Maternal polyunsaturated fatty acids and allergic disease development in the offspring

To the Editor,

The increasing global prevalence of allergic diseases makes it imperative to identify modifiable risk factors for allergic disease development. Maternal antenatal plasma fatty acid composition has been proposed as a risk factor of infant allergic disease. Polyunsaturated fatty acids (PUFAs) are key components of cell membranes and influence immune cell function by regulating membrane fluidity, intracellular signaling, and gene expression. They can be classified into n-3 and n-6 PUFAs, which are linked to production of anti-inflammatory and pro-inflammatory molecules, respectively. The fetoplacental unit lacks the desaturase enzymes required to synthesize long chain PUFAs so that, during pregnancy, the fetus is dependent on transplantal supply of PUFAs from the mother.

Only three studies conducted in European countries have examined the association of the ratio of PUFA precursors to products in the maternal bloodstream (e.g., in plasma phospholipids) with offspring allergic disease development and these have reported conflicting results. Dietary n-3 PUFA alpha-linolenic acid (ALA) undergoes desaturation to form longer chain n-3 PUFAs, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Similarly, dietary n-6 PUFA linolenic acid (LA) competes for the same enzymes to form arachidonic acid (AA). These metabolites are further converted into immunomodulatory oxylipin mediators such as eicosanoids. Through their effects on the cell membrane, cell signaling, gene expression, and oxylipin production, PUFAs can influence production of cytokines involved in allergic disease. The ratios of ALA and LA to their respective unsaturated products indicate metabolism efficiency of the precursors. The balance of n-3 to n-6 PUFAs as well as PUFA precursors to their products may influence the risk of allergic disease development.

In this study, we investigated long-term associations between maternal PUFAs in plasma phospholipids during pregnancy and the risk of offspring rhinitis, wheeze, eczema, and allergic sensitization up to age 8 years in the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort. We hypothesized that higher n-3 metabolites is protective against inflammation and allergy and that higher total n-3:total n-6 PUFAs, higher (DHA + EPA):AA and LA:AA ratios and lower ALA:(EPA + DHA) during pregnancy are associated with decreased pro-inflammatory cord blood cytokines at birth and consequently decreased risk of offspring allergic diseases in the first 8 years of life.

Demographic data were gathered by interviewer-administered questionnaires. Offspring allergic outcomes were evaluated using modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires (Appendix S1). Offspring allergic sensitization was determined by skin prick testing at ages 18, 36 months, 5 and 8 years for common allergens in Singapore (Appendix S2). Maternal plasma phospholipids at gestational week 26 were measured using gas chromatography–mass spectrometry (Appendix S3) and infant cord blood cytokines were assayed using modified Luminex assay via DropArray multiplex assay (Appendix S4). Ethics approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group (D/2009/021) and the Centralized Institutional Review Board of SingHealth (2018/2767).

Analyses were performed using the Statistical Package for the Social Sciences, Version 27 (IBM Cooperation, New York) (Appendix S5).

After removing subjects with missing data on maternal plasma PUFAs concentrations and offspring allergic outcomes, 920 mother-offspring pairs were included in the study (Table 1). There were no differences between included and excluded participants except there was a higher proportion of nulliparous women among the excluded participants (Table S1).

In multivariate Poisson analysis with adjustment for maternal age, history of allergy, parity, smoke exposure during pregnancy, educational attainment, mode of delivery, offspring’s sex, breastfeeding practices, and offspring fish oil intake (DHA + EPA):AA (adjRR = 2.2, 95% CI = 1.1–4.3) and total n-3:total n-6 PUFAs (adjRR = 2.3, 95% CI = 1.1–4.9) increased the risk of wheeze by 18 months (Table 2). In stratified analyses by exposure to allergic sensitization by 18 months, these associations were only demonstrated in non-atopic children [(DHA + EPA):AA (adjRR = 2.9, 95% CI = 1.3–6.7) and n-3:n-6 PUFA ratios (adjRR = 3.3, 95% CI = 1.3–8.2)]. No associations were observed between maternal ALA:(DHA + EPA), LA:AA, ALA:LA, total

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**TABLE 1** Demographics of study population

|                          | n     | Median (IQR) or n (%)                  |
|--------------------------|-------|---------------------------------------|
| **Ethnicity**            | 920   |                                       |
| Chinese                  | 501   | (54.5%)                               |
| Indian                   | 171   | (18.6%)                               |
| Malay                    | 247   | (26.8%)                               |
| **Maternal allergy history** | 920   |                                       |
| Yes                      | 352   | (38.3%)                               |
| No                       | 543   | (60.7%)                               |
| **Mother’s educational attainment** | 920   |                                       |
| Post-secondary and higher | 635   | (69.9%)                               |
| Secondary school education or less | 273   | (30.1%)                               |
| **Maternal exposure to smoke during pregnancy week 26** | 920   |                                       |
| Yes                      | 337   | (38.3%)                               |
| No                       | 543   | (61.7%)                               |
| **Parity**               | 920   |                                       |
| Parous                   | 533   | (57.9%)                               |
| Nulliparous              | 387   | (42.1%)                               |
| **Mode of delivery**     | 920   |                                       |
| Vaginal delivery         | 647   | (70.3%)                               |
| Caesarean section        | 273   | (29.7%)                               |
| **Mother’s age at delivery (years)** | 920   | 31.0 (27.5–34.8)                      |
| **Sex of offspring**     | 920   |                                       |
| Female                   | 439   | (47.7%)                               |
| Male                     | 481   | (52.3%)                               |
| **Feeding practices**    | 877   |                                       |
| Mainly formula           | 383   | (43.7%)                               |
| Mainly breastfeeding     | 110   | (12.5%)                               |
| Mixed                    | 384   | (43.8%)                               |
| **Maternal plasma PUFA ratios during pregnancy** | 920   |                                       |
| ALA:(DHA+ EPA)            | 0.03  | (0.02–0.05)                           |
| LA:AA                    | 2.80  | (2.29–3.37)                           |
| ALA:LA                   | 0.01  | (0.01)                                |
| (DHA + EPA):AA           | 0.67  | (0.54–0.84)                           |
| Total n-3 PUFAs (mcg/ml) | 140.15| (101.82–199.08)                       |
| Total n-6 PUFAs (mcg/ml) | 794.04| (621.39–1006.95)                      |
| Total n-3:n-6 PUFA ratio | 0.18  | (0.14–0.22)                           |
| Total PUFAs (mcg/ml)     | 941.96| (733.07–1192.02)                      |
| **Cord blood cytokines at birth (pg/ml)** |       |                                       |
| IL-10                    | 646   | 0.88 (0.61–1.32)                      |
| IL-6                     | 634   | 2.91 (1.70–6.23)                      |
| TNF-α                    | 647   | 3.64 (3.14–4.21)                      |
| Eotaxin                  | 693   | 57.36 (39.29–89.43)                   |
| IL-1RA                   | 670   | 373.81 (239.53–668.35)                |
| IP-10                    | 693   | 68.04 (49.13–97.91)                   |
| MCP-1                    | 690   | 99.76 (69.90–146.96)                  |
| MIG                      | 642   | 12.66 (8.37–18.55)                    |
| MIP-1alpha               | 689   | 6.40 (4.75–8.46)                      |

**Rhinitis by 18 months** | 750   |                                       |
| Yes                      | 396   | (52.8%)                               |
| No                       | 354   | (47.2%)                               |

**Rhinitis by 36 months** | 748   |                                       |
| Yes                      | 472   | (63.1%)                               |
| No                       | 276   | (36.9%)                               |

**Rhinitis by 5 years** | 724   |                                       |
| Yes                      | 491   | (67.8%)                               |
| No                       | 233   | (32.2%)                               |

**Rhinitis by 8 years** | 798   |                                       |
| Yes                      | 515   | (64.5%)                               |
| No                       | 283   | (35.5%)                               |

**Wheeze by 18 months** | 672   |                                       |
| Yes                      | 97    | (14.4%)                               |
| No                       | 575   | (85.6%)                               |

**Wheeze by 36 months** | 651   |                                       |
| Yes                      | 169   | (26.0%)                               |
| No                       | 482   | (74.0%)                               |

**Wheeze by 5 years** | 601   |                                       |
| Yes                      | 211   | (35.1%)                               |
| No                       | 390   | (64.9%)                               |

**Wheeze by 8 years** | 703   |                                       |
| Yes                      | 226   | (32.1%)                               |
| No                       | 477   | (67.9%)                               |

**Eczema by 18 months** | 705   |                                       |
| Yes                      | 156   | (22.1%)                               |
| No                       | 549   | (77.9%)                               |

**Eczema by 36 months** | 666   |                                       |
| Yes                      | 193   | (29.0%)                               |
| No                       | 473   | (71.0%)                               |

**Eczema by 5 years** | 611   |                                       |
| Yes                      | 207   | (33.9%)                               |
| No                       | 404   | (66.1%)                               |

**Eczema by 8 years** | 715   |                                       |
| Yes                      | 233   | (32.6%)                               |
| No                       | 482   | (67.4%)                               |

**Sensitization by 18 months** | 759   |                                       |
| Yes                      | 106   | (14.0%)                               |
| No                       | 653   | (86.0%)                               |

**Sensitization by 36 months** | 700   |                                       |
| Yes                      | 211   | (30.1%)                               |
| No                       | 489   | (69.9%)                               |

**Sensitization by 5 years** | 661   |                                       |
| Yes                      | 324   | (49.0%)                               |
| No                       | 337   | (51.0%)                               |

**Sensitization by 8 years** | 668   |                                       |
| Yes                      | 472   | (70.7%)                               |
| No                       | 196   | (29.3%)                               |
|                          | Month 18 |                      | Month 36 |                      | Year 5  |                      | Year 8  |                      |
|--------------------------|----------|----------------------|----------|----------------------|---------|----------------------|---------|----------------------|
|                          | n        | RR (95% CI)          | p-value  | n        | RR (95% CI)          | p-value  | n        | RR (95% CI)          | p-value  |
| **Allergic rhinitis**    |          |                      |          |          |                      |          |          |                      |          |
| Ln(ALA(DHA + EPA))       | 686      | 0.92 (0.79–1.08)     | .318     | 643      | 0.94 (0.81–1.09)     | .408     | 537      | 0.92 (0.78–1.08)     | .300     |
| Ln(LA:AA)                | 686      | 1.1 (0.8–1.6)        | .550     | 643      | 1.1 (0.8–1.5)        | .627     | 537      | 1.1 (0.7–1.6)        | .653     |
| Ln(ALA:LA)               | 686      | 0.94 (0.81–1.10)     | .463     | 643      | 0.95 (0.82–1.11)     | .534     | 537      | 0.92 (0.78–1.08)     | .319     |
| Ln(DHA + EPA):AA         | 686      | 1.2 (0.9–1.6)        | .284     | 643      | 1.1 (0.8–1.5)        | .399     | 537      | 1.1 (0.8–1.5)        | .611     |
| Ln(Total n-3:n-6 PUFAs)  | 686      | 1.1 (0.8–1.5)        | .618     | 643      | 1.1 (0.8–1.5)        | .697     | 537      | 1.0 (0.7–1.4)        | .943     |
| Ln(Total n-3 PUFAs)      | 686      | 1.0 (0.8–1.3)        | .922     | 643      | 1.0 (0.8–1.2)        | .960     | 537      | 0.96 (0.77–1.21)     | .757     |
| Ln(Total n-6 PUFAs)      | 686      | 0.95 (0.69–1.30)     | .745     | 643      | 0.96 (0.71–1.29)     | .766     | 537      | 0.92 (0.67–1.27)     | .618     |
| Ln(Total PUFAs)          | 686      | 0.96 (0.71–1.30)     | .788     | 643      | 0.96 (0.72–1.29)     | .806     | 537      | 0.92 (0.67–1.27)     | .627     |
| **Wheeze with nebulizers** |          |                      |          |          |                      |          |          |                      |          |
| Ln(ALA(DHA + EPA))       | 620      | 0.87 (0.62–1.22)     | .433     | 586      | 0.93 (0.71–1.22)     | .616     | 479      | 0.97 (0.74–1.26)     | .795     |
| Ln(LA:AA)                | 620      | 1.1 (0.5–2.4)        | .754     | 586      | 1.1 (0.6–2.0)        | .767     | 479      | 1.0 (0.5–1.8)        | .988     |
| Ln(ALA:LA)               | 620      | 1.0 (0.7–1.5)        | .779     | 586      | 0.97 (0.74–1.26)     | .793     | 479      | 1.0 (0.8–1.3)        | .917     |
| Ln(DHA + EPA):AA         | 620      | 2.2 (1.1–4.3)        | .019     | 586      | 1.2 (0.7–2.0)        | .482     | 479      | 1.2 (0.7–2.0)        | .494     |
| Ln(Total n-3:n-6 PUFAs)  | 620      | 2.3 (1.1–4.9)        | .023     | 586      | 1.1 (0.6–2.0)        | .661     | 479      | 1.2 (0.7–2.1)        | .469     |
| Ln(Total n-3 PUFAs)      | 620      | 1.4 (0.9–2.3)        | .151     | 586      | 0.92 (0.64–1.33)     | .671     | 479      | 0.97 (0.68–1.39)     | .883     |
| Ln(Total n-6 PUFAs)      | 620      | 0.97 (0.50–1.87)     | .930     | 586      | 0.77 (0.46–1.28)     | .319     | 479      | 0.81 (0.49–1.32)     | .391     |
| Ln(Total PUFAs)          | 620      | 1.1 (0.6–2.1)        | .791     | 586      | 0.79 (0.48–1.31)     | .362     | 479      | 0.83 (0.51–1.35)     | .464     |
| **Eczema**               |          |                      |          |          |                      |          |          |                      |          |
| Ln(ALA(DHA + EPA))       | 645      | 1.1 (0.8–1.3)        | .687     | 601      | 0.97 (0.77–1.23)     | .805     | 491      | 1.0 (0.8–1.3)        | .856     |
| Ln(LA:AA)                | 645      | 1.6 (0.9–2.8)        | .119     | 601      | 1.3 (0.8–2.3)        | .308     | 491      | 1.3 (0.7–2.4)        | .362     |
| Ln(ALA:LA)               | 645      | 1.0 (0.8–1.3)        | .833     | 601      | 0.98 (0.78–1.24)     | .886     | 491      | 1.0 (0.8–1.3)        | .842     |
| Ln(DHA + EPA):AA         | 645      | 1.3 (0.8–2.1)        | .348     | 601      | 1.3 (0.8–2.0)        | .298     | 491      | 1.2 (0.7–2.0)        | .430     |
| Ln(Total n-3:n-6 PUFAs)  | 645      | 1.1 (0.6–1.8)        | .842     | 601      | 1.1 (0.7–1.8)        | .616     | 491      | 1.1 (0.6–1.8)        | .773     |
| Ln(Total n-3 PUFAs)      | 645      | 1.0 (0.7–1.4)        | .894     | 601      | 1.1 (0.8–1.5)        | .601     | 491      | 1.1 (0.8–1.6)        | .572     |
| Ln(Total n-6 PUFAs)      | 645      | 1.0 (0.6–1.6)        | .998     | 601      | 1.1 (0.7–1.7)        | .790     | 491      | 1.1 (0.7–1.8)        | .600     |
| Ln(Total PUFAs)          | 645      | 1.0 (0.6–1.6)        | .969     | 601      | 1.1 (0.7–1.7)        | .747     | 491      | 1.1 (0.7–1.8)        | .588     |

(Continues)
TABLE 2 (Continued)

| Month 18 | Year 8 |
|----------|--------|
| n | RR (95% CI) | p-value |
| 902 | 1.0 (0.8–1.2) | .903 |
| 848 | 1.0 (0.8–1.2) | .867 |
| 829 | 1.0 (0.8–1.2) | .829 |
| 889 | 0.97 (0.84–1.13) | .598 |
| 928 | 0.97 (0.84–1.13) | .506 |
| 947 | 0.97 (0.84–1.13) | .416 |
| 998 | 0.97 (0.84–1.13) | .326 |
| 998 | 0.97 (0.84–1.13) | .236 |
| 998 | 0.97 (0.84–1.13) | .146 |

Note: Benjamini-Hochberg correction with false discovery rate at 0.40 and n = 32 was applied to each outcome. Significant p-values are in bold.

a Adjusted for maternal age at delivery, history of allergy, parity, educational attainment, smoke exposure during pregnancy, mode of delivery, breastfeeding practices, offspring’s sex, and year 3 fish oil intake.

b Adjusted for maternal age at delivery, history of allergy, parity, educational attainment, smoke exposure during pregnancy, mode of delivery, breastfeeding practices, offspring’s sex, and year 5 fish oil intake.

We next determined if maternal plasma (DHA + EPA):AA and total n-3:n-6 PUFAs were related to cord blood cytokines; only higher total n-3:n-6 PUFAs ratio was negatively associated with eotaxin (adjβ = −0.25, 95% CI = −0.44 to −0.08) and weakly associated with interleukin-12 subunit p40 (IL-12p40) (adjβ = −0.12, 95% CI = −0.24 to 0, Table 3). There was no mediation effect by any cord blood cytokine in the associations between (DHA + EPA):AA or total n-3:n-6 PUFAs ratios and offspring allergic disease in mediation analysis (Table S2).

In this study, we observed that maternal plasma ALA:(DHA + EPA) and LA:AA were not associated with the development of offspring allergic diseases by the 8-year follow-up. The results are supported by the Generation R study and Avon Longitudinal Study of Parents and Children studies. Conversely, the Southampton Women's Survey found that ratios of ALA and LA to their products in maternal plasma phosphatidylcholine associated with the risks of wheeze and skin sensitization at 6 years of age, respectively.

It is possible that downstream metabolites of DHA, EPA, and AA may be key to controlling allergy development as their inflammatory activities may differ from one another. The above studies included all unsaturated metabolic products of ALA and LA in the computation of precursor: metabolite ratios while we only included the major metabolites DHA and EPA and AA, respectively. For example, LA is metabolized to form AA, which in turn produces pro-inflammatory prostaglandins promoting allergic sensitization and to anti-inflammatory lipoxins promoting the resolution of allergy.

Thus, the overall effect of an individual PUFA or of groups or ratios of PUFAs is difficult to predict. The effect of maternal PUFAs might also be outweighed by other environmental factors which are more relevant to allergy development in our cohort, such as smoking exposure and childcare center attendance during infancy.

We observed that higher maternal total n-3:n-6 PUFAs and (DHA + EPA):AA ratios were associated with a higher risk of early life wheeze by 18 months, especially in non-atopic children. This finding is supported by the Southampton Women's Survey which reported that AA was inversely associated with non-atopic persistent/late wheeze. We postulate that lower maternal n-6 PUFAs levels may increase susceptibility to infections, especially since wheeze in early life is largely caused by viruses or bacteria rather than allergy development. In particular, AA has the strongest antibacterial and antiviral effect in the lungs, as compared to other PUFAs, possibly by disrupting the microbial cell membrane integrity. Early exposure to n-6 PUFAs and AA in utero may promote robust immune system development, which protects against infections later in infancy. Further research is needed to elucidate the underlying mechanisms, with our study suggesting the association between n-3:n-6 PUFA and (DHA + EPA):AA ratios and offspring wheeze by 18 months is not mediated by cord blood cytokine concentrations.

Strengths of this study include the long-term follow-up of participants and the collection of data on allergic diseases, as well as skin
plasma (n-3 to n-6 PUFA) is protective, nor that n-6 PUFA increases the risk of offspring allergy development. However, our results suggest that higher n-3 to n-6 PUFA ratios may be linked to increased risk of early life wheezing illness.

We found no convincing evidence to suggest that maternal plasma n-3 PUFA is protective, nor that n-6 PUFA increases the risk of offspring allergy development. However, our results suggest that higher n-3 to n-6 PUFA ratios may be linked to increased risk of early life wheezing illness.

### Table 3

| Cytokines (pg/ml) | n | B (95% CI) | p-value | n | B (95% CI)* | p-value* |
|------------------|---|-----------|---------|---|-------------|---------|
| **Ln(DHA + EPA):AA** | | | | | | |
| ln(LL-10) | 645 | 0 (-0.15 to 0.14) | .965 | 566 | -0.03 (-0.19 to 0.13) | .680 |
| ln(LL-6) | 634 | 0 (-0.23 to 0.22) | .966 | 556 | 0 (-0.24 to 0.24) | .983 |
| ln(TNF-α) | 647 | -0.04 (-0.09 to 0.01) | .128 | 568 | -0.03 (-0.08 to 0.03) | .341 |
| ln(Eotaxin) | 693 | -0.17 (-0.31 to -0.02) | .024 | 614 | -0.17 (-0.33 to -0.01) | .033 |
| ln(IL-1RA) | 670 | -0.03 (-0.24 to 0.17) | .753 | 592 | -0.09 (-0.32 to 0.14) | .456 |
| ln(IP-10) | 693 | 0.05 (-0.08 to 0.18) | .458 | 614 | 0.06 (-0.09 to 0.20) | .441 |
| ln(MCP-1) | 690 | -0.06 (-0.21 to 0.09) | .432 | 611 | -0.09 (-0.25 to 0.08) | .288 |
| ln(MIG) | 642 | -0.03 (-0.20 to 0.15) | .772 | 569 | -0.01 (-0.2 to 0.18) | .911 |
| ln(MIP-1alpha) | 689 | -0.02 (-0.13 to 0.09) | .687 | 610 | -0.03 (-0.15 to 0.09) | .590 |
| ln(MIP-1beta) | 643 | -0.01 (-0.16 to 0.14) | .877 | 568 | -0.02 (-0.18 to 0.15) | .834 |
| ln(VEGF-A) | 693 | -0.12 (-0.29 to 0.06) | .203 | 614 | -0.13 (-0.33 to 0.06) | .185 |
| ln(IL-12p40) | 693 | -0.04 (-0.14 to 0.06) | .459 | 614 | -0.09 (-0.20 to 0.02) | .112 |
| ln(PAI-1) | 693 | -0.06 (-0.17 to 0.05) | .293 | 614 | -0.08 (-0.21 to 0.04) | .207 |
| ln(CRP) | 691 | -0.01 (-0.19 to 0.17) | .887 | 612 | -0.08 (-0.28 to 0.11) | .407 |

| **Ln(total n-3:total n-6 PUFA)** | | | | | | |
| ln(LL-10) | 645 | -0.06 (-0.21 to 0.10) | .466 | 566 | -0.10 (-0.28 to 0.07) | .255 |
| ln(LL-6) | 634 | -0.18 (-0.43 to 0.06) | .135 | 556 | -0.12 (-0.38 to 0.14) | .381 |
| ln(TNF-α) | 647 | -0.04 (-0.10 to 0.01) | .134 | 568 | -0.04 (-0.11 to 0.02) | .159 |
| ln(Eotaxin) | 693 | -0.2 (-0.36 to -0.05) | .010 | 614 | -0.25 (-0.42 to -0.08) | **.004** |
| ln(IL-1RA) | 670 | -0.08 (-0.30 to 0.14) | .459 | 592 | -0.15 (-0.40 to 0.10) | .229 |
| ln(IP-10) | 693 | 0.03 (-0.10 to 0.17) | .640 | 614 | 0.02 (-0.14 to 0.17) | .823 |
| ln(MCP-1) | 690 | -0.07 (-0.23 to 0.09) | .381 | 611 | -0.12 (-0.30 to 0.06) | .177 |
| ln(MIG) | 642 | -0.07 (-0.26 to 0.11) | .436 | 569 | -0.08 (-0.29 to 0.13) | .449 |
| ln(MIP-1alpha) | 689 | -0.01 (-0.13 to 0.10) | .816 | 610 | -0.06 (-0.19 to 0.07) | .397 |
| ln(MIP-1beta) | 643 | -0.06 (-0.22 to 0.11) | .500 | 568 | -0.12 (-0.3 to 0.06) | .182 |
| ln(VEGF-A) | 693 | -0.07 (-0.26 to 0.12) | .467 | 614 | -0.10 (-0.32 to 0.11) | .332 |
| ln(IL-12p40) | 693 | -0.05 (-0.16 to 0.06) | .352 | 614 | -0.12 (-0.24 to 0.0) | **.047** |
| ln(PAI-1) | 693 | -0.09 (-0.21 to 0.03) | .138 | 614 | -0.12 (-0.26 to 0.01) | .073 |
| ln(CRP) | 691 | -0.06 (-0.26 to 0.13) | .531 | 612 | -0.10 (-0.31 to 0.12) | .368 |

*Note: Benjamini-Hochberg correction with false discovery rate at 0.40 and n = 14 was applied to adjusted models of each outcomes and significant p-value in bold.

*Adjusted for maternal age at delivery, history of allergy, parity, educational attainment, smoke exposure during pregnancy, mode of delivery, breastfeeding practices, and offspring’s sex.

### Author Contributions

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