RESEARCH ARTICLE

Twinship and childhood atopic disease: understanding early-life factors among discordant twins

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ABSTRACT

Parents often question why one of their children would have asthma while their siblings do not. With twins, this is especially perplexing. The gene-environment interaction hypothesis suggests that early-life environmental exposures interact with genes, leading to asthma and atopic diseases. This study sought to investigate twins for potential early-life risk factors that modify the risk of asthma, allergic rhinitis, and eczema. A paired population-based open cohort study was conducted using health administrative data between April 1, 2004 and March 31, 2019 from Ontario, Canada. The study population consisted of Ontario twins born between 2004-2017. Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for associations between discordance of allergic conditions and early-life factors. 24,392 twin-pairs from Ontario Canada aged 1 to 15 years were included. 15.7%, 17.9%, and 31.9% of twin-pairs had discordant asthma, allergic rhinitis, and eczema, respectively. Compared to female-female twin-pairs, male-female and male-male twin-pairs had 69% (95% CI:1.54-1.84) and 35% (95% CI:1.23-1.49) higher odds of asthma discordance, respectively. Twins delivered by Caesarean-section, compared to vaginal deliveries, had significantly higher odds of asthma (aOR:1.09, 95% CI:1.01-1.18) and allergic rhinitis (aOR:1.11, 95% CI:1.04-1.20), while associations were strongly suggested for eczema discordance (aOR:1.05, 95% CI:1.00-1.12). This population-based study found associations of various early-life factors and discordances of asthma, allergic rhinitis, and eczema between twins, though we lacked data for control of zygosity and variance. While early-life factors were associated with disease risks in children, other factors played an underlying role.

HIGHLIGHTS BOX

What is already known about this topic? Genetic factors play a key role in twin discordance of asthma and atopic disease but knowledge of early life environment is limited. **What does this article add to our knowledge?** Preterm births, older mothers, urban settings at birth, higher income, birthweight difference, and early childhood air pollution play significant roles in twin discordance of atopic diseases. **How does this study impact current management guidelines?** Future research should explore the differences between twins, especially hereditary factors, that could address gene-environment interaction, leading to better management and atopic disease prevention.

KEY WORDS

Asthma; twin; discordant; allergic rhinitis; eczema; Ontario.

INTRODUCTION

Parents often question why one of their children would have asthma while their siblings do not. For parents, this is especially perplexing with twins. Monozygotic twins fully share their genetic makeup and dizygotic twins share half their genetics, on average (1). Additionally, twins often strongly share an early-life environment. Despite these similarities, asthma discordance between twins, where one twin has asthma and the other does not, still occurs.

The "gene-environment" interaction hypothesis proposes that early-life environmental exposures (or lack thereof) interact with genes, leading to asthma and atopic diseases (2). Previous twin studies of asthma have found a strong genetic component, with estimates ranging up to 60-90% (3, 4). One twin study over ten years suggested that environmental factors played an increasing role in modified gene expression for asthma and asthma heritability (5). Previous singleton and twin epidemiologic studies have also found various maternal, environmental, and perinatal predictors for childhood asthma and atopic disease including maternal smoking, parental asthma history, air pollution, urban areas, and preterm birth (6-9). Twin births differ from singleton births as twins are often born earlier, to older mothers, at lighter birthweights (10), and have factors of atopic disease risk. By using twins for co-twin matching, twin studies can underestimate the effects of shared environment (11), but better control for potential confounding that may not be effectively controlled for in non-twin studies.

Thus, the objective of this study is to examine early-life risk factors that modify the risk of asthma, allergic rhinitis, and eczema in twins.

METHODS

Study Design and Population

A paired population-based open cohort study was conducted using health administrative data between April 1, 2004 and March 31, 2019 from Ontario, Canada. The study population consisted of Ontario twins born between 2004-2017 with a gestational age of 28-42 weeks to mothers aged between 13-45 years (inclusive). Individuals were excluded if they had missing or inconsistent birth data, had less than one year of follow-up, had no valid Ontario health card number or Ontario residence code, did not have a sibling after other exclusions, or were part of a family with more than one set of twins. Individuals were followed from birth until they moved out of the province, died, or reached the end of study period.

Data Sources

This study used routinely gathered health administrative data linked through unique coded identifiers, collected through Ontario's publicly funded universal single-payer healthcare system and stored at ICES (formerly the Institute for Clinical Evaluative Sciences). Health administrative databases used in this study included: hospital admissions (Canadian Institute for Health Information Discharge Abstract Database), emergency department visits (National Ambulatory Care Reporting System), outpatient physician visit claims (Ontario Health Insurance Plan Claims Database), sociodemographic information (Provincial Registered Persons Database, Ontario Marginalization Index), asthma (Ontario Asthma Surveillance Information System), and maternal and newborn hospital birth abstracts (MOMBABY).

Environmental data was also obtained from the Canadian Urban Environmental Health Research Consortium (12). Annual nitrogen dioxide (NO_2), ozone (O_3), fine particulate matter of <2.5 μm diameter ($PM_{2.5}$), and normalized difference vegetation index (NDVI) data were obtained for each Ontario Local Health Integration Network (LHIN). Data on population counts for each LHIN were obtained from the 2016 Canadian census from Statistics Canada (13).

Outcome Definitions

In this study, discordance was defined as a difference in disease outcome between twins (i.e., one twin was diagnosed with asthma and the other was not). Individuals with physician diagnosed asthma were identified using a validated health administrative definition of at least one hospitalization for asthma or at least two outpatient visits for asthma in two consecutive years. This case definition has been validated (14) and used in previous studies (15-17). Allergic rhinitis and eczema were physician diagnosed and identified by a single health-service use claim.

Statistical Analysis

In this paired cohort study, logistic regression models were used to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for associations between discordance of conditions (asthma, allergic rhinitis, and eczema) and early-life factors. Individuals were paired with their twin and each twin-pair was treated as a single observation unit. Income and Ontario marginalization indices, NO_2, O_3, $PM_{2.5}$ and NDVI data were linked to twin-pairs by postal code and year of birth. Covariates for models were selected a priori and assessed using a forward building method. All models were controlled for sex pair (Male-Male (MM), Male-Female (MF), Female-Female (FF)), birthweight difference (g), LHIN, population, age (years), rurality at birth (rural, urban), preterm birth (yes, no), mode of delivery (vaginal, Caesarean-section (C-section)), mother's age at birth (13-20, 21-25, 26-30, 31-35, 36-38, 39-45), ethnic concentration (quintile), income (quintile), dependency (quintile), residential instability (quintile), NO_2 (ppb), O_3 (ppb), $PM_{2.5}$ (μg/m^3), and NDVI. **Table S1** has further definitions.

Interactions between sex pair and age, sex pair and NO_2, sex pair and O_3, and sex pair and $PM_{2.5}$ were assessed. Age was also assessed for a non-linear relationship using a 3-, 4-, and 5-knot restricted cubic spline for each model. Tests for linear trend used the Wald test with $\chi 2$ where categories of intake were modelled as a continuous variable. Model differences were assessed using likelihood ratio tests. Model fitting was also assessed by plotting residuals and fitted values and assessed for multicollinearity with variance inflation factors. All covariates had <1.5% missing. Sensitivity analyses were conducted with those with missing values removed. Statistical significance was defined where p-values were <0.05. All regression analyses were performed in SAS Enterprise Guide software (v7.15; SAS Institute Inc., Cary, NC). Graphics were created using R software (v.4.0.2) (18) and SAS Enterprise Guide software (v7.15).

RESULTS

Descriptive Results

Among the 24,392 twin-pairs, 3,817 (15.5%), 4,362 (17.9%), and 7,779 (31.9%) twin-pairs were asthma, allergic rhinitis, and eczema discordant respectively. Approximately half of all twins were male, where 32.6% of twin-pairs were male-male and 35.4% were male-female. **Table 1** shows a summary of characteristics by chosen covariates used in multivariate models. The average age of the twin-pairs was 8.2 years, they were more likely at higher income quintiles, to be born pre-term, and delivered by C-section.

Univariate Regression Results

Univariate analysis between asthma discordance and early-life factors found several significant associations including sex pair, rurality at birth, birth type, pre-term at birth, and exposures to O_3, $PM_{2.5}$, and NDVI. Similar univariate associations were found for allergic rhinitis and eczema discordance.

Multivariate Regression Results – Demographic Factors

After adjusting for covariates, asthma discordance was significantly associated with the sexes of twins.

Table S1. *Variable definitions*

Variable	Definition
Pre-term birth	Birth before 37 weeks of gestational age.
Rurality	An area with a population of less than 10.000 people.
Ontario Marginalization Indices †	
Residential Instability	Area-level concentrations of people who experience high rates of family or housing instability.
Dependency	Area-level concentrations of people who do not have income from employment.
Ethnic Concentration	High area-level concentrations of people who are recent immigrants and/or people belonging to a "visible minority" group (defined by Statistics Canada as "persons, other than aboriginal peoples, who are non-Caucasian in race or non-white in colour").

† Matheson FI, van Ingen T. 2016 Ontario marginalization index: user guide. Toronto, ON: St. Michael's Hospital; 2018. Joint publication with Public Health Ontario.

Table 1. *Descriptive statistics of Ontario twin-pairs by chosen covariates.*

		All
N		24392
Age of diagnosis (Years) (mean(SD))		8.2 (3.7)
Sex pair (n(%))	**Male-Male**	7958 (32.6)
	Male-Female	8638 (35.4)
	Female-Female	7796 (32)
BIRTH FACTORS		
Birthweight difference (g) (mean (SD))		293 (253)
Preterm birth (n(%))	**Yes**	13178 (54.0)
Mode of delivery (n(%))	**C-section**	15251 (62.5)
Mother's age at birth (n(%))	**13-20**	495 (2.0)
	21-25	2314 (9.5)
	26-30	6575 (27.0)
	31-35	9330 (38.3)
	36-38	3548 (14.6)
	39-45	2130 (8.7)
DEMOGRAPHIC FACTORS		
Income quintile (n(%))	**1 (lowest)**	4391 (18.0)
	2	4586 (18.8)
	3	4939 (20.3)
	4	5603 (23.0)
	5 (highest)	4793 (19.7)
Rurality at birth(n(%))	**Rural**	2216 (9.1)
ENVIRONMENTAL FACTORS		
NDVI (mean (SD))		0.4 (0.1)
NO_2 (ppb) (mean (SD))		11.5 (6.2)
O_3 (ppb) (mean (SD))		25.9 (3.4)
$PM_{2.5}$ (ug/m^3) (mean (SD))		8.1 (1.6)

Compared to FF twin-pairs, MF and MM twin-pairs had 69% (95% CI: 1.54-1.84) and 35% (95% CI: 1.23-1.49) higher odds of asthma discordance, respectively. Similarly, after adjusting for covariates, MF twin-pairs were significantly associated with 29% (95% CI: 1.19-1.40) and 13% (95% CI: 1.04-1.24) increased odds of allergic rhinitis and eczema discordance, respectively, while MM twin-pairs were significantly associated with higher odds of allergic rhinitis discordance (aOR: 1.16, 95% CI: 1.09-1.24) but not for eczema discordance (aOR: 1.04, 95% CI: 0.97-1.11), compared to FF twin-pairs (**Figure 1**).

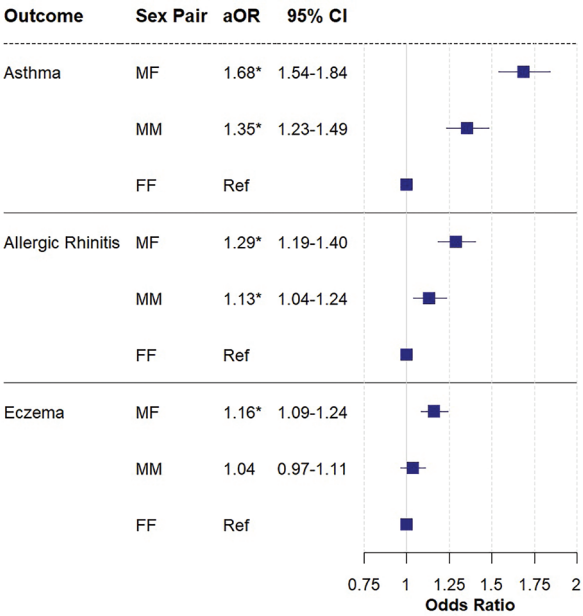

Figure 1. *Adjusted odds ratios of discordant atopic conditions by sex pair. Adjusted for age, birthweight difference, LHIN, population, rurality at birth, preterm birth, mode of delivery, mother's age at birth, ethnic concentration, income, dependency, residential instability, NO_2, O_3, $PM_{2.5}$, and NDVI. * $p < 0.01$.*

Age was found to have a significant non-linear association where each year of increase in age increased discordance odds before age eight (aOR: 1.17, 95% CI: 1.13-1.20; aOR: 1.38, 95% CI: 1.33-1.43; aOR: 1.07, 95% CI: 1.05-1.10) and decreased odds after age eight (aOR: 0.99, 95% CI: 0.99-0.99; aOR: 0.98, 95% CI: 0.98-0.99; aOR: 0.995, 95% CI: 0.99-1.00) for asthma, allergic rhinitis, and eczema discordances, respectively, after adjusting for covariates (**Figure 2**). Additionally, twin-pairs who lived in urban areas had significantly increased odds of allergic rhinitis and eczema discordances by 21% (95% CI: 1.03-1.43) and 28% (95% CI: 1.14-1.45), respectively, compared to twin-pairs who lived in rural areas, after adjusting for covariates.

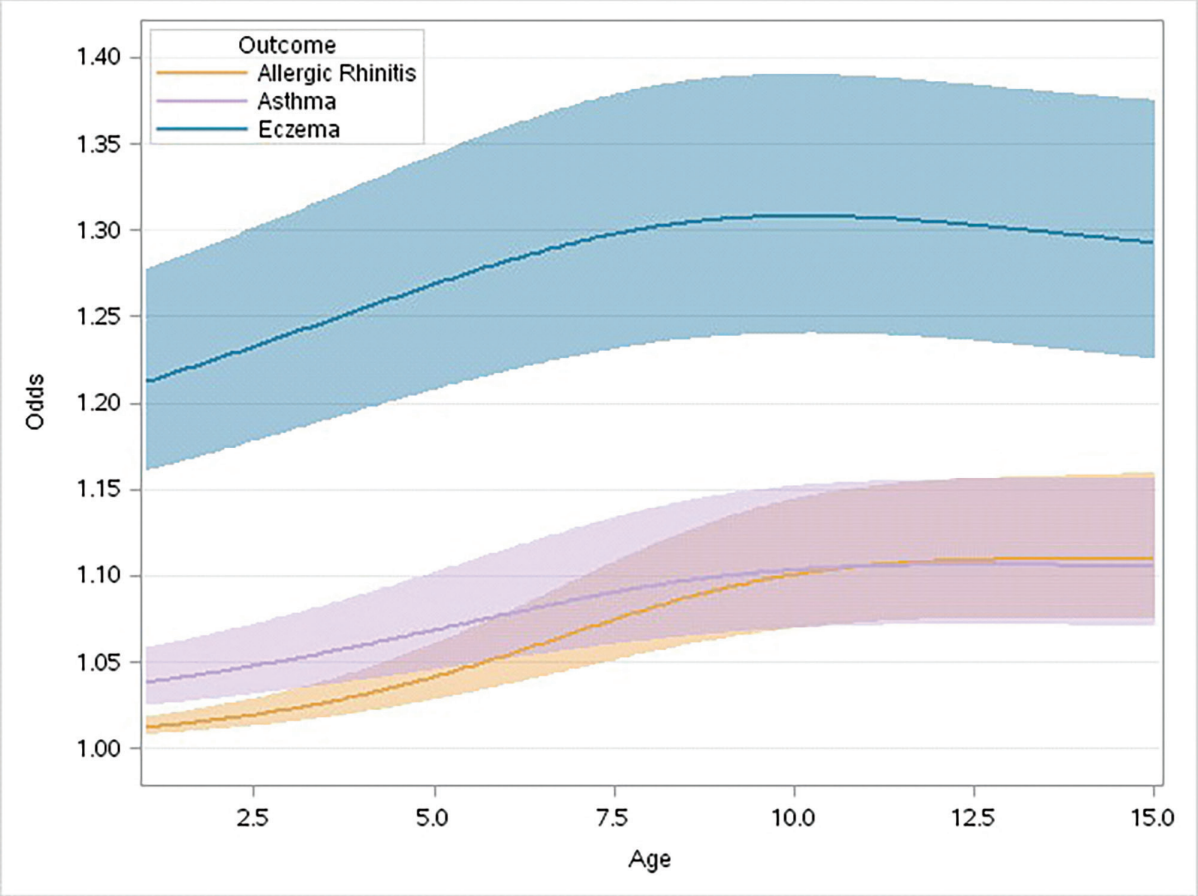

Figure 2. *Odds of twin-pair discordance by disease outcome and age for asthma (purple), allergic rhinitis (orange), and eczema (dark blue). Adjusted for sex pair, birthweight difference, LHIN, population, age, rurality at birth, preterm birth, mode of delivery, mother's age at birth, ethnic concentration, income, dependency, residential instability, NO_2, O_3, $PM_{2.5}$, and NDVI.*

Multivariate Regression Results – Birth and Environmental Factors

Twins who were delivered via C-section had significantly higher odds of asthma (aOR: 1.09, 95% CI: 1.01-1.18) and allergic rhinitis (aOR: 1.11, 95% CI: 1.04-1.20) discordances, compared to pairs who were delivered vaginally, after adjusting for covariates. An association with eczema discordance (aOR: 1.05, 95% CI: 1.00-1.12) was also suggested (p = 0.067). Preterm birth was also a significant factor where twins that were born preterm had 23% (95% CI: 1.15-1.33) increased odds of asthma discordance compared to twins who were not, adjusting for covariates. O_3 levels at birth were negatively associated with asthma discordance and $PM_{2.5}$ levels at birth were strongly suggested to be positively associated with asthma discordance (p = 0.051) (**Table 2**). Mother's age at time of birth (p-trend: <0.01) was also a significantly associated factor for allergic rhinitis discordance while higher income quintiles (p-trend: 0.09) and birthweight difference were significantly and positively associated with eczema discordance (**Table 2**).

Multivariate Regression Results – Interactions and Splines

No significant interactions between sex pairs and NO_2, O_3, or $PM_{2.5}$ were found in any of the models. Non-linear models with a 3-knot spline for age were found to be a better fit than the linear, 4-knot, and 5-knot models in full multivariate analysis. Sensitivity analyses showed our findings to be robust.

DISCUSSION

This study, comprised of 16 years of population-based data, examined over 24,000 twin-pairs and associated asthma, allergic rhinitis, and eczema discordance

Table 2. *Adjusted odds ratios and 95% confidence intervals of chosen variables for atopic discordance. Adjusted for sex pair, age, LHIN, population, ethnic concentration, dependency, residential instability, and other variables listed.*

		Asthma Discordant		Allergic Rhinitis Discordant		Eczema Discordant	
		aOR	95% CI	aOR	95% CI	aOR	95% CI
Birthweight difference	Per 100g	1.01	0.99-1.02	1.00	0.99-1.02	1.01[a]	1.00-1.02
Rurality at birth	Urban	1.12	0.95-1.32	1.21[a]	1.03-1.43	1.28[a]	1.14-1.45
Preterm birth	Yes	1.23[a]	1.15-1.33	1.04	0.97-1.11	0.96	0.91-1.02
Mode of delivery	C-section	1.09[a]	1.01-1.18	1.11[a]	1.04-1.20	1.05	1.00-1.12
Mother's age at birth	13-20	Ref	-	Ref	-	Ref	-
	21-25	1.32	0.98-1.78	1.22	0.90-1.65	1.02	0.82-1.28
	26-30	1.26	0.94-1.68	1.44[a]	1.08-1.91	1.12	0.91-1.38
	31-35	1.25	0.94-1.67	1.61[a]	1.21-2.14	1.01	0.90-1.35
	36-38	1.20	0.90-1.62	1.58[a]	1.18-2.12	1.00	0.81-1.24
	39-45	1.20	0.88-1.63	1.60[a]	1.19-2.18	1.14	0.91-1.42
Income quintile	1 (lowest)	Ref	-	Ref	-	Ref	-
	2	0.98	0.87-1.11	1.10	0.98-1.24	1.10[a]	1.00-1.21
	3	1.00	0.88-1.14	0.99	0.87-1.12	1.11[a]	1.01-1.23
	4	1.04	0.91-1.19	1.12	0.98-1.27	1.14[a]	1.03-1.27
	5 (highest)	1.04	0.90-1.20	1.12	0.97-1.28	1.07	0.96-1.20
NDVI		0.76	0.55-1.07	0.86	0.62-1.19	1.01	0.78-1.30
NO_2	Per ppb	0.99	0.98-1.00	1.01	0.997-1.02	0.99	0.99-1.00
O_3	Per ppb	0.98[a]	0.96-0.99	0.99	0.97-1.00	1.01	0.996-1.02
$PM_{2.5}$	Per µg/m^3	1.04	1.00-1.09	1.02	0.98-1.07	1.02	0.99-1.06

[a] $p < 0.05$.

with early-life factors including newborn, maternal, social, and environmental factors. To our knowledge, this study is one of few that used population-based data to examine twins' discordance of diseases as a primary point of analysis and the first population-based Canadian cohort study that examined factors associated with differences in asthma and atopic disease risks between twins. Our study found strong and significant positive associations between sexes, birth type, age, and discordance of atopic diseases in multivariate analysis. Preterm births were positively associated with asthma discordance, older mothers, and urban settings at birth with allergic rhinitis discordance, and higher income, urban settings at birth, and birthweight difference with eczema discordance. O_3 levels at birth had significant negative associations on asthma discordance and $PM_{2.5}$ levels at birth had a strongly suggested positive association with asthma discordance.

For the discordance of atopic conditions, MM and MF sex pairs displayed significant associations, with opposing sexes having a stronger effect. Previous studies have established similar findings that male gender is a larger risk factor compared to females at young ages (10, 19-21). While this study could not account for differences in zygosity between twin-pairs, it has been shown that dizygotic twin-pairs are more likely to be disease-discordant than monozygotic pairs with certain risk factors (22). This could explain some of the differences of associations between MF and MM/FF since MF twin-pairs are dizygotic, but MM and FF pairs can be monozygotic. Hence, sex may be a potential confounder for disease.

Similar patterns of change over age have been found in other studies. One Danish study on twins aged 3-71 found that hereditary factors of asthma susceptibility decreased with age while another on Danish

twins aged 20-70 showed that onset of asthma in one twin led to the decreased risk of asthma in the co-twin (4, 23). Another twin study in Puerto Rico also found that asthma had a more significant genetic component at age three than age one (24).

The perinatal risk factors of atopic disease discordance observed in this study are largely in line with previous findings of atopic conditions. In particular, this study found that birth by C-section was a significant factor for discordance of asthma and allergic rhinitis but not eczema. In agreement, meta-analyses have found C-sections increased risk by 20% for asthma (25, 26) and allergic rhinitis, but not eczema (26). Some (27, 28), but not all (6), twin studies have found similar increases in risk of asthma. While this study could not explore this interaction further, it is suggested that there was a strong interaction between mode of delivery and genetic factors (family allergy history) that modifies the risk of asthma (29).

Our study also found that twins born preterm had higher chances of asthma discordance. While preterm birth is a risk factor for atopic disease in singleton studies (9), our findings contrast those of Rasanen *et al.* (21). Finnish twin study which found no significant association with asthma. However, Kahr *et al.* (6). Danish twin study also found a similar association with asthma among twins born prematurely (gestational age <32 weeks). Evidence suggests that maternal genetic makeup may causally link preterm birth and children's asthma, where some mothers with asthma have shorter pregnancies, or that preterm birth may result in underdeveloped lungs either anatomically or immunologically, possibly causing children to be more susceptible to risk factors of asthma later in life (9). However, birthweight difference between twins was not found to be significant factor for discordant asthma or allergic rhinitis in this study, only eczema. One previous twin study found similar results with discordant asthma (21). Another contrasts our finding, where there was a significant association with higher birthweight differences and higher asthma risk in monozygotic twins than dizygotic twins (10).

Environmental factors had mixed results in this study. Twins born in urban settings had greater odds of allergic rhinitis and eczema discordance but not asthma. However, two Canadian studies previously found that farming environments reduced the risk of childhood asthma (7, 20). O_3 was found to reduce the chance of asthma discordance while $PM_{2.5}$ was strongly suggested to be associated with increased chances of asthma discordance. It is unclear whether environmental factors in a shared environment can contribute to discordance between twins. Previous works have found that NO_2, O_3, and $PM_{2.5}$ are risk factors for asthma (8), allergic rhinitis (30), and eczema (8) incidence, though evidence is inconsistent (31, 32). There may be unmeasured or residual confounding that contributes to the differences in odds of outcomes in twins that is beyond the shared genetics and environment.

The strength of this study is the use of population-based health administrative data, allowing this study to collect information on atopic conditions, healthcare use, and births on all Ontario twin residents over a 15-year period with minimal missing data. The use of this data source created a large population set that also minimized selection or response bias. However, this study has limitations. This study could not examine and control for certain factors, such as maternal smoking and parental asthma history, as data were not available. Most notably, the lack of genetic data prevented this study to stratify by zygosity, to further control for genetic variance, and to detect gene-environment modifications from early life exposures. As such, there is a risk that each twin may have significantly different life habits. Furthermore, this study only had environmental data based on the birth year of each twin-pair and had no location-based data in twin-pairs' older years, limiting this study's ability to examine the cumulative effects of the environment on health outcomes. Moreover, given that the air pollution data used was by LHIN, the distance from the measurement station to children's schools and homes may lead to potential measurement bias. While there are regional variations in air quality, a previous study by To *et al.* suggested that the variation is relatively small across Ontario (33). Therefore, we do not expect a significant level of measurement bias. Finally, comparison of this study's results to previous research was limited given that there have been only a few publications on early-life factors and atopic disease discordance.

CONCLUSIONS

In summary, this study associated various early-life factors with: 1) the incidence of asthma and atopic conditions and 2) the differences in condition outcomes between twins. Although early-life factors were associated with asthma and atopic condition discordance, genetic factors played a strong underlying role, though we lacked the genetic data to further control for zygosity and variance. Despite strong overlaps in genetic and environmental factors, residual factors remained to create condition discordance between twins. Future research should continue to examine twin discordance to further explore and identify risk factors of disease.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

All the Authors listed in the manuscript have contributed to the conception and planning of the work, through the acquisition of the patient's clinical data, choice of cases, preparation procedure of the preparations, and interpretation of the results. All the Authors participated in the drafting of the manuscript and in the definitive approval of the version to be published.

Ethical approval

Human studies and subjects

Ethics approval for this study was obtained from the Hospital for Sick Children Research Ethics Board in Toronto, Ontario.

Animal studies

N/A.

Data sharing and data accessibility

We are not able to provide a minimal data set for this study due to privacy, legal, prescribed entity designations, and ethical restrictions. All data used in this study are securely housed at ICES, Ontario, Canada in coded form and are subject to their privacy, legal, prescribed entity designations, and ethical governance, available at: www.ices.on.ca/Data-and-Privacy/Privacy-at-ICES (e-mail: privacy@ices.on.ca). While legal data sharing agreements between ICES and data providers (*e.g.*, healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at: https://www.ices.on.ca/use-ices-data/ (e-mail: das@ices.on.ca).

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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