BMC Public Health

RESEARCH

Open Access

Breastfeeding, genetic susceptibility, and the risk of asthma and allergic diseases in children and adolescents: a retrospective national population-based cohort study

Wenyan Hou[1†], Fengjun Guan[2†], Wenying Chen[1], Jike Qi[1], Shuiping Huang[1,3*] and Ping Zeng[1,3*]

Abstract

Background Asthma and allergic diseases (such as allergic rhinitis) are multifactorial chronic respiratory diseases, and have many common pathogenic mechanisms. This study aimed to assess the joint effects of breastfeeding and genetic susceptibility on asthma, allergic disease in children and adolescents and sought to examine whether the effect of breastfeeding was consistent under distinct levels of genetic risk.

Methods A total of 351,931 UK Biobank participants were analyzed. Firstly, Cox proportional hazards model was used to evaluate the relation between breastfeeding and asthma, allergic disease and their comorbidity. Next, we incorporated the polygenic risk score as an additional covariate into the model. Then, we explored the role of breastfeeding at each stage of asthma and allergic disease through a multi-state model. Meanwhile, several sensitivity analyses were conducted to evaluate the robustness of our results. Finally, we calculated the attributable protection and population attributable protection of breastfeeding.

Results Breastfeeding was related to a reduced risk of occurring asthma (adjusted hazard ratio [HR] = 0.89, 95% confidence interval [CI] 0.86 ~ 0.93), allergic disease (HR = 0.89, 95%CI 0.87 ~ 0.91) and comorbidity (HR = 0.89, 95%CI 0.83 ~ 0.94). The effect of breastfeeding was almost unchanged after considering PRS and did not substantially differ across distinct genetic risk levels. Breastfeeding showed a stronger risk-decreased impact on individuals who developed from allergic rhinitis to comorbidity (HR = 0.83, 95%CI 0.73 ~ 0.93). Further, the influence of breastfeeding was robust against covariates considered and the confounding influence of adolescent smoking. Finally, due to breastfeeding, 12.0%, 13.0% or 13.0% of the exposed population would not suffer from asthma, allergic diseases and the comorbidity, while 7.1%, 7.6% or 7.6% of the general population would not suffer from these diseases.

†Wenyan Hou and Fengjun Guan are co-first authors.

*Correspondence:
Shuiping Huang
hsp@xzhmu.edu.cn
Ping Zeng
zpstat@xzhmu.edu.cn

Full list of author information is available at the end of the article

Conclusions This study provided supportive evidence for the risk-reduced effect of breastfeeding on asthma, allergic diseases, and the comorbidity in children and adolescents, and further revealed that such an influence was consistent across distinct genetic risk levels.

Keywords Breastfeeding, Asthma, Allergic diseases, Comorbidity, Polygenic risk score, Multi-state model

Introduction

Asthma [1] and allergic diseases (such as allergic rhinitis [2]) are multifactorial chronic respiratory diseases, and have many common pathogenesis. These two types of diseases affect all age groups. In the past few years, their prevalence rate has continued to increase in many countries (especially among children) [2, 3], which has led to serious global health problems, including impaired quality of life, school or work performance, and significant economic impact [4]. The causes of asthma and allergic diseases include genetic and environmental factors, and it is generally believed that the early living environment (such as nutrition) has a considerable influence on the risk of developing asthma and allergies [5].

Nutrition in the very early years of life (such as neonatal period) can be provided through breastfeeding or formula milk, followed by complementary foods, but the immunomodulatory components of breast milk, such as maternal antibodies, are not available in formula milk [6]. Many studies have demonstrated that breastfeeding can significantly prevent and reduce the risk of asthma and allergic diseases in children [7–9]; therefore, exclusive breastfeeding is recommended to last at least four to six months [10]. Unfortunately, not all studies have confirmed the preventive and protective effects of breastfeeding on asthma and allergic diseases [11, 12].

On the other hand, genetic susceptibility also plays an important role in the development of asthma and allergic diseases [13], with the heritability estimated to be 25 ~ 80% for asthma [14] and up to 90% for allergic rhinitis [15]. Recently, large-scale genome-wide association studies (GWASs) discovered a large number of genetic variations related to the risk of asthma and allergic diseases [14, 16], and found that there was a high degree of genetic overlap among these diseases [13, 17].

However, thus far, few studies have investigated the joint effects of breastfeeding and genetic susceptibility on asthma and allergic diseases, or examined whether the effect of breastfeeding may be affected by genetic susceptibility. In addition, previous studies that reported the protective association of breastfeeding only focused on allergic response in early childhood (for example, before 6 years old [18] or 4 ~ 12 years old [19]), and very limited studies explored its long-term effect on asthma and allergic diseases among older children. Thereby, the role of breastfeeding throughout adolescence needs further investigation [20].

To handle the above problems, in the present study we sought to evaluate the association between breastfeeding and the onset of asthma and allergic diseases up to the age of 18 years using the UK Biobank cohort data [21]. In particular, we studied the joint effects of breastfeeding and genetic susceptibility on asthma and allergic diseases, and further evaluated whether the effect of breastfeeding are consistent at different levels of genetic susceptibility.

Methods and materials

UK Biobank cohort

Our research is a retrospective national population-based cohort study that relies on the UK Biobank, which collected an unprecedented amount of biological and medical data resource on more than 500,000 participants in 22 centers across the UK aged 40 ~ 69 years since 2006 [21]. Most of the participants were British whites, who had been to the center at baseline, but some visited it more than three times during the follow-up period. In our analysis, we only considered participants of white ancestry. The UK Biobank has approval from the North West Multi-Center Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval, meaning other researchers do not require separate ethical clearance and can operate under this approval.

Ascertainment of breastfeeding, asthma, and allergic diseases

Breastfeeding was defined as a binary variable (yes or no) by the answer to the following question: "were you breastfeed when you were a baby?" We chose individuals who had a physician-diagnosed asthma and hay fever, allergic rhinitis, or eczema as cases, which were defined by the question: "has your doctor ever told you that you have had any of the following conditions?" Because hay fever, allergic rhinitis and eczema are classified into one category, we considered them together by following a previous study [22] and referred to as HAE.

Breastfeeding, asthma and allergic diseases were determined according to the baseline information, and if the baseline information was missing, the follow-up data were used instead. We also analyzed the comorbidity of asthma and HAE, and referred to it as AHAE. We ensured each selected case had the onset age and only focused on children/adolescent cases (age at onset ≤ 18 years old) as the protective role of breastfeeding appeared difficult to persist into adulthood [23]. Therefore, individuals with age at onset larger than 18 were excluded.

Finally, 351,931 participants were kept. The flow diagram of data processing is displayed in Fig. 1.

Covariate selection

According to our previous work [24], we included birthweight, maternal smoking during pregnancy, smoking/smokers in household, average total household income before tax, diet score and gender as potential covariates, which either conceptually had an impact on or showed statistically significant connection with our analyzed diseases [25]. The diet score was calculated based on baseline self-reported dietary data (such as intake of fruits, vegetables, meat, etc.). We also included the top ten genetic principal components (GPC) in our analysis to explain possible relatedness among selected participants [26]. We imputed missing values of covariates by multivariate imputation by chained equations (MICE) [27], but ruled out participants with missing values in breastfeeding, asthma, HAE or AHAE.

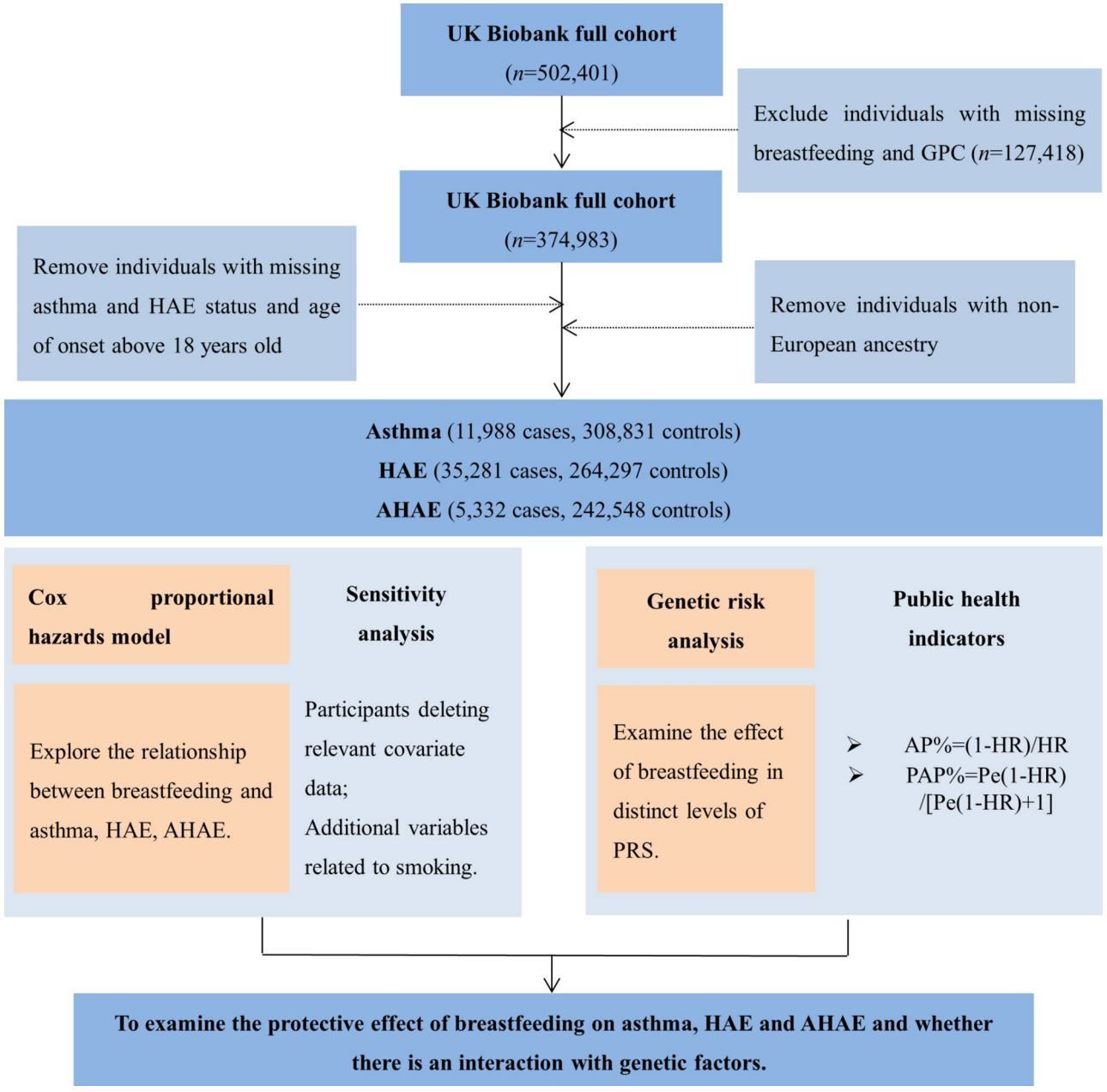

Fig. 1 Flow diagram of data processing and statistical analysis for the present study using the UK Biobank cohort data. PRS, polygenic risk score; HAE, hay fever, allergic rhinitis, and eczema; AHAE, the comorbidity of asthma and HAE. AP, attributable protection; PAP, population attributable protection

Calculation of polygenic risk score

Considering the pervasive polygenic and multi-local nature of disease associations and the relatively small influence of a single genetic variant, PRS has been proposed to evaluate the cumulative impact of multiple risk-related single nucleotide polymorphisms (SNPs) [28, 29]. For each analyzed disease, we calculated its PRS with genetic effect sizes available from summary statistics via PRS-CS [30], with the 1000 Genomes Project European samples ($n=503$) as the external linkage disequilibrium (LD) reference panel. We obtained the summary statistics of white ancestors from the hitherto largest genome-wide association studies (GWASs) (Table S1). According to previous studies [31–34], we performed strict quality control for these summary statistics data.

Statistical analysis

Cox proportional hazards model

We applied the onset age (0 ~ 18 years old) to represent the occurrence time of asthma, HAE or AHAE [35], and set the occurrence time of these non-cases to 18 years old. Cox proportional hazards model was applied to assess the relationship between breastfeeding and asthma (HAE or AHAE) while adjusting for the covariates mentioned before. According to Schoenfeld's residual method [36], we did not find any evidence that violated the proportional hazards hypothesis ($P>0.05$).

We next incorporated standardized PRS into the model as another covariate. PRS was further divided into deciles and tertiles to explore how much the risk of disease changed as the genetic risk increased and to examine whether the breastfeeding effect was different across distinct genetic risk levels. Hazard ratio (HR) and its 95% confidence interval (CI) were reported.

We also conducted stratified analyses based on different levels of covariates. For instance, we divided age at onset into three groups (0 ~ 6 years, 7 ~ 12 years, and 13 ~ 18 years) following previous studies [18, 24], and classified birthweight as low (<2.5 kg), normal (2.5–4.0 kg), and high (≥4.0 kg) levels according to pediatric and existing studies [37–39].

Sensitivity analyses

We conducted two sensitivity analyses to evaluate the robustness of our results. First, because it was uncertain whether current household smoking status, income, or diet could be substituted for exposure before the age of 18, we conducted a similar analysis without considering smoking/smokers in household, average total household income before tax and diet score. Second, we also adjusted for adolescent smoking [40, 41] because smoking can cause asthma and aggravate the symptoms of allergic rhinitis. Because adolescent smoking was not directly available in the UK Biobank, we generated a new variable (yes or no) via the age at smoking and age at quitting before the age of 18.

Multi-state model

Here, we implemented the multi-state model [42, 43] to assess the role of breastfeeding in each stage of disease progression from baseline to a disease (asthma or HAE) and to comorbidity (AHAE) or from baseline to comorbidity. The multi-state model provides a unique advantage by treating various diseases as different transitional states, and can investigate the influence of exposure on different stages of disease progress in the presence of competitive risks. This analysis was conducted in a similar way via Cox proportional hazards model with the above six variables as covariates.

Attributable protection and population attributable protection

Finally, in order to further quantify the risk-reduced influence of breastfeeding on asthma and allergic diseases, attributable protection (AP%) and population attributable protection (PAP%) were calculated to estimate the percentage of cases reduction [44]. Briefly, AP%=(1-HR)/HR and PAP%=P_e(1-HR)/[P_e(1-HR)+1], where P_e was the breastfeeding rate, which varied across the three diseases' data.

Results

Description of the used dataset

We reserved 11,988 asthma cases and 308,831 non-asthma participants, 35,281 HAE cases and 264,297 non-HAE participants, and 5,332 AHAE cases and 242,548 non-AHAE participants. The cumulative incidences of the three types of diseases increasing as age are shown in Figure S1. Summary information of involved variables is shown in Table S2. In the asthma, HAE and AHAE datasets, the breastfeeding rates were 71.4%, 71.3% and 71.7%, respectively, and the breastfeeding rates of non-case participants were generally higher than those of cases.

Estimated effect of breastfeeding on Asthma, HAE, and AHAE

We found that breastfed children had a lower risk of developing asthma compared to those not breastfed (the crude HR=0.91, 95%CI 0.88 ~ 0.95), the effect was almost unchanged after taking covariates into account (the adjusted HR=0.89, 95%CI 0.86 ~ 0.93) (Table 1). The significant association of breastfeeding was also consistently observed for HAE (the crude HR=0.90, 95%CI 0.88 ~ 0.92) and AHAE (the crude HR=0.90, 95%CI 0.85 ~ 0.96), with the adjusted HR=0.89 (95%CI 0.87 ~ 0.91) for HAE and 0.89 (95%CI 0.83 ~ 0.94) for AHAE when covariates were considered.

Table 1 HR and 95%CI for the association of breastfeeding with the risk of Asthma, HAE, and AHAE

Models	Asthma (11,988/308,831)		HAE (35,281/264,297)		AHAE (5,332/242,548)	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Breastfeeding (without any covariates)	0.91 (0.88 ~ 0.95)	1.61×10^{-6}	0.90 (0.88 ~ 0.92)	3.40×10^{-19}	0.90 (0.85 ~ 0.96)	7.33×10^{-4}
Breastfeeding adjusted with covariates	0.89 (0.86 ~ 0.93)	1.51×10^{-8}	0.89 (0.87 ~ 0.91)	2.12×10^{-25}	0.89 (0.83 ~ 0.94)	5.31×10^{-5}
Breastfeeding adjusted with covariates and PRS	0.89 (0.86 ~ 0.93)	1.09×10^{-8}	0.89 (0.87 ~ 0.91)	4.12×10^{-25}	0.89 (0.84 ~ 0.94)	7.18×10^{-5}
PRS adjusted with covariates and breastfeeding	1.52 (1.49 ~ 1.55)	< 0.001	1.08 (1.07 ~ 1.09)	4.49×10^{-45}	1.39 (1.35 ~ 1.43)	2.88×10^{-127}

Note HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score; HAE, hay fever, allergic rhinitis, and eczema; AHAE, the comorbidity of asthma and HAE. $P<0.001$, the *P*-value is too small to be exactly displayed

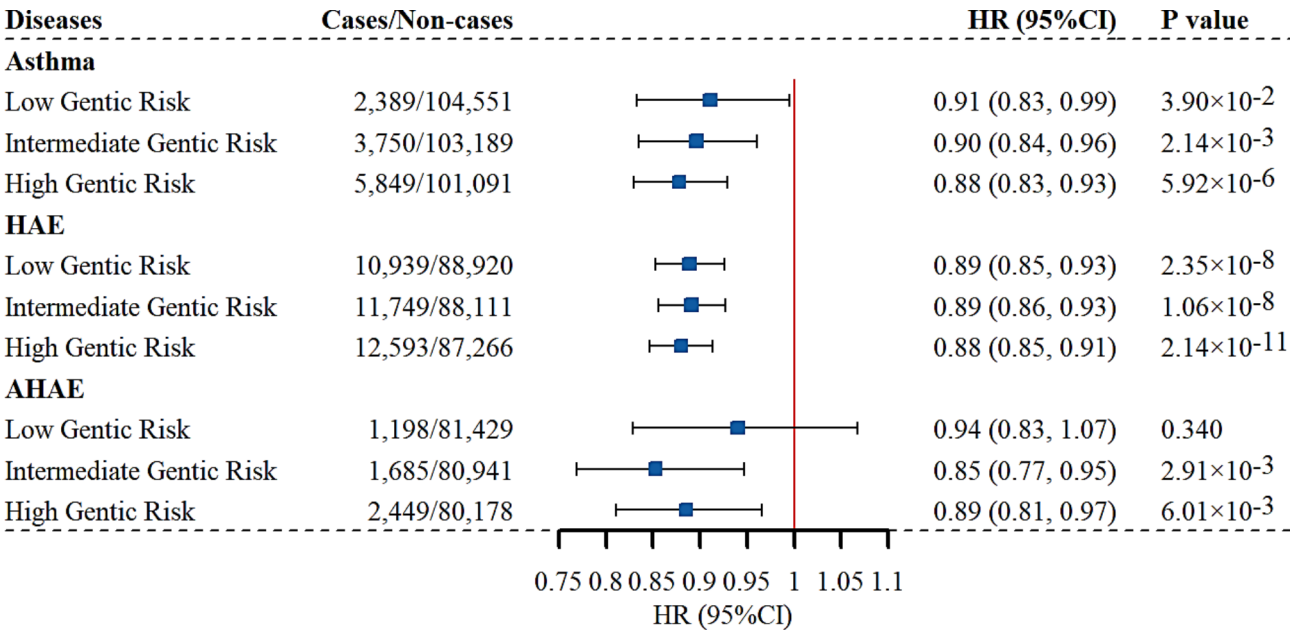

Fig. 2 Forest plot of effects of breastfeeding on Asthma, HAE and AHAE in children under 18 years old when stratified by PRS. HR, hazard ratio; CI, confidence interval; HAE, hay fever, allergic rhinitis, and eczema; AHAE, the comorbidity of asthma and HAE

The stratified analysis showed that the effects of breastfeeding on asthma, HAE, and AHAE were essentially similar across different levels of covariates (Table S3). When stratified by age at onset, we discovered the association of breastfeeding with HAE ($P_{heterogeneity}$=0.170) or AHAE ($P_{heterogeneity}$=0.799) persisted across distinct onset age groups (Table S4); however, breastfeeding exhibited the strongest effect on asthma adolescents aged 13 ~ 18 years ($P_{heterogeneity}$=0.004).

The adjustment of adolescent smoking did not significantly change the influence of breastfeeding on asthma, HAE, or AHAE (Table S5). The estimated effects were also nearly consistent after excluding smoking/smokers in household, diet score and average total household income before tax (Table S5).

Estimated effect of breastfeeding on Asthma, HAE, and AHAE when taking PRS into account

The effects of breastfeeding on asthma, HAE, and AHAE were almost unchanged when PRS was included to explain the impact of genetic risk (Table 1). For example, the HRs of breastfeeding were 0.89 (95%CI 0.86 ~ 0.93) for asthma, 0.89 (95%CI 0.87 ~ 0.91) for HAE, and 0.89 (95%CI 0.84 ~ 0.94) for AHAE, respectively. In terms of the stratified analysis by PRS, there was no significant difference in the association of breastfeeding across various genetic risk levels (Fig. 2).

We observed that per SD increase in PRS had a significant influence on the risk of asthma (HR = 1.52, 95%CI 1.49 ~ 1.55), HAE (HR = 1.08, 95%CI 1.07 ~ 1.09) and AHAE (HR = 1.39, 95%CI 1.35 ~ 1.43), and there existed a progressively elevated impact on the risk of encountering asthma, HAE, or AHAE as PRS increased (Figure S2). Participants with high genetic risk (top tertile) showed a 151% (95%CI 139 ~ 163%), 17% (95%CI 14 ~ 20%), and 106% (95%CI 93 ~ 121%) higher risk of developing asthma, HAE or AHAE compared to those with low genetic risk (bottom tertile), respectively. These effects did not significantly change after additional adjustment for breastfeeding (Table S6).

Estimated effect of breastfeeding in each stage of AHAE progression in the multi-state model

The results of the path analysis from baseline to one disease or two diseases are shown in Fig. 3. For the transition from baseline to one disease, the impact of breastfeeding on HAE was comparable to that for asthma shown above. For the transition from one disease to AHAE, participants with asthma seemed more likely (15.0%) to further develop AHAE compared with the transition from allergic diseases to AHAE (3.7%). However, the influence of breastfeeding seemed slightly more evident for the path from allergic diseases to AHAE (HR = 0.83, 95%CI 0.73 ~ 0.93) relative to the path from asthma to AHAE (HR = 0.90, 95%CI 0.81 ~ 1.00).

Population attributable protection of incident Asthma, HAE and AHAE

In terms of the breastfeeding rates and the estimated HRs, we showed that AP% of asthma, HAE and AHAE was 12.0%, 13.0% and 13.0%, while PAP% of asthma, HAE and AHAE was 7.1%, 7.6% and 7.6%. Taking asthma for example, the incidence of asthma was expected to reduce by 12.0% in the breastfed population and 7.1% in the general population if they were breastfed.

We then calculated AP% and PAP% after stratifying by PRS, and found a similar risk-reduced influence of breastfeeding on participants across various levels of genetic predisposition in the HAE population. However, for asthma and AHAE, breastfeeding showed more evident influence on those with high PRS (Table S7). For example, breastfeeding substantially reduced AHAE from 13.0% for participants with the highest PRS to 6.4% for those with the lowest PRS.

Discussion

Summary of our results

In this study, we have demonstrated that breastfeeding could lead to a decreased risk of suffering from asthma, hay fever, allergic rhinitis, and eczema in children and adolescents, as well as the comorbidity of these diseases. In terms of the transition from a disease to the comorbidity, we discovered that participants with asthma were more likely to progress to comorbidity and breastfeeding had a stronger risk-reduced effect on individuals who developed from allergic rhinitis to comorbidity. Further, the effects of breastfeeding on asthma and allergic diseases were still significant after PRS was included to explain the effect of genetic risk and remained nearly consistent across distinct genetic risk levels.

Comparison with previous studies

Our work supported and complemented the previous research in three aspects. First, some previous studies have proved the relationship between breastfeeding and asthma as well as between breastfeeding and hay fever, allergic rhinitis, or eczema [18, 45]; however, other

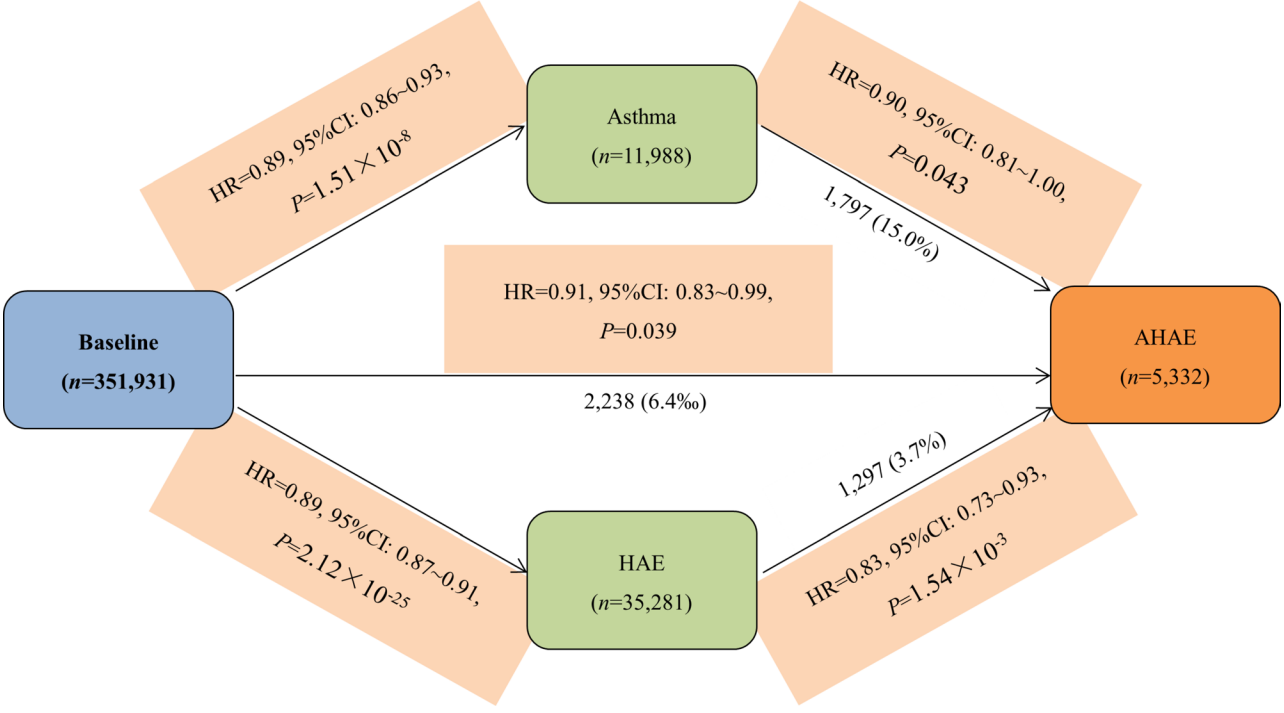

Fig. 3 Analysis path from baseline to the occurrence of one disease and then to the existence of two diseases. HR, hazard ratio; CI, confidence interval; HAE, hay fever, allergic rhinitis, and eczema; AHAE, the comorbidity of asthma and HAE

population-based studies generated inconsistent conclusions. For example, it was discovered that breastfeeding (any or exclusive) showed an insignificant effect on asthma and allergic disease in the IoW cohort [5]. Relying on the large-scale UK Biobank cohort, we offered substantial evidence supporting the association of breastfeeding with asthma and hay fever, allergic rhinitis, and eczema.

Second, some studies on food allergy showed that it was important to consider individual genetic variation when evaluating the relation between breastfeeding and food allergy [46]. In this spirit, we included PRS to explain the effect of genetic risk, and discovered that the effect of breastfeeding did not change much at various genetic risk levels.

Third, contrary to existing studies which demonstrated a possible interaction between breastfeeding and genetic risk [47, 48], we found that the associations between breastfeeding and asthma, hay fever, allergic rhinitis, and eczema, and the relationship between breastfeeding and the comorbidity of these diseases were very similar across all dimensions of genetic risk, which indicated the pervasive benefit of breastfeeding for the whole population under 18 years old.

Advantages of this work

Compared with the previous work, our research has four main advantages. First, the data we analyzed were obtained from the UK Biobank cohort and had a much larger sample size than existing studies; therefore, the sampling error has little influence on the results [49, 50]. Second, we further considered the comorbidity of asthma and allergic diseases, which was very common in practice [51] but rarely discussed before. Third, for the first time, we combined breastfeeding and PRS together to evaluate their joint influences. Fourth, the multi-state model was conducted, which allowed us to explore the effects of breastfeeding on the different stages of the full disease process.

Limitations of this work

There are also some limitations that need to be highlighted. First, due to potential recall bias, breastfeeding, asthma and allergic diseases might be wrongly classified [52, 53]. Meanwhile, we did not consider other important confounders such as length and exclusivity of breastfeeding, family history, maternal gestational age, and maternal/paternal educational level because they cannot be accurately available in the UK Biobank cohort [54, 55]. In addition, we had to employ some adult variables (smoking/smokers in household and average total household income before tax) as the proxies of covariates which needed to adjust for because the relevant information was unavailable for children and adolescents in the UK Biobank cohort. However, through some additional analyses, we found that doing this seemed not to have a substantial influence on our findings. Nevertheless, we cannot rule out the possibility that those unmeasured covariates likely biased our results.

Second, there might exist a reverse relationship [56]; that is to say, early symptoms of asthma and allergic diseases had existed during breastfeeding, which prompted the mothers to continue breastfeeding. This may weaken the impact of breastfeeding and even lead to the spurious conclusion that breastfeeding will increase the risk of asthma, hay fever, allergic rhinitis, or eczema.

Third, the UK Biobank consists mainly of Caucasians from developed countries, and there are large differences in breastfeeding rates across various national races [57], which likely limits the generalization of our findings to populations with other genetic backgrounds and relatively low socio-economic levels.

Public health implications of our findings

Although the risks of not breastfeeding have been widely documented, breastfeeding initiation rates remain relatively low in many high-income countries, particularly among women from low-income regions [58]. The decision of breastfeeding is influenced by multiple and complex factors at the individual, family, health system and societal levels [59]. In view of the health benefits of breastfeeding observed in current research, our findings are of great significance for strengthening breastfeeding suggestions and improving the health status of future generations [46].

In addition, our results offered a deep understanding of the impact of breastfeeding on allergic diseases, regardless of the background of individual genetic variation. Our results also indicate that there is an opportunity to prevent asthma and allergic diseases in children from the beginning (as early as lactation), and to reduce the risk of developing these diseases in the future.

Conclusions

We provided supportive evidence for the significant association of breastfeeding with the reduced risk of asthma, allergic diseases, and comorbidities in children and adolescents less than 18 years of age, and further revealed that this influence was not affected by various genetic susceptibility levels. These findings were helpful in encouraging mothers to initiate and prolong breastfeeding.

Abbreviations

PRS	Polygenic Risk Score
HR	Hazard Ratio
CI	Confidence Interval
GWASs	Genome-Wide Association Studies
MREC	Multi-Center Research Ethics Committee
RTB	Research Tissue Bank

HAE	Hay fever, Allergic rhinitis, and Eczema
AHAE	Comorbidity of Asthma and Hay fever, Allergic rhinitis, and Eczema
GPC	Genetic Principal Components
MICE	Multivariate Imputation by Chained Equations
SNPs	Single-Nucleotide Polymorphisms
AP%	Attributable Protection
PAP%	Population Attributable Protection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20501-0.

Supplementary Material 1

Acknowledgements

This study was also based on the UK Biobank resource under application number 88159. The UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government, and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government, British Heart Foundation and Diabetes UK. The data analyses in the present study were carried out with the high-performance computing cluster that was supported by the special central finance project of local universities for Xuzhou Medical University. We thank the Editor, Associate Editor, and three anonymous reviewers for their constructive comments which substantially improved our manuscript.

Author contributions

PZ conceived the idea for the study. PZ obtained the data. PZ, FG and WH cleared up the datasets and performed the data analyses. PZ, SH, JQ, WC and WH interpreted the results of the data analyses. PZ and WH wrote the manuscript with the participation of other authors.

Funding

The research of Ping Zeng was supported in part by the National Natural Science Foundation of China (82173630), the Natural Science Foundation of Jiangsu Province of China (BK20241952), the QingLan Research Project of Jiangsu Province for Young and Middle-aged Academic Leaders, and the Six-Talent Peaks Project in Jiangsu Province of China (WSN-087).

Data availability

This study used the UK Biobank resource with the application ID 88159. Researchers can access to the UK Biobank dataset by applying to the UK Biobank official website (https://www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate

The UK Biobank had approval from the North West Multi-Centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. All participants provided written informed consent before enrolment in the study, which was conducted in accordance with the Declaration of Helsinki. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Biostatistics, School of Public Health, Xuzhou Medical University, Xuzhou, Jiangsu 221004, China
[2]Department of Pediatrics, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221004, China
[3]Jiangsu Engineering Research Center of Biological Data Mining and Healthcare Transformation, Xuzhou Medical University, Xuzhou, Jiangsu 221004, China

Received: 19 August 2023 / Accepted: 23 October 2024
Published online: 05 November 2024

References

1. Laulajainen-Hongisto A, Lyly A, Hanif T, Dhaygude K, Kankainen M, Renkonen R, et al. Genomics of Asthma, allergy and chronic rhinosinusitis: novel concepts and relevance in airway mucosa. Clin Transl Allergy. 2020;10(1):45. https://doi.org/10.1186/s13601-020-00347-6.
2. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol. 2008;122(2 Suppl):S1–84. https://doi.org/10.1016/j.jaci.2008.06.003.
3. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: executive Summary and Rationale for Key Changes. Am J Respir Crit Care Med. 2022;205(1):17–35. https://doi.org/10.1164/rccm.202109-2205PP.
4. Nur Husna SM, Tan HT, Md Shukri N, Mohd Ashari NS, Wong KK. Allergic rhinitis: a clinical and pathophysiological overview. Front Med (Lausanne). 2022;9:874114. https://doi.org/10.3389/fmed.2022.874114.
5. Bion V, Lockett GA, Soto-Ramírez N, Zhang H, Venter C, Karmaus W, et al. Evaluating the efficacy of breastfeeding guidelines on long-term outcomes for allergic disease. Allergy. 2016;71(5):661–70. https://doi.org/10.1111/all.12833.
6. Sjogren YM, Duchen K, Lindh F, Bjorksten B, Sverremark-Ekstrom E. Neutral oligosaccharides in colostrum in relation to maternal allergy and allergy development in children up to 18 months of age. Pediatr Allergy Immunol. 2007;18(1):20–6. https://doi.org/10.1111/j.1399-3038.2006.00486.x.
7. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):38–53. https://doi.org/10.1111/apa.13132.
8. Xue M, Dehaas E, Chaudhary N, O'Byrne P, Satia I, Kurmi OP. Breastfeeding and risk of childhood asthma: a systematic review and meta-analysis. ERJ Open Res. 2021;7(4):00504–2021. https://doi.org/10.1183/23120541.00504-2021.
9. Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. J Allergy Clin Immunol. 2001;107(4):567–74. https://doi.org/10.1067/mai.2001.112943.
10. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy. 2014;69(5):590–601. https://doi.org/10.1111/all.12398.
11. Kramer MS, Matush L, Vanilovich I, Platt R, Bogdanovich N, Sevkovskaya Z, et al. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. BMJ. 2007;335(7624):815. https://doi.org/10.1136/bmj.39304.464016.AE.
12. Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of parents and children (ALSPAC). J Allergy Clin Immunol. 2008;122(1):49–54. https://doi.org/10.1016/j.jaci.2008.04.001. e1-3.
13. Zhu Z, Lee PH, Chaffin MD, Chung W, Loh PR, Lu Q, et al. A genome-wide cross-trait analysis from UK Biobank highlights the shared genetic architecture of asthma and allergic diseases. Nat Genet. 2018;50(6):857–64. https://doi.org/10.1038/s41588-018-0121-0.
14. Demenais F, Margaritte-Jeannin P, Barnes KC, Cookson WOC, Altmuller J, Ang W, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. Nat Genet. 2018;50(1):42–53. https://doi.org/10.1038/s41588-017-0014-7.
15. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011;242(1):10–30. https://doi.org/10.1111/j.1600-065X.2011.01029.x.
16. Waage J, Standl M, Curtin JA, Jessen LE, Thorsen J, Tian C, et al. Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. Nat Genet. 2018;50(8):1072–80. https://doi.org/10.1038/s41588-018-0157-1.
17. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet. 2017;49(12):1752–7. https://doi.org/10.1038/ng.3985.
18. Silvers KM, Frampton CM, Wickens K, Pattemore PK, Ingham T, Fishwick D et al. Breastfeeding protects against current asthma up to 6 years of age. J Pediatr. 2012;160(6):991-6 e1. https://doi.org/10.1016/j.jpeds.2011.11.055

19. Nathan N, Sileo C, Calender A, Pacheco Y, Rosental P-A, Cavalin C, et al. Paediatric sarcoidosis. Paediatr Respir Rev. 2019;29:53–9. https://doi.org/10.1016/j.prrv.2018.05.003.
20. Duncan JM, Sears MR. Breastfeeding and allergies: time for a change in paradigm? Curr Opin Allergy Clin Immunol. 2008;8(5):398–405. https://doi.org/10.1097/ACI.0b013e32830d82ed.
21. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779. https://doi.org/10.1371/journal.pmed.1001779.
22. Olafsdottir TA, Theodors F, Bjarnadottir K, Bjornsdottir US, Agustsdottir AB, Stefansson OA, et al. Eighty-eight variants highlight the role of T cell regulation and airway remodeling in asthma pathogenesis. Nat Commun. 2020;11(1):393. https://doi.org/10.1038/s41467-019-14144-8.
23. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. Thorax. 2012;67(12):1046–51. https://doi.org/10.1136/thoraxjnl-2012-202150.
24. Hou W, Guan F, Xia L, Xu Y, Huang S, Zeng P. Investigating the influence of breastfeeding on asthma in children under 12 years old in the UK Biobank. Front Immunol. 2022;13:967101. https://doi.org/10.3389/fimmu.2022.967101.
25. Nwaru BI, Takkinen HM, Niemela O, Kaila M, Erkkola M, Ahonen S, et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. J Allergy Clin Immunol. 2013;131(1):78–86. https://doi.org/10.1016/j.jaci.2012.10.028.
26. Zeng P, Zhao Y, Qian C, Zhang L, Zhang R, Gou J, et al. Statistical analysis for genome-wide association study. J Biomed Res. 2015;29(4):285–97. https://doi.org/10.7555/JBR.29.20140007.
27. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67. https://doi.org/10.18637/jss.v045.i03.
28. Visscher PM, Yengo L, Cox NJ, Wray NR. Discovery and implications of polygenicity of common diseases. Science. 2021;373(6562):1468–73. https://doi.org/10.1126/science.abi8206.
29. Kullo IJ, Lewis CM, Inouye M, Martin AR, Ripatti S, Chatterjee N. Polygenic scores in biomedical research. Nat Rev Genet. 2022;23(9):524–32. https://doi.org/10.1038/s41576-022-00470-z.
30. Ge T, Chen CY, Ni Y, Feng Y-CA, Smoller JW. Polygenic prediction via bayesian regression and continuous shrinkage priors. Nat Commun. 2019;10(1):1776. https://doi.org/10.1038/s41467-019-09718-5.
31. Lu H, Qiao J, Shao Z, Wang T, Huang S, Zeng P. A comprehensive gene-centric pleiotropic association analysis for 14 psychiatric disorders with GWAS summary statistics. BMC Med. 2021;19(1):314. https://doi.org/10.1186/s12916-021-02186-z.
32. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47(11):1228–35. https://doi.org/10.1038/ng.3404.
33. Altshuler DM, Durbin RM, Abecasis GR, Bentley DR, Chakravarti A, Clark AG, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–. https://doi.org/10.1038/nature15393.
34. Wang T, Lu H, Zeng P. Identifying pleiotropic genes for complex phenotypes with summary statistics from a perspective of composite null hypothesis testing. Brief Bioinform. 2022;23(1):bbab389. https://doi.org/10.1093/bib/bbab389.
35. Tan CH, Hyman BT, Tan JJX, Hess CP, Dillon WP, Schellenberg GD, et al. Polygenic hazard scores in preclinical Alzheimer disease. Ann Neurol. 2017;82(3):484–8. https://doi.org/10.1002/ana.25029.
36. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69(1):239–41. https://doi.org/10.2307/2335876.
37. Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. Birth weight and childhood wheezing disorders: a systematic review and meta-analysis. J Epidemiol Community Health. 2015;69(5):500–8. https://doi.org/10.1136/jech-2014-204783.
38. Azad MB, Vehling L, Lu Z, Dai D, Subbarao P, Becker AB, et al. Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. Eur Respir J. 2017;49(5):1602019. https://doi.org/10.1183/13993003.02019-2016.
39. Zhao Y, Wang SF, Mu M, Sheng J. Birth weight and overweight/obesity in adults: a meta-analysis. Eur J Pediatr. 2012;171(12):1737–46. https://doi.org/10.1007/s00431-012-1701-0.
40. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med. 2000;162(3 Pt 1):920–4. https://doi.org/10.1164/ajrccm.162.3.9912030.
41. Saulyte J, Regueira C, Montes-Martinez A, Khudyakov P, Takkouche B. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. PLoS Med. 2014;11(3):e1001611. https://doi.org/10.1371/journal.pmed.1001611.
42. de Wreede LC, Fiocco M, Putter H. Mstate: an R Package for the analysis of competing risks and multi-state models. J Stat Softw. 2011;38(7):1–30. https://doi.org/10.18637/jss.v038.i07.
43. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed. 2010;99(3):261–74. https://doi.org/10.1016/j.cmpb.2010.01.001.
44. Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. Int J Epidemiol. 2004;33(6):1389–97. https://doi.org/10.1093/ije/dyh276.
45. Rosas-Salazar C, Forno E, Brehm JM, Han YY, Acosta-Perez E, Cloutier MM, et al. Breastfeeding duration and asthma in Puerto Rican children. Pediatr Pulmonol. 2015;50(6):527–34. https://doi.org/10.1002/ppul.23061.
46. Hong X, Wang G, Liu X, Kumar R, Tsai HJ, Arguelles L et al. Gene polymorphisms, breast-feeding, and development of food sensitization in early childhood. J Allergy Clin Immunol. 2011;128(2):374 – 81 e2. https://doi.org/10.1016/j.jaci.2011.05.007
47. Siltanen MKM, Poussa T, Saarinen KMSE. A dual long-term effect of breastfeeding on atopy in relation to heredity in children at 4 years of age. Allergy. 2003;58(6):524–30. https://doi.org/10.1034/j.1398-9995.2003.00150.x.
48. Kauffmann F, Demenais F. Gene-environment interactions in asthma and allergic diseases: challenges and perspectives. J Allergy Clin Immunol. 2012;130(6):1229–40. https://doi.org/10.1016/j.jaci.2012.10.038. quiz 41 – 2.
49. Sedgwick P. Uncertainty in sample estimates: sampling error. BMJ. 2015;350:h1914. https://doi.org/10.1136/bmj.h1914.
50. Chen Z, Lin L. Bias caused by sampling error in meta-analysis with small sample sizes. PLoS ONE. 2018;13(9):e0204056. https://doi.org/10.1371/journal.pone.0204056.
51. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol. 2000;106(5 Suppl):S201–5. https://doi.org/10.1067/mai.2000.110151.
52. Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal Recall of Breastfeeding Practice. Nutr Rev. 2005;63(4):103–10. https://doi.org/10.1111/j.1753-4887.2005.tb00128.x.
53. Mortz CG, Andersen KE, Bindslev-Jensen C. Recall bias in childhood atopic diseases among adults in the Odense Adolescence Cohort Study. Acta Derm Venereol. 2015;95(8):968–72. https://doi.org/10.2340/00015555-2128.
54. Ek WE, Karlsson T, Hernándes CA, Rask-Andersen M, Johansson Å. Breastfeeding and risk of asthma, hay fever, and eczema. J Allergy Clin Immunol. 2018;141(3):1157–e99. https://doi.org/10.1016/j.jaci.2017.10.022.
55. Elbert NJ, van Meel ER, den Dekker HT, de Jong NW, Nijsten TEC, Jaddoe VWV, et al. Duration and exclusiveness of breastfeeding and risk of childhood atopic diseases. Allergy. 2017;72(12):1936–43. https://doi.org/10.1111/all.13195.
56. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95(Suppl 1):S144–50. https://doi.org/10.2105/AJPH.2004.059204.
57. Jones KM, Power ML, Queenan JT, Schulkin J. Racial and ethnic disparities in breastfeeding. Breastfeed Med. 2015;10(4):186–96. https://doi.org/10.1089/bfm.2014.0152.
58. Balogun OO, O'Sullivan EJ, McFadden A, Ota E, Gavine A, Garner CD, et al. Interventions for promoting the initiation of breastfeeding. Cochrane Database Syst Rev. 2016;11(11):CD001688. https://doi.org/10.1002/14651858.CD001688.pub3.
59. Dyson L, Renfrew MJ, McFadden A, McCormick F, Herbert G, Thomas J. Policy and public health recommendations to promote the initiation and duration of breast-feeding in developed country settings. Public Health Nutr. 2010;13(1):137–44. https://doi.org/10.1017/S136898000999067X.

Publisher's note