner (Statens Serum Institut). The consent given by the participants does not cover storage of data on an individual level in repositories or journals. Researchers who wish to apply for access to data sets for replication purposes should apply through the DNBC Secretariat (see www.dnbc.dk). Access to data sets requires approval from the DNBC organisation, the local Data Protection Agency (in a Danish context. "Fortegnelsen") at the researcher's institution, the Danish Regional Committees on Biomedical Research Ethics (if biological samples are involved), and an agreement with the DNBC at Statens Serum Institut.

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