

Greenness and Incident Childhood Asthma: A 10-Year Follow-up in a Population-based Birth Cohort

To the Editor:

Reduced access to greenspace for children has been linked to higher relative prevalence of asthma (1), and increased access to greenspace has been linked to higher physical activity (2), which is itself associated with decreased asthma development. However, in a birth cohort study conducted in New York, asthma at age 7 years and sensitization to tree pollen were significantly increased in those residing on streets with higher tree canopy coverage (3). We report on the effect of early-life exposure to surrounding residential greenness on asthma incidence, using data from a 10-year follow-up of more than 65,000 children in a population-based birth cohort study in British Columbia, Canada.

Linked administrative data were used to establish the study cohort comprising all 1999–2002 single births in the metropolitan area of Vancouver, British Columbia, to mothers registered with the provincial universal health insurance program and who resided for their complete pregnancy in the study area (4). Individual covariates obtained through administrative records (5, 6) include the month/year of birth, sex, First Nations status, and maternal parity, age, smoking during pregnancy, and initiation of breastfeeding. Participants were assigned neighborhood-level socioeconomic indicators (household income and maternal education) from Census data, based on their residential census dissemination area (7), a unit representing a target population of 400–700 persons.

Using linked physician billing and hospital discharge records (8), children were defined as cases after a validated case definition of asthma (9) of two physician diagnoses in a rolling 12-month period or a minimum of one hospital admission.

Cases were sex- and age-matched to five randomly chosen controls. Using a nested conditional logistic regression, incident asthma during preschool-age (0–5 yr old) and school-age (6–10 yr old) periods was examined in relation to surrounding greenness based on a satellite-derived normalized difference vegetation index (NDVI). As seasonal values were highly correlated ($r > 0.9$), average yearly greenness indices during pregnancy were calculated for 100-m areas around residential postal codes (4).

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Author Contributions: H.S., M.B., and M.K. defined the research theme. L.T. prepared administrative health data linkages provided by Population Data BC. H.S. and L.T. designed analytical and statistical methods. H.S. analyzed the data, interpreted the results, and wrote the paper. All authors discussed analyses, interpretation and presentation. All authors have contributed to, seen, and approved the manuscript. All inferences, opinions, and conclusions drawn in this research article are those of the authors, and do not reflect the opinions or policies of the Data Steward or Stewards.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

This buffer size typically reflects a city block and is at a similar spatial scale as within-city air pollution variation for which exposure estimates were developed and evaluated in the study region.

The mean (SD) age at time of incidence was 2.6 (1.4) and 7.0 (1.2) years in the preschool (6,948 cases) and school age (1,711 cases) groups, respectively (see Table E1 in the online supplement).

Average greenness levels in metropolitan Vancouver were relatively high (median NDVI = 0.24) and inversely correlated with land use regression models estimates of air pollution ($r \approx -0.4$; $P = 0.07$) (4).

In adjusted models, we observed during preschool years a decreased risk of asthma per interquartile (0.11) NDVI increase (adjusted odds ratio [aOR] = 0.96; 95% confidence interval [CI], 0.93–0.99). Accounting for contemporaneous co-exposures to air pollutants and road proximity measures enhanced the effect of greenness (Figure 1). No such associations were observed during the school age period (see Figure E1 in the online supplement).

Suggestive evidence of effect modification by birth weight was indicated, as surrounding greenness reduced the odds of new asthma onset during preschool years by 44% for children with term birth weight $< 2,500$ g compared with those weighing $\geq 2,500$ g at birth. Children born to mothers with low educational attainment were also more likely to benefit from greenness exposure (aOR = 0.92; 95% CI, 0.86–0.97). However, no effect modification by neighborhood-level household income was found (Table 1). The lack of extensive individual level covariate data remains a limitation; however, this may be balanced by the large population-based study design.

Although pediatric asthma diagnosis is challenging, especially in very young children, ascertainment bias is unlikely, as 77% of children diagnosed during preschool years remained asthmatic in later childhood.

The inverse association between surrounding greenness and development of asthma in preschool-age children may support a hypothesis that biodiversity loss (10), reflected for instance by less interaction with natural spaces, leads to immune dysfunction, inflammation, and asthma. Stress reduction may be another pathway by which greenness influences asthma development.

As the protective effect of greenness was enhanced in models including air pollution exposure, despite the absence of a significant interaction term between these covarying exposures, the positive confounding by air pollution may represent a case of variance suppression. Our observations of an association between greenness and incident asthma among preschool children are unlikely to be mediated by increased physical activity, as no association was found between incident asthma and distance to the nearest park (aOR = 0.98; 95% CI, 0.95–1.00). Interaction models confirmed an effect of surrounding greenness that was independent of park proximity.

The possible protective effect of surrounding greenness on children weighing less than 2,500 g and for those born in areas of lower socioeconomic status raises the prospect of preventive public health interventions during pregnancy.

In one of the largest birth cohort studies to examine within-community NDVI-based contrasts, we found that the

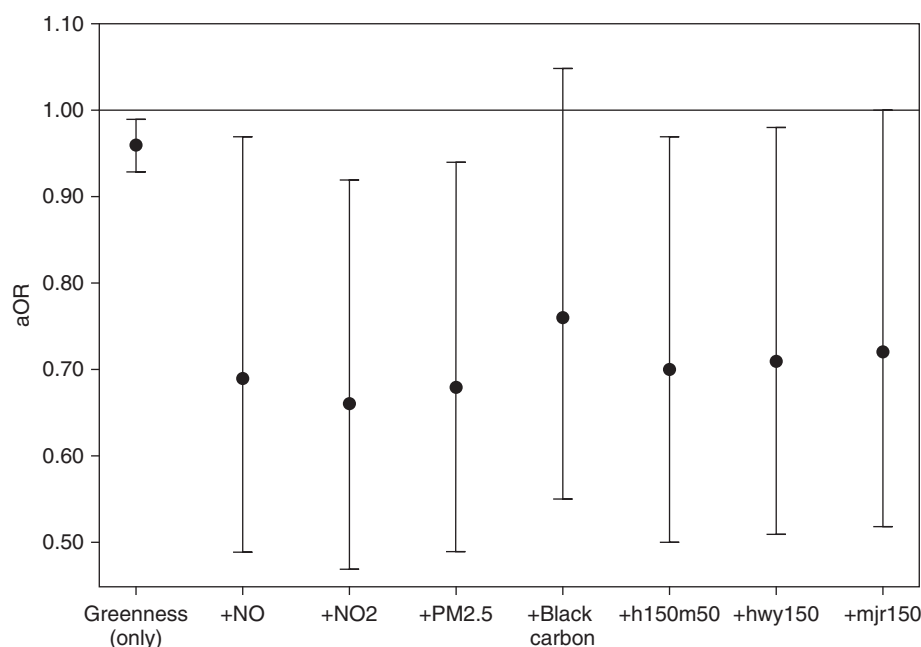


Figure 1. Effects of perinatal exposure to surrounding greenness in a 100-m buffer around home address on incident asthma risk, without and with adjustment for road proximity and air pollutants estimated using land use regression in preschool-age (0–5 yr old) children. All models are adjusted for the following risk factors: maternal age at delivery, birth weight, gestational length, neighborhood-level household income, neighborhood-level maternal education, parity, and breastfeeding. aOR = adjusted odds ratio; hwy50 = within 50 m of highway; h150m50 = within 150 m of highway or 50 m of major road; mjr150 = within 150 m of major road; $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than or equal to 2.5 μm .

Table 1. Effects of Socioeconomic Indicators (Neighborhood-Level Maternal Education and Household Income), Prematurity, and Term Birth Weight on the Association between Perinatal Exposure to Greenness in a 100-m Buffer around the Home Address and Asthma Incidence during the Preschool Period

	Cases (n)	OR	95% CI
Maternal education*			
Low	3,504	0.92	0.86–0.97
High	3,444	1.00	0.95–1.05
Household income†			
Low	3,390	1.00	0.93–1.05
High	3,558	0.98	0.93–1.03
Term birth weight			
≥2,500 g	7,772	0.97	0.93–1.00
<2,500 g	442	0.66	0.39–1.13
Gestational length			
≥37 wk	7,596	0.98	0.95–1.02
<37 wk	618	1.15	0.82–1.63

Definition of abbreviations: CI = confidence interval; OR = odds ratio. Bold indicates statistically significant result ($P < 0.05$). ORs and 95% CIs are presented per interquartile increase in greenness exposure. Models are adjusted for covariates that were significantly associated with incident asthma in bivariate analyses: maternal age at delivery, parity, breastfeeding status at discharge, birth weight, gestational period, household income, and maternal education.

*Low maternal education < median of neighborhood-level maternal educational attainment.

†Low neighborhood-level household income < 40th percentile.

majority of incident asthma occurred during preschool years, a period during which greenness surrounding the residential address was associated with reduced incidence. ■

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Hind Sbihi, Ph.D.
Lillian Tamburic, B.Sc.
Mieke Koehoorn, Ph.D.
Michael Brauer, Sc.D.
University of British Columbia
Vancouver, British Columbia, Canada

ORCID IDs: 0000-0002-4288-7258 (H.S.); 0000-0002-5376-7489 (M.K.); 0000-0002-9103-9343 (M.B.).

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Role of NOD2 Pathway Genes in Sarcoidosis Cases with Clinical Characteristics of Blau Syndrome

To the Editor:

Blau syndrome, a rare autosomal dominant disorder, presents in early childhood with granulomatous arthritis, dermatitis, and uveitis (1). Blau has been strongly associated with mutations in the *NOD2* gene (nucleotide-binding oligomerization domain-containing protein 2) (2), a member of the NOD-like receptor family involved in innate immunity. Blau shares similarities in phenotype and histological findings (presence of noncaseating granulomas) with sarcoidosis, another multisystemic granulomatous disorder. However, it differs in mode of inheritance, onset age, and pattern of organ involvement. Sarcoidosis rarely presents in childhood (3) and involves the lungs in more than 90% of cases, although any organ may be affected (e.g., bone/joints, skin) (3).

Despite these similarities, studies of patients with adult sarcoidosis have failed to find an association with *NOD2* (4). In this study, we assess the role of genes within the *NOD2* pathway in patients with adult sarcoidosis exhibiting similar pattern of organ involvement to Blau (eye, skin, bone/joint).

Methods

Analysis was performed independently for European American (EA) and African American (AA) sarcoidosis cases. AA cases ($n = 1273$) were compiled from the Sarcoidosis Genetic Analysis study population (5) and the National Heart, Lung, and Blood Institute's ACCESS (A Case Controlled Etiologic Study of Sarcoidosis) study (6), and a cohort from the Detroit Henry Ford Health System. EA cases ($n = 442$) were obtained from the ACCESS study. Analysis of each cohort involved the comparison of cases positive for both skin and bone/joint involvement to those negative for both. Using EMMAX (Efficient Mixed-Model Association eXpedited) (7), single-marker sex-adjusted association tests were performed for the single-nucleotide polymorphisms

(SNPs) in a number of genes selected from the *NOD2* pathway (Figure 1). The *NOD2* pathway has a total of 30 components, but our analysis excluded genes encoding pathway byproducts (e.g., chemokines), leaving 23 genes (covering 7,615 SNPs for AA and 2,612 for EA). The effective number of independent tests (N_{eff}) was estimated by computing the number of linkage disequilibrium (LD) blocks (LD threshold: $r^2 = 0.5$) in our SNP data, and Bonferroni correction was used to adjust for multiple testing. Thresholds for suggestive associations in each analysis were chosen on the basis of the expectation of a single false-positive association per analysis.

Results and Discussion

No significant associations were seen in *NOD2* in both AA and EA analyses. For EA, we observed novel significant associations in four variants within the *TAB2* gene. These variants were in complete LD ($r^2 = 1$). For AA, we observed a significant genetic association in a *MAPK13*, a gene encoding p38- δ , one of the four isoforms of the p38 MAP kinase.

Table 1 provides information on the SNPs, and Figure 1 provides a graphical overview of the pathway components harboring significant and/or suggestive variants in either cohort.

The four perfectly correlated SNPs identified in the EA cohort analysis reside in a large haplotype block within the *TAB2* (TAK1-binding protein 2) gene. In the AA cohort, we also discovered a suggestive association in the *TAB2* gene. Although there is no overlap between the *TAB2* SNPs identified in either cohort, the association of this gene in both race groups suggests its potential relevance to the subphenotype of interest and provides evidence of “gene-level replication.” Our AA analysis also revealed suggestive associations for SNPs in *TAB1* (TAK1-binding protein 1), a functional counterpart of *TAB2*. *TAB1* and *TAB2* bind to *TAK1* to form a complex that functions as a single unit. These results suggest a key role for the TAK1–TAB1–TAB2 complex in the intracellular signaling cascade initiated by *NOD2*. The complex is known to be involved in macrophage (a component of granulomas) activation, and deletion of *TAB1/TAB2* results in macrophage death (8). Studies have also shown this complex plays regulatory roles in the epidermal and intestinal epithelium (9) and in joint and cartilage development (10).

We also observed a suggestive associated variant in *TNFAIP3* (tumor necrosis factor α -induced protein 3), a gene encoding A20, a ubiquitin-editing enzyme that has been shown to inhibit NF- κ B activation as well as TNF-mediated apoptosis.

All variants showing significant/suggestive associations were located in noncoding regions. Functional annotation using HaploReg and RegulomeDB revealed enrichment for transcription factor binding sites, enhancer/promoter histone modification, and DNase hypersensitivity in different cell types.

This study is the first to fully explore the *NOD2* signaling pathway in search of downstream components that might play a role in the granulomatous inflammation common to Blau and sarcoidosis. Our findings will guide further investigations into the mechanisms leading to Blau-like manifestations of sarcoidosis. Although we further confirm that the *NOD2* gene itself is not a contributor to sarcoidosis, we do provide evidence indicating the *NOD2* pathway is involved. ■

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Greenness and incident childhood asthma: 10 year follow-up in a population-based birth cohort

Hind Sbihi, Lillian Tamburic, Mieke Koehoorn, Michael Brauer

Online Data Supplement

Table E1- Covariates and exposure descriptives among cases and matched controls by time window (n (%) for categorical covariates; mean (standard deviation) for continuous variables).

		Pre-school		School	
		Control (34621)	Cases (6948)	Control (8577)	Cases (1711)
Gender	Female	13143 (38)	2646 (38)	3480 (41)	690 (40)
	Male	21478 (62)	4302 (62)	5097 (59)	1021 (60)
Breastfeeding at discharge					
	No breastfeeding	2430 (7)	545 (8)	626 (7)	141 (8)
	Breastfeeding	32028 (93)	6358 (92)	7911 (93)	1561 (92)
	Unknown	163 (0)	45 (0)	40 (0)	9 (1)
Maternal post-secondary education quartiles					
	1 (lowest)	7670 (22)	1882 (27)	1959 (22)	459 (27)
	2	7973 (23)	1622 (23)	1996 (23)	411 (23)
	3	9407 (27)	1781 (26)	2270 (27)	421 (26)
	4	9571 (28)	1663 (24)	2352 (28)	420 (24)
Area-based household income quintiles					
	1 (poorest)	7468 (22)	1693 (24)	1833 (21)	392 (23)
	2	7719 (22)	1697 (24)	1905 (22)	425 (25)
	3	7178 (21)	1460 (21)	1893 (21)	377 (22)
	4	6799 (20)	1185 (17)	1629 (19)	301 (18)
	5	5457 (16)	913 (13)	1317 (16)	216 (13)
Parity	0	15504 (45)	3332(52)	3879(45)	892 (48)
	1+	19117 (55)	3616(48)	4698(55)	819 (52)
Gestation length (weeks)		39.4 (1.15)	38.9 (1.94)	39.1 (1.68)	39.0 (1.8)
Maternal age (years)		31.5 (5.06)	31.2 (5.09)	31.5 (5.12)	30.8 (5.3)
Birth Weight (g)		3510 (458)	3362 (567)	3437 (527)	3385 (538)
Exposure (NDVI)		0.23 (0.09)	0.23 (0.09)	0.23 (0.09)	0.24 (0.09)

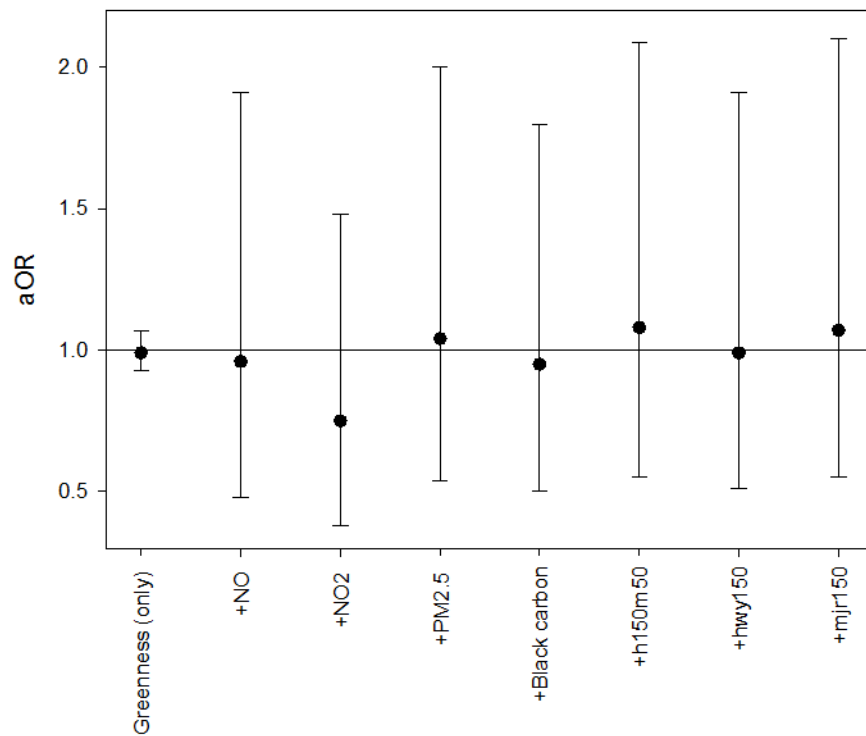


Figure E1: Effects of perinatal exposure to surrounding greenness in a 100m buffer around home address on incident asthma risk (controlling for maternal age at delivery, parity, breastfeeding status at discharge, birth weight, gestational length, neighborhood-level maternal education and household income), without and with adjustment for road proximity^{ss} and air pollutants estimated using Land Use Regression (LUR) in school (6-10) age children

^{ss} hwy50: within 50m of highway; mjr150: within 150m of major road; h150m50: within 150m of highway or 50m of major road