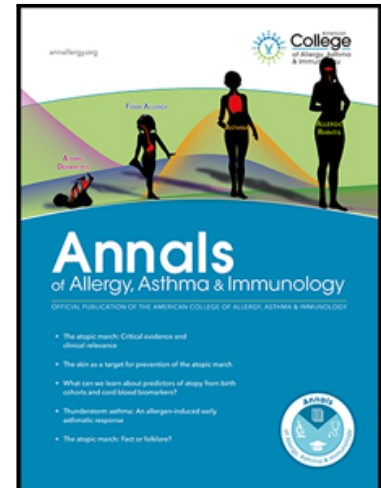


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Safiya Soullane MDc , Phillipe Bégin MD PhD FRCPC ,
Antoine Lewin PhD , Ga Eun Lee MScPH ,
Nathalie Auger MD MSc FRCPC

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Increased risk of allergy hospitalization after cesarean delivery: a longitudinal study of 950,000 children

Safiya Soullane MDc,¹ Phillipe Bégin MD PhD FRCPC,^{2,3} Antoine Lewin PhD,^{4,5} Ga Eun Lee MScPH,^{6,7}
Nathalie Auger MD MSc FRCPC⁶⁻⁹

¹Faculty of Medicine, McGill University, Montreal, Quebec, Canada

²Sainte-Justine Hospital Research Centre, Montreal, Quebec, Canada

³Division of Clinical Immunology, University of Montreal, Montreal, Quebec, Canada

⁴Medical Affairs and Innovation, Hema-Quebec, Montreal, Quebec, Canada

⁵Department of Obstetrics and Gynecology, University of Sherbrooke, Sherbrooke, Quebec, Canada

⁶University of Montreal Hospital Research Centre, Montreal, Quebec, Canada

⁷Institut national de santé publique du Québec, Montreal, Quebec, Canada

⁸Department of Social and Preventive Medicine, School of Public Health, University of Montreal,
Montreal, Quebec, Canada

⁹Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal,
Quebec, Canada

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Corresponding author: Nathalie Auger, 190 Cremazie Blvd. E., Montreal, Quebec H2P 1E2, Canada,
nathalie.auger@inspq.qc.ca, Tel +1.514.864.1600 ext 3717, Fax +1.514.864.1616

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Abbreviations: HR = Hazard ratio; CI = Confidence interval

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Cesarean delivery is increasingly implicated in the development of childhood allergies.¹⁻³ In newborns, cesarean delivery prevents colonization by maternal vaginal and intestinal flora and is associated with mucosal dysbiosis.⁴ Mucosal dysbiosis is thought to impair immune tolerance and facilitate allergic sensitization.^{4,5} However, recent data suggesting that operative vaginal delivery is also associated with asthma and allergy challenge this hypothesis.^{2,6} Operative vaginal delivery does not cause mucosal dysbiosis as fetuses born with forceps or vacuum instrumentation pass through the vagina and are colonized by maternal flora. Because mucosal dysbiosis cannot explain the association between operative vaginal delivery and allergy, it is possible that the relationship with cesarean delivery is confounded by unmeasured patient characteristics. We evaluated the association between cesarean delivery and risk of allergy before 13 years of age, and assessed the extent to which the relationship was confounded by environmental or genetic factors.

We studied a retrospective longitudinal cohort of 954,754 singleton children born at term in hospitals of Quebec, Canada between 2006 and 2019. Data were collected from the Maintenance and Use of Data for the Study of Hospital Clientele registry which contains discharge abstracts for all hospitalized patients in Quebec. We used diagnostic and procedure codes in the International Classification of Diseases-10 and Canadian Classification of Health Interventions to identify exposures and outcomes. The exposures were cesarean delivery, operative vaginal delivery (forceps or vacuum), and nonoperative vaginal delivery (spontaneous or induced). The outcome was allergy hospitalization before 13 years of age, including allergic asthma, anaphylaxis, and nonasthmatic allergy (allergic rhinitis, allergic dermatitis, urticaria, granulomatous angiitis, and other allergic disorders). We used in-hospital diagnoses of clinically

significant allergic events that required confirmatory testing, rather than parent reports of allergy that may be unconfirmed or affected by recall.

Using health insurance numbers, we followed the children from birth until the first allergy hospitalization, death, or the study end on March 31, 2019. We calculated the incidence of allergy hospitalization and used multivariable Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between delivery mode and allergy hospitalization. We adjusted the models for known confounders, including maternal age at birth, parity, maternal atopy, pregnancy-related morbidity, infant sex, socioeconomic disadvantage,⁷ and time period. We analyzed death as a competing event, accounted for correlation of outcomes in siblings, and verified the proportionality of hazards.

To determine if the associations were confounded by unmeasured environmental or genetic factors, we repeated the analysis using a sibling design with stratified Cox regression. Unmeasured environmental factors such as nutrition, obesity, and breastfeeding, as well as genetic factors, have the potential to confound the relationship between cesarean delivery and childhood allergy.^{3,8} Accounting for these factors in sibling strata with discordant exposure helps eliminate residual confounding.⁹ We conducted the analyses in SAS 9.4 (SAS Institute Inc., Cary, NC). We obtained an ethics waiver for the study as the data were anonymized.

During the study, 216,547 children (23%) were born by cesarean and 92,780 (10%) by operative vaginal delivery (Table 1). Children born by cesarean and operative vaginal delivery had a higher incidence of childhood allergy (46.5 and 44.8 per 10,000 person-years, respectively), compared with nonoperative

vaginal delivery (41.4 per 10,000 person-years). Compared with nonoperative vaginal delivery, cesarean delivery was associated with 1.14 times the risk (95% CI 1.10-1.17) and operative vaginal delivery with 1.12 times the risk (95% CI 1.07-1.17) of any allergy hospitalization in the full cohort of children. Associations were similar for siblings in the unstratified analysis, and were present for both allergic asthma and nonasthmatic allergy.

Cesarean delivery remained associated with allergy when we repeated the analysis using a stratified sibling design. In stratified Cox models that accounted for environmental and genetic confounders, cesarean delivery was associated with 1.16 times the risk of any allergy (95% CI 1.06-1.27) and 1.27 times the risk of nonasthmatic allergy (95% CI 1.10-1.45). However, the association between operative vaginal delivery and allergy disappeared (HR 0.99, 95% CI 0.93-1.05). Operative vaginal delivery was not associated with any type of allergy after accounting for environmental and genetic confounders in sibling strata.

Stratified sibling designs are effective to control for the effect of shared confounders such as family history, smoking, indoor allergens, nutritional habits, and socioeconomic conditions.^{1,8,9} In this study, cesarean delivery was associated with nonasthmatic allergy hospitalization even after accounting for these environmental and genetic confounders. In contrast, the association of operative vaginal delivery with allergy disappeared. Few studies of cesarean delivery and allergy have used sibling designs in past research. Previous analyses have been limited to asthma only.^{1,8} In these studies, associations with elective¹ and emergency⁸ cesarean delivery persisted after accounting for environmental and genetic confounders, whereas associations with operative vaginal delivery disappeared.^{1,8}

The data support the notion that infants who do not pass through the birth canal and are deprived of mucosal colonization by maternal flora have a greater risk of allergy. Because cesarean delivery prevents full exposure to vaginal flora, growth of beneficial bacterial species is inhibited, resulting in mucosal dysbiosis.^{4,5} Dysbiosis may impede the growth of microbes that stimulate T cells involved in regulating atopic responses.^{4,5} Other mechanisms specific to cesarean delivery, including reduced labour hormones and exposure to perinatal antibiotics, may also contribute to allergic sensitization in childhood.^{4,10}

The study has limitations. We controlled for environmental and genetic confounders using stratified sibling analysis, but residual confounding due to factors not shared in families may remain. We lacked data on potential confounders such as breastfeeding and perinatal antibiotic use. We evaluated allergy hospitalization and could not include less severe allergies that did not require admission.

In this study of more than 950,000 children followed from birth to 13 years of age, cesarean delivery was associated with the risk of childhood allergy independently of environmental and genetic factors. While the results cannot confirm the mucosal dysbiosis hypothesis, they support initiatives to determine the role of delivery mode in the development of allergy. Clinicians may maintain a higher index of suspicion for allergic disorders in children born by cesarean delivery.

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Table 1 Incidence of allergy hospitalization in children born at term by cesarean, operative vaginal, and nonoperative vaginal delivery

	Total no. children	No. with allergy	Allergy incidence per 10,000 person-years (95% CI)	Hazard ratio (95% confidence interval)		
				Full cohort ^a	Siblings unstratified analysis ^a	Siblings stratified analysis ^b
Any allergy						
Cesarean	216,547	6,220	46.5 (45.8-47.1)	1.14 (1.10-1.17)	1.13 (1.09-1.17)	1.16 (1.06-1.27)
Operative vaginal	92,780	2,685	44.8 (43.8-45.8)	1.12 (1.07-1.17)	1.09 (1.04-1.15)	0.99 (0.93-1.05)
Nonoperative vaginal	645,427	16,959	41.4 (41.0-41.7)	Reference	Reference	Reference
Allergic asthma						
Cesarean	216,547	3,873	28.7 (28.2-29.2)	1.15 (1.11-1.19)	1.14 (1.08-1.19)	1.07 (0.96-1.20)
Operative vaginal	92,780	1,678	27.8 (27.0-28.5)	1.14 (1.08-1.20)	1.11 (1.04-1.19)	0.99 (0.92-1.07)
Nonoperative vaginal	645,427	10,457	25.3 (25.0-25.6)	Reference	Reference	Reference
Anaphylaxis						
Cesarean	216,547	385	2.82 (2.66-2.98)	1.04 (0.93-1.17)	1.05 (0.91-1.22)	1.35 (0.94-1.94)
Operative vaginal	92,780	163	2.66 (2.44-2.91)	0.96 (0.81-1.14)	0.91 (0.73-1.12)	0.95 (0.74-1.21)
Nonoperative vaginal	645,427	1,108	2.65 (2.56-2.74)	Reference	Reference	Reference

Nonasthmatic allergy^c

Cesarean	216,547	2,582	19.0 (18.6-19.5)	1.12 (1.07-1.17)	1.12 (1.06-1.19)	1.27 (1.10-1.45)
Operative vaginal	92,780	1,114	18.3 (17.7-19.0)	1.11 (1.04-1.18)	1.08 (0.99-1.17)	0.98 (0.89-1.08)
Nonoperative vaginal	645,427	7,065	17.0 (16.8-17.3)	Reference	Reference	Reference

^aCox regression adjusted for maternal age (<20, 20-24, 25-29, 30-34, ≥35 years), parity (0, 1, ≥2), maternal atopy, pregnancy-related morbidity (hypertensive disorders, gestational or preexisting diabetes, illicit drug, alcohol, and tobacco use), sex, socioeconomic disadvantage (yes, no, unknown), and time period (2006-2010, 2011-2015, 2016-2019).

^bStratified Cox regression adjusted for environmental and genetic confounders (613,751 siblings, including 142,373 siblings with discordant exposure).

^cAllergic rhinitis, allergic dermatitis, urticaria, granulomatous angiitis, and other clinically significant allergic disorders (allergic purpura, allergic alveolitis, allergic gastroenteritis and colitis, allergic arthritis, allergic conjunctivitis, and allergic otitis).