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**Original Article**

# Impact of Delivery Mode on Childhood Asthma and *ADAM33* Methylation: A Birth Cohort Study

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**Abstract:**
Cesarean section (CS) rates and childhood asthma are rising, but the link is unclear. In this nested cohort (N=240), elective CS was associated with neonatal ADAM33 hypomethylation (median 20% vs. 100% in emergency CS, p<0.001). While methylation normalized by preschool age, lower levels correlated with higher asthma risk. These findings reveal a novel epigenetic mechanism linking delivery mode to respiratory health, suggesting early-life programming of asthma susceptibility.
**Keywords: Cesarean section; Asthma; ADAM33; DNA methylation; Epigenetics**

## Introduction

Despite a dramatic demographic declining fertility rates shift in China from 6.0 in 1970 to a historic low of 1.3 in 2020, the prevalence of childhood asthma has paradoxically surged.[1] While the birth rate has fallen, ever asthma-like symptoms prevalence among Chinese children has climbed steadily, rising from 0.69% in 1984 to 5.30% in 2021.[2.] This inverse relationship challenges public health systems and suggests that environmental and perinatal factors are driving the allergic epidemic.[3] Among these factors, the "hygiene hypothesis" remains a leading explanation, positing that reduced exposure to microbial agents and changes in perinatal medical practices disrupt early immune development.[4]

One of the most significant perinatal changes in recent decades is the global rise in Cesarean section (CS) deliveries.[5] In many high-income and rapidly industrializing nations, the increase in CS rates parallels the rise in allergic disease.[6] While numerous studies suggest an association between cesarean delivery and childhood wheezing or asthma, the results remain inconsistent.[7] Furthermore, while the epidemiological link is frequently observed, the underlying biological mechanisms that might translate a surgical birth into long-term respiratory pathology remain largely obscure.

Epigenetic modification offers a plausible biological bridge between perinatal environmental exposures and long-term health outcomes. DNA methylation, in particular, is a key mechanism by which early life stressors can permanently alter gene expression.[8] Recent literature has identified differentially methylated regions (DMRs) associated with asthma,[9] with specific attention drawn to the ADAM33 gene.[10] ADAM33 is integral to the transforming growth factor-beta (TGF-β) signaling pathway, playing a critical role in immune regulation, airway remodeling, and fibrosis.[11] Prior research indicates that hypermethylation of the ADAM33 promoter region is linked to childhood asthma.[12] However, it is unknown whether the mode of delivery itself acts as an environmental stressor capable of inducing these specific methylation changes.

This study aims to bridge the gap between epidemiological observation and molecular mechanism. We assessed the association between the mode of delivery and current childhood asthma within a longitudinal cohort to ensure robust statistical power across heterogeneous settings. Crucially, this investigation is the first to evaluate longitudinal variations in ADAM33 gene methylation profiles in children born via different delivery modes. By examining these epigenetic markers, we seek to determine whether Cesarean delivery induces distinct biological responses to perinatal stress, thereby contributing to the pathogenesis of asthma through lasting epigenetic modifications.

## Materials and Methods

### *Study Design and Population*

This study utilized a nested cohort design derived from the Department of Pediatrics. The study protocol was reviewed and approved by the Medical Ethics Committee of the hospital. Written informed consent was obtained from the parents or legal guardians of all participants.

The study consisted of two phases. **For phase 1, a** total of 240 mother–infant pairs in 2023-2024 were enrolled. Participants were categorized into three groups based on delivery mode: vaginal delivery (n=80), elective cesarean section (n=80), and emergency cesarean section (n=80). Exclusion criteria included multiple gestations, stillbirths, and infants with severe congenital malformations. The second phase is to investigate the molecular mechanisms underlying the epidemiological findings, a subset of 26 children was randomly selected for longitudinal methylation analysis from 2021. Biological samples were collected at two critical developmental time points: birth and preschool age (3–4 years). This subset included 10 children from the elective cesarean group, 6 from the emergency cesarean group, and 10 from the vaginal delivery group.

### *Data Collection and Outcome Definitions*

For the full cohort, clinical data were collected via standardized questionnaires and electronic medical records. The primary exposure was the mode of delivery. The primary outcomes were allergic diseases diagnosed or reported within the first year of life, including wheezing, eczema, physician-diagnosed asthma, and atopic dermatitis. Covariates considered as potential confounders included maternal age, parity, infant sex, gestational age, small for gestational age (SGA) status, maternal history of allergy, maternal smoking (active and passive) during pregnancy, maternal education level, annual family income, marital status, breastfeeding duration (6 months), pet ownership, and postnatal passive smoking exposure.

### *Lung Function Assessment (Preschool Sub-cohort)*

For the preschool subset, respiratory health was assessed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Lung function was evaluated via spirometry. The Tiffeneau-Pinelli index (FEV1/FVC) was calculated to assess airway obstruction.

### *DNA Methylation Analysis*

Sample Collection and Extraction: Genomic DNA was isolated from buccal epithelial cells using sterile swabs. DNA extraction was performed immediately following collection using a commercial genomic DNA kit (Tiangen Biotech, Beijing, China) according to the manufacturer's instructions. DNA concentration and purity were quantified using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific).

Bisulfite Conversion and High-Resolution Melting (HRM): Sodium bisulfite modification was performed on 200 ng of genomic DNA using the EZ DNA Methylation-Gold™ Kit (Zymo Research, USA). The methylation status of the ADAM33 gene promoter was quantified using

Methylation-Specific PCR (MSP) coupled with High-Resolution Melting (HRM) analysis.

PCR amplification was conducted in a 10 mL reaction volume containing HRM PCR Master Mix ( Vazyme Biotech, Nanjing, China), 10 pmol of forward and reverse primers, and approximately 10 ng of bisulfite-converted DNA. The analysis was performed on a QuantStudio Real-Time PCR System. Methylation percentages were calculated against standard curves generated from fully methylated and unmethylated controls. Samples with methylation levels <20% were classified as unmethylated.

### *Statistical Analysis*

Data analysis was performed using Stata version 15.0 (StataCorp, USA) and SPSS version 29.0 (IBM Corp, USA). Baseline characteristics were compared using Pearson's chi-square test. Multivariable logistic regression models were constructed to estimate crude (cOR) and adjusted odds ratios (aOR) with 95% confidence intervals (CIs). Model 1 adjusted for perinatal and socioeconomic factors (maternal age, parity, sex, gestational age, SGA, maternal allergy, prenatal smoking, education, income, marriage). Model 2 further adjusted for postnatal environmental factors (breastfeeding, pets, postnatal smoking).

For methylation data, continuous variables were described as medians with interquartile ranges (IQR) due to non-normal distribution. Differences between delivery groups were analyzed using the Kruskal-Wallis test followed by Dunn's post-hoc test. The relationship between methylation levels and lung function (FEV1/FVC) was assessed using Spearman's rank correlation coefficient. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant.

## Results

### *Participant Characteristics*

The demographic and clinical characteristics of the 240 participants are summarized in Table 1.

**Table 1. Baseline demographic and clinical characteristics of the study participants**

| | **Vaginal delivery n=80** | | **Cesarean delivery n=160** | | **p value** |
|---|---|---|---|---|---|
| | **n** | % | **n** | % | |
| Maternal age at pregnancy (years) | | | | | 0.14 |
| <20 | 1 | 1.3 | 1 | 0.6 | |
| 20-29 | 32 | 40.0 | 48 | 30.0 | |
| 30-39 | 45 | 56.3 | 99 | 61.9 | |
| >=40 | 2 | 2.5 | 12 | 7.5 | |
| Parity | | | | | 0.972 |
| 0 | 24 | 29.8 | 46 | 28.8 | |
| 1 | 28 | 34.7 | 56 | 35.0 | |
| >=2 | 28 | 35.4 | 60 | 37.5 | |
| Sex(male) | 40 | 50.0 | 82 | 51.3 | 0.849 |
| Gestational age(weeks) | | | | | <0.001 |
| <37 | 2 | 2.5 | 17 | 10.6 | |
| 37 | 6 | 7.5 | 36 | 22.5 | |
| 38 | 14 | 17.5 | 68 | 42.5 | |
| 39-41 | 58 | 72.5 | 39 | 24.4 | |
| SGA | 2 | 2.5 | 8 | 5.0 | 0.361 |
| Maternal allergies | 41 | 51.3 | 82 | 51.3 | 1.00 |

| | | | | | |
|---|---|---|---|---|---|
| Maternal smoking during pregnancy | 3 | 3.8 | 8 | 5.0 | 0.743 |
| passive smoking during pregnancy | 28 | 35.0 | 58 | 36.3 | 0.846 |
| Maternal education periods (year) | | | | | 0.948 |
| <10 | 3 | 3.8 | 6 | 3.8 | |
| 10-12 | 25 | 31.3 | 53 | 33.1 | |
| 13-16 | 51 | 63.8 | 98 | 61.3 | |
| >=17 | 1 | 1.3 | 3 | 1.9 | |
| Annual family income(CNY) | | | | | 0.997 |
| <200,000 | 4 | 5.0 | 9 | 5.6 | |
| 200,000-499,999 | 54 | 67.5 | 106 | 66.3 | |
| 500,000-999,999 | 18 | 22.5 | 37 | 23.1 | |
| >=1,000,000 | 4 | 5.0 | 8 | 5.0 | |
| Marriage | 77 | 96.3 | 155 | 96.9 | 0.811 |
| Breastfeeding at 6 months | 60 | 75.0 | 114 | 71.3 | 0.532 |
| Pet owner | 19 | 23.8 | 29 | 18.1 | 0.344 |
| Passive smoking exposure of infants at 1 mon | 40 | 50.0 | 81 | 50.6 | 0.923 |
| Allergy disease | | | | | |
| Wheezing | 16 | 20.0 | 32 | 20.0 | 1.00 |
| Eczema | 2 | 2.5 | 4 | 2.5 | 1.00 |
| Asthma | 15 | 18.8 | 49 | 30.6 | 0.02 |
| Atopic dermatitis | 4 | 4.4 | 8 | 5.0 | 0.812 |

Data are presented as **n** (%) or mean ± SD. P-values were calculated using the chi-square test. SGA: small gestational age; CNY: Chinese Yuan. The p value was determined using the chi-square test.

Significant differences were observed between delivery groups regarding , gestational age. For allergic disease, significant differences can be found between delivery groups and asthma ($p < 0.05$). Specifically, mothers in the cesarean groups were more likely to be older (>30 years), have higher education and income levels, and were less likely to breastfeed for 6 months compared to the vaginal delivery group.

### *Association Between Delivery Mode and Allergic Outcomes*

We evaluated the risk of allergic diseases across delivery modes. In the fully adjusted analysis (Model 2), cesarean delivery showed no obvious trend toward an increased risk of asthma (aOR = 0.93; 95% CI: 0.55–7.87) compared to vaginal delivery, and this reached statistical significance (Table 2).

**Table 2. Association between cesarean delivery and the risk of allergic diseases (wheezing, eczema, asthma, and atopic dermatitis).**

| | **Outcome** | Wheezing | Eczema | Asthma | Atopic dermatitis |
|---|---|---|---|---|---|
| Vaginal delivery | | Ref | Ref | Ref | Ref |
| Cesarean delivery | **cOR (95% CI)** | 0.25 (0.14-1.00) | 0.03 (0.00-1.0) | 0.23 (1.91−6.13) | 0.05(0.02-0.87) |
| | **aOR*1 (95% CI)** | 0.00 (0.92–2.86) | 0.00 (0.45–1.25) | 0.93 (0.55–7.87) | 0.00(0.17-1.15) |
| | **aOR*2 (95% CI)** | 0.00 (0.93–3.89) | 0.00 (0.51–0.990) | 0.88 (0.65–7.31) | 0.00(0.14-1.13) |

**cOR:** crude odds ratio; **aOR:** adjusted odds ratio; **CI:** confidence interval; **Ref:** reference group (vaginal delivery). ***Model 1:** Adjusted for maternal and perinatal factors (age, parity, infant sex, preterm birth, SGA, maternal allergies/smoking, education, income, and marital status). ***Model 2:** Additionally adjusted for postnatal environmental factors (breastfeeding at 6 months, pet ownership, and infant passive smoking exposure).

Differently, no statistically significant associations were found for wheezing, eczema, or atopic dermatitis in the elective cesarean group. However, elective cesarean delivery was associated with an increased risk of asthma (aOR = 1.88; 95% CI:0.79–4.61) while emergency cesarean did not show the similar results (Table 3).

**Table 3. Risk of allergic outcomes associated with elective versus emergency cesarean delivery.**

| **Outcome** | Wheezing | Eczema | Asthma | Atopic dermatitis |
|---|---|---|---|---|
| **Elective cOR (95% CI)** | 0.25 (0.78–1.25) | 0.03 (1.00–1.00) | 0.23 (1.86–1.97) | 0.05 (0.49–1.27) |
| **Elective aOR*1 (95% CI)** | 0.81 (0.31–2.12) | 0.34 (0.00–4.54) | 1.88 (0.79–4.61) | 1.02 (0.22–5.12) |
| **Elective aOR*2 (95% CI)** | 0.87 (0.33–2.26) | 0.33 (0.00–4.59) | 2.07 (0.86–5.17) | 1.05 (0.22–5.36) |
| **Emergency cOR (95% CI)** | 0.25 (0.78–1.25) | 0.03 (1.00–1.00) | 0.23 (1.86–1.97) | 0.05 (0.49–1.27) |
| **Emergency aOR*1 (95% CI)** | 0.98 (0.42–2.31) | 0.71 (0.12–4.50) | 1.19 (0.53–2.77) | 1.13 (0.16–8.29) |
| **Emergency aOR*2 (95% CI)** | 0.95 (0.40–2.27) | 0.83 (0.14–5.14) | 1.22 (0.53–2.85) | 1.19 (0.18–8.75) |

**cOR:** crude odds ratio; **aOR:** adjusted odds ratio; **CI:** confidence interval; **Ref:** reference group. ***Model 1:** Adjusted for maternal and perinatal factors (as detailed in Table 2). ***Model 2:** Additionally adjusted for postnatal environmental factors (as detailed in Table 2).

### *Longitudinal ADAM33 Methylation Dynamics*

Methylation analysis of the ADAM33 promoter revealed distinct temporal patterns (Table 4).

**Table 4. Comparison of DNA methylation levels at birth and preschool age across different delivery modes.**

| Age | Group | n | Q25 | Median | Q75 | P |
|---|---|---|---|---|---|---|
| Birth | Elective cesarean delivery[a] | 10 | 20 | 20 | 20 | <0.001 |
| | Emergency cesarean delivery[b] | 6 | 100 | 100 | 100 | |
| | Vaginal delivery[a] | 10 | 25.22 | 69.31 | 84.46 | |
| Preschool | Elective cesarean delivery[c] | 10 | 16.95 | 31.92 | 45.34 | 0.712 |
| | Emergency cesarean delivery[c] | 6 | 34.19 | 41.40 | 48.55 | |
| | Vaginal delivery[c] | 10 | 23.42 | 40.04 | 46.81 | |

Data are presented as median [IQR, Q25–Q75]. P-values were determined by the Kruskal-Wallis test followed by Dunn's multiple comparison test.

**(a)** Significant difference between Elective Cesarean and Vaginal delivery groups at birth ($p < 0.05$). **(b)** No significant difference in

Emergency Cesarean compared to other groups at birth. **(c)** No significant differences observed among groups at preschool age.

At birth, there was a highly significant difference in methylation levels among the groups ($p < 0.001$). The emergency cesarean group exhibited the highest median methylation (100%), whereas the elective cesarean group showed the lowest (20%).

However, this epigenetic variation appeared transient. By preschool age, methylation levels converged, and no significant differences were observed among the three groups ($p = 0.712$). This suggests that while delivery mode may influence the neonatal epigenetic landscape, environmental exposures during early childhood might homogenize these profiles over time.

***Correlation with Lung Function and Clinical Phenotypes***

We further explored the functional relevance of ADAM33 methylation in the preschool sub-cohort. There was a trend toward a negative correlation between ADAM33 methylation and airway patency (FEV1/FVC ratio) ($R = -0.005$, $p = 0.9788$), as illustrated in Figure 1. While not statistically significant due to the small sample size, the directionality suggests that higher methylation might be associated with reduced lung function.

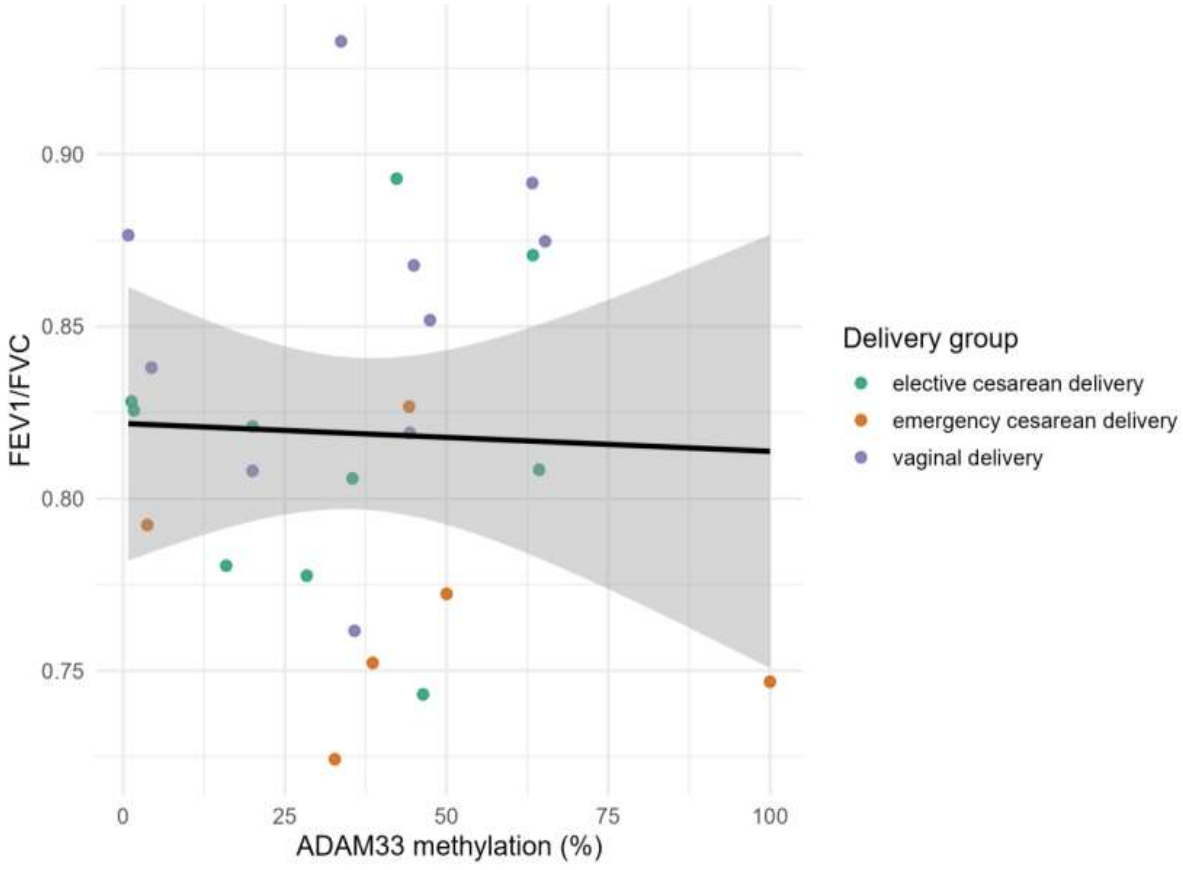


**Fig. 1 Correlation between DNA methylation levels and lung function parameters (FEV1/FVC) across all groups**

ISAAC Risk Stratification: Contrary to the null findings in the overall delivery mode comparison, ADAM33 methylation levels were significantly associated with specific allergic phenotypes (Table 5).

**Table 5 Preschool methylation levels stratified by ISAAC questionnaire risk categories for asthma and rhinitis**

| ISAAC Type | ISAAC Group | | Methylation（%） | | | |
|---|---|---|---|---|---|---|
| | | n | Q25 | Median | Q75 | P |
| Asthma | <5 (low risk) | 20 | 35.48 | 56.82 | 81.91 | 0.001 |
| Asthma | >5 (high risk) | 16 | 20.00 | 20.00 | 20.00 | |
| Rhinitis | <4 (low risk) | 18 | 23.39 | 34.69 | 45.46 | 0.0302 |
| Rhinitis | >4 (high risk) | 18 | 5.15 | 18.78 | 30.36 | |

Data are presented as median [IQR, Q25–Q75]. P-values were calculated using the independent Kruskal-Wallis test. ***Risk definition:** Low- and high-risk groups were categorized based on the established cutoff points.

Children classified as "high risk" for asthma (ISAAC score >5) had significantly lower median methylation levels (20.00%) compared to the low-risk group (56.82%; p = 0.001). Similarly, children at high risk for rhinitis exhibited significantly lower methylation compared to low-risk peers (p = 0.030).

**Discussion**

The primary objective of this study was to disentangle the complex relationship between mode of delivery, childhood asthma, and epigenetic modifications. Our principal finding presents an intriguing nuance: we observed slightly statistically significant association between elective cesarean section and the clinical development of asthma in early childhood, we identified a distinct epigenetic signature at birth. Specifically, children born via elective cesarean delivery exhibited significantly higher methylation levels in the ADAM33 promoter region compared to those born vaginally. Notably, this methylation difference attenuated over time, suggesting that while delivery mode induces an immediate biological response, these epigenetic marks may be transient and subject to environmental plasticity as the child ages.

Our observation that cesarean delivery does not increase the risk of asthma contrasts with the "hygiene hypothesis," which posits that lack of exposure to vaginal flora compromises immune development.[13] While several meta-analyses and cohorts in Canada and Korea have reported no increased risks of wheezing or asthma following cesarean section, [14,15] our results align with population-based studies from the Mexican, China, and Greece that found no such causal link after adjusting for confounders.[16,17,18] The discrepancy in the literature likely stems from heterogeneity in study design, particularly the age of diagnosis. In our study, outcomes were defined within the first year of life. Diagnosing asthma in infancy is notoriously difficult, as recurrent asthma is common and often transient. It is plausible that the "null" association observed here reflects the difficulty of distinguishing true asthma from viral-induced wheezing in infants, rather than a definitive lack of biological risk.

Despite the lack of a clinical phenotype in infancy, the molecular data reveals a biological impact of delivery mode.[19] ADAM33 is a susceptibility gene crucial for airway remodeling and bronchial hyper-responsiveness . Our finding that elective CS leads to hypermethylation of the ADAM33 promoter at birth is significant. Hypermethylation typically suppresses gene expression.[20] However, in the context of ADAM33, the relationship is complex and tissue-specific.[21]

The difference in methylation between elective and emergency CS suggests that the mechanism is not solely related to the surgical bypass of the birth canal (microbiome seeding) but perhaps to the physiological stress of labor.[22,23] Infants born via elective CS lack the surge of stress hormones (catecholamines and cortisol)[24] and inflammatory

cytokines (IL-6, IL-10, TNF-α) that occur during labor.[25] This "immunological silence" at birth might fail to trigger necessary demethylation processes or induce hypermethylation as a compensatory response.[26] However, the fact that these methylation profiles converged with the vaginal delivery group over time indicates that postnatal environmental exposures may override these initial intrauterine or perinatal effects.[27] This highlights the potential reversibility of epigenetic markers and suggests that the "window of opportunity" for immune programming remains open after birth.[28]

This study has several strengths, including its prospective nationwide design and the ability to distinguish between emergency and elective Cesarean sections. Methodologically, the use of oral swabs for genomic DNA collection proved to be a non-invasive, replicable, and effective technique for neonatal populations.

However, several limitations must be acknowledged. First, the clinical follow-up period was limited to the first year of life. As noted, respiratory function tests are unreliable in infants, and "asthma" is rarely definitively diagnosed before age 5 or 6.[29,30] Consequently, our reliance on early-life wheezing may underrepresent the true incidence of atopic asthma that develops later. Second, the sample size for the methylation analysis (PCR) was relatively small compared to the overall cohort, which limits statistical power and generalizability. Third, the reliance on self-reported questionnaires for allergic history introduces the potential for recall bias. Finally, we could not fully account for unmeasured confounders, such as the severity of maternal stress or specific antibiotic usage, which could influence both methylation and asthma outcomes.

**Conclusion**

In summary, while this study did not find a direct correlation between Cesarean delivery and clinical asthma in the first year of life, it provides the first evidence that delivery mode influences the methylation profile of the ADAM33 gene at birth. This suggests that Cesarean delivery acts as a perinatal stressor capable of inducing epigenetic variation, though these changes appear to be dynamic and reversible. Future research should focus on longer-term follow-up to determine if these transient epigenetic "scars" resurface as functional respiratory deficits in later childhood.

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