

Maternal dietary inflammatory potential and quality are associated with offspring asthma risk over 10-year follow-up: the Lifeways Cross-Generation Cohort Study

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ABSTRACT

Background: Asthma is the most common childhood chronic health condition. Maternal antenatal diet has been associated with offspring asthma risk, but studies investigating maternal whole diet quality and inflammatory potential with long-term offspring follow-up (>5 y) are rare.

Objectives: We aimed to elucidate these associations in a prospective cohort study in Ireland.

Methods: Early pregnancy diets were assessed using a validated FFQ from which energy-adjusted Dietary Inflammatory Index (E-DII) and Healthy Eating Index (HEI)-2015 scores were computed. Doctor-diagnosed offspring asthma status (general practitioner or parent reports) for the first 10 y of life was collected at 3-y, 5-y, and 9-y follow-up. A total of 862 mother–child pairs with information on maternal diet and ≥ 1 offspring asthma data points were included. The longitudinal associations between maternal E-DII and HEI scores and offspring asthma status were assessed using generalized estimating equations.

Results: Cumulative offspring asthma incidence was 21% over the 10-y period. In the main models, adjusted for maternal lifestyle and sociodemographic factors, a higher E-DII score, indicating a more proinflammatory diet, was associated with higher risk of offspring asthma (OR: 1.35; 95% CI: 1.10, 1.65; per 1-SD score increment), whereas a higher HEI-2015 score, indicating better dietary quality, was associated with lower risk (OR: 0.77; 95% CI: 0.64, 0.93) (both $P < 0.01$). Results persisted with further adjustment for childhood factors (e.g., breastfeeding, diet, and childcare attendance) and parental asthma history. Similar associations were observed when E-DII and HEI-2015 scores were modeled in quartiles (both P -trend < 0.05). Associations for HEI-2015 were attenuated after adjustment for E-DII, suggesting the importance of anti-inflammatory pathways.

Conclusions: Our results suggest that a proinflammatory and low-quality diet during pregnancy is associated with a higher risk of offspring asthma. Pending confirmation from other studies, optimizing these aspects of maternal diet can be a promising strategy for reducing childhood asthma risk. This prospective observational study was registered at the ISRCTN Registry as ISRCTN16537904. *Am J Clin Nutr* 2019;00:1–8.

Keywords: dietary quality, dietary inflammation, pregnancy, asthma, developmental origin, children

Introduction

Asthma is a complex, heterogeneous disease (1) characterized by bronchial hypersensitivity and eosinophilic airway inflammation that results in episodes of coughing, wheezing, and breathlessness (2–4). Being the most common chronic, noncommunicable disease of childhood (4) and estimated to affect 358 million individuals worldwide (5), asthma imposes personal hardship and substantial financial burden on healthcare systems and other societal resources.

The etiology of asthma is not fully understood but is believed to develop due to the interplay between genetic predisposition and environmental triggers including diet (6–8). In this regard,

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Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval from the Lifeways steering and management team.

Supplemental Figure 1 and Supplemental Tables 1–4 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: DII, Dietary Inflammatory Index; E-DII, energy-adjusted Dietary Inflammatory Index; GEE, generalized estimating equation; GP, general practitioner; HEI, Healthy Eating Index.

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increasing evidence has suggested that in utero nutritional challenges can also affect offspring asthma risk (9). Because the vast majority of organogenesis of the fetal airway takes place in utero and is nearly complete at birth (10), maternal dietary intake during pregnancy can have a major impact on offspring lung and airway development. Furthermore, suboptimal maternal diet can negatively influence the development of the offspring innate and adaptive immune systems and their subsequent interaction with allergens, leading to a higher risk of asthma later in life (7).

Although maternal diet has been investigated in association with offspring asthma, most previous studies focused on individual nutrients and foods such as fruit and vegetables, oily fish, and vitamin D (8, 11–13). However, because people do not consume isolated foods or nutrients, focusing on the quality of whole diets by using predefined indices such as the Healthy Eating Index (HEI) (14–16) can improve the applicability of public health messaging. Limited studies have investigated the influence of maternal dietary quality on offspring asthma risk, and have reported inconsistent findings between maternal adherence to the Mediterranean diet and risk of offspring wheezing (6, 17–19).

Furthermore, because inflammation is an important component in asthma pathogenesis, reducing overall dietary inflammatory potential could also be a promising strategy for lowering asthma risk. In this regard, the Dietary Inflammatory Index (DII), a well-validated literature-based index, can be used to rank an individual's dietary inflammatory potential (20). To our knowledge, no study to date has investigated the potential intergenerational influence of maternal DII during pregnancy on offspring asthma risk.

There is a clear dearth of research on the intergenerational influence of maternal dietary quality and inflammatory potential on offspring asthma risk. Therefore, we aimed to address this research gap by investigating whether maternal whole diet quality and dietary inflammatory potential during pregnancy influenced childhood asthma risk over a 10-y follow-up in Ireland, which has the fourth highest prevalence of asthma worldwide (21).

Methods

The Lifeways Cross-Generation Cohort Study is a prospective, longitudinal cohort study designed to investigate the influence of early-life factors on offspring health (22, 23). Briefly, between the years 2000 and 2003, Irish-born mothers were recruited at 2 maternity hospitals in the Republic of Ireland during their first antenatal visit. A cohort of 1070 singleton live-births was born to the recruited mothers. The current analysis sample consists of mother–child pairs with both pregnancy dietary information and ≥ 1 data point on child asthma health status over a 10-y follow-up ($n = 862$). The detailed participant flow chart is shown in **Supplemental Figure 1**. The Lifeways study has been granted ethical approval by ethical committees of the Coombe University Hospital, Dublin, University College Dublin, Irish College of General Practitioners, and University College Hospital, Galway, Ireland. Written informed consent was collected from all women upon recruitment; an additional assent was obtained from all children at the year 9 follow-up phase.

Exposure

Dietary assessment.

Assessment of habitual dietary intakes of the Lifeways participants has been described in detail previously (24). During their first trimester of pregnancy, the Lifeways mothers completed a self-administered semiquantitative FFQ [based on the European Prospective Investigation into Cancer and Nutrition instrument (25), which has been validated extensively in several populations (26)]. The 149-item FFQ used in Lifeways, adapted to reflect the Irish diet, was originally validated for use in the Irish population using food diaries and a protein biomarker in a volunteer sample (27). The FFQ was subsequently incorporated into the Irish National Surveys of Lifestyle Attitudes and Nutrition 1998, 2002, and 2007. The mothers indicated their average consumption frequency for each food item, ranging from “never or less than once per month” to “6+ per day,” during the first 12–16 wk of pregnancy. These intake frequencies were then converted into intake amounts (grams per day) using standard portion sizes (28). Energy and nutrient intakes were calculated using an in-house software program (FFQ Software Ver 1.0; developed by the National Nutrition Surveillance Centre, School of Public Health, Physiotherapy, and Sports Science, University College Dublin), which linked frequency selections with the food equivalents in McCance and Widdowson food tables (28).

Derivation of HEI scores.

The HEI-2015 scores a diet based on 9 adequacy components (intakes of total fruits; whole fruits; vegetables; greens and beans; total protein-containing foods; seafood and plant protein; whole grains; dairy; and ratio of PUFAs and MUFAs to SFAs) and 4 moderation components (refined grains, sodium, added sugars, and SFAs). With the exception of the fatty acids ratio, each of the components is scored on a density basis out of 1000 kcal, meaning that reported intake amounts of the food components were first converted to amounts per 1000 kcal intake, which were subsequently compared and scored according to criteria detailed elsewhere (29). The theoretical range of the HEI-2015 is 0–100, with a higher score reflecting greater adherence to recommendations in the dietary guideline for Americans (high intakes of foods counting toward adequacy components and low intakes of foods counting toward moderation components) and thus indicative of better dietary quality. For the adequacy components, a maximum score of 5, reflecting a higher intake, can be awarded for intakes of total fruits, whole fruits, vegetables, greens and beans, total protein-containing foods, and seafood and plant protein; the maximum score is 10 for consumption of whole grains, dairy, and fatty acids ratio. All moderation components were subjected to reverse scoring and have a maximum score of 10, reflecting a lower intake.

Derivation of DII scores.

The development of the DII has been described in detail elsewhere (30). To compute the energy-adjusted DII (E-DII) score for the adults, dietary information for each study participant was first linked to a regionally representative database that provides a global estimate of mean and SD of intakes for each of the dietary parameters (i.e., foods, nutrients, and other food

components). Subsequently, *z*-scores for each dietary parameter were derived by subtracting the mean of the energy-adjusted regionally representative database from the participant-reported amount and dividing this value by the parameter's representative SD. These *z*-scores were converted to proportions (i.e., with values ranging from 0 to 1) and then centered by doubling and subtracting 1. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a comprehensive literature review of 1943 peer-reviewed articles). All of these food parameter-specific E-DII scores were then summed to create the overall E-DII score for all participants in the study. Energy adjustment was done using the density approach wherein all the food parameters in the study and in the global database were converted to per 1000 kcal consumption. A total of 29 of the 45 possible food parameters were used for E-DII calculation based on the FFQ in this study (see **Supplemental Table 1**). A higher E-DII score indicates a more proinflammatory diet.

Outcomes

The primary study outcome is doctor-diagnosed asthma in offspring over a 10-y follow-up (at ages 3, 5, and 9 y). Data on asthma diagnosis of the children were reported directly by doctors [general practitioners (GPs)] at follow-ups at year 3. Specifically, GPs were asked, "Has a diagnosis of (the study child) asthma ever been recorded in (your) notes?" The GP answered yes or no to the question. At year 5, information on doctor-diagnosed asthma was obtained through parental report. Specifically, the parents were asked, "Has a diagnosis of asthma ever been made in your Lifeways child?" At year 9, information on asthma diagnosis was obtained through both doctors' and parental reports.

Covariates

Information on maternal age at recruitment, self-reported height and prepregnancy weight, cigarette smoking and alcohol intake during the periconceptional period (including both reported current smokers/drinkers and women who had smoked/consumed alcohol within 3 mo prior to recruitment) was collected using a self-administered questionnaire at recruitment. Using the same questionnaire, information on maternal education attainment (had college or university education compared with no college or university education), socioeconomic status [proxied by eligibility to the General Medical Services Scheme, a robust indicator of social disadvantage in the Irish population (31)], and household damp or condensation was collected. Prepregnancy BMI (kg/m^2) was calculated. Information on parity and child sex was abstracted from hospital records. Information on study children's attendance at child-care/crèche during the first 2 y of life was obtained from study booklets sent to the mothers. At year 5 follow-up, the mothers were asked if they ever breastfed the study children. At the same follow-up, the mothers also reported their children's average time spent outdoors (active) and viewing television (sedentary) (both asked separately for weekday and weekend day, which were then averaged). Dietary quality of the children was assessed using nutritional intake information

from a shorter FFQ completed by their mothers. Parental doctor-diagnosed asthma status, either through self-report or direct report by GPs, was determined at year 9 follow-up.

Statistical analysis

Descriptive statistics were first generated for maternal and child characteristics. Differences in characteristics across quartiles of maternal E-DII and HEI scores were assessed using 1-factor ANOVA for continuous variables and chi-square test for categorical variables.

The longitudinal associations between maternal E-DII and HEI scores and offspring asthma risk over the 10-y follow up were assessed using generalized estimating equations (GEEs), which account for nonindependence of multiple measurements per child, with unstructured covariance structure and a logit link. E-DII and HEI scores were modeled continuously (in *z*-scores) and in quartiles. *P*-trends for quartiles analyses were derived by modeling the median dietary score for each quartile in the models. ORs at individual follow-up time points were also estimated using logistic regressions. In all regression analyses the child's exact age at follow-up was controlled for. Furthermore, the following set of a priori selected confounders and covariates were adjusted: maternal socioeconomic status, education attainment, cigarette smoking and alcohol intake during the periconceptional period, daily total energy intake, age at recruitment, prepregnancy BMI, parity, and child sex. Missing covariates were multiply imputed 20 times using chained equations (32) by including all variables in the planned analysis, with burn-in iterations set to default (i.e., 10), resulting in 20 imputed datasets. The regression coefficients resulting from analyses in the 20 imputed datasets were subsequently pooled. Multiple imputation considers uncertainties of imputation by substituting each missing value with a set of simulated plausible values (33). We tested potential sex-interaction for the associations between maternal E-DII, HEI, and offspring asthma risk by including the multiplicative terms (one at a time) in the models.

In sensitivity analyses, we further adjusted for childhood factors (breastfeeding, childcare attendance, dietary quality, active and sedentary time), damp in house, paternal smoking around the time of maternal pregnancy, and parental asthma history. We also investigated whether further adjustment for indicator of participant recruitment site influenced the effect estimates. We excluded mothers with likely implausible energy intakes based on different cutoffs (<500 and >3500 kcal/d; <500 and >5000 kcal/d) commonly applied for pregnant populations (34, 35). Moreover, we modeled E-DII and HEI-2015 scores simultaneously (including them in the same model) to assess the influence of mutual adjustment. Finally, in a small subset ($n = 293$) of our sample with paternal habitual dietary intake information, we also assessed the relations of paternal dietary quality (during study mother's pregnancy) and inflammatory potential with offspring asthma risk as a negative control analysis. Due to the small sample size and cases and convergence issue with GEEs, the paternal analysis was conducted by using standard logistic regression (not GEEs) with ever asthma diagnosis over the 10-y follow up as the outcome.

All statistical analyses were conducted using the statistical software STATA version 13.1 (StataCorp). A 2-sided *P* value < 0.05 was considered statistically significant.

Results

Overall, the study mothers had a mean age of 30.4 ± 5.8 y at recruitment and a mean prepregnancy BMI of 23.8 ± 4.2 . Maternal E-DII score showed moderate inverse correlation with HEI-2015 score (Pearson $r = -0.56$; $P < 0.001$). Mothers with higher E-DII (more proinflammatory diet) and lower HEI-2015 (lower dietary quality) scores tended to be younger, to smoke cigarettes during early pregnancy, and had lower educational and socioeconomic status (all $P < 0.01$) (Table 1).

As shown in Table 2, an increment of 1-SD higher maternal E-DII score was associated with a 35% higher risk of offspring asthma (OR = 1.35; 95% CI: 1.10, 1.65; $P = 0.004$) in the fully adjusted model. In contrast, a 1-SD higher maternal HEI-2015 score was associated with a 23% lower risk of offspring asthma (OR = 0.77; 95% CI: 0.64, 0.93; $P = 0.006$). In individual follow-up time-point analyses, a higher maternal E-DII score was associated with a higher risk of offspring asthma risk at year 3, 5, and 9 (all $P < 0.05$) (Table 2). Similarly, a higher maternal HEI-2015 score was associated with a lower risk of offspring asthma risk across all follow-up time points, although statistical significance was observed only for year 3 (Table 2).

Similar trends of associations were observed when maternal E-DII and HEI-2015 scores were modeled in quartiles (Figure 1). In the GEE analysis for overall offspring asthma risk over the 10-y follow-up, higher quartiles of maternal E-DII scores were associated with a higher offspring asthma risk (overall P -trend = 0.002; OR_{Q4vsQ1} = 2.28; 95% CI: 1.30, 3.98). Higher maternal HEI-2015 score quartiles, signifying better dietary quality, were associated with an overall lower risk of offspring asthma risk (overall P -trend = 0.029; OR_{Q4vsQ1} = 0.63; 95% CI: 0.38, 1.03). In keeping with the analyses modeling E-DII and HEI-2015 scores continuously, higher E-DII quartiles were associated with a higher offspring asthma risk across all individual time points (P -trends < 0.05 for year 3 and 9, P -trend = 0.077 for year 5). Although inverse associations between higher HEI-2015 quartiles and lower offspring asthma risk were observed across individual time points, statistical significance was observed only for year 3 (P -trend = 0.016).

No sex-interaction was observed for either maternal E-DII–offspring asthma or HEI-2015–offspring asthma relations (all P -interactions > 0.36). In sensitivity analyses, the statistically significant associations between maternal E-DII, HEI-2015, and offspring asthma risk persisted with further adjustment for childhood factors (breastfeeding, childcare attendance, dietary quality, active and sedentary time), dampness in house, paternal smoking around the time of maternal pregnancy, and parental asthma history (Supplemental Table 2). Similarly, results changed little with additional adjustment for participant recruitment site (Supplemental Table 2). Results were also similar when we restricted the analyses to mothers with reported energy intake range of 500–3500 kcal/d or 500–5000 kcal/d (Supplemental Table 2). When E-DII and HEI-2015 scores were included in the models simultaneously, most E-DII associations remained similar and were statistically significant; however, the associations for HEI-2015 were largely attenuated, especially at later time points (Supplemental Table 3). In a small subset ($n = 293$) of our analysis population where paternal dietary information was available, there was little suggestion for associations of paternal dietary inflammatory potential and quality with offspring asthma

risk over the 10-y follow-up (OR = 0.98; 95% CI: 0.73, 1.33, per SD increment of E-DII; and OR = 1.06; 95% CI: 0.79, 1.42, per SD increment of HEI-2015).

Discussion

In this longitudinal cohort study with a 10-y follow-up, a more proinflammatory and lower-quality maternal diet during pregnancy was associated with a higher risk of offspring asthma. These associations were robust to adjustment for a comprehensive list of prenatal and postnatal covariates and in several sensitivity analyses. To the best of our knowledge, our study is the first to investigate the intergenerational influence of maternal dietary inflammatory potential and adherence to HEI-2015 on offspring asthma risk.

Cumulative offspring asthma incidence in our study was 21% over the 10-y period: year 3 = 10.1%, year 5 = 13.3%, and year 9 = 23.2%. These incidence proportions seemed to be comparable to those reported in a study in Manchester, United Kingdom, with similar follow-up time points (36).

Research on intergenerational influence of maternal dietary quality, especially based on adherence to predefined healthy indices, on offspring asthma risk is limited. In this regard, most previous studies have focused on maternal adherence to the Mediterranean diet. Our results are in concordance with the findings in a Spanish cohort where higher maternal adherence to the Mediterranean diet was associated with a lower risk of persistent wheeze in 6.5-y-old offspring (15). A cross-sectional Mexican study in 6–7-y-old children reported no consistent association between maternal adherence to the Mediterranean diet and questionnaire-determined offspring ever asthma and wheezing risks (17). That study, however, assessed maternal diet retrospectively (6–7 y after pregnancy), which could have induced excessive recall bias and limitations. A US study reported an inverse association in unadjusted analysis between adherence to the Mediterranean diet during pregnancy and offspring recurrent wheezing at year 3, which was attenuated by adjustment for confounders; no association was observed for maternal adherence to the Alternate Healthy Eating Index (19). A study involving Spanish and Greek cohorts reported no association between maternal adherence to the Mediterranean diet and offspring wheezing in the first year of life (6). The authors acknowledged that at early ages, the phenotype of wheeze is complex and likely transient, and longer follow-up is needed to preclude the influence of maternal dietary quality on offspring asthma risk at later ages (6). Differences in study design and setting, sample size, and year of follow-up could all have contributed to the heterogeneity in results. Our focus on prospective dietary intake assessment during early pregnancy, a critical period for fetal airway development, in a study population with high prevalence of childhood asthma, and long-term (10-y) follow-up of offspring asthma outcome could be the reasons why we observed an inverse association between maternal dietary quality and offspring asthma risk.

Dietary inflammation, as determined by the DII, has been linked with a range of adverse health outcomes (37). Although no prior research studies have investigated the intergenerational influence of dietary inflammatory potential on offspring asthma risk, research among adults and children suggests that an

TABLE 1 Characteristics of participants according to quartiles of maternal energy-adjusted Dietary Inflammatory Index (E-DII) and Healthy Eating Index (HEI-2015) scores in the Lifeways cohort study¹

<i>n</i>	Total 862 ²	E-DII				HEI				<i>P</i> value ³	<i>P</i> value ³
		Q1 216	Q2 215	Q3 216	Q4 215	Q1 232	Q2 200	Q3 216	Q4 214		
E-DII score	0.4 ± 1.7	-1.8 ± 0.8	-0.3 ± 0.3	0.9 ± 0.4	2.6 ± 0.9	1.5 ± 1.6	0.6 ± 1.4	0.2 ± 1.5	-1.0 ± 1.5	<0.001	<0.001
HEI-2015 score	52.4 ± 8.5	58.3 ± 7.4	54.3 ± 6.4	50.6 ± 7.2	46.2 ± 7.8	41.8 ± 4.5	50.1 ± 1.3	55.2 ± 1.7	63.1 ± 3.8	<0.001	<0.001
Maternal age at recruitment, y	30.4 ± 5.8	32.7 ± 4.5	31.6 ± 5.2	29.3 ± 5.9	27.8 ± 6.3	28.9 ± 6.2	29.6 ± 5.9	31.0 ± 5.6	32.0 ± 5.1	<0.001	<0.001
Maternal prepregnancy BMI, kg/m ²	23.8 ± 4.2	24.0 ± 4.0	23.8 ± 4.0	23.8 ± 4.3	23.7 ± 4.3	23.9 ± 4.5	24.1 ± 4.4	23.7 ± 3.9	23.6 ± 3.8	0.66	0.66
Maternal education status										<0.001	<0.001
Below tertiary	414 (49.1)	79 (36.9)	91 (42.7)	108 (51.9)	136 (65.4)	140 (63.3)	103 (52.3)	98 (46.4)	73 (34.1)		
Tertiary or above	429 (50.9)	135 (63.1)	122 (57.3)	100 (48.1)	72 (34.6)	81 (36.7)	94 (47.7)	113 (53.6)	141 (65.9)		
Parity											
Nulliparous	374 (43.8)	88 (41.3)	86 (40.8)	93 (43.3)	107 (50.0)	107 (46.5)	84 (42.2)	87 (41.0)	96 (45.3)	0.20	0.63
Nonnulliparous	479 (56.2)	125 (58.7)	125 (59.2)	122 (56.7)	107 (50.0)	123 (53.5)	115 (57.8)	125 (59.0)	116 (54.7)		
Cigarette smoking during early pregnancy										<0.001	<0.001
No	613 (72.4)	172 (81.5)	169 (79.7)	138 (64.5)	134 (63.8)	135 (59.5)	132 (66.7)	167 (79.1)	179 (84.8)		
Yes	234 (27.6)	39 (18.5)	43 (20.3)	76 (35.5)	76 (36.2)	92 (40.5)	66 (33.3)	44 (20.9)	32 (15.2)		
Alcohol use during early pregnancy										0.74	0.23
No	261 (30.4)	65 (30.1)	61 (28.6)	64 (29.6)	71 (33.3)	70 (30.3)	70 (35.4)	56 (25.9)	65 (30.5)		
Yes	597 (69.6)	151 (69.9)	152 (71.4)	152 (70.4)	142 (66.7)	161 (69.7)	128 (64.6)	160 (74.1)	148 (69.5)		
Eligibility to join the General Medical Services Scheme										<0.001	0.004
No	719 (84.2)	202 (94.0)	188 (87.9)	172 (81.5)	157 (73.4)	177 (77.6)	165 (82.9)	188 (87.9)	189 (88.7)		
Yes	135 (15.8)	13 (6.0)	26 (12.1)	39 (18.5)	57 (26.6)	51 (22.4)	34 (17.1)	26 (12.1)	24 (11.3)		
Child sex										0.41	0.85
Female	445 (51.6)	102 (47.2)	119 (55.3)	113 (52.3)	111 (51.6)	122 (52.6)	107 (53.5)	107 (49.5)	109 (50.9)		
Male	417 (48.4)	114 (52.8)	96 (44.7)	103 (47.7)	104 (48.4)	110 (47.4)	93 (46.5)	109 (50.5)	105 (49.1)		

¹Values are mean ± SD for continuous variables or *n* (%) for categorical variables. Q, quartile.²Total number might not be 862 due to missing information: maternal age (*n* = 2); prepregnancy BMI (*n* = 137); maternal education status (*n* = 19); parity (*n* = 9); cigarette smoking (*n* = 15); alcohol intake (*n* = 4); eligibility to join the General Medical Services Scheme (*n* = 8).³*P* values were derived from 1-factor ANOVA for continuous variables and chi-square test for categorical variables.

TABLE 2 Associations of maternal energy-adjusted Dietary Inflammatory Index (E-DII) and Healthy Eating Index (HEI-2015) with offspring asthma risk over a 10-y follow-up in the Lifeways cohort study¹

	Over 10-y follow-up (n = 862)	Year 3 (n = 677)	Year 5 (n = 543)	Year 9 (n = 444)
E-DII				
Model 1	1.31 (1.11, 1.55)**	1.33 (1.04, 1.70)*	1.37 (1.06, 1.77)*	1.35 (1.08, 1.71)*
Model 2	1.35 (1.10, 1.65)**	1.44 (1.06, 1.95)*	1.42 (1.04, 1.94)*	1.36 (1.03, 1.79)*
HEI-2015				
Model 1	0.76 (0.64, 0.91)**	0.73 (0.57, 0.94)*	0.72 (0.56, 1.84)*	0.84 (0.67, 1.07)
Model 2	0.77 (0.64, 0.93)**	0.70 (0.53, 0.93)*	0.78 (0.59, 1.03) ^T	0.84 (0.65, 1.08)

¹ Values are OR (95% CI) from generalized estimating equations (for overall estimates over a 10-y follow-up) and logistic regressions for individual follow-up time points at year 3, 5, and 9. Model 1 is adjusted for exact child's age at each follow-up. Model 2 is adjusted for exact child's age at each follow-up, maternal socioeconomic status, educational attainment, cigarette smoking and alcohol consumption during pregnancy, daily total energy intake, age at recruitment, parity, prepregnancy BMI, and child sex. ^TP < 0.10; *P < 0.05; **P < 0.01.

individual's dietary inflammatory potential could alter their own asthma risk. In a cross-sectional analysis, Australian adults with stable asthma had a more proinflammatory diet (higher DII score) compared with healthy controls; after accounting for confounders, a higher DII score was associated with a higher risk of asthma and lower lung function (20). In another cross-sectional study involving 15,791 adults and 8175 children in the United States, a higher E-DII score was associated with current wheeze in adults, and in children with allergic airway inflammation (38).

We have previously reported that higher maternal intakes of certain food groups and nutrients such as oily fish, fruit and vegetables, and vitamin D can be associated with lower

offspring asthma risk, although these associations did not always survive covariate adjustment or achieve statistical significance (8, 12). In the current study we thus focused on DII and HEI-2015, which assess multiple components of diet (including fruit, vegetables, and fatty acids) together, because the influence of isolated nutrients and food groups might be too small to be detected. Our current findings suggest an association between maternal whole diet, especially its inflammatory potential, and asthma in offspring. We noted a moderately strong inverse correlation (Pearson $r = -0.56$) between maternal E-DII and HEI-2015 scores, which is comparable to the magnitude of inverse correlation (-0.45) between DII and Mediterranean diet scores reported in a previous study (39). These results suggest

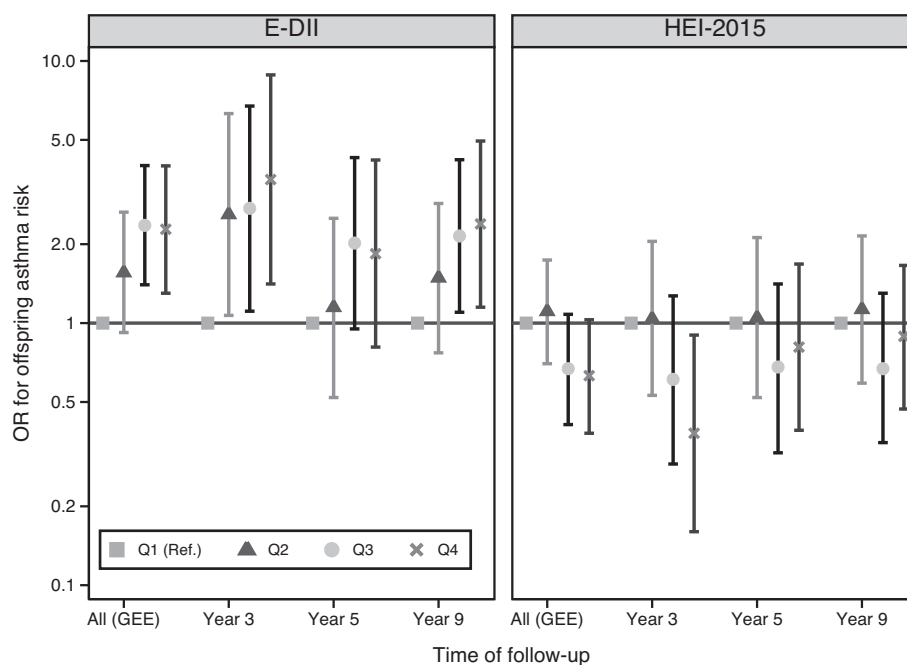


FIGURE 1 Associations of maternal energy-adjusted Dietary Inflammatory Index (E-DII) and Healthy Eating Index (HEI-2015), modeled in quartiles, with offspring asthma risk over a 10-y follow-up in the Lifeways cohort study. Values are ORs (represented by the markers explained in the key) and 95% CIs (represented by the capped vertical lines) from GEEs (for the overall 10-y follow-up) and logistic regression (for individual follow-up time points) with reference to the lowest quartile. The y-axis is log-scaled. The P -trends for E-DII were: $P = 0.002$ (all), $P = 0.012$ (year 3), $P = 0.077$ (year 5), $P = 0.011$ (year 9). The P -trends for HEI were: $P = 0.029$ (all), $P = 0.016$ (year 3), $P = 0.42$ (year 5), $P = 0.50$ (year 9). Regressions were adjusted for maternal socioeconomic status, educational attainment, cigarette smoking and alcohol consumption during pregnancy, daily energy intake, age at recruitment, parity, prepregnancy BMI, and child sex and exact age at follow-up. GEE, generalized estimating equation; Q, quartile; Ref., reference.

that participants with a better dietary quality are also likely to have a diet that is of lower inflammatory potential. However, E-DII likely captures slightly different dimensions of the diet compared with other dietary quality indices because it is designed specifically to reflect dietary potential to influence inflammation, which is implicated in the pathogenesis of many diseases. When we modeled E-DII and HEI-2015 scores simultaneously, the associations for HEI-2015 largely attenuated, suggesting that the protective influence of maternal healthy eating on offspring asthma risk could be principally mediated through the anti-inflammatory pathways.

The mechanisms underpinning the associations of maternal whole dietary quality and inflammatory potential on offspring asthma risk are unclear but could be due to impacts on fetal airway and immune system development (7). In animal studies, normal-weight dams fed a high-fat diet delivered offspring with chronic higher airway inflammation (indicated by elevated proinflammatory cytokine concentrations in lung tissues) and hyperreactivity (40). Other maternal dietary factors also could influence offspring asthma risk through fetal immune system programming. For instance, low maternal vitamin E intake was associated with higher neonatal T-helper cell proliferative responses of cord blood mononuclear cells, which are in turn associated with subsequent development of atopic diseases (41, 42). In addition, fish oil supplementation during pregnancy was associated with lower cord blood T-helper 2 cytokine expression (43) and lower cord plasma IL-13 concentration (44), an inducer for type 1 allergy in humans and animals (45). Taken together, it appears biologically plausible for maternal diet to influence offspring asthma risk, especially because the DII and HEI-2015 focus on whole diet and assess multiple healthful/anti-inflammatory and unhealthful/proinflammatory aspects holistically.

Our study has several strengths. The study children were followed up multiple times for 10 y, a rare follow-up period for a study of intergenerational influence of maternal diet on offspring asthma. We studied diet in holistic ways, thus increasing the applicability to public health messaging. The prospective design of our study also established the temporal sequence of our exposure and outcome, and we were able to adjust for a comprehensive list of maternal and childhood factors. Furthermore, we also investigated potential intergenerational influence of paternal dietary quality and inflammatory potential on offspring asthma risk.

Nonetheless, the study results should be interpreted with some limitations in mind. First, we measured maternal diets only once during early pregnancy, thus precluding investigation of potential differential influence of in utero diets on offspring asthma risk during different developmental stages. However, in a UK study maternal dietary intakes and patterns did not change substantially during pregnancy (46). Similarly, in a US study, a strong correlation (Pearson $r = 0.61$; $P < 0.0001$) was noted between maternal DII scores in the first and second trimester (47). There are also concerns about measurement error using self-reported dietary intake data, though these errors are likely nondifferential (thus more likely to bias effect estimates toward null) given that maternal dietary assessment precedes offspring asthma diagnosis. The authors acknowledge that criteria used by GPs to diagnose asthma could vary. However, it is unlikely that any potential misclassification of asthma would be related to

maternal diet assessed during pregnancy; thus, effect estimates were more likely to have been biased toward null. Although the lack of paternal associations in a small subsample of our study suggests the specificity of in utero dietary influence on offspring asthma risk, these findings should be replicated in studies with a larger sample size of fathers and offspring asthma cases. Compared with participants included in the current analysis, mothers who were not included tended to be younger, had lower educational attainment and socioeconomic status, had a more proinflammatory and less healthy diet, and were more likely to be smokers (**Supplementary Table 4**). These observations suggest that our results may be more applicable to generally healthier mothers in Ireland, and that our observed estimates could have been an underestimation in populations with more proinflammatory and less healthy diets. Last, as with any observational study, residual confounding remains a concern and causality cannot be claimed.

In conclusion, in this relatively large prospective cohort with a long follow-up period, a maternal diet that is of lower quality and higher inflammatory potential is associated with a higher risk of offspring asthma risk. Pending confirmation from randomized controlled trials (which could be resource-intensive and involve time gap of evidence), reducing maternal dietary inflammation and improving overall dietary quality during pregnancy could be a promising strategy for reducing childhood asthma risk and its associated healthcare burden.

The authors' contributions were as follows—L-WC: conceptualized the current study, conducted statistical analysis, interpreted data, and wrote the first draft of the manuscript; BL: conducted literature review and preliminary analysis under the guidance of L-WC and CMP; PN: generated HEI score; NS, JRH: computed DII score; CMM: contributed to data collection and interpretation of results; JM: is the data manager of the Lifeways study who oversaw data management and quality; CCK: conceived and oversaw the Lifeways study at all stages of data collection and analysis and contributed to data interpretation; CMP: conceptualized the current study, supervised the analysis, and contributed to data interpretation; and all authors: critically revised and approved the final manuscript.

JRH owns a controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the DII from the University of South Carolina to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. NS is an employee of CHI. All other authors report no conflicts of interest.

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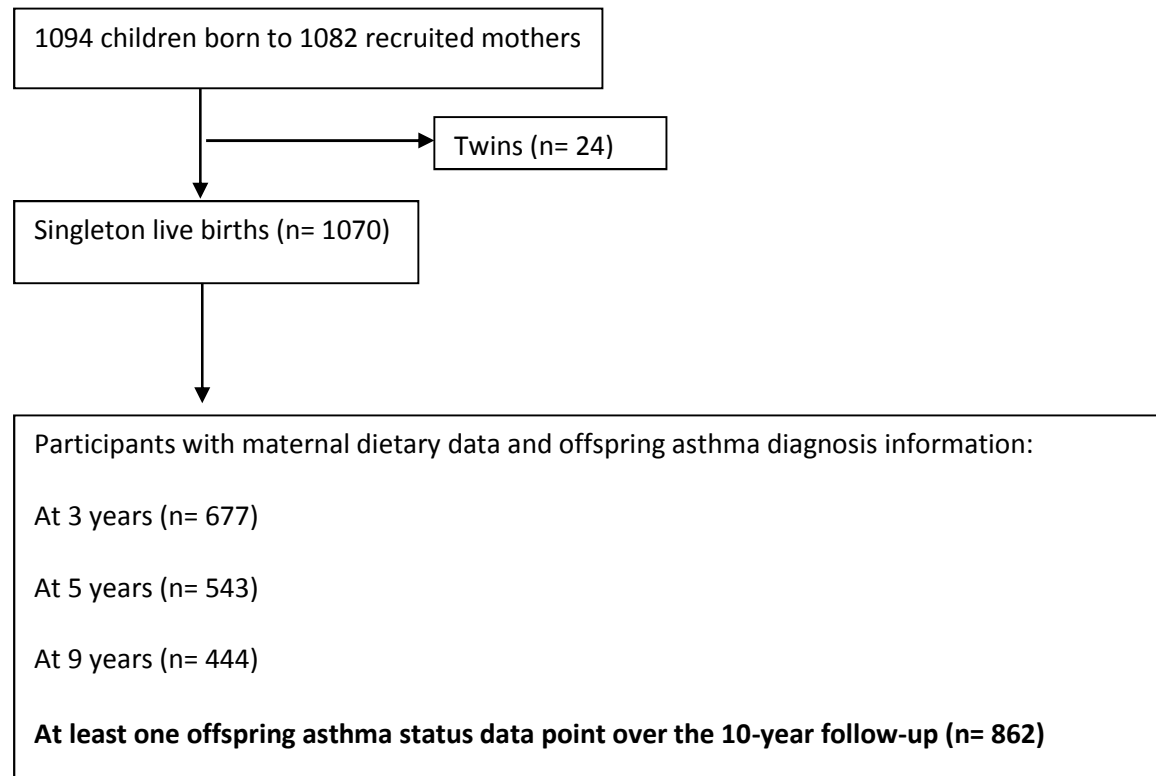
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Ling-Wei Chen, Becky Lyons, Pilar Navarro, Nitin Shivappa, John Mehegan, Celine Murrin, James R. Hébert, Cecily C. Kelleher, Catherine M. Phillips, for the Lifeways Cross Generation Cohort Study

Online Supplementary Material

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Supplemental Figure 1 Participant flow chart



Maternal dietary inflammatory potential and quality are associated with offspring asthma risk over 10-year follow-up: The Lifeways Cross-Generation Cohort Study. Chen *et al.* “Online Supplementary Material”

Supplemental Table 1 *List of components (n= 29) used to calculate the Dietary Inflammatory Index scores in the Lifeways cohort study*

Energy intake	Thiamine	Vitamin A	Iron	Total fat
Carbohydrate	Riboflavin	Beta-carotene	Selenium	SFA
Protein	Niacin	Vitamin D	Magnesium	MUFA
Alcohol	Vitamin B6	Vitamin E	Garlic	PUFA
Tea	Folic acid	Vitamin C	Onion	Cholesterol
Caffeine	Vitamin B12	Zinc	Fibre	

MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids

Maternal dietary inflammatory potential and quality are associated with offspring asthma risk over 10-year follow-up: The Lifeways Cross-Generation Cohort Study. Chen *et al.* “Online Supplementary Material”

Supplemental Table 2 Sensitivity analyses for the associations of maternal energy-adjusted dietary inflammatory index and healthy eating index with offspring asthma risk over a 10-year follow-up in the Lifeways cohort study¹

	Over 10-year follow-up	Year 3	Year 5	Year 9
E-DII				
Further adjustment ²	1.34 (1.09, 1.64)**	1.45 (1.05, 1.98)*	1.35 (0.98, 1.88) ^T	1.33 (0.99, 1.77) ^T
Study site ³	1.35 (1.10, 1.65)**	1.41 (1.04, 1.92)*	1.44 (1.05, 1.98)*	1.37 (1.04, 1.80)*
Exclusion based on <500-3500 kcal/d	1.37 (1.12, 1.68)**	1.38 (1.01, 1.88)*	1.44 (1.05, 1.98)*	1.43 (1.08, 1.89)*
Exclusion based on <500-5000 kcal/d	1.32 (1.08, 1.62)**	1.38 (1.02, 1.88)*	1.36 (1.00, 1.85) ^T	1.40 (1.06, 1.84)*
HEI-2015				
Further adjustment ²	0.78 (0.64, 0.94)*	0.70 (0.52, 0.93)*	0.82 (0.61, 1.10)	0.86 (0.66, 1.12)
Study site ³	0.77 (0.64, 0.93)**	0.70 (0.53, 0.93)*	0.78 (0.59, 1.02) ^T	0.84 (0.65, 1.07)
Exclusion based on <500-3500 kcal/d	0.78 (0.64, 0.95)*	0.73 (0.54, 0.98)*	0.80 (0.60, 1.08)	0.83 (0.63, 1.09)
Exclusion based on <500-5000 kcal/d	0.78 (0.64, 0.94)*	0.73 (0.54, 0.97)*	0.79 (0.60, 1.05)	0.82 (0.64, 1.07)

E-DII, energy-adjusted dietary inflammatory index; HEI-2015, healthy eating index 2015

¹Values are OR (95% CI) from generalized estimating equations (for overall estimates over a 10-year follow-up) and logistic regressions for individual follow-up time points at Year 3, 5, and 9. Regressions are adjusted for exact child’s age at each follow-up, maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during pregnancy, daily total energy intake, age at recruitment, parity, pre-pregnancy body mass index, and child sex.

²Additionally adjusted for childhood factors (breastfeeding, childcare attendance, dietary quality, active and sedentary time), dampness in house, paternal smoking around the time of maternal pregnancy, and parental asthma history.

³Additionally adjusted for indicator of participants’ recruitment site.

^T*P* <0.10; **P* <0.05; ***P* <0.01

Supplemental Table 3 Mutual adjustment analyses for the associations of maternal energy-adjusted dietary inflammatory index and healthy eating index with offspring asthma risk over a 10-year follow-up in the Lifeways cohort study¹

	Over 10-year follow-up	Year 3	Year 5	Year 9
E-DII				
Continuous	1.22 (0.95, 1.57)	1.23 (0.85, 1.79)	1.34 (0.90, 1.98)	1.37 (0.96, 1.97) ^T
Q1	Ref	Ref	Ref	Ref
Q2	1.52 (0.88, 2.61)	2.27 (0.92, 5.59) ^T	1.20 (0.53, 2.67)	1.67 (0.84, 3.30)
Q3	2.22 (1.26, 3.91)**	2.14 (0.83, 5.55)	2.13 (0.94, 4.85) ^T	2.58 (1.23, 5.40)*
Q4	2.09 (1.10, 3.94)*	2.59 (0.94, 7.11) ^T	1.97 (0.76, 5.12)	3.01 (1.26, 7.18)*
<i>P-trend</i>	0.019	0.14	0.12	0.010
HEI-2015				
Continuous	0.86 (0.69, 1.09)	0.79 (0.55, 1.12)	0.92 (0.64, 1.30)	1.02 (0.73, 1.41)
Q1	Ref	Ref	Ref	Ref
Q2	1.21 (0.76, 1.94)	1.11 (0.56, 2.22)	1.15 (0.56, 2.36)	1.34 (0.68, 2.64)
Q3	0.78 (0.47, 1.30)	0.70 (0.32, 1.49)	0.80 (0.37, 1.73)	0.87 (0.43, 1.77)
Q4	0.89 (0.50, 1.59)	0.53 (0.21, 1.37)	1.17 (0.50, 2.76)	1.54 (0.72, 3.28)
<i>P-trend</i>	0.48	0.17	0.93	0.41

E-DII, energy-adjusted dietary inflammatory index; HEI-2015, healthy eating index 2015; Q, quartile; Ref, reference

¹Values are OR (95% CI) from generalized estimating equations (for overall estimates over a 10-year follow-up) and logistic regressions for individual follow-up time points at Year 3, 5, and 9. Regressions are adjusted for exact child's age at each follow-up, maternal socio-economic status, education attainment, cigarette smoking and alcohol consumption during pregnancy, daily total energy intake, age at recruitment, parity, pre-pregnancy body mass index, and child sex; E-DII and HEI-2015 were mutually adjusted (included in the same model) for the estimates presented in this table.

^T*P* < 0.10; **P* < 0.05; ***P* < 0.01

Supplemental Table 4 Comparison of characteristics between included and not-included mother-child pairs¹

	Included in the analysis (<i>n</i> = 862)	Not included in the analysis (<i>n</i> = 208)	<i>P</i> -value ²
E-DII score	0.4 ± 1.7	0.8 ± 1.8	0.003
HEI-2015 score	52.4 ± 8.5	50.7 ± 9.2	0.014
Maternal age at recruitment, y	30.4 ± 5.8	27.6 ± 6.0	<0.001
Maternal pre-pregnancy BMI, kg/m ²	23.8 ± 4.2	23.7 ± 4.3	0.64
<i>Maternal education status</i>			0.024
Below tertiary	414 (49.1%)	117 (57.9%)	
Tertiary or above	429 (50.9%)	85 (42.1%)	
<i>Parity</i>			0.13
Nulliparous	374 (43.8%)	100 (49.8%)	
Non-nulliparous	479 (56.2%)	101 (50.2%)	
<i>Cigarette smoking during early pregnancy</i>			<0.001
No	613 (72.4%)	119 (57.8%)	
Yes	234 (27.6%)	87 (42.2%)	
<i>Alcohol use during early pregnancy</i>			0.37
No	261 (30.4%)	69 (33.7%)	
Yes	597 (69.6%)	136 (66.3%)	
<i>Eligibility to join the General Medical Services Scheme</i>			<0.001
No	719 (84.2%)	151 (72.9%)	
Yes	135 (15.8%)	56 (27.1%)	
<i>Child sex</i>			0.24
Female	445 (51.6%)	98 (47.1%)	
Male	417 (48.4%)	110 (52.9%)	

E-DII, energy-adjusted dietary inflammatory index; HEI-2015, healthy eating index 2015

¹Values are mean ± SD or *n* (%).

²*P*-values were derived from independent *t*-test for continuous variables and chi-square test for categorical variables.