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Early Life Exposure to Phthalates and Organophosphate Esters and the Development of Childhood Asthma and Wheeze

Garthika Navaranjan, PhD

Occupational and Environmental Health Seminar

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CHILD COHORT STUDY

Conflicts of Interest

- None to declare

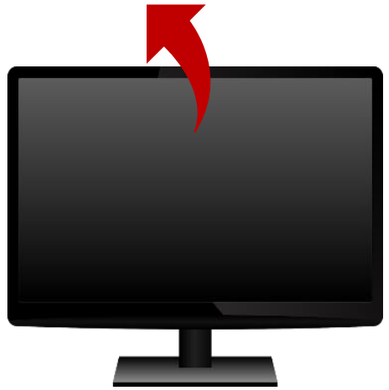
Childhood asthma

- Asthma most common chronic disease among children
- Rapid increase in prevalence of childhood asthma thought be explained by environmental factors
- Children spend most of their early life in the indoor environment

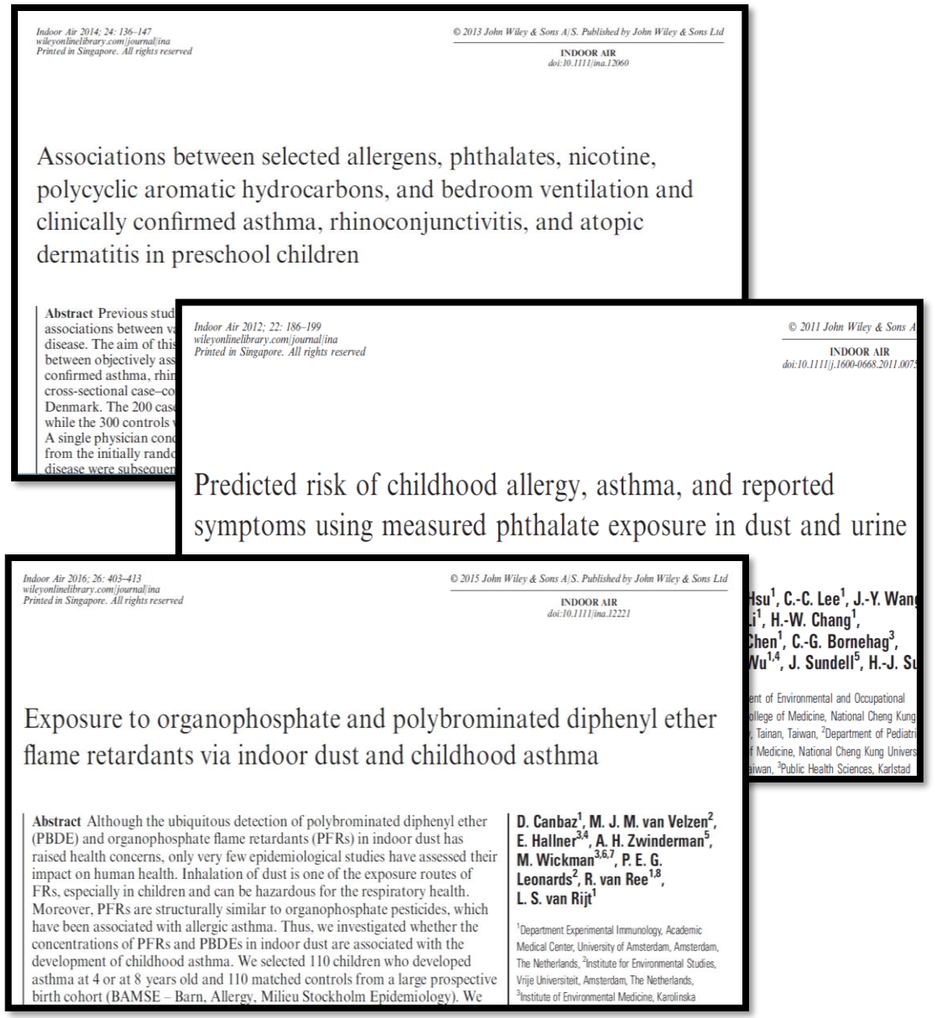
Phthalates and organophosphate esters (OPEs)

- Phthalates used primarily as plasticizers, and as solvents and lubricants

- OPEs used as flame retardants and plasticizers



Phthalates, and OPEs and childhood asthma



Indoor Air 2014; 24: 136–147
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INDOOR AIR
doi:10.1111/ina.12060

Associations between selected allergens, phthalates, nicotine, polycyclic aromatic hydrocarbons, and bedroom ventilation and clinically confirmed asthma, rhinoconjunctivitis, and atopic dermatitis in preschool children

Indoor Air 2012; 22: 186–199
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INDOOR AIR
doi:10.1111/j.1600-0668.2011.007

Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine

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INDOOR AIR
doi:10.1111/ina.12221

Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma

Abstract Although the ubiquitous detection of polybrominated diphenyl ether (PBDE) and organophosphate flame retardants (PFRs) in indoor dust has raised health concerns, only very few epidemiological studies have assessed their impact on human health. Inhalation of dust is one of the exposure routes of FRs, especially in children and can be hazardous for the respiratory health. Moreover, PFRs are structurally similar to organophosphate pesticides, which have been associated with allergic asthma. Thus, we investigated whether the concentrations of PFRs and PBDEs in indoor dust are associated with the development of childhood asthma. We selected 110 children who developed asthma at 4 or at 8 years old and 110 matched controls from a large prospective birth cohort (BAMSE – Barn, Allergy, Milieu Stockholm Epidemiology). We

D. Canbaz[1], M. J. M. van Velzen[2], E. Hallner[3,4], A. H. Zwinderman[5], M. Wickman[3,6,7], P. E. G. Leonards[2], R. van Ree[1,8], L. S. van Rijt[1]

[1]Department Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Institute for Environmental Studies, Vrije Universiteit, Amsterdam, The Netherlands, [3]Institute of Environmental Medicine, Karolinska

- Studies found association between phthalates, particularly DEHP, and childhood asthma, although inconsistent
  - No longitudinal studies examining early life exposure
  - Lack of examination of chronic exposure
  - Few studies examined gene-environment interactions
- Few studies have examined OPE exposure and childhood asthma
  - Limited exposure data

Research objectives

1. Assess level of exposure to phthalates and OPEs among Canadian children during early life

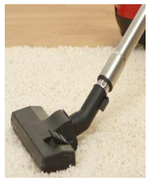
2. Examine the association between early life exposure to phthalates and OPEs, using house dust, and the development of childhood asthma and wheeze

3. Elucidate gene-environment interactions in the development of childhood asthma and wheeze

CHILD Cohort Study

- Canadian population-based birth cohort
- Families recruited from 2008 to 2012
- 3455 eligible children followed from pregnancy
- Examining development of asthma and allergy

Exposure and outcome assessments in CHILD

House dust collected at 3-4 months from most used living area (floor) and child's sleeping area (floor and mattress sheet/cover)

Expsoure








BIRTH | 3 months | 1 year | 2 years | 3 years | 4 years | 5 years

Health Outcomes





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Objective 1: Assess level of exposure to phthalates among Canadian children during early life using urine samples

- **Spot urine samples** collected at 3 months, 1 year and 3 years analyzed for 8 phthalate metabolites
- **Questionnaires** administered at several time points on multiple risk factors (demographic, home environment, nutrition)

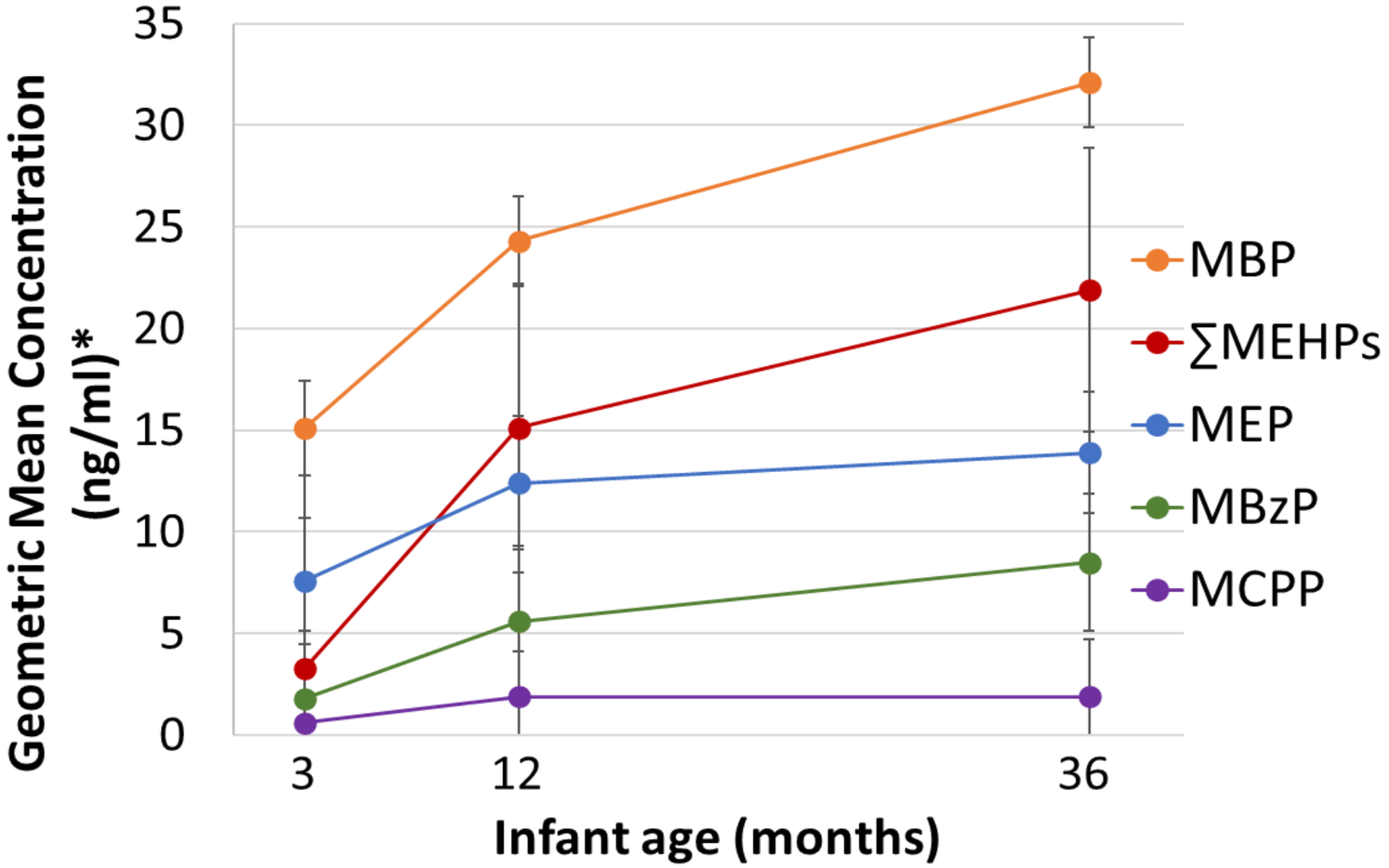
Parent Compound	Metabolite Measured
Dimethyl phthalate (DMP)	Mono-methyl phthalate (MMP)
Diethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)
Dibutyl phthalate (DBP)	Mono-butyl phthalate (MBP) (∑ mono-n-butyl (MnBP) & mono-iso-butyl phthalate (MiBP))
Benzyl butyl phthalate (BzBP)	Mono-benzyl phthalate (MBzP)
Di(2-ethyl-hexyl) phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP) Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
Di-n-octyl phthalate (DOP)	Mono-3-carboxypropyl phthalate (MCPP)

Statistical analysis: Assess level of exposure to phthalates among Canadian children during early life using urine samples

- Geometric means and standard deviation calculated
- Trends in concentration across age examined using linear mixed models with random intercept
- Differences in concentrations within key factors at each age assessed using ANOVA

Results: Assess level of exposure to phthalates among Canadian children during early life using urine samples

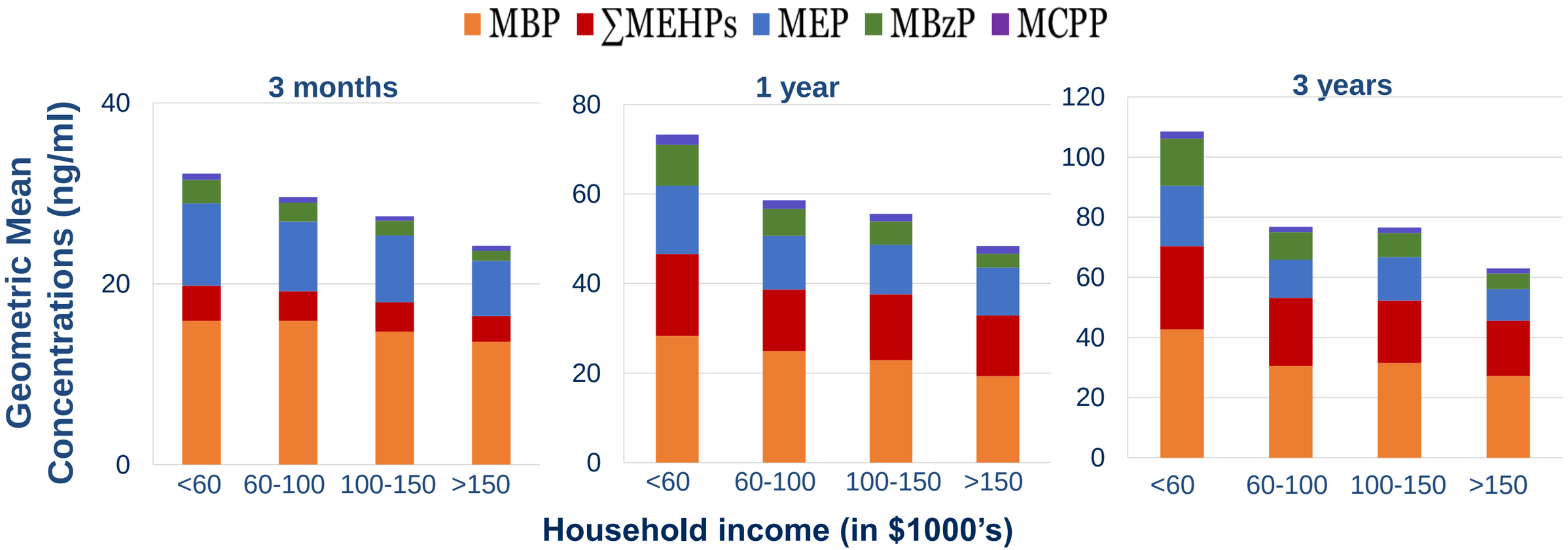
- High detection frequency (70-100%) for all phthalate metabolites, except MMP



*adjusted for specific gravity

Navaranjan et al. *J Expo Sci Environ Epidemiol* 2020

Results: Assess level of exposure to phthalates among Canadian children during early life using urine samples



p<0.05 for difference in concentration across income for all phthalate metabolites, at all time points, except MBP at 3 months

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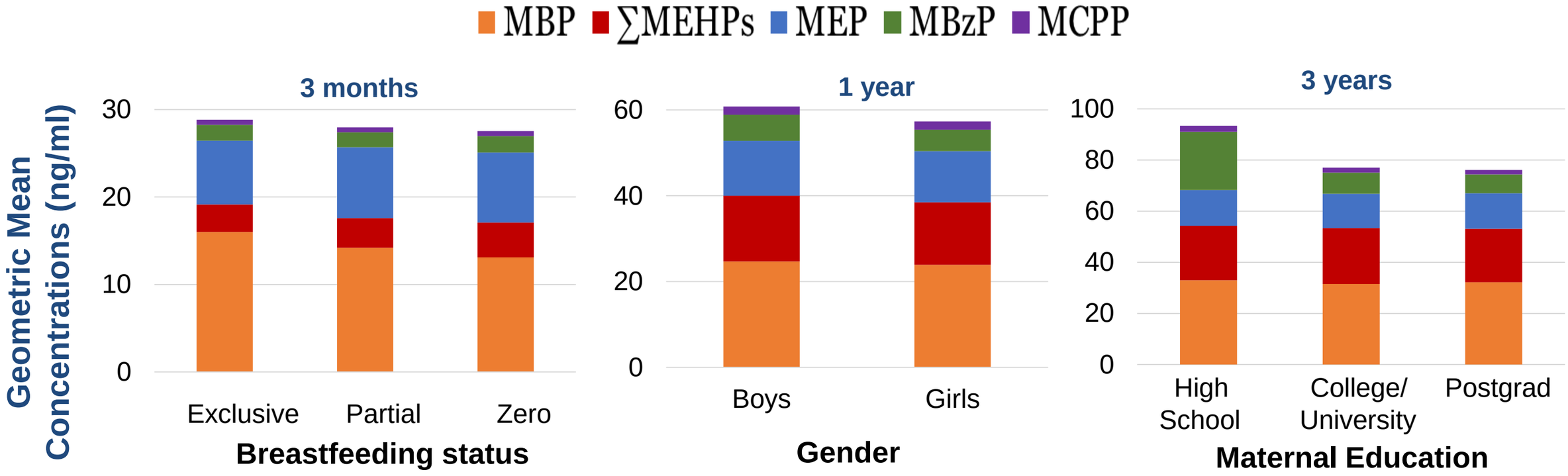
Results: Assess level of exposure to phthalates among Canadian children during early life using urine samples



- No consistent and significant differences in concentration observed by breastfeeding status, gender, study site, maternal age, maternal education, child's ethnicity

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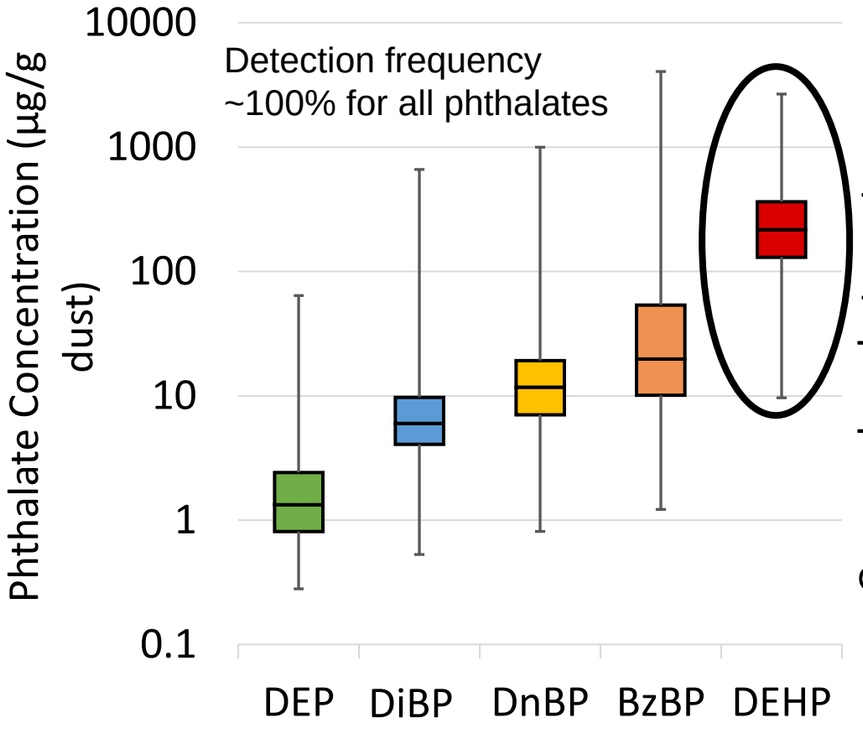
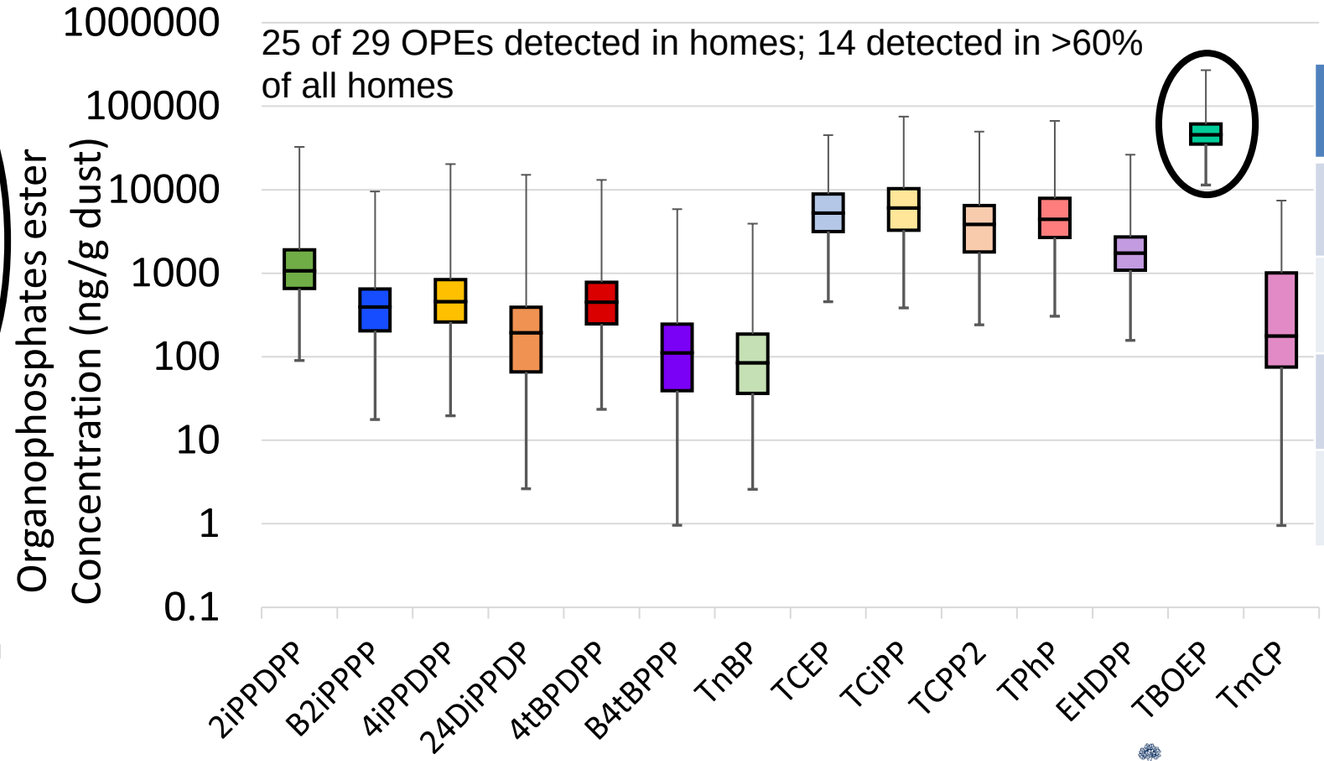
Objective 1: Assess exposure to phthalates and OPEs exposure during early life using house dust samples

- House dust samples from the most used room and child's sleeping area combined and analyzed for 5 phthalates and 29 OPEs for 726 children

Phthalates



OPEs



Room	∑OPE (ng/g)
Bedroom Most Used	82700 47200
Bedroom Most Used	58900 48500
Bedroom Most Used	263000 237000
Bedroom Most Used	94300 86800

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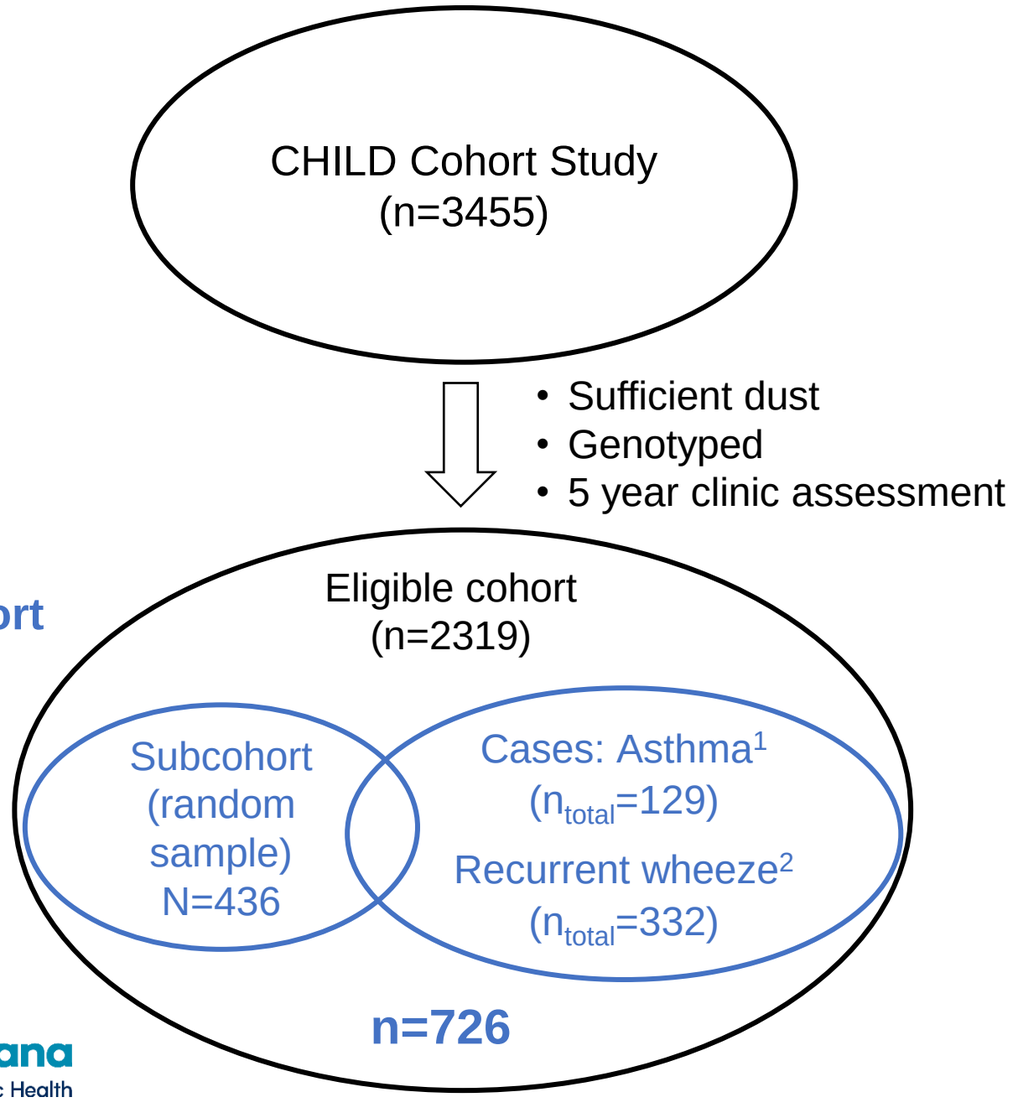
Objective 2: Early life exposure to phthalates and OPEs and development of childhood asthma and wheeze



- Exposure assessed using house dust samples collected at 3-4 months (Objective 1)
- Outcomes of interest:

1. Physician diagnosed definite asthma at 5 years
2. Defined as 2 or more occurrences of wheeze between 2 to 5 years, based on either parental report or physician assessment

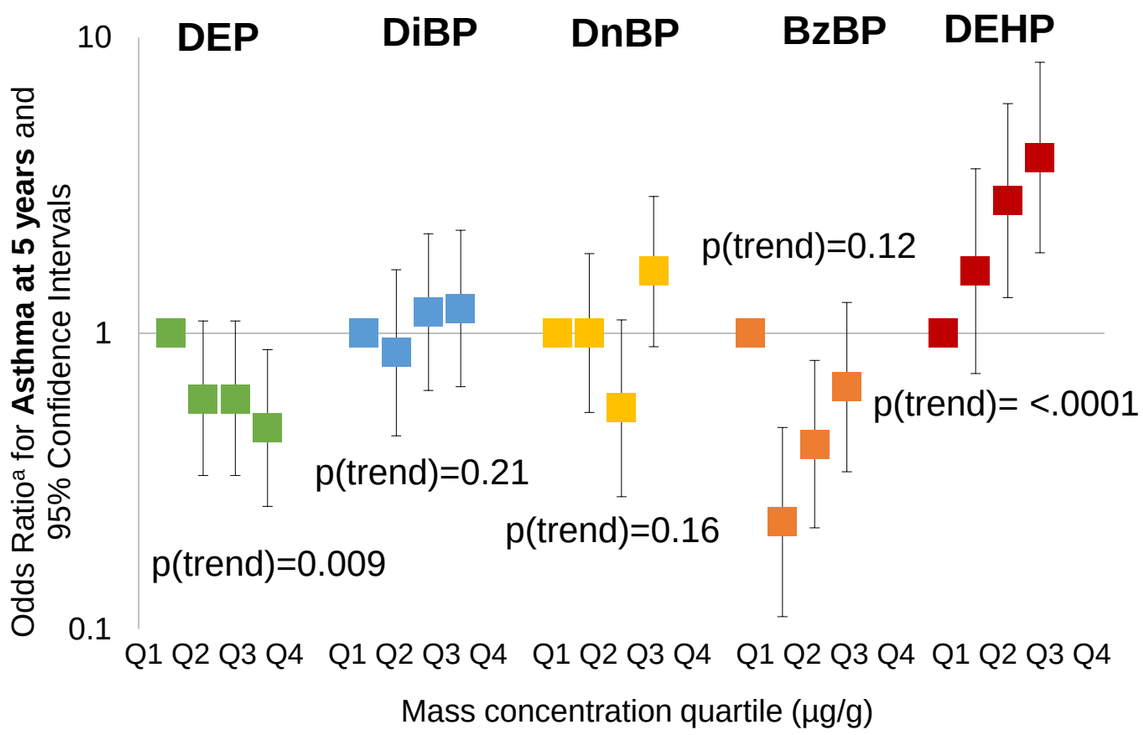
Statistical Analysis: Early life exposure to phthalates and OPEs and development of childhood asthma and wheeze

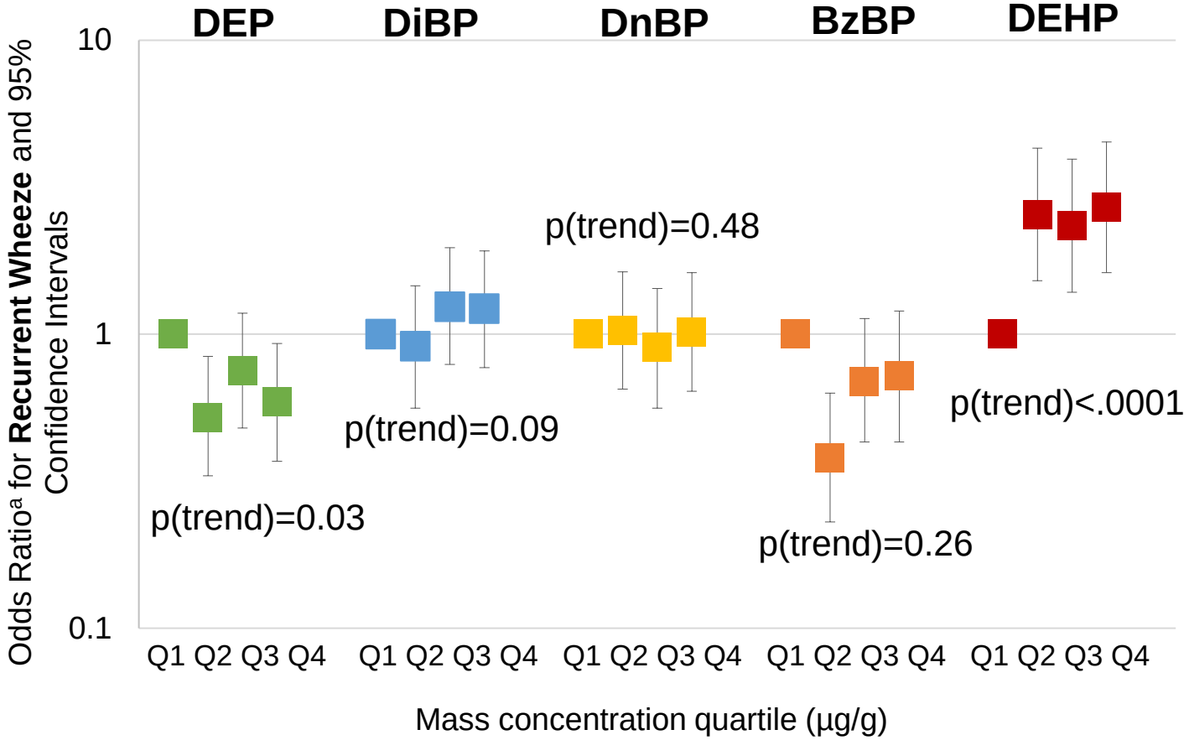
- Logistic regression to determine odds ratio with 95% CI
- Potential confounders examined using questionnaire data:
  - Gender, study site, household income
  - Smoking inside home
  - Parental history of asthma
  - Flooring type, home volume, period home built
- Interaction between exposure to each phthalate and sex examined in logistic regression models

Study population: Early life exposure to phthalates and OPEs and development of childhood asthma and wheeze

- Representation across all study sites among cases (asthma & recurrent wheeze) and non-cases
- Higher proportion of cases (> 60%) were boys
- Low prevalence of indoor smoking (< 3%) among cases and non-cases
- Roughly 50% of cases and non-cases had an annual income >$100 000

Results: Association between early life exposure to phthalates and development of childhood asthma and wheeze





[a] odds ratios adjusted for study site, gender, parental history of asthma, household income

- No differences in risk observed by sex, p(interaction) > 0.05

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Navaranjan et al. *Environ. Res* 2021 https://doi.org/10.1016/j.envres.2021.110981

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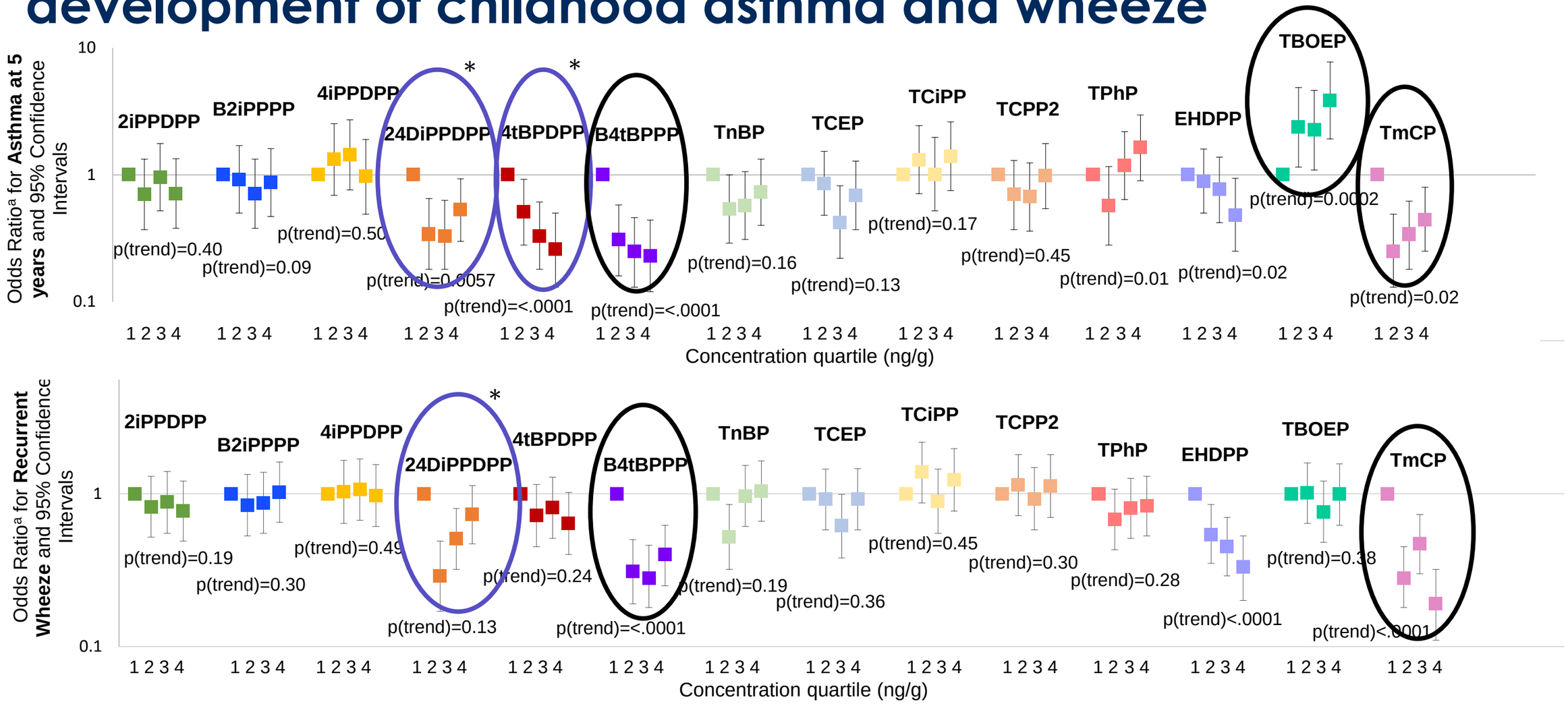
Results: Association between early life exposure to OPEs and development of childhood asthma and wheeze



[a] odds ratios adjusted for study site, gender, parental history of asthma, household income

*Those associations circled in purple were not statistically significant when adjusting for other OPEs

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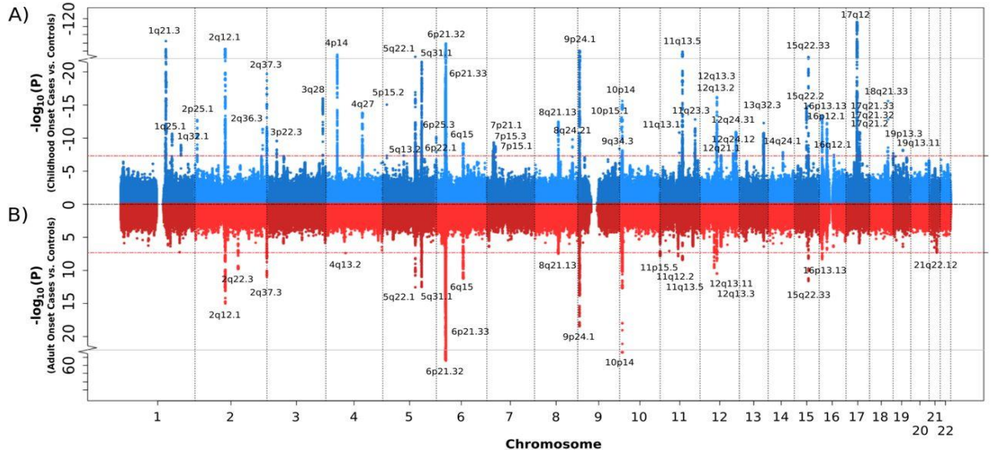
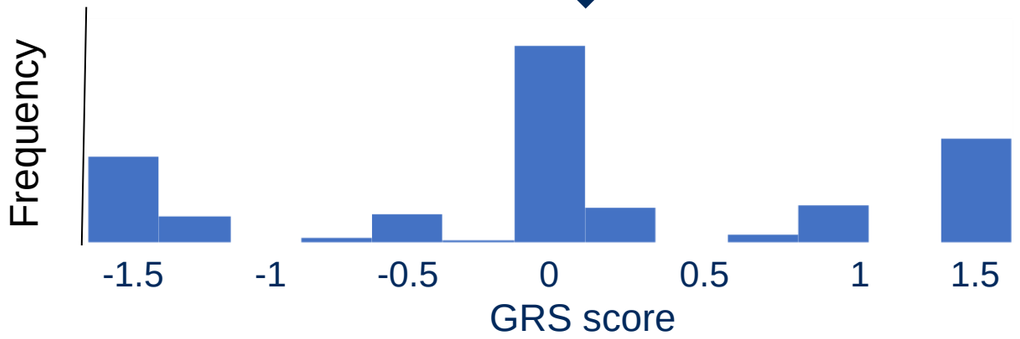
Objective 3: Elucidate gene-environment interactions in the development of childhood asthma

- Genetic risk examined using genetic risk scores (GRS)
  - Genome-wide association study by Pividori et al. 2019 used to identify genetic variants
  - Four variants (rs3816470, rs3902920, rs8076131, rs12603332) found to be strongest predictors of asthma in CHILD
  - Variants weighted according to their effect size for asthma and summed to assign a GRS
  - GRS further categorized into tertiles: low, moderate and high risk



Pividori et al. *Lancet Respir Med.* 2019

GRS = (# risk alleles of variant A)*(weight of variant A) + (# of risk alleles of variant B)*(weight of variant B) + …….



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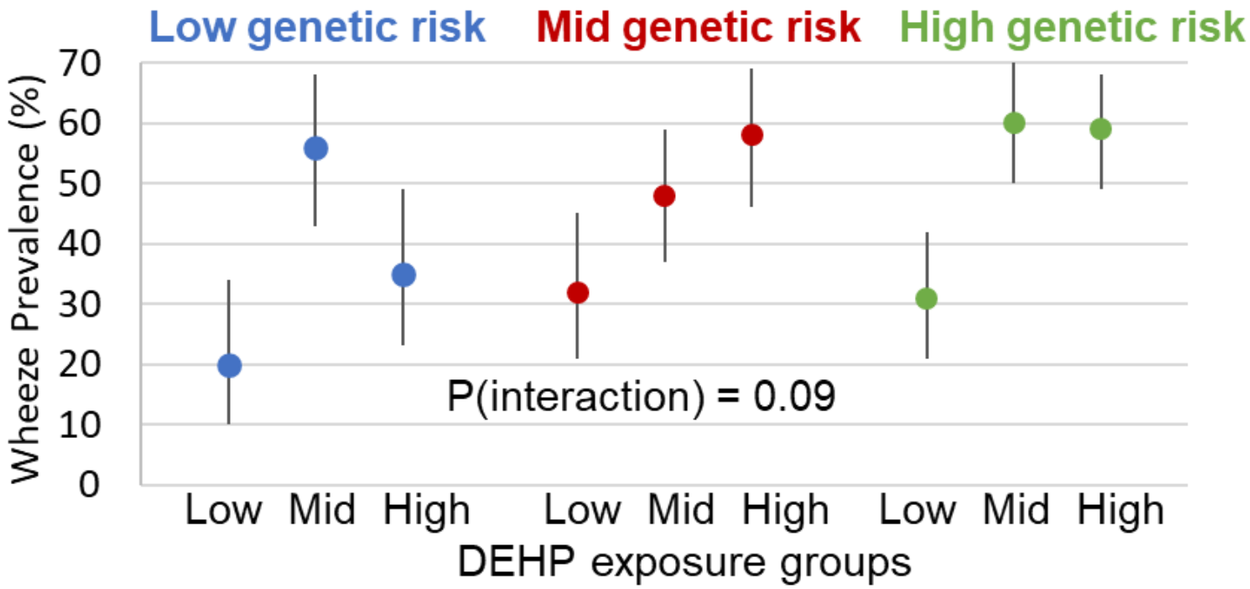
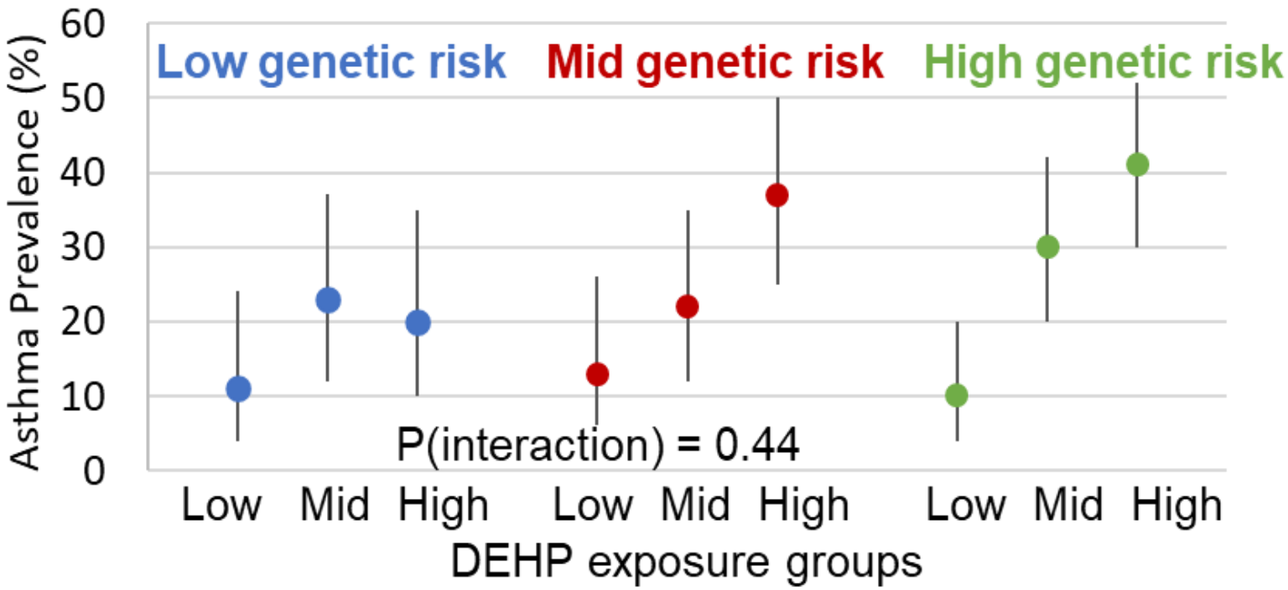
Statistical Analysis: Elucidate gene-environment interactions in the development of childhood asthma

- Prevalence of asthma and recurrent wheeze estimated for phthalate exposure tertiles by GRS group
- Interaction between exposure to each phthalate and GRS examined in logistic regression models
    - Models adjusted for key confounders: sex, study site, ethnicity

Results: Elucidate gene-environment interactions in the development of childhood asthma





- Interaction term between each phthalate and GRS not significant for asthma or recurrent wheeze ($p_{interaction} > 0.05$)

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Conclusions

- Children have ubiquitous early life exposure to phthalates and OPEs
- Higher concentrations of phthalate metabolites observed with lower income households
- Higher concentrations of OPEs observed likely due to sleeping environment
- Increased risk of asthma associated with early life DEHP exposure and TBOEP exposure and increased risk of recurrent wheeze associated with DEHP exposure
- Reduced risk observed between DEP exposure and BzBP exposure and asthma development; 24DiPPDPP*, B4tBPPP, and TmCP and risk of recurrent wheeze; and between 4tBPDPP* and risk of asthma
- Genetic risk, based on our GRS, did not modify relationship between phthalate exposure and asthma or recurrent wheeze risk

Recommendations

- Investigate sources of phthalates and OPEs driving high levels of exposure in Canadian homes, particularly in sleeping environment
- Examine early life exposure to mixtures of chemicals and with other early life exposures (e.g. allergens)
- Examine exposure to phthalates and OPEs during early life for other health outcomes (e.g. neurodevelopmental)
- Explore gene-phthalate interactions with a GRS developed with genetic variants involved in oxidative stress pathways
- Investigate early life exposure to chemicals among lower SES Canadian children and subsequent risk of disease

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Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

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Thank you!

Questions?

Garthika.Navaranjan@utoronto.ca