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Breastfeeding can relieve asthma: A two-sample Mendelian analysis and genetic database mining

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Abstract: *Pediatric asthma, a highly heterogeneous disorder, poses significant health risks to children and strains healthcare systems worldwide. While breastfeeding is recognized as a pivotal early-life factor, its impact on childhood asthma development remains contentious. Using a two-sample Mendelian randomization approach, we identify instrumental variables significantly associated with breastfeeding and assess their impact on pediatric asthma risk. Our results indicate a significant negative correlation between breastfeeding and childhood asthma, suggesting that breastfeeding acts as a protective factor. Sensitivity analysis confirms the robustness of our findings. Furthermore, we conduct differential gene expression analysis to elucidate the genetic mechanisms underlying asthma occurrence and its association with breastfeeding. Through reanalysis of existing genetic data and gene set enrichment analysis, we identify key genes and pathways implicated in asthma pathogenesis, shedding light on the potential molecular mechanisms underlying breastfeeding's protective effects. In conclusion, our study provides compelling evidence supporting breastfeeding as a crucial factor in mitigating pediatric asthma risk.*

Keywords: *breastfeeding; pediatric asthma; Mendelian randomization analysis; Expression of differential genes*

1. Introduction

Pediatric asthma is a highly heterogeneous disorder with multiple clinical phenotypes and can have very serious consequences for children's health, their families, and the health care system[1-3].It refers to the global increase[4-6].in the incidence of childhood asthma and highlights the close correlation between childhood asthma and various early life factors. Numerous maternal exposures significantly contribute to the health problems of offspring[7]. In addition, it acknowledges that breastfeeding is one of the key factors in early life exposure[8], but notes that there has been controversy regarding the impact of breastfeeding on the development of asthma in children.

It is claimed that exposing infants to food allergens, especially dairy protein, may increase the likelihood of developing atopic conditions and asthma. In the absence of excluding confounding factors such as maternal asthma, breastfeeding may increase the risk of pediatric asthma.[9-13]However, there is still substantial evidence from various other studies and cohort research indicating that breastfeeding during infancy can significantly reduce the likelihood of asthma in children under the age of six[14-16].

Currently, there is limited clinical retrospective research on the relationship between breastfeeding and pediatric asthma, and the conclusions drawn from these studies are controversial. There is currently no precise statistical evidence regarding the causal relationship in this regard. [17].This article aims to use Mendelian randomization analysis to investigate the causal relationship between pediatric asthma and breastfeeding during infancy and further explore this relationship at the gene expression level using differential gene expression analysis methods[18].

2. Methods

2.1 MR Verification Ideas

To select appropriate instrumental variables in the two-sample MR study, this research establishes

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three key hypotheses(Figure 1):

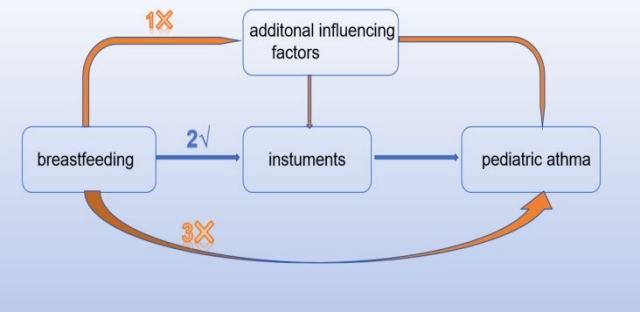

Figure 1: Mendelian Three Verification Ideas

2.2 MR Data Sources

The genetic data concerning infant breastfeeding practices originate from the Neil Laboratory (UKB-A-33), comprising a European cohort with a sample size of 255,881 individuals and encompassing 10,894,596 variants. Data pertaining to pediatric asthma were sourced from the European Bioinformatics Institute (EBI-A-GCST90018895), with a sample size of 438,843 subjects and a total of 24,166,696 SNPs identified through genome-wide association studies (GWAS). Given the utilization of publicly available databases, no supplementary ethical approval was deemed necessary.

2.3 Selection of MR Instrumental Variables

In this study, instrumental variables significantly associated with breastfeeding were preselected based on a significance threshold of $p < 1 \times 10^{-5}$. A parameter setting of an r^2 threshold of 0.1 and a kilobase pair (kb) of 500 were established to mitigate interference from linkage disequilibrium (LD). Consequently, breastfeeding-associated SNPs exhibiting statistical significance were identified. Harmonization, as described by Reference was performed by aligning SNPs with identical alleles between the GWAS datasets of breastfeeding and pediatric asthma, ensuring correspondence of exposure and outcome effect estimates.

2.4 Statistical Analysis Use

This study primarily employed version 4.1.2 of the R programming language and conducted Two Sample Mendelian Randomization (MR) using five regression models: MR-Egger regression, random-effects inverse variance weighted method, ratio estimate method, weighted median method, and weighted mode method to validate the causal relationship between breastfeeding and pediatric asthma. The Inverse Variance Weighted (IVW) method was utilized to estimate the causal effects of genes on traits.

2.5 Sensitivity Analysis

Sensitivity analysis primarily involved heterogeneity testing and the leave-one-out method.

2.6 Differential Gene Analysis

This study conducted a DEG analysis on asthma and control groups based on the GEO database to discover key genes associated with the occurrence of asthma and their relationship with breastfeeding. Airway epithelial brushings were obtainedfor microarray analysis by research bronchoscopy in 62 subjects with mild-to-moderateasthma not on inhaled steroids and 43 healthy controls. Asthma subjects were stratified into 2 subgroups, Th2 high and Th2 low asthma, based on their expression of a three-gene signature of Type 2 inflammation: POSTN, SERPINB2, and CLCA1.This data set is based on the BergeM HijaziK[19] study (GSE67472).

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3. Results

3.1 Instrumental Variables

After comparing with confounding factors such as age, gender, frequency of breastfeeding during childhood, and family history of hereditary diseases, and calculating their F values, F = 0.632 (>0.05), indicating the exclusion of confounding factors. In this study, a total of 70 significant instrumental variables were finally identified for breastfeeding during infancy. A regression model intercept test was conducted, yielding a regression intercept term of b = -0.005 and P = 0.361 for breastfeeding SNPs(see Table 1), indicating no horizontal pleiotropy (P > 0.05). Thus, the screened SNPs do not exhibit genetic pleiotropy, rendering Mendelian Randomization an effective method for causal inference in this study.

Table 1: Intercept Test of Regression Model

Method	Variable	Intercept	Standard Error	P
MR-Egger	Infant Breastfeeding	-0.005	0.006	0.361

3.2 Mendelian Randomization Analysis Results

Using the IVW method, a total of 70 instrumental variables were found to be significantly associated with childhood asthma. After multiple-method correction, as shown in Table 2, the directions of Beta were inconsistent; therefore, the results from IVW should be considered definitive. Among these, P=0.01 (P<0.05), indicating a significant causal relationship. The correlation coefficient was -0.591, demonstrating a negative correlation. Subsequently, after causal directionality verification, the variance of childhood breastfeeding SNPs was 0.006, for childhood asthma it was 0.0002, and the Steiger test yielded a P-value of 0.000. These results indicated an established exposure, a valid causal relationship, correct causal directionality, and significance. The results of the MR regression analysis are depicted in Figure 2:

Table 2: Mendelian Randomization Analysis Results

Method	**SNP Quantity**	**b**	**se**	**Pval**
MR Egger	70	0.007	0.695	0.991
Weighted median	70	-0.441	0.292	0.110
Inverse variance weighted	70	-0.592	0.240	0.013
Simple mode	70	-0.327	0.777	0.013
Weighted mode	70	-0.327	0.719	0.651

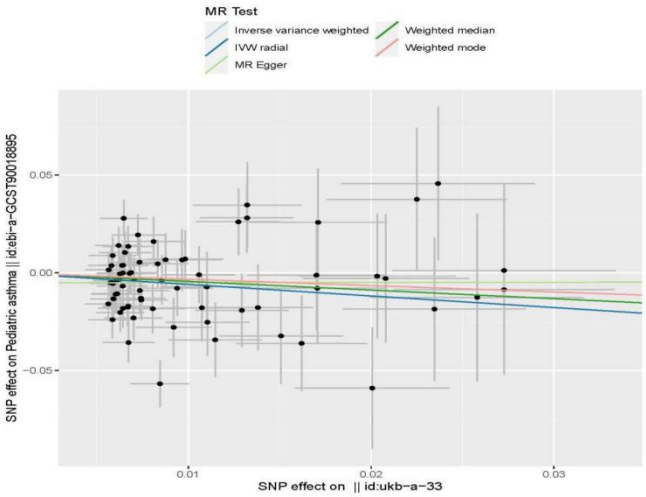

Figure 2: Regression Analysis Graph under Different Statistical Methods

3.3 Sensitivity Analysis

Sensitivity analysis was conducted using leave-one-out method (see Figure 3). When breastfeeding during infancy was considered as the exposure factor, the results after excluding each SNP individually

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were consistently on the left side of zero and on the same side as the null line. This indicates robustness of the results. According to the funnel plot depicted in Figure 4, there were no significant outliers, further supporting the stability of the results.

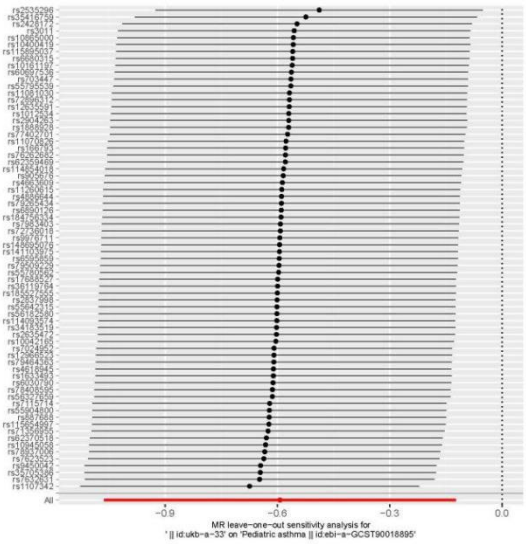

Figure 3: Leave-One-Out Method

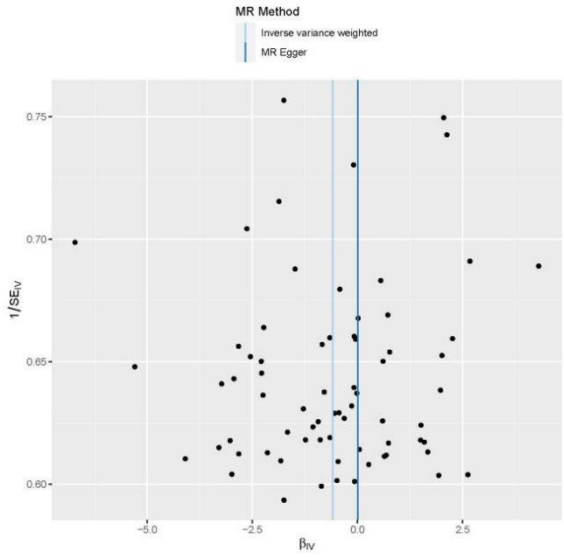

Figure 4: MR Funnel Plot

3.4 Differential Gene Expression Results

The bubble chart visualizes the analysis results. The results obtained are shown in Figure 5, in the figure, larger bubble size and darker color indicate greater differential expression levels. The significant pathways, response to stimuli, and other main findings are presented in Table 3.

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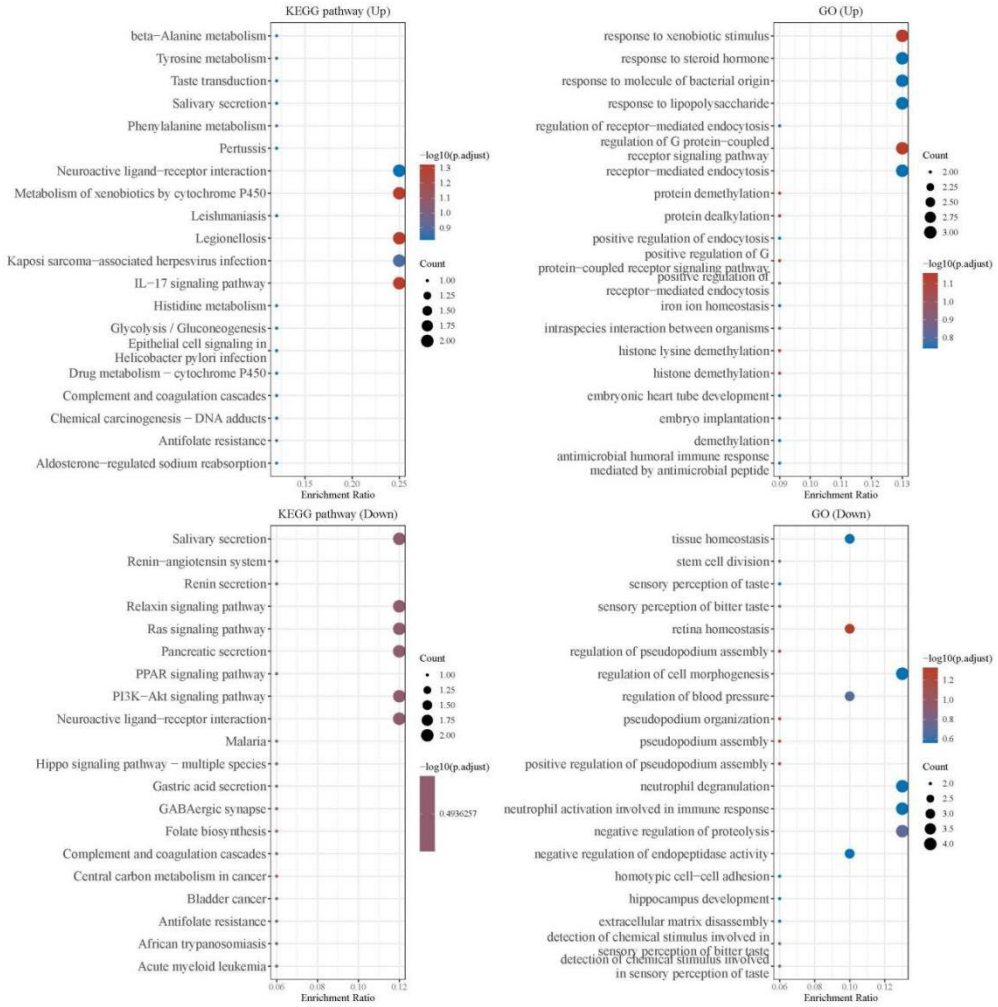

Figure 5: KEGG analysis

Table 3: Gene Expression Analysis

Name	up/down	Associations with breastfeeding	References
IL-17signaling pathway	up	Breast milk contains numerous immune-modulating(IL-10),reduce IL-17 levels	[20]
legionellosis	up	Breast milk provides antibodies (such as IgA) and immune cells against legionellosis	[21]
The metabolism of xenobiotics by CYP450	up	Breast milk contains various substances that can influence the activity of CYP450 enzymes.(Enzyme Induction and Inhibition)	[22]
Keposi sarcoma-associated Herpevirus infection	up	Vertical Transmission: KSHV can be transmitted from mother to child during pregnancy, childbirth, and possibly through breastfeeding	[23]
Response to xenabitic stimulus	up	Breast milk has anti-inflammatory properties that can modulate the infant's immune response to xenobiotics, potentially reducing adverse reactions.	[24]
Regulation of G protein - coupled	up	Breast milk is rich in DHA,AA,prolactin, leptin that can modulate GPCR activity.	[25]

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Resonds to steried horone	up	Breastfeeding influences an infant's response to steroid hormones through multiple pathways, including immune modulation, endocrine system development, metabolic regulation, neurodevelopment, and hormonal interactions.	[26]
Receptor-medated endocytosis	up	Breast milk supports this process by supplying essential nutrients, immune factors, growth factors, and hormones, all of which contribute to the efficient functioning and development of the infant’s cellular systems.	[27]
Salivary serection	down	Breastfeeding positively influences salivary secretion by providing essential nutrients, supporting hydration, boosting immune protection, aiding developmental processes, promoting a healthy oral microbiota, and potentially delivering beneficial hormones.	[28]
Relaxin signaling pathway	down	Bresat milk cintains relaxin	[29]
Ras signaling pathway	down	it's reasonable to speculate that breastfeeding, through its effects on hormone levels, tissue remodeling, and immune function, could influence Ras pathway activity	[30]
Pancreatie serection	down	Breastfeeding triggers the release of gastrointestinal hormones like CCK	[31]
P13k-akt signaling pathway	down	The PI3K-Akt-mTOR pathway senses nutrient availability and energy status,affacted by breastfeeding	[32]
Neuroactive ligand-receptor interaction	down	Breastfeeding can indeed have effects on the neuroactive ligand-receptor interaction, particularly in relation to the oxytocinergic and opioidergic systems	[33]
Regulation of cell morphogenes	down	Matrix Metalloproteinases (MMPs)	[34]
Neutrophil activation involved in immue response	down	Breastfeeding influences neutrophil activation and the overall immune response in infants by providing a range of immune factors in breast milk.Enhance the phagocytic activity of neutrophils	[35]
Nagative regulation of proteolysis	down	influences the negative regulation of proteolysis through the presence of proteinase inhibitors and other bioactive components in breast milk.	[36]
Neutrophil degranulation	down	Breastfeeding influences neutrophil degranulation and the overall immune response in infants by providing a range of immune factors in breast milk.	[37]

The volcano plot (see Figure 6) illustrates the most pronounced downregulated gene expression in the upper left quadrant and the most pronounced upregulated gene expression in the lower right quadrant. Additionally, the heatmap of differentially expressed genes (see Figure 6) depicts downregulated expression in blue and upregulated expression in red.Summarize the gene names and functions with significant differences as shown in Table 4.

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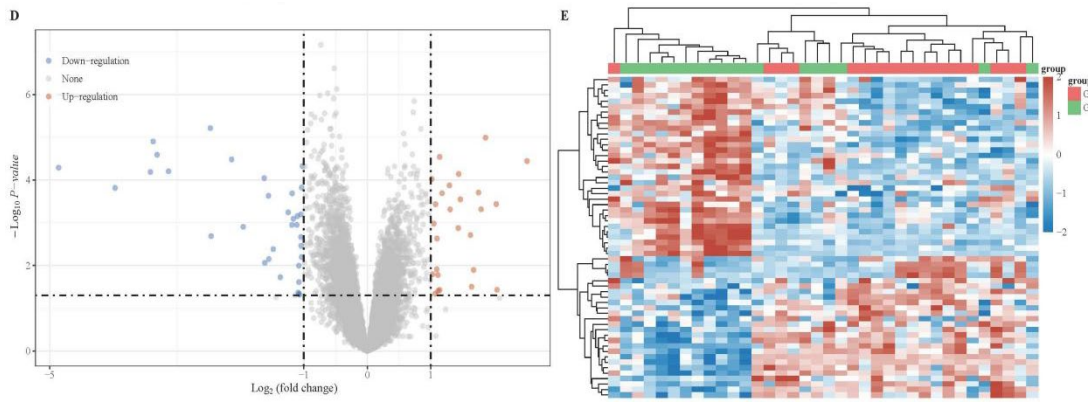

Figure 6: D Volcano Plot of Differentially Expressed Genes E Heatmap of Differentially Expressed Genes

Table 4: Key Genes

Genes	up/down	Function	Reference
muc5b	up	encodes mucin 5B protection and lubrication of mucosal surfaces	[38]
cyp2a1320	up	an enzyme primarily expressed in the respiratory tract and is involved in the metabolism of xenobiotics	[39]
scgb3a122	up	encodes Secretoglobin Family 3A Member 2 Anti-inflammatory Properties Immune Modulation and Tumor Suppression	[40]
best423	up	encodes a protein involved in ion transport and is primarily expressed in the retinal pigment epithelium	[41]
Lrrc7025	up	signal transduction, cell adhesion, and the immune response	[42]
serpinb226	down	Protease Inhibition Regulation of Immune Responses andProtection of Tissues	[43]
prr4	down	encodes Proline Rich 4 have roles in maintaining the integrity and function of epithelial tissues	[44]
cst427	down	encodes Cystatin S helps regulate proteolytic activities that are crucial for various cellular processes, including protein degradation, tissue remodeling, and immune responses	[45]
c16orf54	down	a gene located on chromosome 16	[46]
p2ry14	down	encodes the P2Y purinoceptor 14 G protein-coupled receptors	[47]

4. Conclusions

It is noteworthy that, supported by other studies, breastfeeding exhibits substantial potential in regulating the incidence of pediatric asthma at both the pathway and gene levels.Regarding the key genes and pathways involved in the occurrence of asthma, one of the recognized factors in breast milk that influences metabolism and weight gain is kynurenic acid (KYNA). KYNA is an agonist of the G-protein coupled receptor (GPR35) and reduces the incidence of asthma.[48]There is research evidence indicating that breast-feeding induces the transportation of membrane-incorporated FcRn from its perinuclear localization to the apical plasma membrane domain. This transportation is achieved through the membrane system, which mediates apical receptor-mediated transcytosis via the trans-Golgi network. Subsequently, the apical plasma membrane containing the FcRn binds to maternal IgG, is endocytosed into the absorptive cells, and is transported to the basolateral membrane domain.[49]Breastfeeding can

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regulate receptor-mediated endocytosis. The roles of the different breast milk components are far from being completely understood. Of note, immune cells such as B and T lymphocytes, regulatory cells, monocytes/macrophages, neutrophils, natural killer cells and IgA, IgG and IgM antibodies are found in the breast milk.[50]The systematic reviews have shown the breastfeeding protection of infants against the development of atopic diseases such as eczema and food and respiratory allergy, especially when there is a family history.[11,51]Purified mucins MUC1 and MUC4 from breast milk, as well as cervical mucus from pregnancy (MUC2, MUC5AC, MUC5B, and MUC6), have been shown to inhibit infectious agents such as viruses in in vitro assays.[52]Additionally, breastfeeding can significantly regulate bone metabolism processes[53], neutrophil degranulation, and negative regulation of proteolysis. This aligns with the key genes and pathways we have identified as being involved in the occurrence of asthma. For expectant mothers with a family history of asthma, the conclusions remain controversial. However, for healthy mothers, breastfeeding can effectively prevent the occurrence of pediatric asthma on multiple levels. Research evidence indicates that this protective effect can last up to six years.[50]

Through Mendelian randomization experiments, we have discovered that, using European samples as an example, breastfeeding acts as a direct mitigating factor for pediatric asthma. Breastfeeding, unaffected by other confounding factors, serves as a direct causal factor in preventing pediatric asthma, demonstrating a high level of significance. However, this study, relying on genetic samples from European populations, still carries certain limitations, as indicated by statistical analysis revealing a highly causal relationship.

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