

Letter to the Editor

Breast-feeding and risk of asthma, hay fever, and eczema

To the Editor:

The World Health Organization recommends breast-feeding for at least 6 months after delivery because of general health benefits for the child.¹ However, studies on breast-feeding have yielded inconsistent results regarding its association with the risks for developing asthma, hay fever, and eczema.²⁻⁴ A large homogeneous population-based cohort, such as the one used in this study (UK Biobank; N = 502,682), provides statistical power to fill in unaddressed gaps in the knowledge on the effects of breast-feeding on the risks of developing asthma, hay fever, and eczema. A total of 336,364 Caucasian participants, born between 1937 and 1969, with self-reported information about being breast-fed or not were included in this study. Information on length and exclusivity of breast-feeding was not available. Baseline characteristics and prevalences are presented in Table E1 in this article's Online Repository at www.jacionline.org.

In the main analysis we included all 336,364 participants. We compared the odds of self-reported asthma, hay fever, and eczema diagnosis separately and hay fever/eczema combined, depending on breast-feeding using logistic regression. When not adjusting for possible confounders, a decreased risk of asthma (odds ratio [OR] = 0.88; $P < 2.10 \times 10^{-16}$; Fig 1, A) and hay fever/eczema (OR = 0.94; $P = 1.89 \times 10^{-10}$; Fig 1, B) was found for the breast-fed population. We then reanalyzed all disease phenotypes and included covariates that we identified to be associated with these phenotypes (see Table E2 in this article's Online Repository at www.jacionline.org). To evaluate the effect of the covariates, each covariate was first included in the model separately (see Table E3 in this article's Online Repository at www.jacionline.org). By including year of birth in the model we can see that breast-feeding changes from having a protective effect on hay fever and/or eczema, to increasing the risk for disease. This suggests that year of birth operates as a strong qualitative confounder in the unadjusted analyses, that is, change the effect in the opposite direction. This suggests that the opposite directions of the secular trends of breast-feeding and hay fever/eczema represent an ecologic fallacy (see Fig E1 in this article's Online Repository at www.jacionline.org), which might be resolved by adjustment for year of birth. Therefore, not adjusting for year of birth will give a negative association (as seen in the univariate analysis). The full model, adjusting for all covariates, showed that the effect of breast-feeding on the odds of being diagnosed with asthma was no longer significant (OR = 0.99; $P = .96$; Fig 1, A), while associated with higher odds for hay fever/eczema (OR = 1.06; $P = 7.80 \times 10^{-6}$) (Fig 1, B). Breast-feeding also increased the odds for eczema and hay fever diagnosed separately (see Fig E2, A and B, in this article's Online Repository at www.jacionline.org).

We could see an effect of socioeconomic status (for which Townsend deprivation index [TDI] is used as a proxy) on asthma and hay fever in the full model. Higher TDI (lower socioeconomic status) was associated with increased odds for asthma (OR = 1.02; $P = 9.01 \times 10^{-11}$) while associated with lower odds for hay fever (OR = 0.098; $P = 7.46 \times 10^{-8}$). Note that the effect size denotes the change in OR per unit of TDI

($-6 < \text{TDI} < 10$). By comparing the groups with lowest and highest TDI, the effect would be larger. The decreased odds for hay fever are in line with the "hygiene hypothesis," which suggests that a lack of endemic infections increases the risk of being diagnosed with allergies due to a lack of early childhood exposure to, for example, microorganisms.⁵ Endemic infections might be related to socioeconomic status indirectly (eg, by crowding). Maternal smoking around birth and smoking in house seem to be risk factors for developing asthma (OR = 1.03; $P = .047$), while having a protective effect on hay fever and eczema (OR = 0.94; $P = 3.54 \times 10^{-6}$). High body mass index was significantly associated with increased odds for asthma (OR = 1.04; $P < 2 \times 10^{-16}$) and hay fever/eczema (OR = 1.004; $P = .00024$). Higher birth weight lowered the odds for asthma (OR = 0.93; $P = 3.13 \times 10^{-11}$) and hay fever/eczema (OR = 0.97; $P = .0039$).

To measure the robustness of these links between asthma, hay fever, and eczema with being breast-fed, we did additional subgroup analyses of all 336,364 participants, which confirmed the same results as the full model (Fig 1, A and B; see Fig E2, A and B). Interestingly, females showed a significant association between breast-feeding and decreased odds for asthma in the subgroup analysis ($P = .046$), with an opposite effect as compared with males (Fig 1, A). This might be due to a difference between atopic asthma (more common in males) and nonatopic asthma (more common in females). When analyzing participants with asthma without hay fever/eczema (proxy for nonatopic asthma), breast-feeding is significantly protective (OR = 0.95; $P = .02$) against asthma. Also, no difference (P value for interaction = .52) was seen between males and females. When analyzing breast-feeding with participants with asthma with hay fever/eczema (proxy for atopic asthma), we see increased odds for disease associated with breast-feeding (OR = 1.053; $P = .018$). Even though the P values would not hold for multiple testing, it indicates that breast-feeding may have a different direction of effect on nonatopic asthma compared with atopic asthma.

Identifying the actual effect of breast-feeding on disease outcome is a challenge because there may be unknown or unobserved differences between breast-fed and non-breast-fed participants. For example, nonlinear effects and interactions between covariates could mask or distort the effect of breast-feeding. To overcome such problems, and to strengthen the results from our main analysis, we matched breast-fed and non-breast-fed participants for suspected confounders (see Fig E3 in this article's Online Repository at www.jacionline.org). We matched breast-fed and non-breast-fed individuals in 16 subgroups. To make the groups as homogeneous as possible, we excluded individuals with extreme body mass index values (obese and underweight) and low birth weights (<2.5 kg). After meta-analyzing the results from the matched subgroups, the results were still significant with the same direction of effect as in the main adjusted analysis. This strengthens our conclusion that breast-feeding is associated with increased odds of being diagnosed with hay fever and eczema (see Table E4 in this article's Online Repository at www.jacionline.org).

Observational studies do not allow for clinical recommendations because residual confounding might still be an issue.

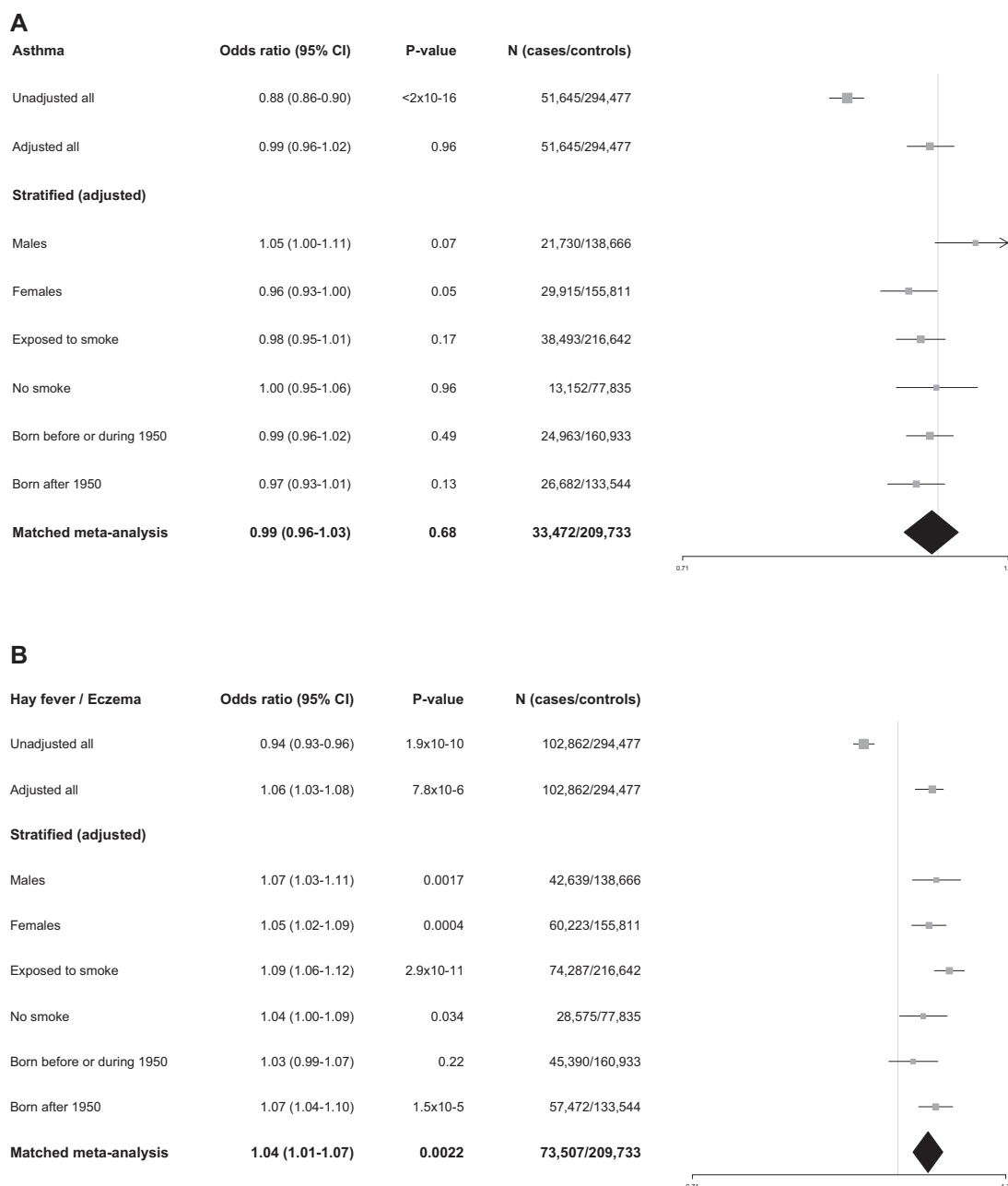


FIG 1. Forest plots for the effect of breast-feeding for asthma (**A**) and hay fever/eczema (**B**) for the unadjusted model, the adjusted model, the adjusted subgroup analysis, and the matched meta-analysis. The matched meta-analysis is adjusted for body mass index, birth weight, TDI, home area, and year of birth.

Observed effects might also be due to reversed causality, that is, that individuals with a known risk of developing disease may not have been breast-fed or had a higher chance of being breast-fed due to recommendations. Today, women with higher socioeconomic status and high education level seem to breast-feed more often.⁶ If TDI does not fully cover socioeconomic status, and because we did not have information on maternal education, socioeconomic status and education might drive the association between breast-feeding and the increased risk for hay fever and eczema. However, during the period 1950 to 1960 this trend seems to have been the opposite,

that is, that breast-feeding rates were lower for women with a high school education than for those with less education,⁷ and so the use of TDI and the lack of maternal education in the regression model would rather have a diminishing effect on the estimates.

In summary, this study reports evidence that breast-feeding is associated with an increased risk for hay fever and eczema. Because of the high power achieved by the large sample size and the rigorous information on confounding variables, we conclude that breast-feeding is not likely to have a large effect on the risk of developing asthma.

This research was conducted using the UK Biobank Resource under Application Number 15479. The computations were performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under project b2016021203.

Weronica E. Ek, PhD

Torgny Karlsson, PhD

Carlos Azuaje Hernández, BSc

Mathias Rask-Andersen, PhD

Åsa Johansson, PhD

From the Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden. E-mail: Weronica.ek@igp.uu.se.

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METHODS

Participants

The UK Biobank database includes 502,682 participants recruited from all across the United Kingdom. Participants were aged 37 to 73 years at the time of recruitment between 2006 and 2010. Most participants visited the center once, but some individuals visited the center at up to 3 instances. This population-based cohort includes information on medical conditions, diet, and lifestyle factors. The UK Biobank database was approved by the National Research Ethics Committee (REC reference no. 11/NW/0382). Application for using data from UK Biobank had been approved (application no. 15479). In this study, we included participants of Caucasian ancestry, defined as those reporting that they were “white,” “white British,” “Irish,” or “other white” during all instances. A total of 5568 individuals were removed because of conflicting answers on asthma (622 individuals), hay fever (2,143 individuals), and eczema (2,738 individuals) and 65 individuals because of conflicting answers on both hay fever and eczema.

Disease phenotypes: Asthma and hay fever/eczema

Self-reports of asthma and hay fever and/or eczema (combined) were collected through touch screen questionnaire. The primary data used in this study were from the touch screen question number 6152: “has a doctor ever told you that you have had any of the following conditions? (You can select more than one answer)”: (1) asthma and (2) hay fever, allergic rhinitis, or eczema, (3) none of the above, or (4) prefer not to answer. Hay fever and eczema diagnosis could not be separated and this variable is therefore called hay fever/eczema in our study. Controls were selected as individuals answering “none of the above” in question 6152, and those who did not report asthma, hay fever, or eczema during the verbal interview (see below). Some individuals visited the center more than once and we included participants who reported disease at any or all visits.

Disease phenotypes: Hay fever and eczema separately

Trained staff followed up individuals who answered that they had been told by a doctor that they had 1 or more of the following diseases: heart attack, angina, stroke, high blood pressure, blood clot in leg, blood clot in lung, emphysema/chronic bronchitis, asthma, or diabetes, with a verbal interview. During this interview, the nurse confirmed with each participant that the data they selected on the screen or questionnaire were correct. If yes, the nurses asked them the approximate age at diagnosis. The nurses could also add diagnoses (via a drop-down menu) if the participant wanted to add other medical conditions. These were later coded to *International Classification of Diseases, Tenth Revision* before being made publicly available. These diagnoses (UK Biobank data field 20002) were used to define hay fever and eczema cases separately. Because only 379,887 participants were followed up for an interview, and this selection was not random, diseases reported here have a bias in prevalence. Therefore, data from individuals who did not report that they had eczema or hay fever are uncertain and the same controls were therefore used as for the touch screen variables above. If there were any conflicting answers between the variables from the interview and the touch screen, the phenotype was set to missing. For example, individuals who reported that they had eczema/hay fever in the touch screen questionnaire, but had not reported either eczema or hay fever in the interview, were removed from the analyses.

Discussion/limitations

It is remarkable and quite unexpected that we see an association between breast-feeding and an increased risk for hay fever and eczema. One hypothesis of a causal mechanism for such an effect can be the transfer of contaminants present in breast milk from the mother to the infant. Previous studies have identified increased level of contaminants in breast milk,^{E1-E3} which agrees with this finding. Both hay fever and eczema are also heritable^{E4} and it is possible that mothers with allergies more often breast-fed their babies

compared with mothers without any allergy. It is also important to remember that the observed effects might be due to reversed causality, that is, that individuals with a known risk of developing atopic diseases (eg, participants with atopic disease within their family) might not have been breast-fed or had a higher chance of being breast-fed due to recommendations. The understanding of the immune system began during the 1950s, and in 1958, Hanson^{E5} described how antibodies in human milk were active against enteric bacteria and viruses, which culminated in an increased understanding of the biological role of human milk. However, we have not found any reports in the literature about recommendations for allergic/atopic mothers to breast-feed their babies before 1970, when breast-feeding campaigns started to develop.^{E6} In the early 1980s, the general knowledge of breast-feeding health benefits quickly increased.^{E7} We therefore have no reason to believe that maternal history of allergy would have increased both breast-feeding and risk of hay fever/eczema during the time period 1937 to 1969, when the UK Biobank participants included in this study were born. One previous study has also shown that breast-feeding effects are not affected by parental history of hay fever or asthma.^{E8} We are unable to make any statements on potentially different effects of breast-feeding between different risk groups depending on the level of prevalence, or lack of disease in families.

After 1950, there was a faster increase in disease incidence combined with a decline in the incidence of being breast-fed (Fig E1). For that reason, stratifying for being born before or after 1950 was done. Breast-feeding showed significantly increased odds for hay fever/eczema in participants being born after 1950. In participants being born during or before 1950, the effect was in the same direction, but not significant (Fig 1, B).

Even though this study showed a protective effect of maternal smoking around birth and being exposed to tobacco smoke at home on the risk of being diagnosed with hay fever and eczema in the full model, there are a number of important reasons not to expose other people to tobacco smoke, for example, the fact that second-hand smoke increases the risk of lung cancer^{E9} and heart disease.^{E10} Smoking is also associated with socioeconomic status and it cannot be ruled out that the higher odds of being diagnosed with hay fever/eczema result from a residual effect of socioeconomic status that is not picked up by TDI.

Because of the dichotomous nature of the data, we could not investigate the effects of duration of breast-feeding (more than 2 months), a dose-response effect (2, 4, or 6 months), or the effect of exclusive breast-feeding. Both duration and exclusivity of breast-feeding are important because dose-response is well established for many breast milk benefits, especially for child mortality.^{E11,E12} However, in previous studies that have investigated the association between breast-feeding and atopic diseases, it appears as dose and duration do not change the direction of effect, rather only increasing the effect size, which, in turn, influence the size of the *P* values.^{E8,E13,E14} Even though the phenotypes are self-reported in the UK Biobank database, which may lead to an overestimation of disease incidence, the questions are well defined and identical for all participants. However, the need for strict diagnosis criteria is less important due to the large statistical power of a large population-based cohort such as the UK Biobank cohort.

Understanding the limitations of this study should not limit the value of it, which is an important contribution to the literature on breast-feeding and risk prevention of atopic disease. The authors of the present study do not take any positions as to whether breast-feeding represents the best source of nutrition for newborns.

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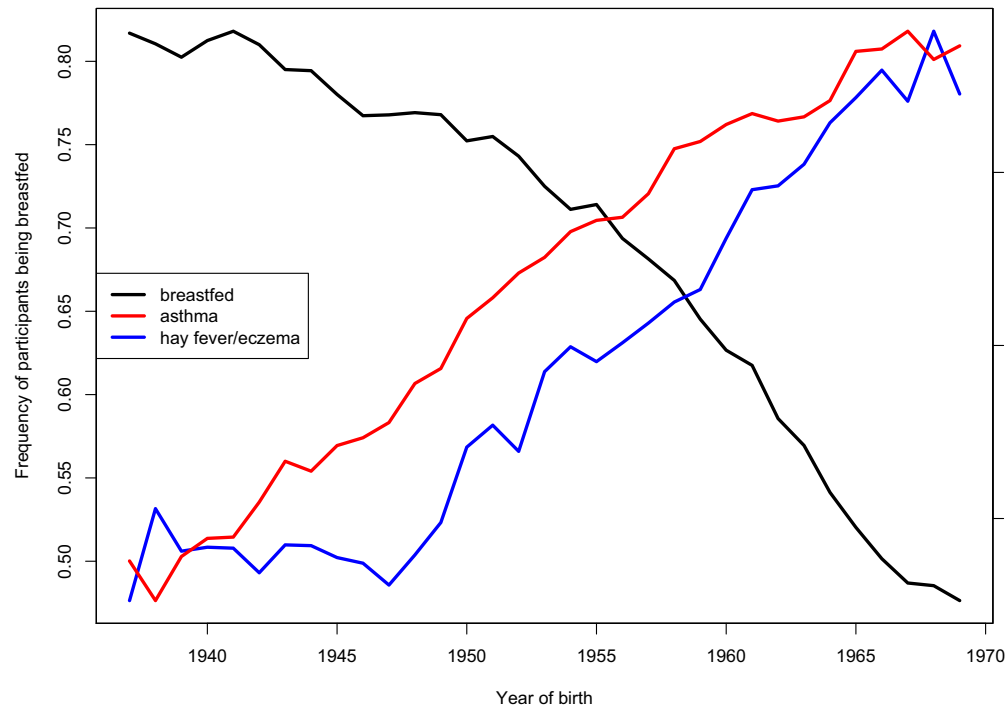
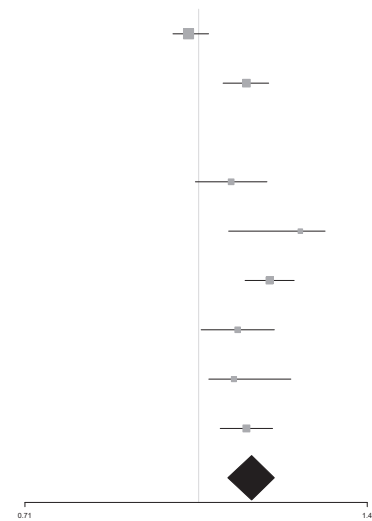


FIG E1. Frequency of participants being breast-fed and the incidence of asthma and hay fever/eczema for year of birth from 1934 to 1970. By not adjusting for year of birth, it appears as if the non-breast-fed population experiences a strongly increased risk of asthma and hay fever/eczema.

A

Hay fever	Odds ratio (95% CI)	P-value	N (cases/controls)
Unadjusted all	0.98 (0.95-1.02)	0.34	22,919/294,477
Adjusted all	1.10 (1.05-1.15)	1.8x10 ⁻⁵	22,919/294,477
Stratified (adjusted)			
Males	1.07 (0.99-1.15)	0.075	10,532/138,666
Females	1.23 (1.06-1.29)	4.8x10 ⁻⁵	12,387/155,811
Exposed to smoke	1.15 (1.10-1.21)	1.6x10 ⁻⁸	16,152/216,642
No smoke	1.08 (1.01-1.16)	0.036	6,767/77,853
Born before or during 1950	1.07 (1.02-1.20)	0.014	9,738/160,933
Born after 1950	1.10 (1.04-1.16)	0.0004	13,181/133,544
Matched meta-analysis	1.11 (1.06-1.16)	6.2x10⁻⁵	16,646/209,733

**B**

Eczema	Odds ratio (95% CI)	P-value	N (cases/controls)
Unadjusted all	0.95 (0.91-1.00)	0.06	9,578/294,477
Adjusted all	1.09 (1.02-1.17)	0.012	9,578/294,477
Stratified (adjusted)			
Males	0.94 (0.91-1.14)	0.81	4,088/138,666
Females	1.13 (1.04-1.23)	0.004	5,490/155,811
Exposed to smoke	1.10 (1.02-1.18)	0.013	7,021/216,642
No smoke	1.13 (1.01-1.27)	0.035	2,557/77,835
Born before or during 1950	1.06 (0.94-1.21)	0.337	4,062/160,933
Born after 1950	1.11 (1.02-1.20)	0.012	5,517/33,544
Matched meta-analysis	1.05 (1.03-1.18)	0.0088	6,863/209,733

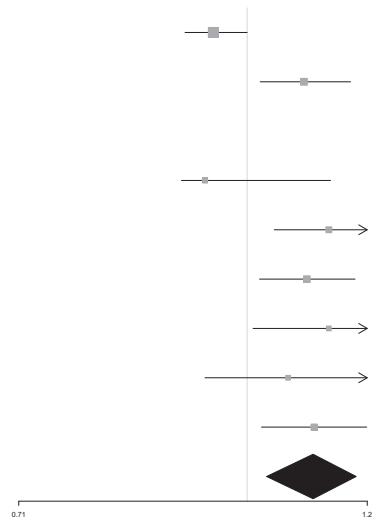


FIG E2. Forest plots for the effect of breast-feeding on each disease for the unadjusted model, the adjusted model, the adjusted subgroup analysis, and the matched meta-analysis for hay fever (**A**) and eczema (**B**). The matched meta-analysis is adjusted for body mass index, birth weight, TDI, home area, and year of birth.

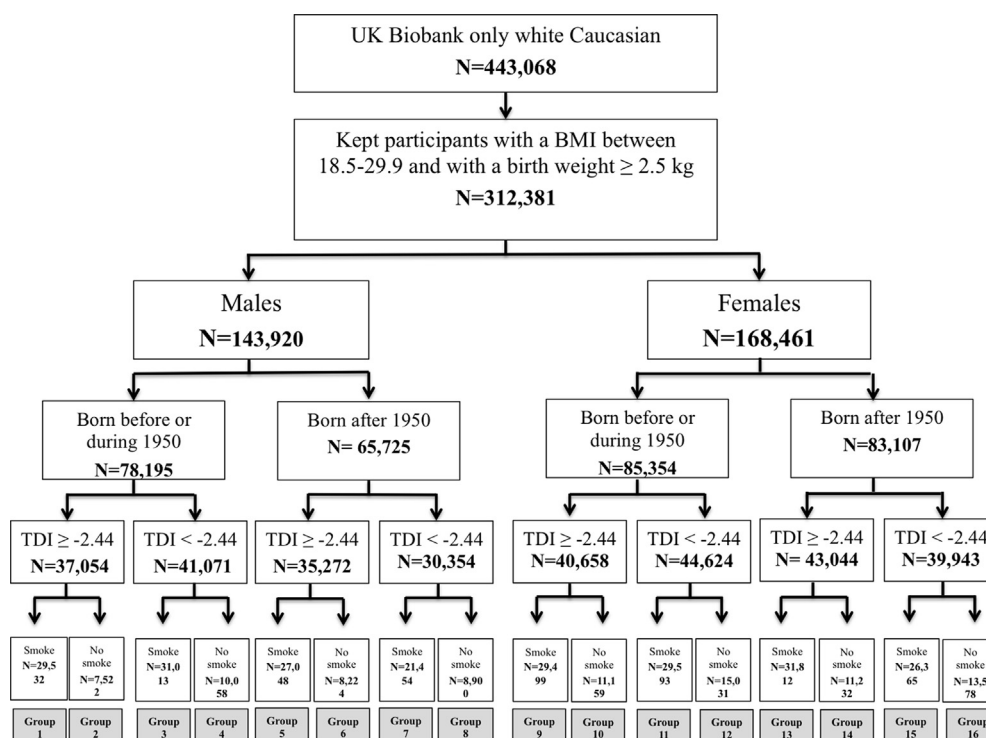


FIG E3. Flow chart of all 16 matched groups. The groups were also adjusted for year of birth, birth weight, and BMI. *BMI*, Body mass index.

TABLE E1. Baseline characteristics for the participants included in the study

Variable	All participants (N = 443,068)	Breast-fed (N = 239,239 [71.2%])	Not breast-fed (N = 97,125 [28.8%])
	N (percentage of total)	N (percentage of N breast-fed)	N (percentage of N not breast-fed)
Sex: male	202,574 (45.7)	105,963 (44.3)	36,808 (37.9)
Asthma	51,645 (11.7)	27,286 (11.4)	12,292 (12.7)
Hay fever/eczema*	102,862 (23.2)	57,091 (23.9)	24,066 (24.8)
Hay fever†	22,919 (5.2)	12,880 (5.4)	5,211 (5.4)
Eczema‡	9,578 (2.2)	5,403 (0.9)	2,256 (2.3)
Maternal smoking at birth	117,518 (26.5)	58,462 (24.4)	30,915 (31.8)
Smoking in house	40,470 (9.1)	21,369 (8.9)	9,745 (10.0)
Ever smoked	266,432 (60.1)	145,645 (60.9)	55,189 (56.8)
Birth weight (kg), range (mean)	0.45-8.16 (3.32)	0.45-7.48 (3.37)	0.45-8.16 (3.23)
Age (y), range (mean)	38-73 (56.86)	38-73 (57.18)	39-70 (53.56)
BMI, range (mean)§	12.12-74.68 (27.42)	12.12-68.41 (27.31)	12.65-74.8 (27.41)
Home area (urban living)	375,045 (84.6)	200,173 (83.7)	83,512 (86.0)
TDI, range (mean)§	-6.26 to 10.88 (-1.52)	-6.26 to 10.56 (-1.65)	-6.26 to 10.88 (-1.35)

All variables were self-reported, except BMI, TDI, and home area.

BMI, Body mass index.

*Self-reported hay fever/eczema information was collected from the touch screen question 6152: "has a doctor ever told you that you have had any of the following conditions? (You can select more than one answer)": (1) asthma and (2) hay fever, allergic rhinitis, or eczema, (3) none of the above, or (4) prefer not to answer. Hay fever and eczema diagnosis could not be separated and this variable is therefore called hay fever/eczema in our study.

†Information on hay fever and eczema separately was collected from an interview (UK Biobank data field 20002). Because only 379,887 participants were followed up for an interview, and this selection was not random, diseases reported here have a bias in prevalence.

‡The BMI value was constructed from height and weight measured during the initial assessment center visit.

§TDI was calculated immediately before participant joining UK Biobank. Each participant is assigned a score corresponding to the output area in which his or her postcode is located. Home area was derived by combining each participant's home postcode with data generated from the 2001 Census from the Office of National Statistics, using the Geoconvert tool from Census Dissemination Unit.

TABLE E2. Associations between individual covariates and asthma, hay fever, eczema, and breast-feeding

Covariate	Asthma		Hay fever/eczema		Hay fever		Eczema		Breast-feeding	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex	0.816 (0.801-0.832)	$<2 \times 10^{-16}$	0.796 (0.784-0.807)	$<2 \times 10^{-16}$	0.955 (0.930-0.981)	.0009	0.837 (0.803-0.872)	$<2 \times 10^{-16}$	1.302 (1.283-1.323)	$<2 \times 10^{-16}$
TDI	1.029 (1.026-1.032)	$<2 \times 10^{-16}$	0.990 (0.987-0.992)	$<2 \times 10^{-16}$	0.960 (0.956-0.965)	$<2 \times 10^{-16}$	0.993 (0.986-1.000)	.038	0.966 (0.964-0.968)	$<2 \times 10^{-16}$
Birth weight	0.918 (0.901-0.935)	$<2 \times 10^{-16}$	0.974 (0.961-0.988)	.0002	0.978 (0.952-1.003)	.087	0.994 (0.956-1.034)	.78	1.401 (1.381-1.421)	$<2 \times 10^{-16}$
Year of birth	1.012 (1.016-1.019)	$<2 \times 10^{-16}$	1.030 (1.029-1.031)	$<2 \times 10^{-16}$	1.033 (1.032-1.035)	$<2 \times 10^{-16}$	1.034 (1.031-1.036)	$<2 \times 10^{-16}$	0.946 (0.945-0.947)	$<2 \times 10^{-16}$
Maternal smoke	1.123 (1.099-1.147)	$<2 \times 10^{-16}$	0.962 (0.946-0.978)	4×10^{-6}	0.902 (0.874-0.932)	3×10^{-10}	0.940 (0.896-0.986)	.011	0.665 (0.654-0.676)	$<2 \times 10^{-16}$
Smoke in house	1.107 (1.073-1.142)	$<2 \times 10^{-16}$	0.972 (0.948-0.997)	.027	0.920 (0.878-0.965)	.0006	0.947 (0.881-1.018)	.141	0.864 (0.842-0.886)	$<2 \times 10^{-16}$
Ever smoked	0.998 (0.978-1.017)	.91	0.923 (0.910-0.937)	$<2 \times 10^{-16}$	0.990 (0.958-1.024)	.57	1.021 (0.979-1.065)	.33	1.184 (1.166-1.202)	$<2 \times 10^{-16}$
Home area*	1.031 (1.004-1.059)	.025	0.984 (0.964-1.004)	.122	0.818 (0.789-0.848)	$<2 \times 10^{-16}$	0.912 (0.86-0.95)	.001	0.969 (0.966-0.972)	$<2 \times 10^{-16}$
BMI	1.035 (1.033-1.037)	$<2 \times 10^{-16}$	0.996 (0.995-0.998)	4×10^{-7}	0.99 (0.988-0.99)	10×10^{-8}	0.996 (0.993-1.000)	.035	0.992 (0.988-0.995)	9×10^{-7}

BMI, Body mass index.

*Home area is either rural or urban.

TABLE E3. Association between breast-feeding and each disease when including a single covariate

Included covariate	Asthma		Hay fever/eczema		Hay fever		Eczema	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex	0.893 (0.873-0.914)	$<2 \times 10^{-16}$	0.957 (0.940-0.974)	9×10^{-7}	0.985 (0.953-1.019)	.379	0.963 (0.916-1.012)	.138
TDI	0.891 (0.870-0.912)	$<2 \times 10^{-16}$	0.942 (0.925-0.959)	3×10^{-11}	0.975 (0.942-1.008)	.133	0.951 (0.904-1.000)	.048
Birth weight	0.918 (0.893-0.944)	2×10^{-10}	0.977 (0.956-0.997)	.026	1.007 (0.968-1.048)	.713	0.970 (0.913-1.029)	.310
Year of birth	0.935 (0.913-0.957)	3×10^{-8}	1.047 (1.028-1.066)	8×10^{-8}	1.113 (1.076-1.152)	10×10^{-10}	1.080 (1.026-1.137)	.003
Maternal smoke	0.899 (0.877-0.921)	$<2 \times 10^{-16}$	0.938 (0.921-0.956)	3×10^{-10}	0.982 (0.947-1.017)	.309	0.948 (0.899-1.000)	.051
Smoke in house	0.888 (0.866-0.909)	$<2 \times 10^{-16}$	0.940 (0.922-0.957)	3×10^{-11}	0.971 (0.938-1.005)	.093	0.949 (0.901-0.999)	.047
Ever smoked	0.883 (0.863-0.904)	$<2 \times 10^{-16}$	0.948 (0.931-0.964)	2×10^{-9}	0.990 (0.958-1.024)	.566	0.955 (0.908-1.004)	.069
BMI	0.888 (0.868-0.909)	$<2 \times 10^{-16}$	0.944 (0.927-0.961)	1×10^{-10}	0.984 (0.952-1.018)	.345	0.952 (0.905-1.001)	.053
Home area	0.884 (0.905-0.864)	$<2 \times 10^{-16}$	0.944 (0.927-0.961)	2×10^{-10}	0.978 (0.946-1.012)	.195	0.948 (0.902-0.997)	.021

BMI, Body mass index.

TABLE E4. Results from meta-analyzing the matched groups for the fixed-effect model (*P* and OR) and for the random-effect model (*P*(R) and OR(R))

Disease	<i>P</i>	<i>P</i> (R)	OR	OR(R)	<i>Q</i>	<i>I</i>	N
Asthma	.656	.684	0.992	0.990	0.114	31.1	16
Hay fever/Eczema	.00012	.0022	1.052	1.048	0.2485	17.92	16
Hay fever	6.23×10^{-5}	6.23×10^{-5}	1.112	1.112	0.807	0.0	16
Eczema	.0088	.0088	1.105	1.105	0.792	0.0	16

Each group is defined in [Fig 1](#). *Q* is the *P* value for the Cochran *Q* statistics, *I* is the *I*² heterogeneity index (0-100), and N is the number of included groups.