**Maternal diet in pregnancy and child’s respiratory outcomes: an individual participant data meta-analysis of 18,000 children**

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**Contribution of authors to the study**

SMB, EM, VJ and LD contributed to the conception and design, acquisition of data, analyses and interpretation of the data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published.

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**Ethical approvals**

Specific cohort approvals are for ALSPAC by the ALSPAC Ethics and Law Committee (IRB00003312) and Local Research Ethics Committees, informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time; for EDEN by the Ethics Committee (CCPPRB) and CNIL (Commission Nationale Informatique et Liberté), the French data privacy institution; for Generation R by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam; for Lifeways by the University College Dublin Research Ethics Committee and St. Vincent’s University Hospital Research Ethics Committee; for REPRO\_PL by the Ethical Committee of the Nofer Institute of Occupational Medicine, Łódź, Poland (Decisions No. 7/2007, 3/2008, 22/2014); for ROLO by the Ethics Committee of the National Maternity Hospital, Dublin, Ireland; and for SWS by the Southampton and South West Hampshire Research Ethics Committee.

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**Conflict of interest**

The study sponsors had no role in the study design, data analysis, interpretation of data, or writing of this report.

**Disclosure**

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

**Take home message**

A suboptimal maternal diet in pregnancy, as defined by a higher inflammatory potential or low quality of the diet, does not play an important role in the development of respiratory diseases in childhood.

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**ABSTRACT**

**Rationale** Severe fetal malnutrition has been related to an increased risk of respiratory diseases later in life, but evidence for the association of a suboptimal diet during pregnancy with respiratory outcomes in childhood is conflicting. We aimed to examine whether a pro-inflammatory or low-quality maternal diet during pregnancy was associated with child’s respiratory health.

**Methods** We performed an individual participant meta-analysis among 18,326 mother-child pairs from seven European birth cohorts. Maternal pro-inflammatory and low-quality diet were estimated by energy-adjusted Dietary Inflammatory Index (E-DIITM) and Dietary Approaches to Stop Hypertension (DASH) scores. Preschool wheezing and school-age asthma were measured by questionnaires and lung function by spirometry.

**Results** After adjustment for lifestyle and sociodemographic factors, we observed that a higher maternal E-DII score (a more pro-inflammatory diet) during pregnancy was associated only with a lower FVC in children (Z-score difference (95% confidence interval (CI)): -0.05 (-0.08, -0.02), per IQR increase). No linear associations of the maternal E-DII or DASH score with child’s wheezing or asthma were observed. When exploratively examining the extremes, a very low DASH score (<10th percentile) (a very low dietary quality) was associated with an increased risk of preschool wheezing and a low FEV1/FVC (z-score <-1.64) (OR (95% CI) 1.20 (1.06, 1.36), 1.40 (1.06, 1.85), compared to ≥10th percentile), with corresponding population attributable risk fractions of 1.7% and 3.3%.

**Conclusion** Main results from this individual participant data meta-analysis do not support the hypothesis that maternal pro-inflammatory or low-quality diet in pregnancy are related to respiratory diseases in childhood.

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**Key words** diet; pregnancy; asthma; pulmonary function test; meta-analysis

**INTRODUCTION**

Asthma is a common disorder in childhood, and associated with respiratory health problems in adulthood [1, 2]. It is therefore important to identify early-life modifiable risk factors. Fetal exposure to a suboptimal diet during pregnancy might affect the maturation of the lungs and immune system, leading to a lower lung function and a higher risk of wheezing and asthma in childhood [3]. Severe malnutrition in pregnancy has previously been associated with an increased risk of respiratory diseases later in life [4]. Studies examining maternal diet during pregnancy and childhood respiratory health mainly focused on the intake of specific nutrients or food groups [5]. However, examining the overall diet might take the interactions within the diet into account and be better translatable to dietary guidelines [6]. The E-DIITM (energy-adjusted Dietary Inflammatory Index) [7] and DASH (Dietary Approaches to Stop Hypertension) [8] provide dietary scores for the inflammatory potential and overall quality of the diet, respectively. Cohort studies showed that a higher maternal E-DII score in pregnancy was associated with a higher risk of an early wheeze trajectory and a lower mid-expiratory flow or a higher risk of asthma in childhood [9, 10]. The relation of the DASH score with respiratory outcomes has been studied only in adults, where a DASH-promoting behavioural intervention seemed to improve asthma control [11]. To date, a pooled analysis across cohorts which examines the relation of the inflammatory potential and overall quality of maternal diet during pregnancy with child’s respiratory health is lacking.

We performed an individual participant data meta-analysis among 18,326 children, participating in seven European birth cohort studies. We assessed the associations of maternal diet during pregnancy, as summarized by the E-DII and DASH score, with preschool wheezing, school-age asthma and lung function, and estimated the impact of these associations on the general population by calculating the population attributable fraction (PAF).

**METHODS**

This meta-analysis was performed among seven European prospective birth cohorts participating in the ALPHABET consortium, which aims to examine the early-life nutritional programming of non-communicable diseases (supplemental methods) [12, 13]. We included 18,326 mother-child pairs for the current analyses (supplemental methods).

**Maternal diet** Information obtained from food frequency questionnaires (FFQs) before or during pregnancy was used to generate the maternal E-DII and DASH scores (Table E1, Table E2), as previously described (supplemental methods) [7, 13]. To control for the effect of the total energy intake the E-DII, calculated per 1,000 kilocalories (kcal) of food consumed, was used. The E-DII in ALPHABET was generated from 20-28 dietary parameters, out of 44 possible parameters. A higher E-DII score characterizes a more pro-inflammatory diet [7]. For the seven cohorts in the ALPHABET project, a DASH score was generated. This score was composed of eight food components, based mainly on the Fung method with a scoring system based on quintile rankings in each cohort [8, 13]. A lower DASH score characterizes a lower dietary quality. For the main analyses, we used data collected at one time-point, preferably in early-pregnancy (first or second trimester) (Generation R, Lifeways, REPRO\_PL, ROLO, SWS) since this period is of specific importance for lung disease development later in life [14], or, if not available, in late-pregnancy (third trimester) (ALSPAC, EDEN).

**Respiratory health** Data on preschool wheezing and school-age asthma was mainly obtained from questions adapted from the International Study on Asthma and Allergy in Childhood questionnaire [15]. We defined preschool wheezing as ‘‘ever reported wheezing during the first 4 years of life’’ and school-age asthma as ‘‘asthma diagnosis reported between 5 and 10 years’’ [16]. Cohort-specific information is shown in supplemental methods and Table E1. All cohorts obtained lung function measures by spirometry according to the ATS/ERS guidelines [17]. Lung function measures included forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC and forced expiratory flow at 25–75% of FVC (FEF25–75), and were converted into sex-, age-, height-, and ethnicity adjusted Z-scores based on the Global Lung Initiative reference values [18].

**Covariates** Information on lifestyle and sociodemographic related confounders, intermediates and effect modifiers was mainly obtained by questionnaires or clinical examinations at the research center (supplemental methods, Table E1).

**Statistical analyses** Dietary scores were analysed as continuous variables to study the linear associations, and additionally as dichotomous variables to explore the effect of the extremes. We first conducted one-stage meta-analyses by using multilevel linear regression models or multilevel logistic regression models to study the associations of the maternal E-DII and DASH scores with child’s respiratory outcomes. In these models, individual participant data from all cohorts were combined and modeled simultaneously, taking into account clustering of participants within cohorts [19]. We included a random intercept at cohort level, which allows intercepts to vary across cohorts. More information on the used models is provided in the supplemental methods. As explorative analyses to examine the effect of an extreme adverse diet in pregnancy, we additionally studied the dichotomous relationships and examined the associations of a very high E-DII score (>90th percentile) or low DASH score (<10th percentile) with wheezing and asthma, and with lung function below the lower limit of normal (LLN) (<5th percentile, equals z-score of -1.64). The highest and lowest 10th percentile cut off for the dietary scores is a common epidemiological approach, in the absence of clinical cut-offs. If consistent associations were observed, we subsequently calculated the population attributable risk fraction (PAF) based on the adjusted odds ratio (OR) and the prevalence of a high E-DII or low DASH score, which indicates the proportion of wheezing, asthma or lung function measures below the LLN attributable to a high E-DII or low DASH score [20]. We considered the linear confounder models as the main models and applied several additional analyses to these models as described in the supplemental methods.

P-values are two-tailed, statistical significance was defined at p-values <0.05. We did not adjust for multiple testing since respiratory outcomes are strongly interrelated [21]. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and RevMan version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and R version 3.6.1 (‘mediation’ package).

**RESULTS**

**Subject characteristics** Table 1 shows the main characteristics, maternal dietary scores and child’s respiratory outcomes of the cohorts, and Table E3 and Table E4 the corresponding information on maternal and child related baseline characteristics. The median age of the included children at lung function measurement was 8.6 years (95% range 5.4-10.2). Of all participants, 51.9 % (n=8,018) had preschool wheezing and 15.6% (n=2,193) had school-age asthma. The correlation between the E-DII and DASH score was moderate (range Pearson r -0.49 to -0.60, p<0.001).

**Maternal E-DII and DASH score and child’s respiratory outcomes** Table 2 shows that after adjustment for confounders, only an association of a higher maternal E-DII score during pregnancy with a lower FVC in the children was observed (Z-score difference (95% CI): -0.05 (-0.08, -0.02)). A lower DASH score was not associated with preschool wheezing, school-age asthma, or lung function measures. We observed no consistent associations for both the maternal E-DII and DASH score with FEF25-75 (results not shown).

When exploratively examining the extremes, we observed after adjustment for confounders no associations of a very high maternal E-DII score (>90th percentile) with child’s respiratory outcomes compared to a normal maternal E-DII score (≤90th percentile) (Figure 1). A very low DASH score (<10th percentile) was associated with a higher risk of preschool wheezing and an FEV1/FVC below the LLN, and borderline associated with a higher risk of asthma (OR (95% CI) 1.20 (1.06, 1.36), 1.40 (1.06, 1.85), 1.17 (1.00, 1.39), respectively, as compared to a DASH score ≥10th percentile)). The estimated proportions of wheezing, a FEV1/FVC below the LLN and asthma attributable to a low DASH score were 1.7%, 3.3% and 1.4%, respectively.

**Additional analyses** Additional adjustment for early growth factors, lower respiratory tract infections, child’s BMI, or child’s E-DII score did not materially change the effects (results not shown). Further mediation analyses showed that early growth factors and child’s E-DII score only explained 6.2% (95% CI: 2.3, 21.0) and 17.8% (2.6, 48.0) of the association of the E-DII score with FVC. We observed a consistent interaction between the maternal DASH score and child’s sex (range p-values interaction terms <0.001 – 0.549), but not between maternal dietary scores and child’s atopic predisposition. After stratification by sex, no consistent differences between boys and girls in the association of the maternal E-DII or DASH score with child’s respiratory outcomes were observed (Table E5). The two-stage random effect meta-analyses indicated at most moderate heterogeneity (range I2 0% - 52%) and similar effects as the one-stage meta-analyses (Figure E2, Figure E3). When we examined the dietary scores per time period of assessment in pregnancy, directions of the associations with respiratory outcomes were similar for all time periods (Table E6). Examining the associations of maternal dietary scores with lung function measures in age groups of children showed that among children ≥8 years, a higher maternal E-DII score was associated with a lower FEV1 and FVC, and a lower maternal DASH score with a lower FEV1 (Table E7). We repeated the main models restricted to complete cases, to mothers with a European birthplace/ethnic background, and excluding one cohort at a time, and mainly observed similar sizes and directions of the effect estimates (Table E7, Table E8a, Table E8b). Excluding only the intervention arm of the ROLO study did not materially change our results (results not shown).

**DISCUSSION**

In this individual-participant data meta-analysis among 18,326 children from seven European birth cohorts, we observed that only a more pro-inflammatory diet during pregnancy was associated with a lower FVC in childhood. When studying the extremes, a very low maternal dietary quality was associated with a higher risk of preschool wheezing and a FEV1/FVC below the LLN in the children, and borderline higher risk of school-age asthma.

**Comparison with previous studies** To our best knowledge, our study is the first individual participant meta-analysis of prospective birth cohorts that examined the associations of the maternal E-DII score with child’s respiratory outcomes. Previous studies showed that a higher E-DII score during pregnancy or in childhood was associated with a higher risk of early wheezing, wheezing trajectories, or asthma, and a lower FEF25-75, but not with other lung function measures or in high risk children only [9, 10, 22]. Differences between results of these studies and our meta-analysis might be due to other definitions of respiratory outcomes. Asthma is difficult to diagnose in children younger than 5 years, and the wheezing pathogenesis including the role of specific viruses in the development of a lower lung function and asthma might differ between age periods [23, 24]. Therefore, we used both preschool wheezing and school-age asthma as outcomes. The association of the E-DII with a lower FVC did not attenuate after additional adjustment for lower respiratory tract infections. However, further studies on the effect of the maternal E-DII score on harmonized longitudinal asthma-symptom phenotypes in the children are needed.

Our study showed no linear associations of the maternal DASH score with child’s respiratory outcomes, but a very-low-quality-diet, defined by a very-low DASH score capturing the intake of multiple food groups, was associated with a higher risk of wheezing and airway obstruction. A Mediterranean diet in pregnancy partly overlaps with the high DASH score diet (DASH diet) and has been associated with a lower risk of wheezing, whereas other dietary patterns, defined based on principal component analysis, were not associated with respiratory outcomes [25, 26]. The advantage of the DASH diet, as compared to these approaches, is that it might better reflect the dietary habits in a non-Mediterranean population and is easy to translate into public health guidelines [6].

**Interpretation of the results** The E-DII score takes many food parameters into account, of which main pro-inflammatory components are trans-fat, saturated fat and cholesterol, and main anti-inflammatory components are nutrients derived from fruits and vegetables and n-3 fatty acids [7]. Underlying mechanisms might be that a high-fat maternal diet leads to fetal lung inflammation and remodelling, which could make the lungs more susceptible to developing asthma later in childhood [27]. Obesity is another factor that is associated with inflammation [28], and this might be the reason why the associations with wheezing and asthma attenuated after adjustment for lifestyle factors including maternal BMI. Also, an indirect effect through early growth factors may play a role in the association of the maternal E-DII score with child’s FVC as shown by the moderate percentage of change of the effect estimates [29]. However, the effect of the association of the maternal E-DII score with child’s FVC was small and might therefore reflect a subclinical change or chance finding.

A DASH diet is mainly characterized by a high intake of fruits and vegetables which are rich in anti-oxidants, and a low intake of added sugars and sodium [13]. Antioxidants might make the lungs less vulnerable to oxidative stress, and thereby may reduce the risk of asthma and airway obstruction [30]. The DASH diet has also been shown to lower the blood pressure [31]. A higher blood pressure in pregnancy, which might reflect a poorer vascular health, has been associated with a higher risk of wheezing and asthma and a lower FEV1/FVC in children [32, 33]. We only observed in our explorative analyses that a very low DASH score was associated with a higher risk of preschool wheezing, airway obstruction and borderline with asthma. However, we were not able to take the DASH score of child’s current diet into consideration. Also, the effect of maternal diet on child’s respiratory outcomes may differ between different periods of pregnancy. Since lung development already starts in the fourth week of pregnancy, adverse exposures in early pregnancy are considered to be specifically important for lung disease development later in life [14]. Further research is needed to understand the effect of maternal diet at different gestational ages during pregnancy and in different periods of early life after birth on lung development across the life course.

Although previous studies showed that high maternal intake of single nutrients including vitamin D and n-3 fatty acids may be beneficial for child’s respiratory health [34, 35], we observed no consistent association of the maternal E-DII or DASH score with respiratory outcomes. This suggests that specific supplements may be of more importance than a balanced diet for asthma development.

The moderate correlation between the E-DII and DASH scores suggest that these scores partly represent different factors of the diet. The scores differ in concept as the E-DII is mainly nutrient based and focusses on the inflammatory effects of the diet whereas the DASH defines the overall quality of the diet based on food components. Our hypothesis for the effect of maternal diet on child’s respiratory outcomes was based on a population with an extreme adverse diet [4]. The distribution of maternal diet during pregnancy in Western countries might be within optimal ranges, and any potential adverse effect might lay in the extremes. Therefore, we studied the extremes by using a common epidemiological cut-off approach, the highest and lowest 10th percentiles, since clinical cut-offs are lacking. Categorization is prone to bias and our analyses are explorative and should be considered as hypothesis-generating. Results suggesting that the associations of an adverse diet with clinically relevant respiratory outcomes only exist in those exposed to an extreme adverse diet should therefore be carefully interpreted. In addition, if we assume that these relationships are causal, the average proportions of wheezing, asthma and an FEV1/FVC below the LLN attributable to a low DASH are tenuous. Whether targeting maternal diet, in addition to other lifestyle and sociodemographic factors, improves child’s respiratory outcomes, could be the subject for future intervention trials but in a population of mothers with an extreme adverse diet only.

**Strengths and limitations** A major strength of this meta-analysis is the use of individual participant data. This resulted in a large sample size and enabled us to harmonize the data, and to reduce the risk of publication bias. However, some limitations do apply. First, dietary scores as well as wheezing and asthma were defined based on questionnaires which could have led to reporting errors. FFQs may also not adequately assess the intake of specific nutrients, such as sodium, a component of the DASH score or the specific food parameters for the E-DII score. Also, missing data in the FFQs might have biased the estimation of the dietary scores. Clearly, we cannot know the effect of foods eaten that are not on the FFQ. Nevertheless, most cohorts used validated questionnaires [13, 15]. Second, although the dietary scores were calculated in all cohorts according to the same methods, there were differences in the included food parameters, length and content of the FFQs, assessed time periods in pregnancy and assessment years. However, two-stage meta-analyses gave similar results and showed limited heterogeneity between the cohort estimates. Although none of the cohorts had information on all 44 possible parameters for the E-DII score, a previous validation study showed that an DII score based on 28 parameters had a good predictive ability, and an additional study showed that a score based on 17 parameters was related to inflammatory markers [36, 37]. Thus, our E-DII score gives a valid, if imprecise, estimation of the inflammatory potential of the diet. We were not able to take potential changes in a mothers diet due to seasonal variation or food aversions into consideration. Also, we did not have information for all cohorts on the exact gestational age at which diet was assessed. However, FFQs are considered an adequate method to measure the usual dietary intake over an extensive period of time, and dietary patterns are suggested not to change much during pregnancy [38, 39]. Thus, our dietary measurements across cohorts were appropriate and support our findings. Third, although the participating cohorts were carefully selected based on a priori power calculations, data availability, and spread throughout Europe, most participants come from two cohorts and have a European birthplace/ethnic background. Therefore, results may not be generalizable to mothers in other geographical regions. Fourth, we did not measure changes in the associations of maternal diet with child’s respiratory outcomes over time. Fifth, to date, no validated method to calculate child’s DASH score is available. Although results remained similar after adjustment for child’s BMI, potential mediating effect of child’s DASH score cannot be fully ruled out. Last, we adjusted for major potential confounders but, as in all observational studies, residual confounding due to unmeasured or insufficiently harmonised factors, such as other socio-demographic factors, environmental pollution, the use of supplements or medication in pregnancy or the duration of breastfeeding, remains an issue. Future randomized controlled intervention trials might minimise the risk of confounding factors influencing the results, but should be carefully considered given the absence of a consistent association in our current study.

**CONCLUSION**

A more pro-inflammatory diet of mothers during pregnancy was only related to a lower FVC in childhood. Both the inflammatory potential and quality of the diet were not consistently related to wheezing or asthma in childhood. Main results from this individual participant data meta-analysis do not support the hypothesis that maternal pro-inflammatory or low-quality diet in pregnancy are related to respiratory diseases in childhood.

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**Table 1.** Characteristics of participating cohorts

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **ALSPAC**  **(United Kingdom)** | **EDEN**  **(France)** | | **Generation R**  **(The Netherlands)** | **Lifeways**  **(Ireland)** | **REPRO\_PL**  **(Poland)** | **ROLO**  **(Ireland)** | **SWS**  **(United Kingdom)** | | |
| Total participants | 10,130 | 843 | | 4,263 | 224 | 523 | 301 | 2,042 | | |
| Inclusion years | 1990-1992 | 2003-2006 | | 2002-2006 | 2001-2003 | 2007-2011 | 2007-2011 | 1998-2002 | | |
| **Pregnancy** |  |  | |  |  |  |  |  | | |
| FFQ (GA in weeks)\*\*\* | 32 | 24-28 | Birth | <24 | 12-16 | 20-24 | ≤28 | PP | 11 | 34 |
| FFQ assessed period | LP | PP | LP | EP | EP | EP | EP | PP | EP | LP |
| E-DII score\* | 0.51 (1.82) | 0.76 (1.65) | | -0.43 (1.10) | -0.12 (1.43) | -1.10 (1.54) | 0.12 (1.74) | 0.27 (1.49) | | |
| DASH score\* | 24.1 (4.0) | 24.3 (4.1) | | 24.4 (4.4) | 25.2 (4.5) | 24.1 (4.4) | 24.2 (4.1) | 24.1 (4.3) | | |
| **Preschool wheezing** |  |  | |  |  |  |  |  | | |
| N | 9,313 | 840 | | 2,876 | NA | 370 | NA | 2,037 | | |
| Age (years)\*\*\* | 0-3.5 | 0-4 | | 1-4 | NA | 1,2 | NA | 0-3 | | |
| Yes %, (N) | 54.4 (5,070) | 36.8 (309) | | 49.7 (1,429) | NA | 18.4 (68) | NA | 56.1 (1,142) | | |
| **School-age asthma** |  |  | |  |  |  |  |  | | |
| N | 7,506 | 842 | | 3,510 | 224 | 275 | 301 | 1,421 | | |
| Age (years)\*\*\* | 8 | 5,8 | | 9 | 9 | 7-8 | 5 | 5 | | |
| Yes %, (N) | 20.3 (1,525) | 12.1 (102) | | 8.9 (312) | 5.4 (12) | 6.2 (17) | 7.6 (23) | 14.2 (202) | | |
| **Lung function** |  |  | |  |  |  |  |  | | |
| N | 5,766 | 838 | | 3,651 | NA | 264 | NA | 730 | | |
| Age (years)\*\* | 8.6 (8.3 - 9.5) | 5.6 (5.4 - 6.0) | | 9.8 (9.4 - 10.7) | NA | 7.2 (7.0 - 8.8) | NA | 6.5 (6.2 - 6.9) | | |
| FEV1 (z-score)\* | -0.03 (1.01) | -0.70 (1.45) | | 0.17 (0.98) | NA | -0.32 (1.74) | NA | 0.09 (0.98) | | |
| FVC (z-score)\* | -0.04 (1.02) | -1.00 (1.48) | | 0.21 (0.93) | NA | -0.44 (1.85) | NA | 0.15 (1.06) | | |
| FEV1/FVC (z-score)\* | 0.05 (1.07) | 0.87 (1.06) | | -0.11 (0.95) | NA | 0.30 (1.25) | NA | -0.08 (1.06) | | |
| FEF25-75 (z-score)\* | -0.15 (1.02) | -0.39 (1.09) | | 0.43 (1.08) | NA | -0.14 (1.01) | NA | -0.25 (0.92) | | |

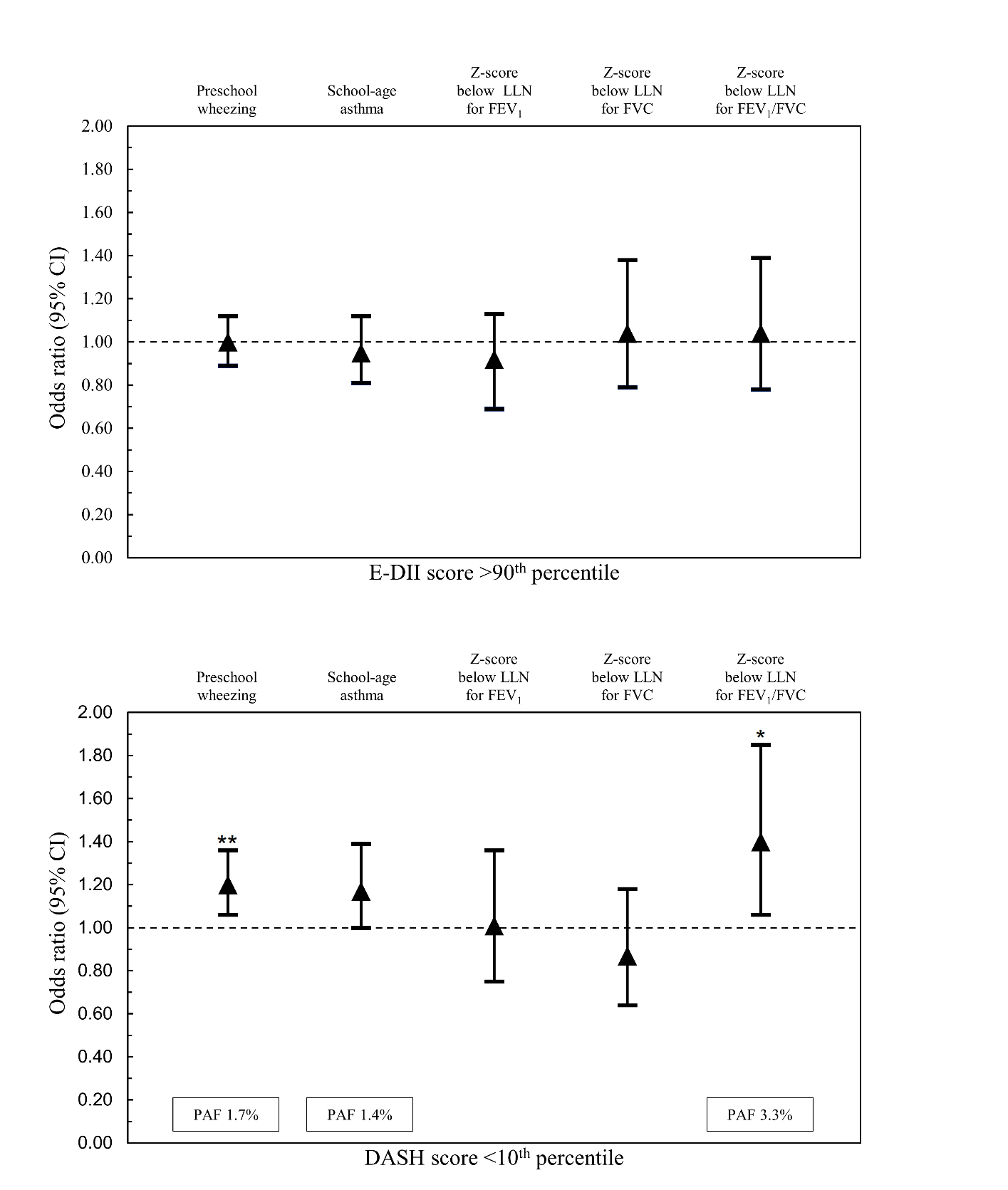
Values are valid percentages (absolute numbers), \*means (SD), \*\*medians (95% range), or \*\*\*time period of questionnaire assessment. Number of participants (N). Food frequency questionnaire (FFQ). Pre pregnancy (PP), early pregnancy (EP): first or second trimester, late pregnancy (LP): third trimester. Gestational age (GA). Forced Expiratory Flow in 1 second (FEV1), Forced Vital Capacity (FVC). Not available (NA).

**Table 2.** Linear associations of maternal E-DII and DASH score with preschool wheezing and school-age asthma and lung function

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Preschool**  **wheezing**  **OR**  **(95% CI)**  **n = 15,436** | **School-age**  **asthma**  **OR**  **(95% CI)**  **n = 14,079** | **FEV1**  **Z-score**  **change**  **(95% CI)**  **n = 11,249** | **FVC**  **Z-score**  **change**  **(95% CI)**  **n = 11,249** | **FEV1/FVC**  **Z-score**  **change**  **(95% CI)**  **n = 11,249** |
| **E-DII score, per IQR increase** | |  |  |  |  |
| Basic model | **1.14 (1.09, 1.20)\*\*** | **1.07 (1.00, 1.15)\*** | -0.03 (-0.05, 0.00) | **-0.04 (-0.07, -0.01)\*** | 0.02 (-0.01, 0.05) |
| *P-value* | *<0.001* | *0.047* | *0.082* | *0.010* | *0.11* |
| Confounder model | 1.02 (0.97, 1.07) | 1.00 (0.93, 1.07) | -0.03 (-0.06, 0.00) | **-0.05 (-0.08, -0.02)\*\*** | 0.03 (-0.00, 0.06) |
| *P-value* | *0.484* | *0.883* | *0.057* | *0.003* | *0.051* |
| **DASH score, per IQR decrease** | |  |  |  |  |
| Basic model | **1.15 (1.10, 1.21)\*\*** | **1.16 (1.08, 1.24)\*\*** | -0.01 (-0.04, 0.02) | -0.01 (-0.04 0.02) | -0.02 (-0.05, 0.01) |
| *P-value* | *<0.001* | *<0.001* | *0.421* | *0.865* | *0.122* |
| Confounder model | 1.04 (0.98, 1.09) | 1.06 (0.99, 1.14) | -0.02 (-0.05, 0.01) | -0.01 (-0.04, 0.02) | -0.02 (-0.05, 0.01) |
| *P-value* | *0.180* | *0.123* | *0.250* | *0.506* | *0.170* |

Values are derived from multilevel logistic or linear regression models and reflect Odds ratios or changes in Z-scores with their corresponding 95% confidence interval (95% CI) per inter quartile range (IQR) increase in the E-DII score or per IQR decrease in the DASH score. Forced Expiratory Flow in 1 second (FEV1), and Forced Vital Capacity (FVC). Basic models are adjusted for child’s sex, and basic models with DASH as exposure are additionally adjusted for maternal energy intake. The main models are additionally adjusted for maternal BMI, education, birthplace/ethnic background, smoking during pregnancy and parity, and child’s breastfeeding. \*P-value <0.05. **\*\***P-value <0.01.

**Figure 1.** Associations of a high E-DII and low DASH score in pregnancy with preschool wheezing, and school-age asthma and lung function

**~~~~**

Values are derived from multilevel logistic regression models and reflect changes in Odds ratios with 95% confidence interval (95% CI) as compared to the reference group (≤90th percentile for the E-DII score and ≥10th percentile for the DASH score). The population attributable risk fractions (PAFs) indicate the proportion of preschool wheezing, school-age asthma or FEV1/FVC below the lower limit of normal (LLN) attributable to a low DASH score. LLN is defined as z-score for lung function outcome <1.64. Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC). The models are adjusted for maternal BMI, education, birthplace/ethnic background, smoking during pregnancy and parity, and child’s sex and breastfeeding, and the models with DASH as exposure are additionally adjusted for maternal energy intake. \*P-value <0.05. \*\*P-value<0.01.