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To cite this article: Danny Wadden, Jamie Farrell, Mary Jane Smith, Laurie K. Twells & Zhiwei Gao (2019): Maternal history of asthma modifies the risk of childhood persistent asthma associated with maternal age at birth: Results from a large prospective cohort in Canada, Journal of Asthma, DOI: [10.1080/02770903.2019.1658207](https://doi.org/10.1080/02770903.2019.1658207)

To link to this article: <https://doi.org/10.1080/02770903.2019.1658207>



Published online: 03 Sep 2019.



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Maternal history of asthma modifies the risk of childhood persistent asthma associated with maternal age at birth: Results from a large prospective cohort in Canada

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ABSTRACT

Background: Asthma is a prevalent disease that affects many Canadians. Persistent asthma can affect quality of life, and has multiple health implications. Maternal age at birth has been associated with many adverse health outcomes in children. Conflicting study results exist regarding maternal age at birth and childhood asthma. The association between maternal age at birth and persistent asthma in children is still unknown.

Objective: To investigate the relationship between maternal age at birth and persistent asthma in children at ten years of age.

Methods: This is a prospective cohort study including all children aged 0-2 years who took part in the first cycle of the National Longitudinal Survey of Children and Youths (NLSCY) and were followed every two years until eight to ten years of age in Cycle 5. An interaction term between maternal age at birth and maternal asthma history was introduced in a multivariate model to examine modification effects of maternal asthma history on the association.

Results: Multivariate logistic regression demonstrated that older maternal age at birth was significantly associated with an increased risk of childhood persistent asthma in mothers with a history of asthma (OR = 1.20, 95% CI: 1.04–1.40, $p = .016$). No relationship was found in mothers without a history of asthma.

Conclusion: Maternal history of asthma has an impact on the association between maternal age at birth and childhood persistent asthma in children by age ten. The finding may help explain the inconsistent results in the literature regarding the risk of asthma associated with maternal age at birth.

ARTICLE HISTORY

Received 4 June 2019

Revised 1 August 2019

Accepted 17 August 2019

KEYWORDS

Asthma; childhood; Canada

Introduction

Asthma is an obstructive airway disease characterized by periodic symptoms including, cough, wheeze, dyspnea, and chest tightness. The Centers for Disease Control (CDC) estimates the prevalence of asthma for individuals 18 years and over, and for those younger than 18 to be 20.4 million and 6.1 million in the United States, respectively (1). This represents 8.3% of the each of the aforementioned populations (1). The World Health Organization estimated that asthma caused 383 000 deaths globally in 2015 (2).

The diagnosis of asthma for children six years and older, and adults, as per guidelines by the Canadian Thoracic Society (CTS), relies on measurement of pulmonary function by spirometry portraying reversible airway obstruction, variability of peak expiratory flow,

and/or a positive methacholine or exercise challenge test (3). Because the diagnosis of asthma in children under the age of six can be more difficult, the CTS has published guidelines for the diagnosis in this population which focuses more on clinical assessment; airflow reversibility should be observed by the health care provider (i.e. observation after treatment with short acting bronchodilators) as opposed to directly quantified by spirometry (4).

Asthma in childhood is associated with various comorbid conditions (5) including allergic rhinitis (6), obesity (7), psychiatric conditions (8), and Gastroesophageal reflux disease (GERD) (9). Additionally, childhood asthma is an important entity, as it can affect lung function later in life (10). Results from a case-control study demonstrated that asthma in childhood was

related to risk of chronic obstructive pulmonary disease (COPD) as an adult (11). As such, childhood asthma is an important chronic disease. Guidelines by the National Asthma Education and Prevention Program published through the National Heart, Lung and Blood Institute have described phenotypes of asthma based on respiratory impairment (12). The group divides asthma into intermittent and persistent, with persistent asthmatics being further split into mild, moderate and severe (12). These are important phenotypes as exacerbation risk and recommended treatment initiation differ based on these guidelines.

Like other chronic diseases, asthma is a multifactorial condition in which both genetic and environmental factors play a role (13–15). Family history of asthma is also a significant factor; a review of 33 studies by Burke et al., reported that asthma in at least one first-degree relative was a risk factor for developing asthma (16). Maternal history of asthma is one of the most important predictors of childhood asthma (17). Millar and Hill reported that children of a mother with a history of asthma are three times (OR = 2.78, 99% CI: 2.21–3.50, $p < .01$) more likely to be associated with childhood asthma (18). However, the risk of childhood asthma is two times in children of a father with history of asthma (OR = 1.99, 99% CI: 1.48–2.67, $p < 0.01$) (18). Multiple maternal factors have been linked to childhood asthma including maternal obesity (19), maternal diet (20), and exposure to pollutants (21). Work by Deng et al. have explored the relationship of air pollution both during early life and pregnancy (22,23). Interestingly, maternal age at time of birth is a variable which has been investigated regarding risk of asthma in offspring and studies have demonstrated that younger maternal age at time of birth is associated with an increased risk of asthma (24–28). However, other studies have found the opposite finding in that there is a positive relationship between maternal age at birth and risk of asthma (29–31). Furthermore, other studies have found no relationship between maternal age at birth and risk of asthma in offspring (32,33). Given these inconsistent findings, the association between maternal age at birth and asthma phenotype such as persistent asthma in children is still unknown.

Using a Canadian national childhood cohort study, we outlined the following research objectives: (1) to examine the association between maternal age at time of birth and childhood persistent asthma in children by ten years of age; and (2) to assess whether this association, if found, can be modified by a history of maternal asthma.

Methods

Ethics approval

The study was approved by the Health Research Ethics Authority (HREA), at Memorial University in St. John's, Newfoundland and Labrador, Canada (HREB# 2018.240).

Study population

The National Longitudinal Survey of Children and Youths (NLSCY) is a longitudinal survey, conducted by Statistics Canada to follow children from birth to early adulthood. In 1994, 16 903 children aged 0 to 12 years from ten provinces of Canada were included in the first cycle. Of the 16 903 children aged 0–12 years included in the first cycle, our current study included only those children aged 0–2 years ($n = 6,660$). Of these 6,660 children, information was gathered through interviews every two years on 5,040 (76%) children in cycle 2 (aged 2–4 years), 4,900 (74%) children in cycle 3 (aged 4–6 years), 4,400 (66%) children in cycle 4 (aged 6–8 years), and 4,255 (64%) children in cycle 5 (aged 8–10 years). For more information on the methodology and study sample, see [Reference for more information on the study available at https://media.lib.unb.ca/gddm/data/user_docs/nlscyc/cycle1-1994-1995/nlscyc1-gid.pdf (34)].

Outcome variable: persistent asthma

The classification of persistent asthma was determined through responses from the person most knowledgeable (PMK) of the child, to the following questions: a) Ever-asthma- “Does this child have asthma that has been diagnosed by a Health Professional”; b) Current-asthma- “Has he/she had an attack of asthma in the last 12 months?”. *Persistent asthma* was used for a positive response to either question in the earliest cycle and a positive response on the Current-asthma question in all the following cycles.

Main exposure variable

Age of biological mother and father at birth of child was based on self-report responses to the following questions: “Age of biological mother at birth of child?” and “Age of biological father at birth of child?” A history of asthma in the biological mother or father was based on a self-report response to the following question: “Do(es) you/he/she have any of the

following long-term conditions that have been diagnosed by a health professional: e.g., ASTHMA?”

Covariates

Age and sex of child, premature delivery (≤ 258 days) were included as predictors of asthma early in life or during pregnancy. The PMK and spousal current smoking status, highest level of education of PMK and spouse, PMK total annual income, PMK/spouse cigarette usage/day, and Household Socio-Economic Status (HSES) were included as parental predictors of asthma. HSES was defined by Statistics Canada using the following five sources for each household: PMK level of education, spouse/partner level of education, PMK's occupation prestige, spouse/partner occupation prestige, and household income. Other household predictors included dwelling ownership, and dwelling in need of repair. [Reference for more information on the study available at https://media.lib.unb.ca/gddm/data/user_docs/nlscy/cycle1-1994-1995/nlscyc1-gid.pdf (34)]. Studies have found these cofounders to be important in regards to the risk of childhood asthma (35–38).

Statistical analysis

Data analyses were conducted using SAS[®] version 9.4. Descriptive statistics including mean, standard deviation (STD) and count (frequency) were provided for continuous and categorical variables. To detect significant risk factors for persistent asthma, *PROC SURVEYLOGISTIC* was utilized in univariate and multivariate analysis. Clinically important factors in addition to variables with a p values lower than 0.20 in the univariate analysis were used in the multivariate model. All statistical analyses included sampling weights. Due to the complex survey design issues and different methods involved in selecting Primary Sampling Unit (PSU) in different type of areas (urban, rural and remote areas), longitudinal sampling weights and 1,000 bootstrap weights (provided by Statistics Canada) were used in all the statistical analysis to obtain unbiased estimates of coefficients and variances. To examine the possible impact of maternal history of asthma on the risk of persistent asthma associated with biological mother age at birth of child, an interaction term between maternal history of asthma and biological mother age at birth of child was introduced into multivariate model. The level of significance $\alpha = 0.05$ was used for the multivariate logistic regression.

Results

Descriptive statistics are presented in Table 1. The study population consisted of 1,121 020 children (subjects with sample weights) with an almost even distribution between boys (51.0%) and girls (49.0%). The average age of children in cycle 1 was 1.02 years

Table 1. Descriptive stats of study cohort.^a

Variable	N	%
Gender of child		
Female	5,49,230	49.0
Male	5,71,790	51.0
Persistent asthma status		
Persistent asthma	29,640	2.6
No persistent asthma	10,91,380	97.4
Mother asthma status		
Maternal asthma	57,640	5.7
No maternal asthma	95,6720	94.3
PMK daily smoking status		
Smoker	2,64,280	23.7
Non-smoker	8,50,480	76.3
PMK's spouse smoking status		
Smoker	2,59,820	27.2
Non-smoker	6,96,570	72.8
PMK + spouse smoking status		
Smoker	2,60,640	23.4
Non-smoker	8,54,120	76.6
House ownership status		
Home owner	7,36,990	65.7
Non home owner	3,84,030	34.3
Home repair status		
Minor repairs needed	1,77,680	15.9
Major repairs needed	74,630	6.7
No repairs needed	8,68,360	77.5
Highest level of education (spouse/PMK)		
Secondary school and less	2,35,090	21.0
Beyond high school	2,93,080	26.2
College/university & higher	5,90,700	52.8
Premature child		
Premature birth	1,06,060	9.8
Non-premature birth	9,82,230	90.2
Income of PMK		
Less than \$15,000	6,02,290	53.7
\$15,000-\$30,000	2,78,490	24.8
Greater than \$30,000	2,40,240	21.4
Total household income		
Less than \$15,000	1,11,950	10.0
\$15,000-\$30,000	2,17,620	19.4
Greater than \$30,000	7,91,450	70.6
Low birth weight		
No low birth weight	10,18,060	94.1
Low birth weight	64,410	6.0
PMK status		
PMK is biological mother	10,16,010	90.6
PMK is other	1,05,010	9.4
Mean $\pm$ STD		
Age of child at baseline (years)	1.0 $\pm$ 0.8	
Mother's age at birth (years)	29.0 $\pm$ 5.1	
Father's age at birth (years)	31.9 $\pm$ 5.3	
Number of cigarettes/day (Spouse)	5.3 $\pm$ 9.7	
Number of cigarettes/day (PMK)	3.8 $\pm$ 7.4	
Household socio-economic status (HSES) ^b	-0.1 $\pm$ 0.8	
Number of Siblings,	1.0 $\pm$ 1.1	
Number of Siblings, older	0.8 $\pm$ 1.0	

Notes: ^aNumber of subjects without sample weight = 4,255; Number of subjects with sample weights = 1,121 020.

^bData were derived from five sources by Statistics Canada: the level of education of the PMK, the level of education of the spouse/partner, the prestige of the PMK's occupation, the prestige of the occupation of the spouse/partner, and household income.

(STD = 0.81). An estimated 2.6% of children had persistent asthma. Maternal asthma was present in 5.7% of cases. Almost one quarter (23.7%) of person most

Table 2. Univariate analysis results for persistent asthmatics.

Variable	Prevalence	Persistent asthma			
		OR	95% CI		p value
			Low	High	
Sex of child					
Female	1.8%	0.51	0.30	0.88	0.016
Male	3.5%	1			
PMK current daily smoke					
Smoker	2.3%	0.84	0.44	1.60	0.58
Non smoker	2.8%	1			
Spouse current daily smoke					
Smoker	3.1%	1.12	0.61	2.05	0.72
Non Smoker	2.8%	1			
PMK & spouse current daily smoke					
Smoker	3.1%	1.26	0.69	2.30	0.46
Non Smoker	2.5%	1			
House ownership					
Home owner	2.8%	1.20	0.62	2.33	0.59
Non home owner	2.3%	1			
Home repair status					
Minor repairs needed	3.6%	1.49	0.40	3.18	0.31
Major repairs needed	3.0%	1.26	0.59	2.68	0.55
No repairs needed	2.4%	1			
Highest education level					
Secondary school or less	2.0%	0.64	0.24	1.72	0.37
Beyond high school	2.2%	0.71	0.38	1.34	0.29
College/University or higher	3.1%	1			
Mother's (biol) history of asthma					
Maternal asthma	5.4%	2.09	0.88	4.99	0.10
No maternal asthma	2.7%	1			
Child born prematurely					
Premature	2.7%	1.02	0.43	2.41	0.96
Non premature	2.7%	1			
PMK Income					
Less than \$15,000	3.1%	2.49	1.22	5.06	0.012
\$15,000-\$30,000	2.8%	2.27	0.98	5.23	0.06
Greater than \$30,000	1.3%	1			
Total household income					
Less than \$15,000	3.4%	1.21	0.33	4.50	0.78
\$15,000-\$30,000	1.5%	0.50	0.23	1.10	0.08
Greater than \$30,000	2.9%	1			
Low birth weight					
No low birth weight	2.6%	1			
Low birth weight	4.1%	1.57	0.59	4.14	0.37
Child age at baseline		0.68	0.50	0.95	0.021
Household SES		1.12	0.78	1.59	0.55
Mother's (biologic) age at birth		1.04	0.99	1.10	0.13
Father's (biologic) age at birth		1.03	0.99	1.08	0.14
PMK daily cigarettes		0.99	0.95	1.04	0.87
Spouse daily cigarettes		1.00	0.98	1.03	0.76
Number of siblings		1.05	0.81	1.36	0.72
Number of older siblings		1.12	0.87	1.44	0.37

knowledgeable (PMK) reported daily smoking while this number increased to 27.2% for the PMK's spouse and 23.4% when combining PMK + spouse. An estimated 65.7% of respondents lived in a house than was owned. Minor repair needed, major repairs need and no repaired need were reported in 15.9%, 6.7% and 77.5%, of the respondents, respectively. The highest level of education in the home was reported 21.0%, 26.2% and 52.8% for secondary school and less, beyond high-school, and college/university and higher, respectively. 9.8% of children were report as premature and a low birth weight was evident in 6.0% of the cohort.

53.7% of PMK reported an income of less than \$15 000, while the numbers for \$15 000–30 000 and greater than \$30 000 were 24.8% and 21.4% respectively. Total household income was greater than \$30 000 for 70.6% of the population. The PMK was the biological mother of the child in 90.6% of respondents.

Table 1 also reports other continuous variables. Mother's and father's mean age at birth were 29.0 ± 5.1 and 31.9 ± 5.3 , respectively. Mean number of cigarettes smoked per day were 5.30 ± 9.7 for the spouse and 3.80 ± 7.4 for the PMK. Number of siblings were 0.95 ± 1.1 and number of older sibling were 0.83 ± 1.0 .

Univariate analysis for persistent asthmatics is presented in Table 2. Being female was significantly less likely to be associated with persistent asthma than being male (OR = 0.51, 95% CI: 0.30–0.88, $p = .016$). Additionally, being a child from the PMK with income less than \$15 000 was associated with a higher risk of persistent asthma than being a child from the PMK with income greater than \$30 000 (OR = 2.49, 95% CI: 1.22–5.06, p values = .012). Increasing Mother's (biologic) or father's (biologic) age at birth was associated with increased risk of childhood persistent asthma, respectively in the univariate analysis. However, none of the variables was statistically significant at the level of 0.05.

The results from multivariate analyses of persistent asthma are presented in Table 3. In children who had

Table 3. Multivariate analysis of risk of persistent asthma associated with maternal age at birth of child by maternal history of asthma.

	Persistent asthma							
	Maternal asthma history				No maternal asthma history			
	OR	95% CI		p Value	OR	95% CI		p Value
		Low	High			Low	High	
Maternal age at birth	1.20	1.04	1.40	.016	1.05	0.99	1.12	.10

Note: The following confounders were included in the multivariate analysis: age of child, sex of child, low birth weight and PMK income.

a reported history of maternal asthma, a one-year increase in maternal age at birth of child was associated with a more than 20% increased risk of persistent asthma (OR = 1.20, 95% CI: 1.04–1.40, $p = .016$, after controlling for potential confounders. No such association was found for children in which no maternal asthma history was present.

Discussion

The current study investigated the relationship between maternal age at birth of child and childhood risk of persistent asthma by ten years of age in a nation-wide prospective large Canadian cohort. We report the biological mother history of asthma can significantly modify the risk of persistent asthma of her child associated with maternal age at birth. A one-year increase in maternal age at birth of child was associated with a 20% increased risk of persistent asthma by age ten years of age among children whose biological mother had a history of asthma. This association was not observed among children whose biological mother had no history of asthma. The results of our study can help to explain the discrepancy and inconsistent results from published studies in the current literature on the association between maternal age at birth of child and risk of asthma.

Much of the past literature has found an inverse relationship between maternal age at birth of child and risk of asthma in the offspring. Geier et al., investigated 15 436 American childhood asthma cases (against 22 614 controls), and reported childhood asthma cases had significantly younger maternal age than the controls (Mean $\pm$ Std: 29.594 ± 7.117 vs 30.547 ± 7.117 , $p < .0001$) (39). Given the large sample size of this study, although the difference in average maternal age between two groups was highly statistically significant, the less than 1 year difference in the mean age ($30.547 - 29.594 = 0.95$ year) between the two groups is not clinically important. In a cross-sectional study of 4492 schoolchildren from Spain, the authors reported an inverse correlation between mother's age and a physician diagnosis of asthma (40). In another study of 175 children, aged 2–16 years living in Columbia and with a history of asthma, authors demonstrated that a maternal age at birth of ≤ 30 years was a risk factor for severe asthma (41). Similar findings have been reported in several other studies. Aspberg et al., reported a relationship between younger maternal age and an increased risk of childhood asthma in a Swedish cohort of 14 803 children (28). The FinnTwin16 study on 3065 families in

Finland showed decreasing maternal age was associated with an increased risk of asthma (27). Infante-Rivard et al., found in a cohort of 457 children 3–4 years of age and who were newly diagnosed with asthma that the children born to younger mothers had an increased risk of asthma compared to a maternal age of 30 years or older (26). A maternal age at birth of <20 years was linked to childhood asthma in a study of 15 416 children from the 1981 National Health Interview Survey (25). Moreover, another American population based study reported younger maternal age was related to asthma (24).

Studies have also investigated maternal age and asthma later in life; Gomez Real et al., in a study of the European Community Respiratory Health Survey II of 10 692 adult participants (42) showed in females, an increasing maternal age at time of birth was associated with a decreased risk of asthma controlling for confounding factors including maternal history of asthma; no such association was present in males (42). Another study of 16 190 participants aged between 23–54 years old from the European Community Respiratory Health Survey I also reported that every five years increase in maternal age was associated with eight percent decreased risk of asthma (43).

Conversely, studies have found an opposite relationship between maternal age at birth and asthma in offspring. Kashanian et al., in a study of 268 children aged from 7 and 14 (134 children with diagnosis of asthma and 134 children without diagnosis of asthma) found that maternal age at birth and maternal history of asthma increased risk of asthma: OR = 2.54, 95% CI 1.30–4.95, p values = .006 and OR = 11.62, 95% CI 1.38–96.9, $p = .024$, respectively (31). However, the possible effects of interaction between these two risk factors on the risk of asthma were not reported in this study. Dik et al., in a study of 170 960 children from the Canadian province of Manitoba reported a history of maternal asthma was associated with an increased risk of asthma in offspring (29). Additionally, the study found increasing maternal age was associated with offspring being asthmatic; interestingly when time-dependent variables (i.e. onset of allergic and respiratory conditions) were removed from the analyses, the relationship was reversed (29). Abid et al. examined a Latino cohort from the US and Puerto Rico consisting of 1696 asthmatics and 1777 controls ranging from 8 to 21 years of age (30). A mother's age of less than 20 at birth was found to have a decrease risk of asthma in the child, compared to mother's age of 25–29 [30]. No such associated was found comparing a maternal age at birth of 20–24 and greater than

29 with the 25–29 group (30). When subgroup analyses was completed, this relationship was only found in Mexican Americans- a maternal age of less than 20 and offspring asthma (30). Interestingly this relationship in the Mexican American group was only found if the offspring had no siblings (30). Moreover, in the Puerto Rico cohort maternal age >29 was positively associated with decrease risk of offspring asthma (30). Still other studies have found that asthma risk in offspring could not be explained by maternal age (33). A study from Japan found no relationship between mother's age at birth and various allergic disorders (32).

Why an increasing maternal age at birth of a child would be associated with an increased risk of asthma is an important question to explore. Dratva et al., investigated a European based cohort of 12 862 individuals aged 28–73 (44). An older mother's age at delivery was one of many variables associated with more rapid lung function decline (44). Though this cohort was an adult population, it shows that factors influencing lung health may occur early in life (44). Various prenatal and perinatal factors have been postulated to influence respiratory function in offspring (45). Increased maternal age has been linked to numerous adverse obstetric outcomes including need for cesarean delivery and preterm birth (46). Cesarean section has been associated with a greater risk of childhood asthma (47). Some have theorized that gut bacteria is different between cesarean births and vaginal deliveries and this may also influence the immune response by affecting the microbiota of the gut (48). Preterm birth has been shown to affect lung health, specifically early in life (49). Parental stress has also been reviewed as a potential factor in childhood asthma of the offspring (50); whether this plays a role with increasing maternal age is unclear. These are just few postulations of why an increasing maternal age is related to asthma status. The results of our study are important as they demonstrate that the maternal history of asthma can modify the effects of maternal age at birth of a child associated with persistent asthma can help to explain part of the discrepancy and inconsistent conclusion at current literature. More studies are necessary to further elucidate the mechanism of how maternal age at birth influences respiratory status of the offspring.

The current study has strengths and limitations. Strengths include the longitudinal study design and large sample size representative of children in Canada. The methods of data collection are standardized as per Statistics Canada and this will ensure the data

collected are valid and reliable. The large data set allows for the adjustment of confounding, adding strength to the data analysis and the study findings. There are also some limitations. The data collected was self-reported which can be influenced by recall of the person most knowledgeable (PMK). Nevertheless, we feel variables describing age, birth and history of asthma in both mother and child would be accurate. Although the gold standard for asthma diagnosis clinically would be made by a physician, for large epidemiological studies, it would not be feasible to obtain spirometry data on such a large sample size. This study is focused on childhood persistent asthma. The severity of persistent asthma (mild, moderate and severe) is important since each has very specific definition; however, information regarding specific severity categories of childhood persistent asthma was not available in this study.

In summary, utilizing a very large dataset of Canadian children, we found an association between maternal age at time of birth and childhood asthma, which was modified by the mother's history of asthma. As discussed, the current literature is unclear as to reasoning for or the mechanism to describe the relationship between maternal age and childhood asthma, although there are proposed theories. Our key finding is that there appears to be a significant relationship between maternal age and asthma in mothers who report a history of asthma. We therefore theorize that there may be a genetic link to explain part of this association. This unique finding may be helpful in understanding respiratory diseases and the possible potentiation at an early developmental stage. Further studies are needed to confirm these findings and also to uncover other potentially confounding variables which may help explain why maternal age is associated with offspring asthma.

Acknowledgements

The National Longitudinal Survey of Children and Youths (NLSCY) is a product of Statistics Canada. Information is available through Statistics Canada. We gratefully acknowledge Statistics Canada for granting us access to the dataset. We also acknowledge the Memorial University Research Data Centre, a branch of the Canadian Research Data Centre Network for providing space for data analysis.

Conflicts of interest

The authors declare no conflicts of interest.

Contribution statement

Concept and design: ZG, DW. Writing of manuscript: DW. Statistical analysis: ZG. Interpretations of result: DW and ZG. Revision and editing of manuscript: DW, ZG, JF, MJS, LT. Each author provided critical revisions and approved submission.

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