The Built Environment, Metabolomics, and Cancer Risk

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CanPath
Canadian Partnership for Tomorrow's Health

Background

- Breast, prostate, lung, and colorectal cancers contribute most to the public health burden
- Aging population: Canada is expected to face an increased burden of cancer
- Morbidity and mortality can be mitigated by interventions reducing exposure to risk factors
- Interventions to influence individual-level behavior change can be ineffective
- The built environment, which influences behaviors, can be altered to reduce cancer incidence

Research Gap

- Built environment → dietary choices, physical activity, circadian rhythm, hormonal changes, air pollution, and other ambient exposures
- Actual effect of the built environment on cancer risk is unknown
- Air pollution: Group 1 lung carcinogen, worth exploring given the generally low levels of pollution
- Unknown pathways through which built-environment factors influence cancer risk
- Examining the associations between built-environment factors and biomarkers may help elucidate these pathways

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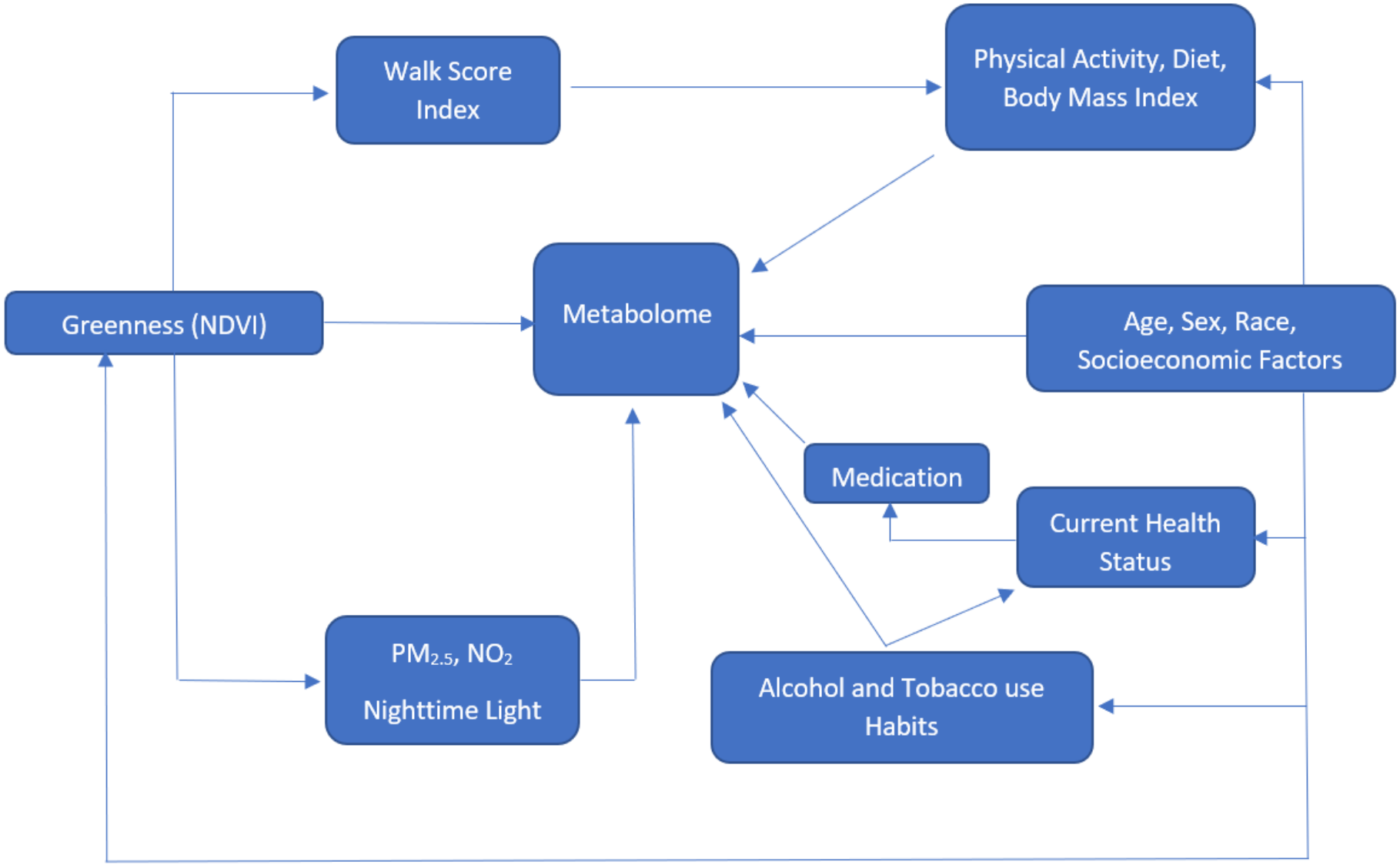
Figure 1b: The Relationship Between the Built Environment, Individual Factors, and the Metabolome



NDVI = Normalized Difference Vegetation Index, $PM_{2.5}$= Particulate Matter ≤2.5µm, NO_2= Nitrogen Dioxide

Data Sources

- BCGP
- ATP
- Cancer Registries
- CANUE
- Where Matters Study: Walkability Index 2006, 2011, 2016

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233 Metabolites

CANUE

Greenness:
- ✓ NDVI (1984-2019)

Air Quality:
- ✓ $PM_{2.5}$ (2000-2016)
- ✓ NO_2 (1984-2016)

Neighborhood:
- ✓ Nighttime Light (1992-2013)
- ✓ Walkability Index 2006

Exposures and Outcomes

Exposures

- Greenness (NDVI)
- Two measures of walkability
- Light at Night
- Air pollution: $PM_{2.5}$, NO_2

Outcomes

- Breast, Prostate, Lung, and Colorectal Cancers
- NDE and NIE of Greenness on cancer risk
- Change in metabolite concentrations

Statistical Methods

Cancer Risk

Cox regression model: association between each exposure and incident cancer

Minimum adjustment set and change in effect estimates

Exposures will be evaluated as continuous and categorical variables

Walkability indices from CANUE and WM will be compared

Mediation Analysis

Contingent on significant findings

Counterfactual method with assumptions of confounding

Model for each cancer type with NDVI values as the primary exposure, and other exposures as mediators. Constructing linear models for environmental mediators with NDVI as the exposure

NDE and NIE

Metabolite Analysis

Cross-sectional analysis: restricted to 1,320 participants in BCGP

Associations with NDVI, nighttime light, and air pollution (PM2.5, NO2) in the year of blood sample collection and both the Where Matters and CANUE 2006 walkability indices will be assessed through individual models

Strengths and Limitations

☑Longitudinal design

☑Highly quantitative spatially-resolved exposure data

☑69,000 individuals from BC and Alberta

☑Expect strong internal validity

☑Exploratory evaluation: insight for larger-scale studies that can be pursued in the future

- Non-probability sampling
- Sample sizes are limited to support analyses of clinically relevant cancer subgroups
- Metabolite analysis: our study does not investigate temporal changes, foregoing any causal inference
  - Focus on lipids
  - Limited generalizability

Relevance & Knowledge Translation

- Potential to inform land use, urban planning, and city development
- Inform policymakers and governmental stakeholders
- Where Matters project publishes reports, website content, and newsletters for dissemination to the public
- Identify biochemical pathways potentially affecting cancer risk and inform researchers of the utility of exploratory metabolomics

Thank You!

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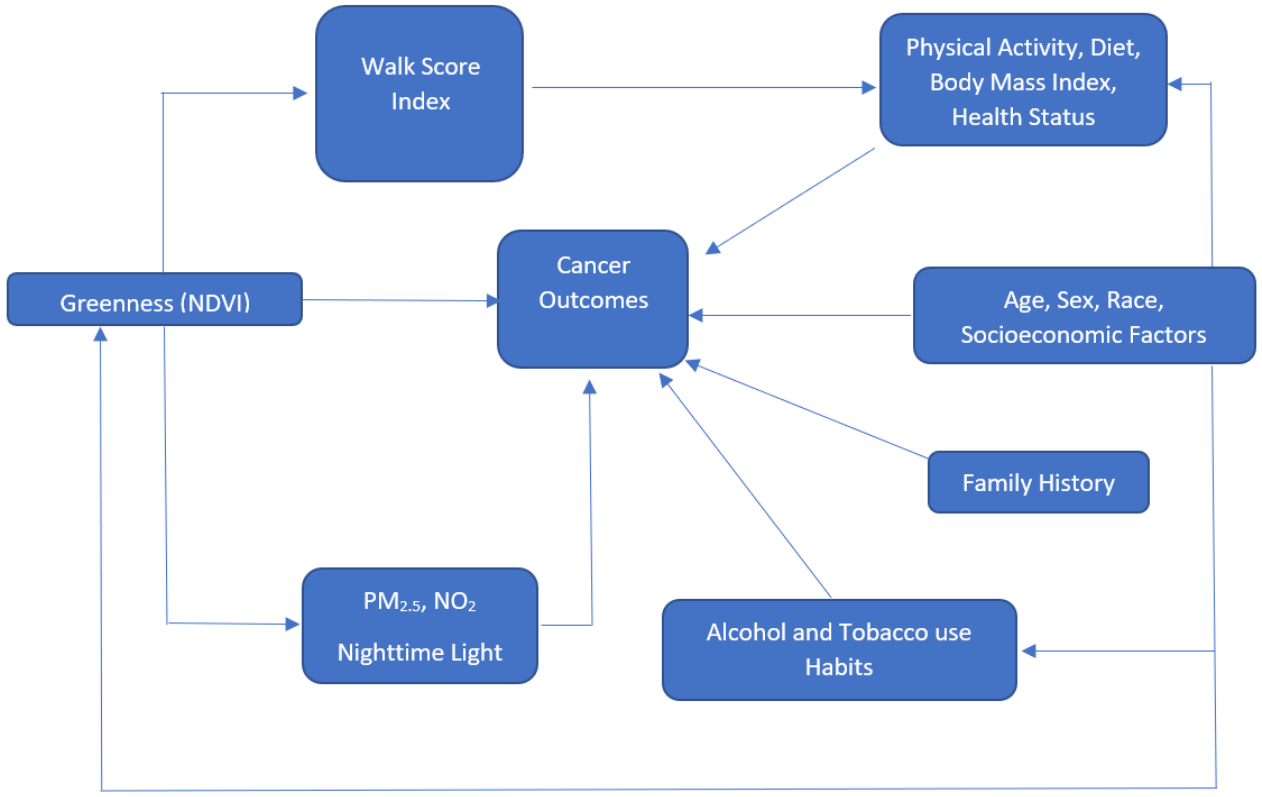
Additional Information – Mediation Analysis

- $log\lambda_T(\mathrm{t}|\mathrm{a},\mathrm{m},\mathrm{c}) = \log\lambda_T(\mathrm{t}|0,0,0) + \gamma_1 a + \sum_{i=1}^{k}\gamma_2^i m^i + \sum_{i=1}^{k}\gamma_3^i a m^i + \gamma_4' c$
- $E\left[M^i = 1 \middle| a, c\right] = \beta_0^i + \beta_1^i a + \beta_2^{i\prime} c$
- $NIE^{HR} = \exp\left(\sum_{i=1}^{k}(\gamma_2^i + \gamma_3^i a)\beta_1^i (a - a^*)\right)$
- $NDE^{HR} = \exp(\{\gamma_1 + \sum_{i=1}^{k}\gamma_3^i\left(\beta_0^i + \beta_1^i a^* + \beta_2^{i\grave{}} c + \gamma_2^i \sigma^{i2}\right)\}(a - a^*) + 0.5(\gamma_2 + \gamma_3 a)'\sum(\gamma_2 + \gamma_3 a) - 0.5(\gamma_2 + \gamma_3 a^*)'\sum(\gamma_2 + \gamma_3 a^*))$

Additional Information – Conceptual Framework 1

Figure 1a: The Relationship Between Environmental Factors and Cancer Outcomes



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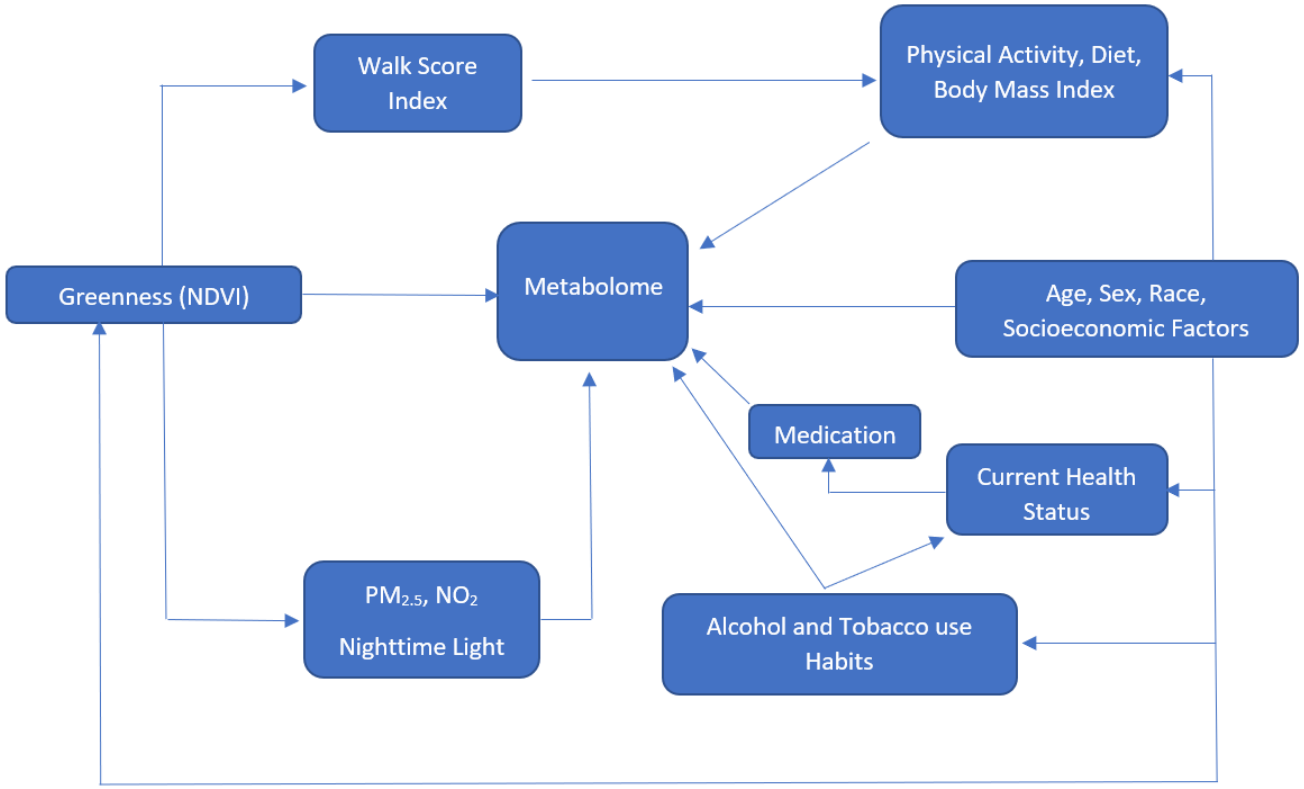

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Additional Information – Conceptual Framework 2