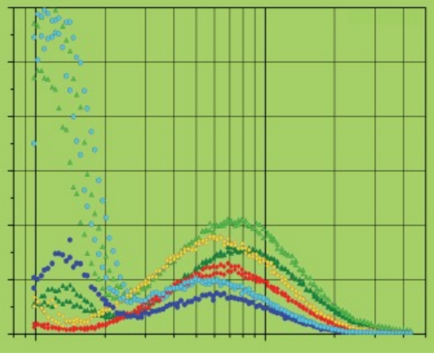
27th ETH-Nanoparticles Conference (NPC-24)
June 10 – 14, 2024
ETH Zürich, Switzerland – on-site

SCS Swiss Chemical Society

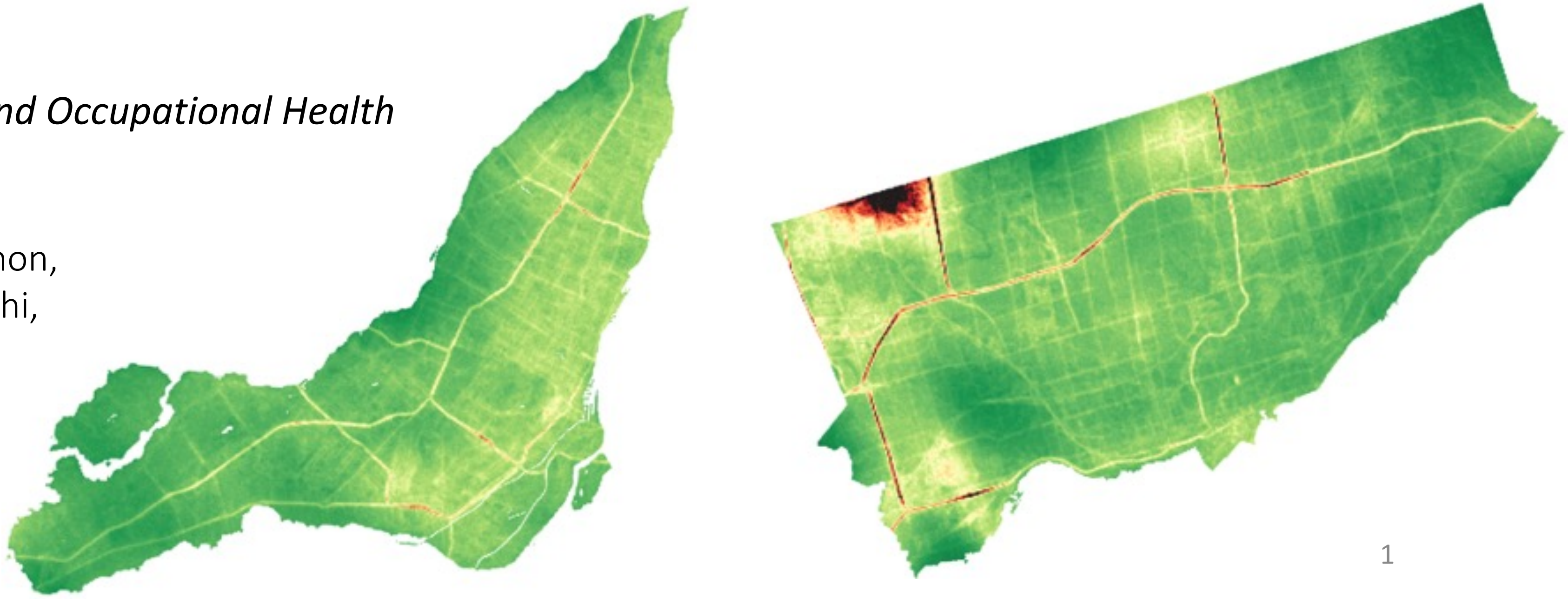


*Session 12: Health Effects*

# Airborne Nanoparticle Concentrations are Associated with Brain Cancer Incidence in Canada's Two Largest Cities

Marshall Lloyd
PhD Candidate
*McGill University*
*Department of Epidemiology, Biostatistics, and Occupational Health*

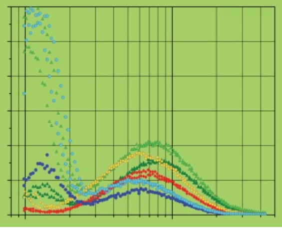
Toyib Olaniyan, Arman Ganji, Junshi Xu, Leora Simon, Mingqian Zhang, Milad Saeedi, Shoma Yamanouchi, An Wang, Richard T. Burnett, Michael Tjepkema, Marianne Hatzopoulou, <u>*Scott Weichenthal*</u>



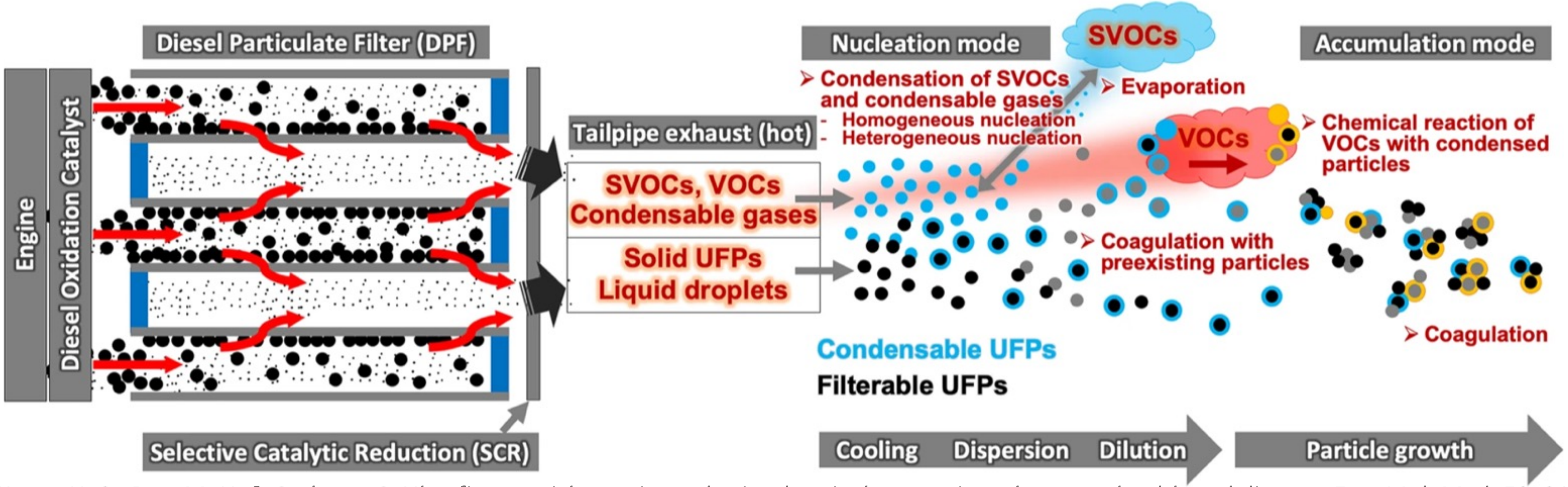
HEI

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

# Outdoor UFPs – Heterogeneity



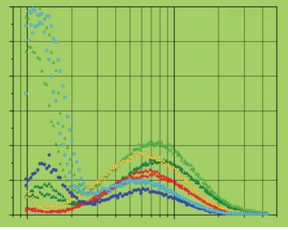
- Outdoor UFPs are a heterogenous mix
- Most epidemiological studies only contrast UFP concentrations
  - assume all UFPs are the same with respect to the outcome



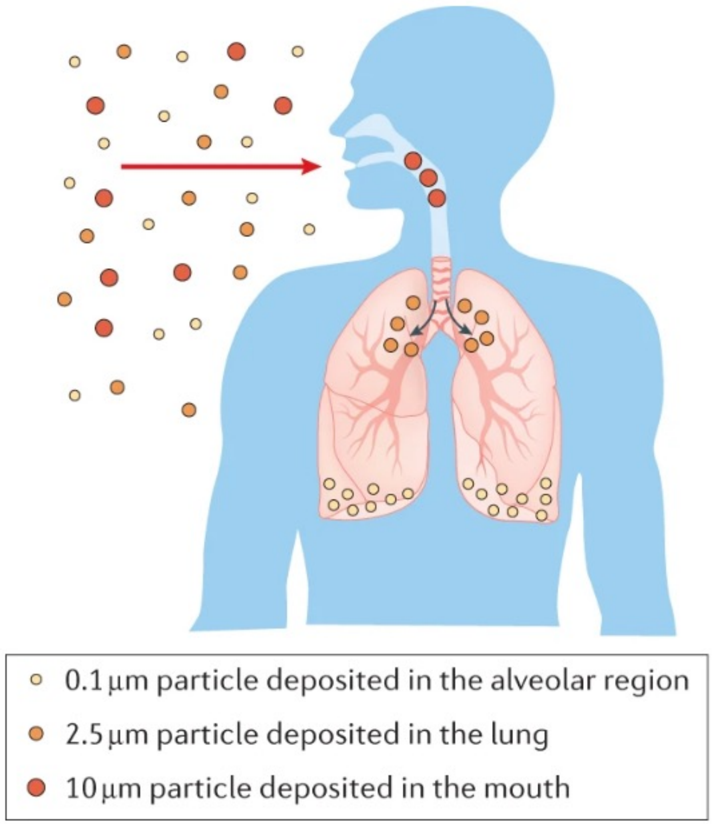



*Kwon, H.-S., Ryu, M. H. & Carlsten, C. Ultrafine particles: unique physicochemical properties relevant to health and disease. Exp. Mol. Med. 52, 318–328 (2020)*

# UFPs and Health – Brain Tumours

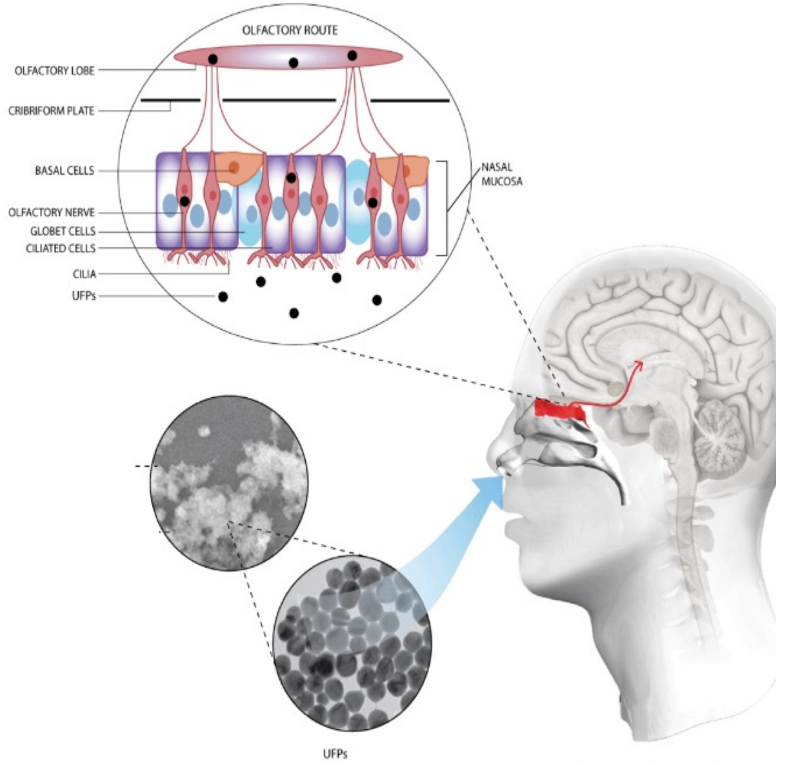


- Deposit deep in the lungs
- Translocate into systemic circulation



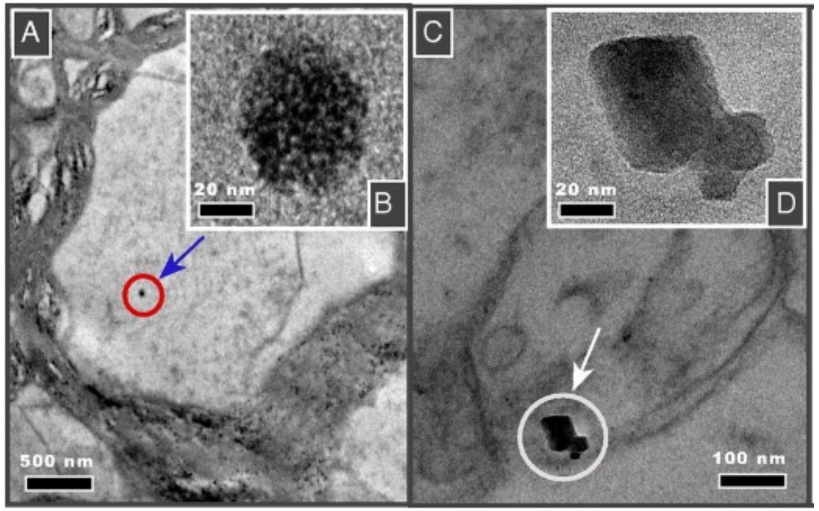

Morawska, L., Buonanno, G. The physics of particle formation and deposition during breathing. *Nat Rev Phys* **3**, 300–301 (2021).

- Deposit in the nasal cavity
- May travel up the olfactory nerve



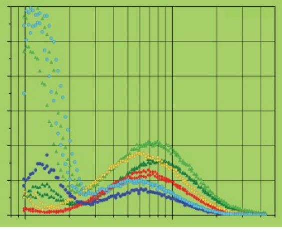

Shang, Y., Chen, R., Bai, R., Tu, J. & Tian, L. Quantification of long-term accumulation of inhaled ultrafine particles via human olfactory-brain pathway due to environmental emissions – a pilot study. NanoImpact **22**, 100322 (2021).

- Have been found in brain tissue
- May predispose, initiate, or encourage the progression of cancerous tumours



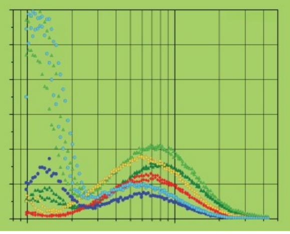

B.A. Maher, I.A. Ahmed, V. Karloukovski, D.A. MacLaren, P.G. Foulds, D. Allsop, D.M. Mann, R. Torres-Jardón, L. Calderon-Garciduenas. Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci*, **113** (39) 10797-10801 (2016).

# Aim



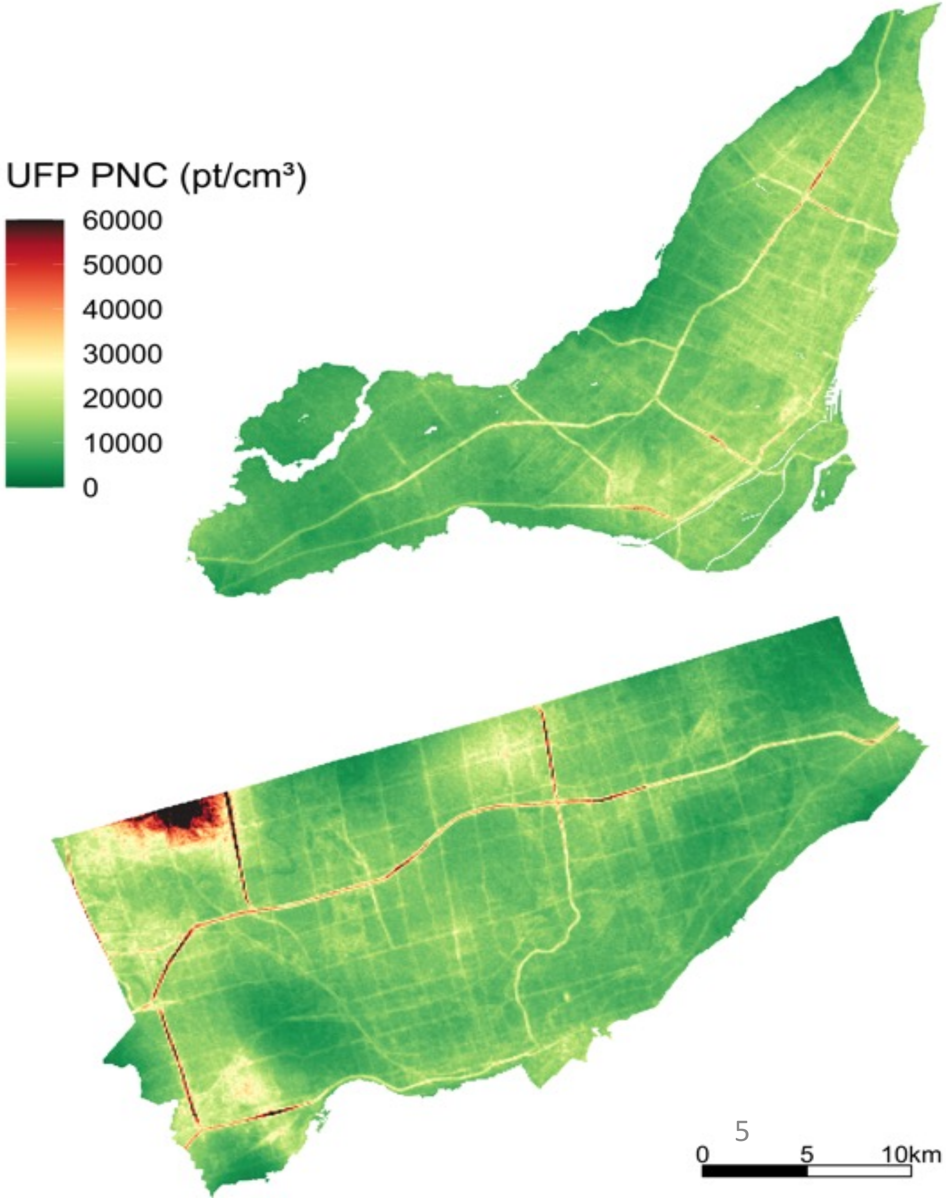
Investigate the relationship between ***long-term exposures*** to ***outdoor UFPs*** and ***malignant brain tumours***

# Methods - Exposure



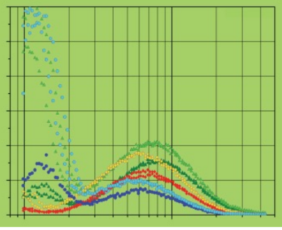
- Year-long mobile monitoring campaign
  - Between 7am and 10pm
  - All days of the week
  - Naneos Partector 2 and Testo DiscMini

- Model predictions of within-city spatial variation in median annual outdoor UFP levels
  - UFP number concentration
  - mean UFP size
  - Models trained on land use and satellite images
  - Historic traffic values used to project predictions into the past (i.e., back-casting)



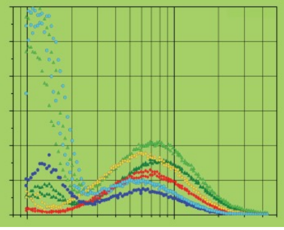

Lloyd M et al. **Predicting spatial variations in annual average outdoor ultrafine particle concentrations in Montreal and Toronto, Canada: Integrating land use regression and deep learning models.** *Environ. Int.* **178**, 108106 (2023)

# Methods – Study Population

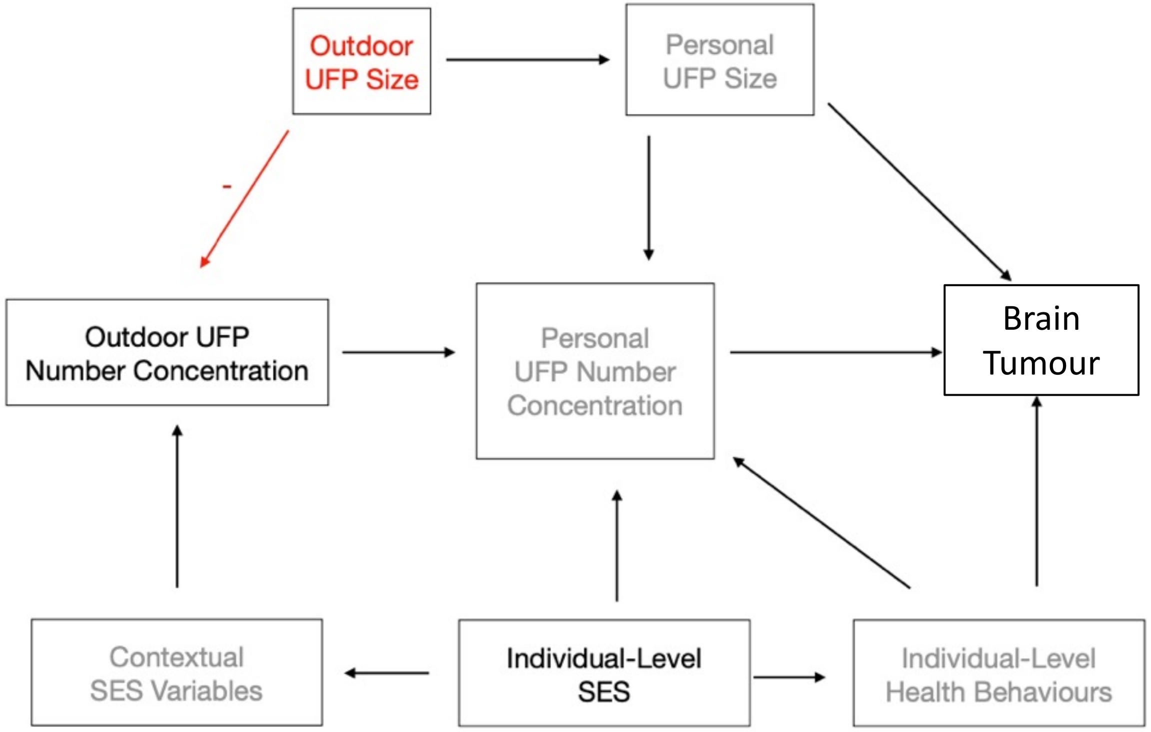


- Population-based cohort: Canadian Census Health and Environment Cohort (CanCHEC)
- Multiple census waves linked to administrative health records (i.e., Canadian Cancer Registry) and residential addresses from tax fillings
- **1.5 million adults** living in Montreal of Toronto
- Residential address (and exposure) updated every year
- Individual-level socioeconomic and demographic data

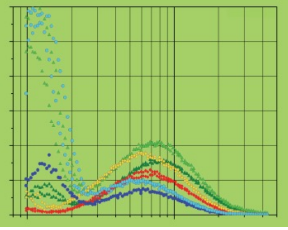
# Methods – Epidemiological Analysis



- Link exposures to study cohort
  - 3-year moving average at residential address
- Follow-up between 2001 and 2016
- Cox Proportional Hazard models
  - Stratified by age, immigrant status, sex, and census cycle
  - Adjusted for education, occupational level, income, marital status, visible minority status
  - Adjusted for outdoor concentrations of black carbon, $PM_{2.5}$, and $O_x$ ($O_3$ + $NO_x$)
  - **Adjusted for mean UFP size (spline)**



# Methods – Epidemiological Analysis



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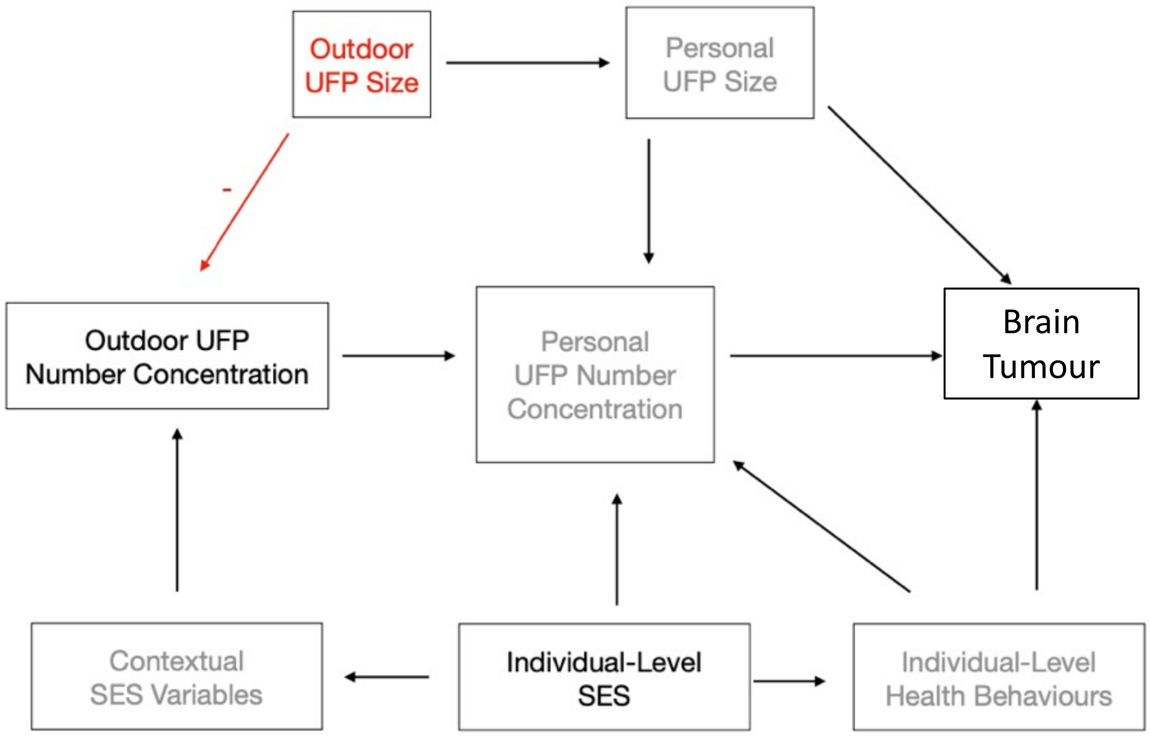
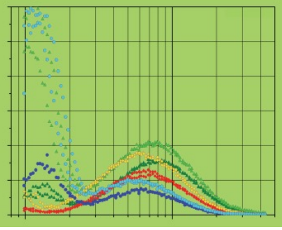
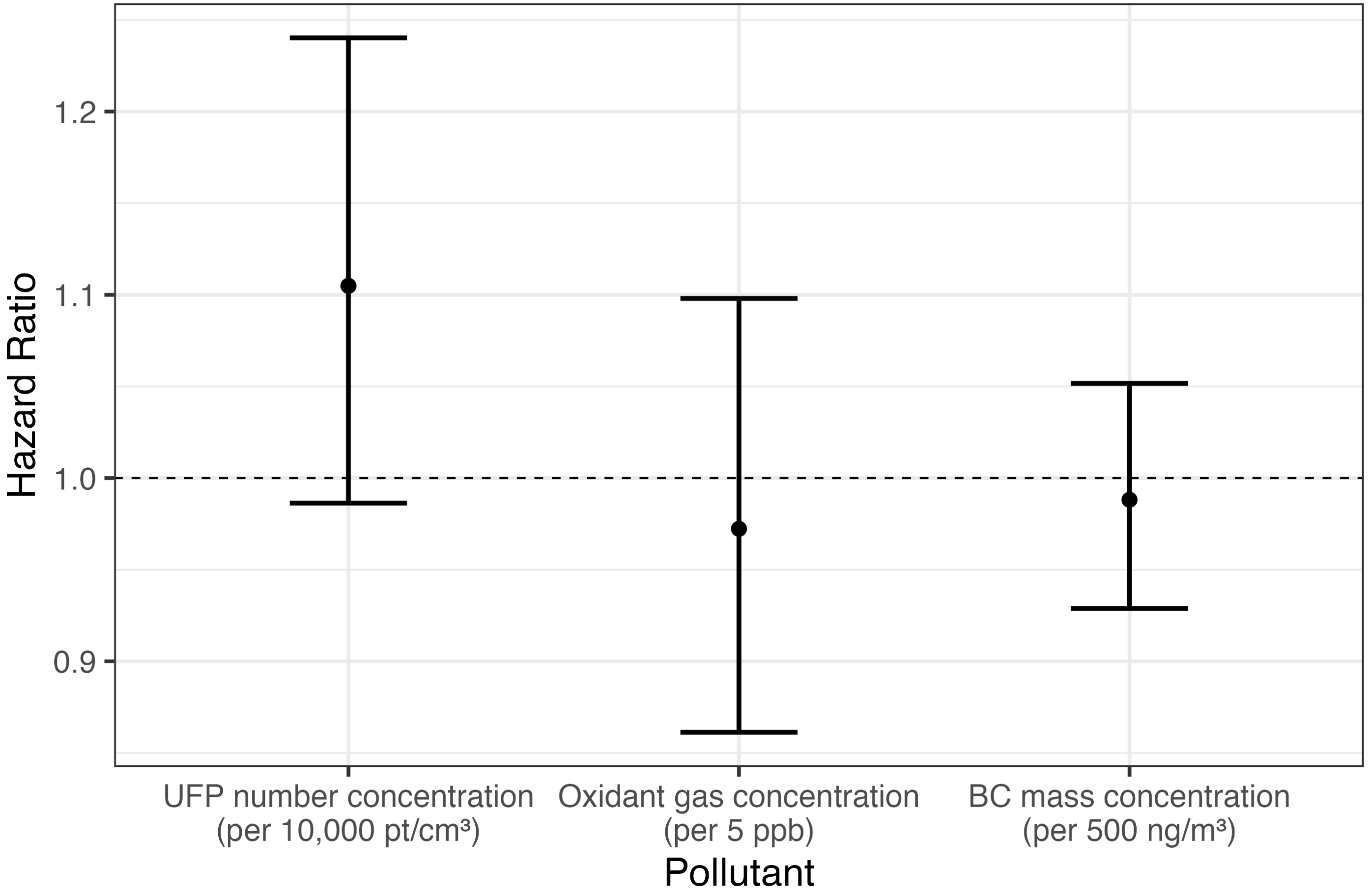



$$HR \sim UFP_{conc} + s(UFP_{size}) + BC_{conc} + Ox_{conc} + PM2.5_{conc} + SES$$

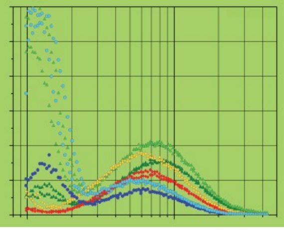
# Results – Main Analysis



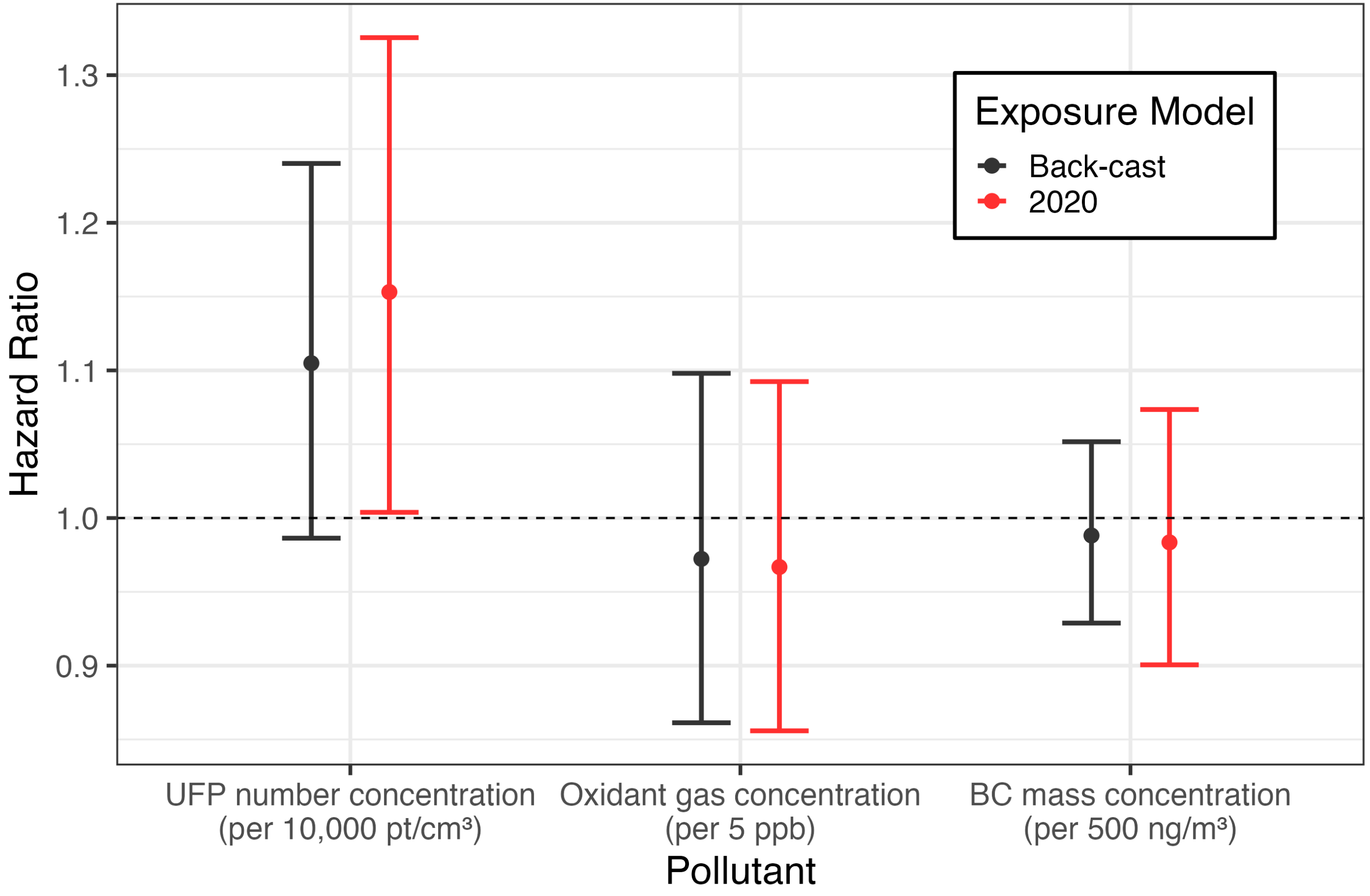
- 1400 new brain tumours during follow-up
  - 1.5 million adults
  - Average follow-up time of 14.7 years
- Every 10,000 pt/cm$^3$ increase in UFPs was associated with ***10% increase in risk*** of incident brain tumours
  - Relatively wide confidence interval



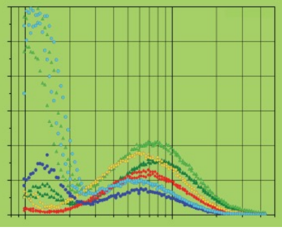
# Results – Alternate Exposure Model



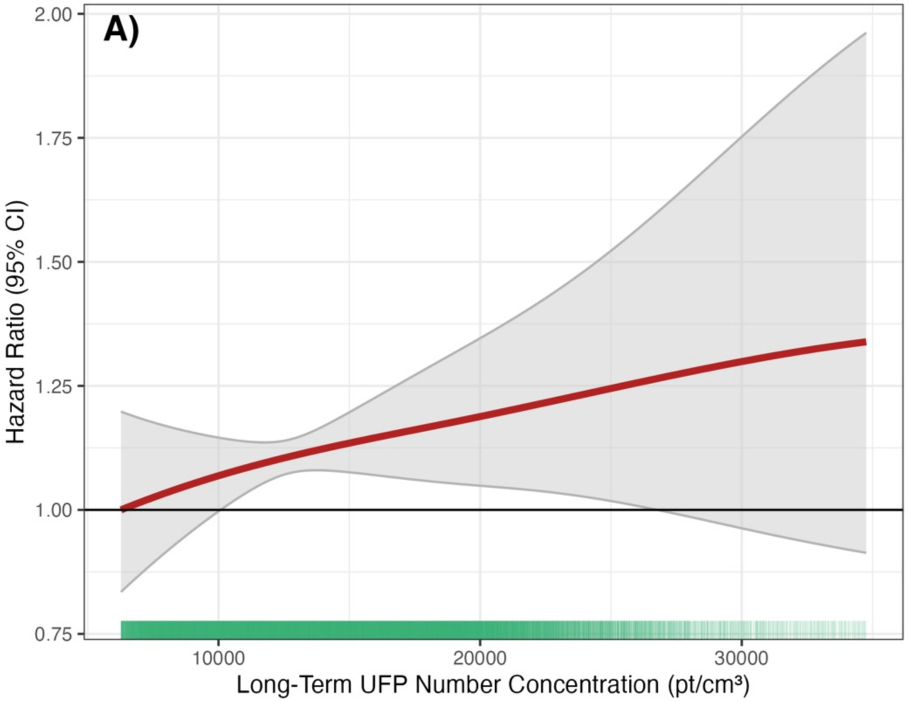
- Main analysis used back-cast model exposures
  - Novel method
  - Used historic traffic data and 2020 land use data
  - Assumed changes in spatial contrasts are captured by changes in historic traffic data
  - May have introduce additional measurement error
- Sensitivity analysis used 2020 exposure model
  - Used traffic and land use data from 2020
  - Assumed spatial contrasts are conserved over time
- UFP and BC air pollution monitoring conducted in 2020



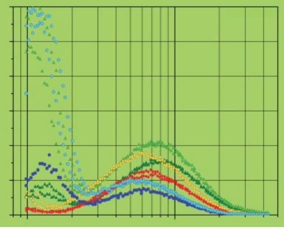
# Results – Concentration Response



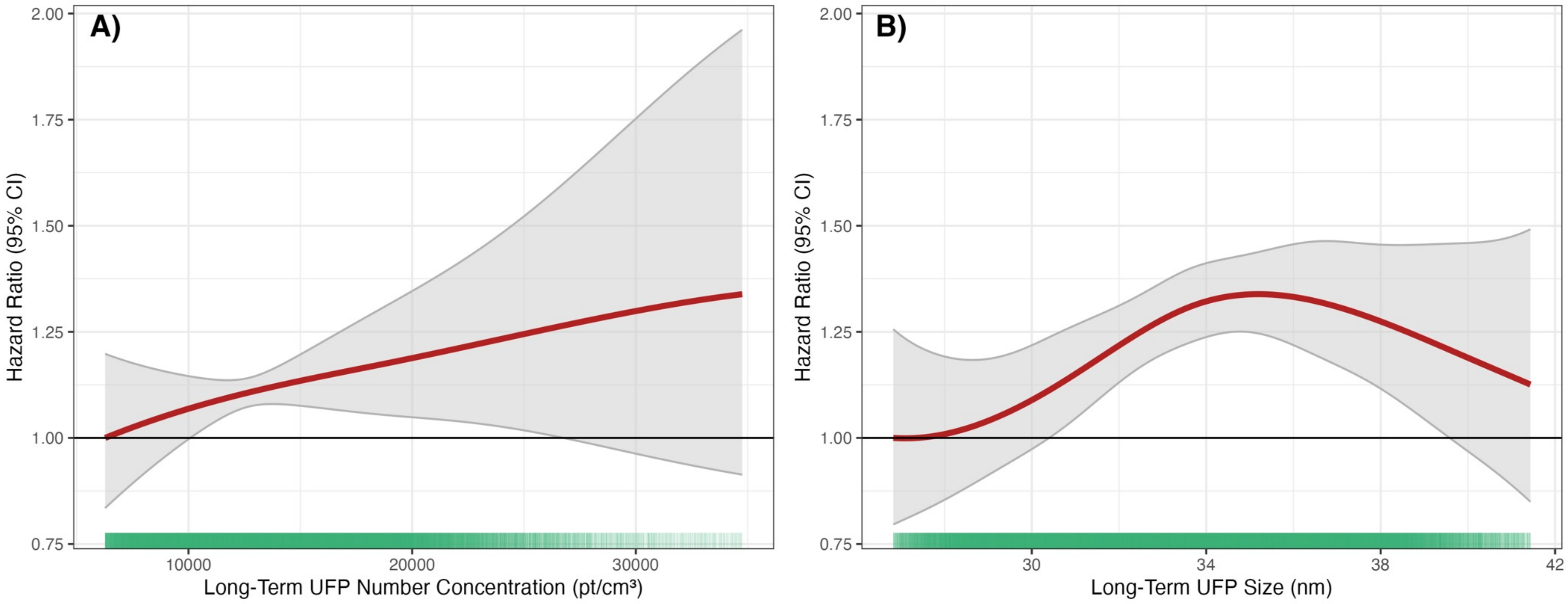
**A)** Elevated UFP concentrations associated with brain tumours



# Results – Concentration Response

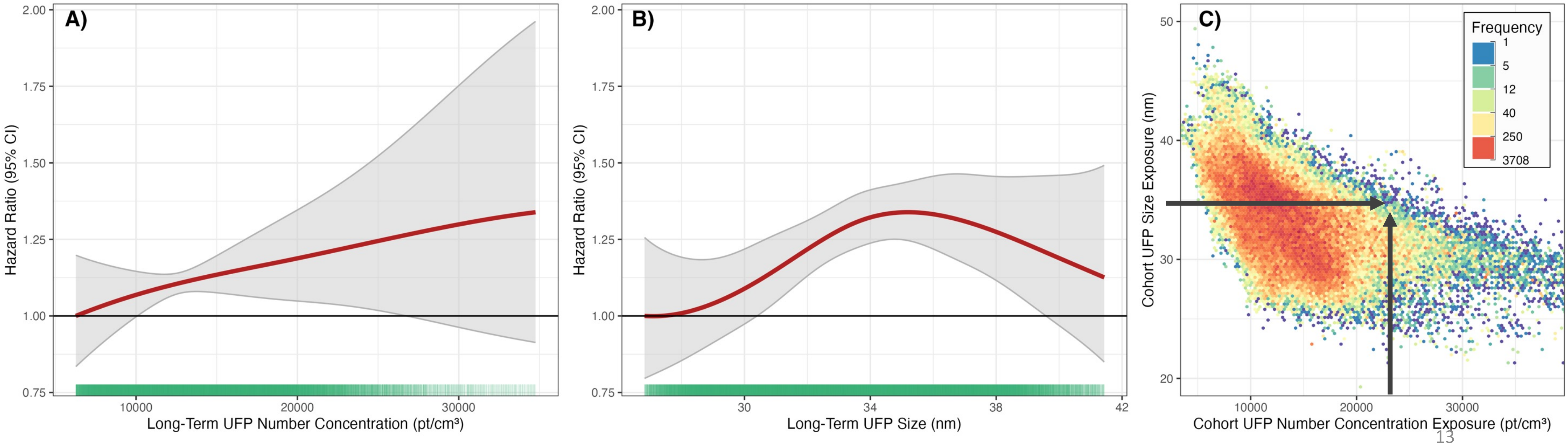


**A)** Elevated UFP concentrations associated with brain tumours
**B)** Larger UFPs associated with brain tumours

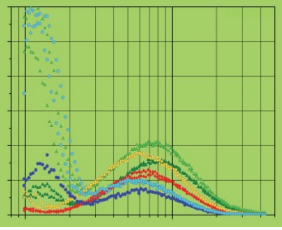


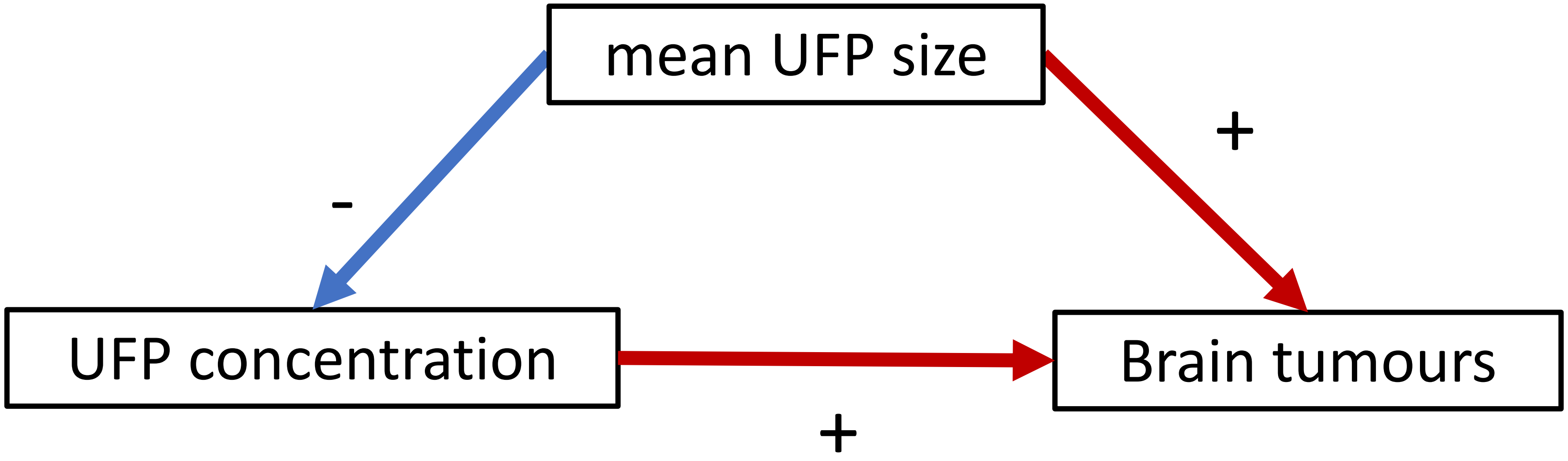
# Results – Concentration Response

**A)** Elevated UFP concentrations associated with brain tumours
**B)** Larger UFPs associated with brain tumours
**C)** Elevated UFP concentrations have smaller UFPs (e.g., fresh emissions)



# Results – UFP Size as a Confounder





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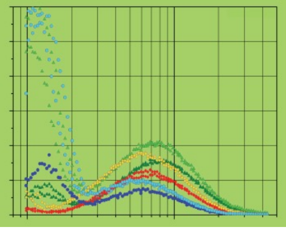

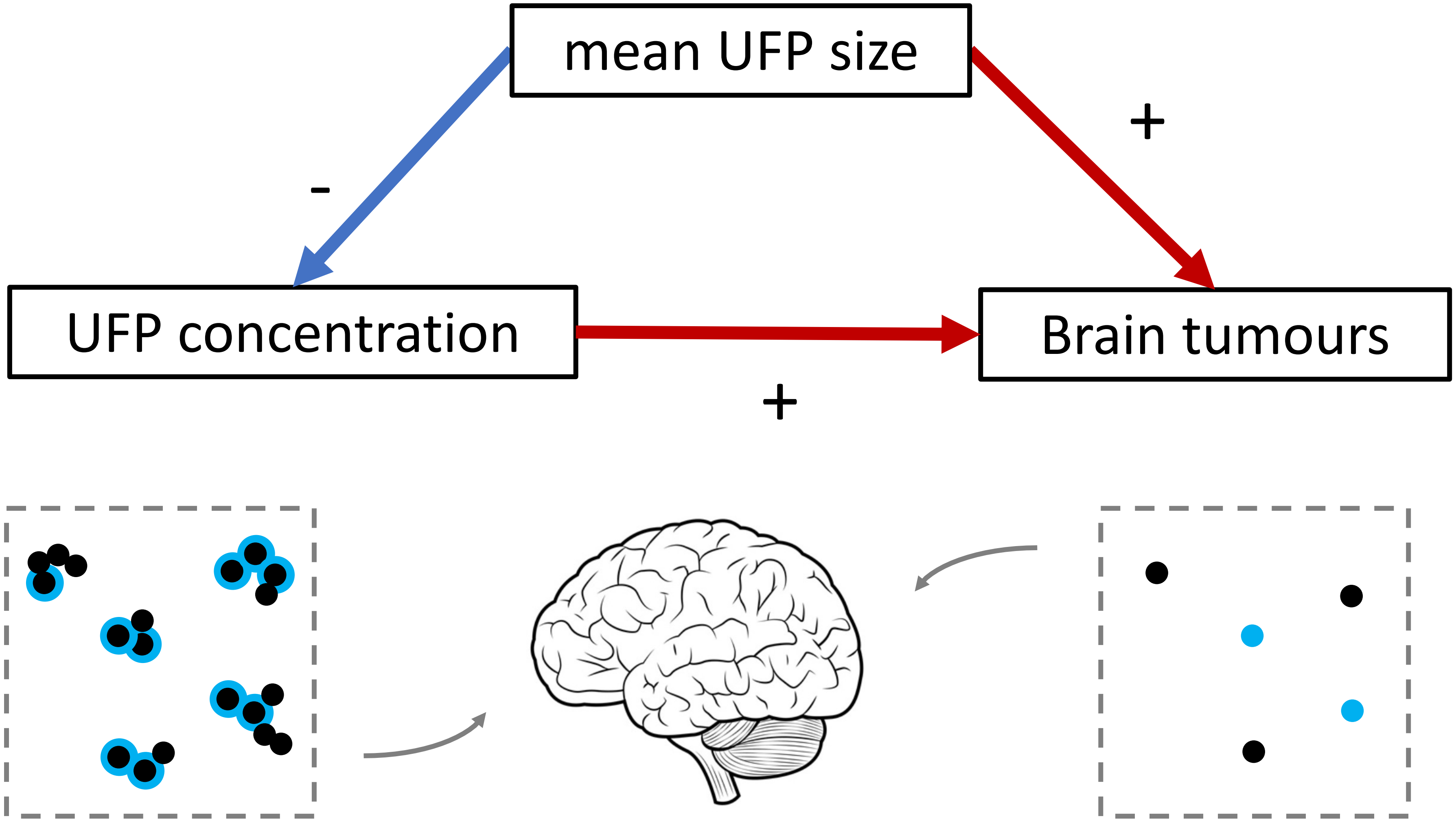

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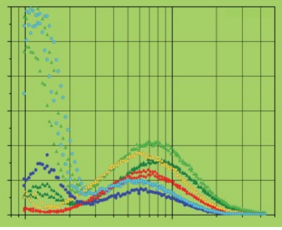
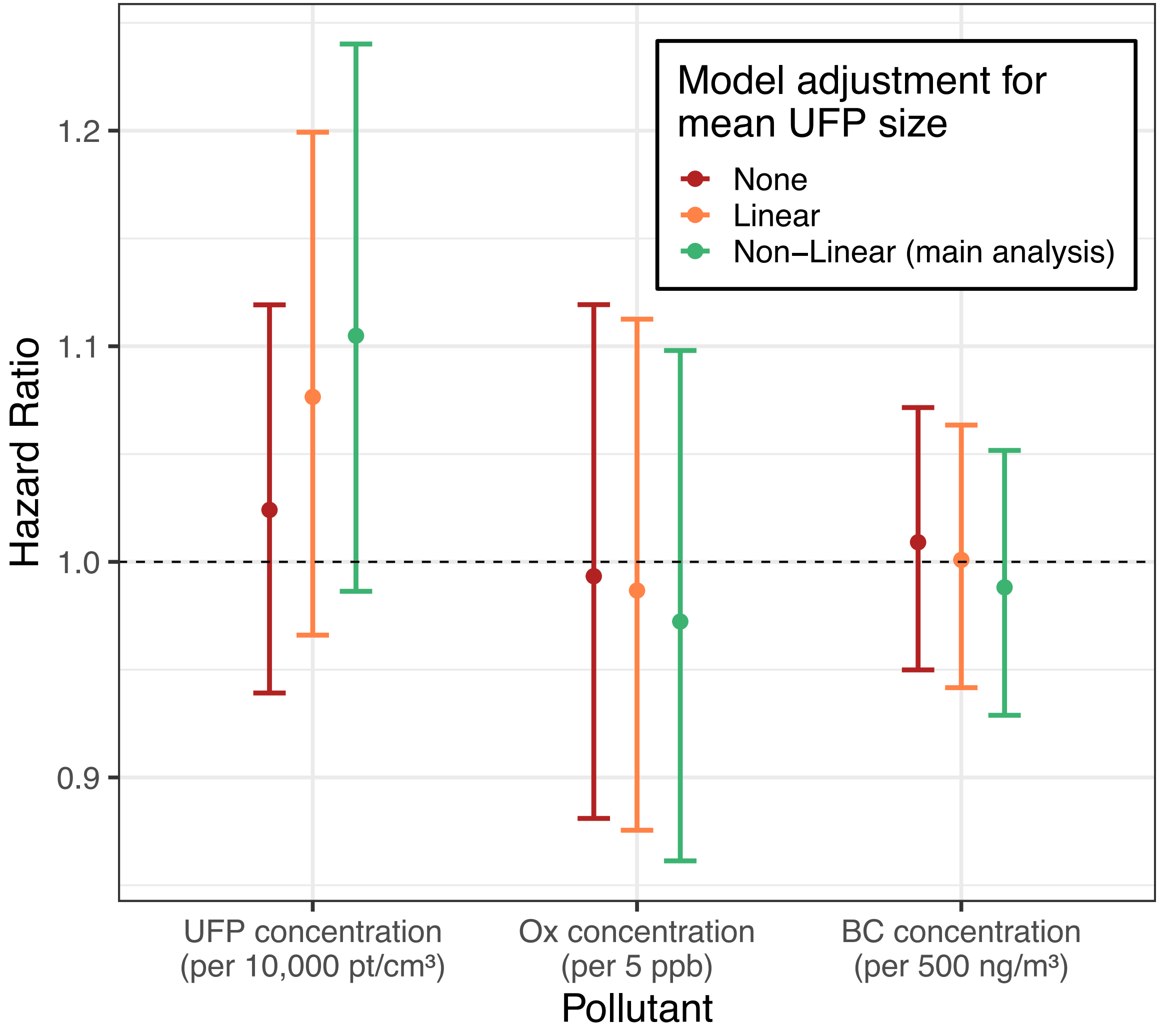


- Not all UFP mixtures are the same
- UFP size confounds the relationship between UFP number concentration and mortality
- Adjusting for UFP size helps control for variation in UFP mixtures

$$HR \sim UFP_{conc} + s(UFP_{size}) + \cdots$$
$$HR \sim UFP_{conc} + UFP_{size} + \cdots$$
$$HR \sim UFP_{conc} + \cdots$$



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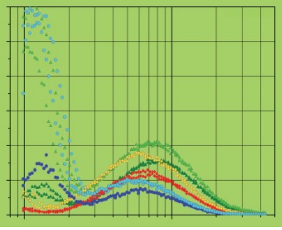
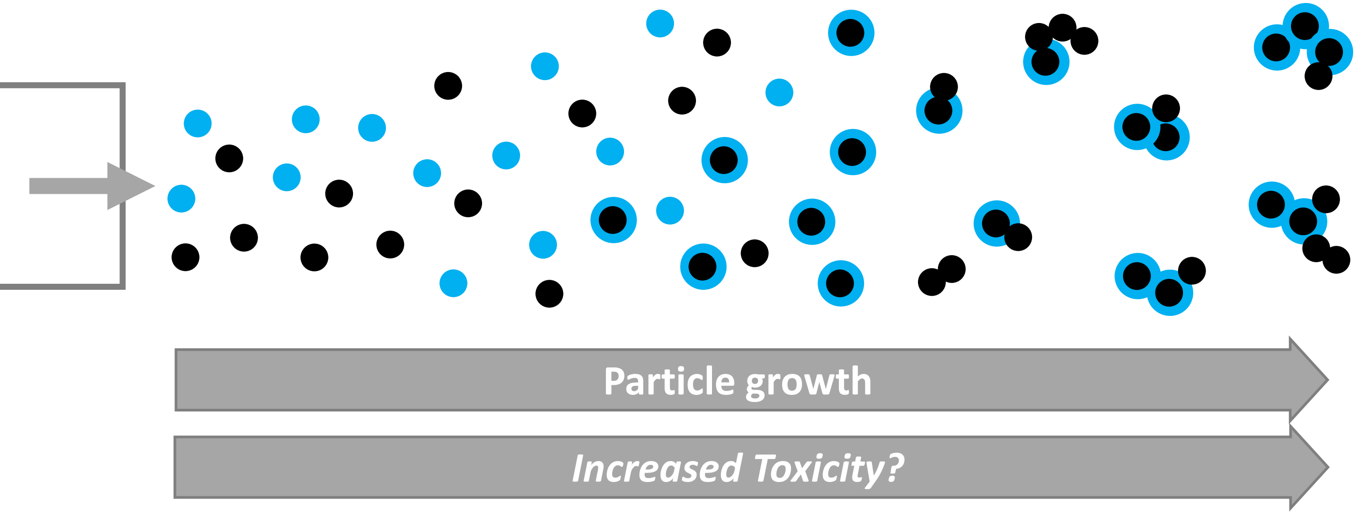
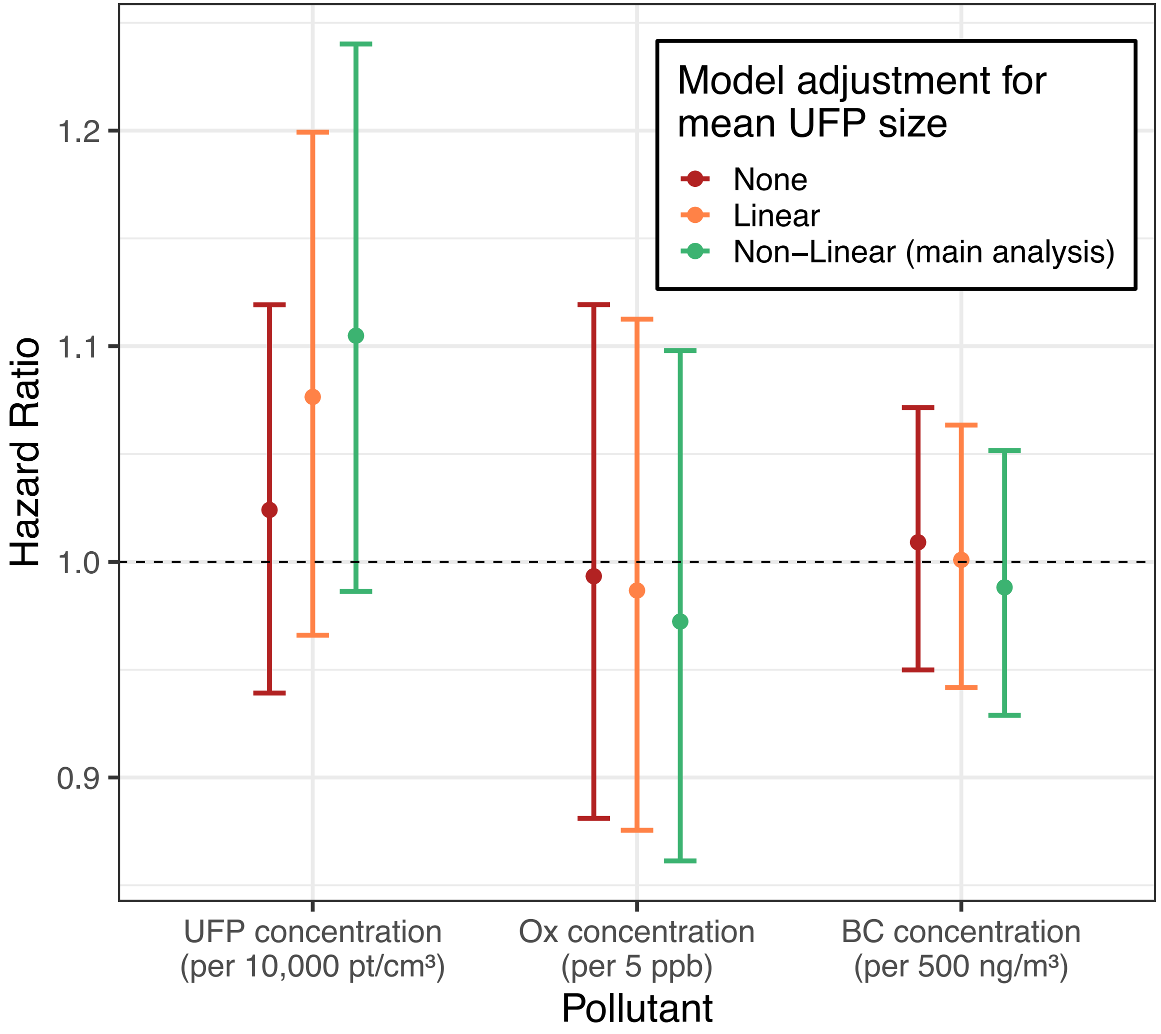
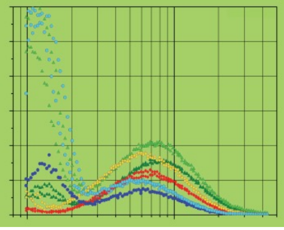


- Not all UFP mixtures are the same
- UFP size confounds the relationship between UFP number concentration and mortality
- Adjusting for UFP size helps control for variation in UFP mixtures
- As UFPs age, they interact with other particles and the environment
    - Particle size increases
    - Toxicity may increase



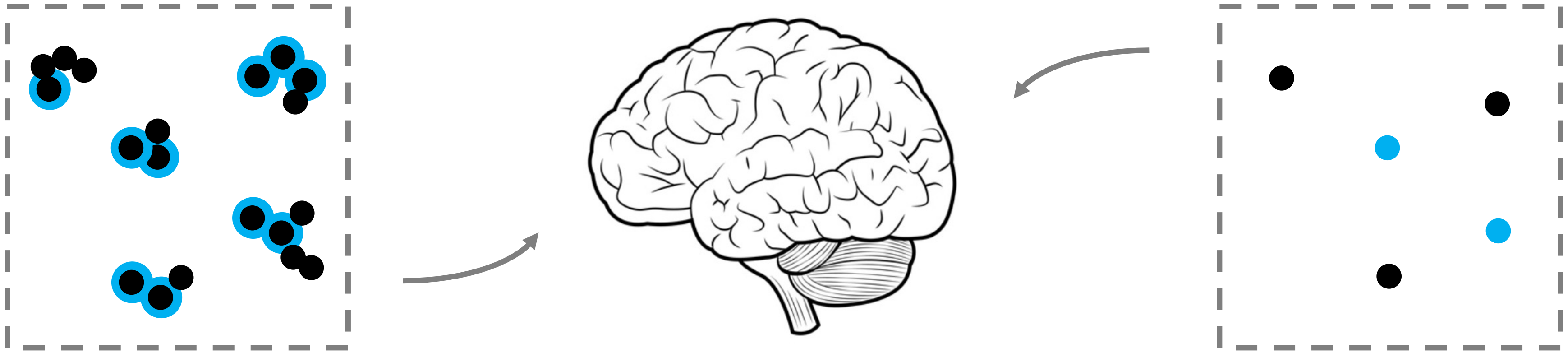
# “mean UFP size” in this study



- Measured by Partector 2 and DiscMini
  - Repeated, on-road sampling
- Modelled and predicted average annual mean UFP size
- Long-term exposure assigned at residential address
- Included in Cox PH model with UFP number concentration
- Very easy and inexpensive to include

# Summary

- Consistent associations between UFPs and incident brain tumours
- Important to adjust for UFP size
  - Different UFP mixtures may have different health effects
  - Within UFPs, the larger UFPs may be more harmful



# Acknowledgements

This work was supported through a ***Canadian Institutes of health Research (CIHR)*** Foundation Grant (Weichenthal PI) and by The United States ***Health Effects Institute (HEI)*** (Grant Number: 4976-RFA19-1/20-10), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award CR 83998101) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

Travel was supported in part by ***McGill University: Ely and Ezequiel Franco Fellowship in Epidemiology travel award.***

*Collaborators:*
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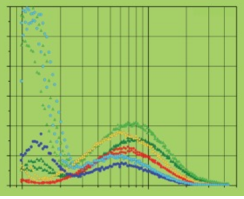

# Questions

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**Commentary**

**Fine Particulate Air Pollution and the "No-Multiple-Versions-of-Treatment" Assumption: Does Particle Composition Matter for Causal Inference?**

**Scott Weichenthal*, Susannah Ripley, and Jill Korsiak**

* Correspondence to Dr. Scott Weichenthal, Department of Epidemiology, Biostatistics and Occupational Health, School of Population and Global Health, McGill University, Montreal, QC H3A 1G1, Canada (e-mail: scott.weichenthal@mcgill.ca).

*Initially submitted February 9, 2022; accepted for publication October 27, 2022.*

Here we discuss possible violations of the "no-multiple-versions-of-treatment" assumption in studies of outdoor fine particulate air pollution (particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$)) owing to differences in particle composition, which in turn influence health. This assumption is part

Current Pollution Reports (2023) 9:590–601
https://doi.org/10.1007/s40726-023-00272-9

Check for updates

**Aging Effects on the Toxicity Alteration of Different Types of Organic Aerosols: A Review**

**Ruoyuan Lei[1] · Ziqian Wei[2] · Meijuan Chen[1] · Haifeng Meng[1] · Yun Wu[1] · Xinlei Ge[1]**

Accepted: 26 May 2023 / Published online: 16 June 2023
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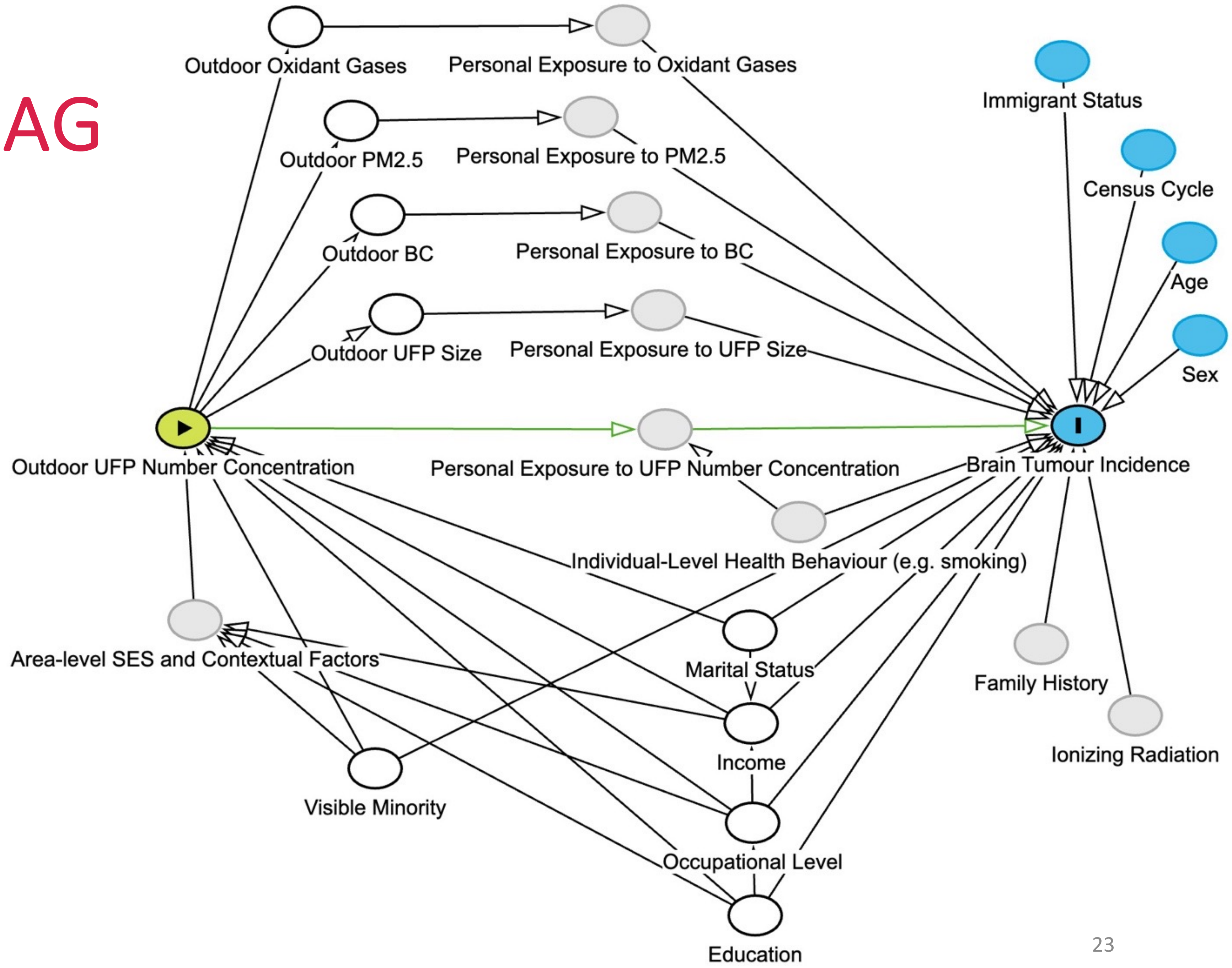
**Abstract**

Numerous epidemiological and toxicological studies have demonstrated the important role of secondary organic aerosol (SOA) in $PM_{2.5}$-related adverse health effects. Primary organic aerosol, volatile organic compounds (VOCs), and intermediate volatile organic compounds (IVOCs) can react with multiple atmospheric oxidants (e.g., $NO_x$ and free radicals) and generate SOA. The chemical composition of SOA varies with precursor identity and aging conditions; however, knowledge

# Methods - Cohort

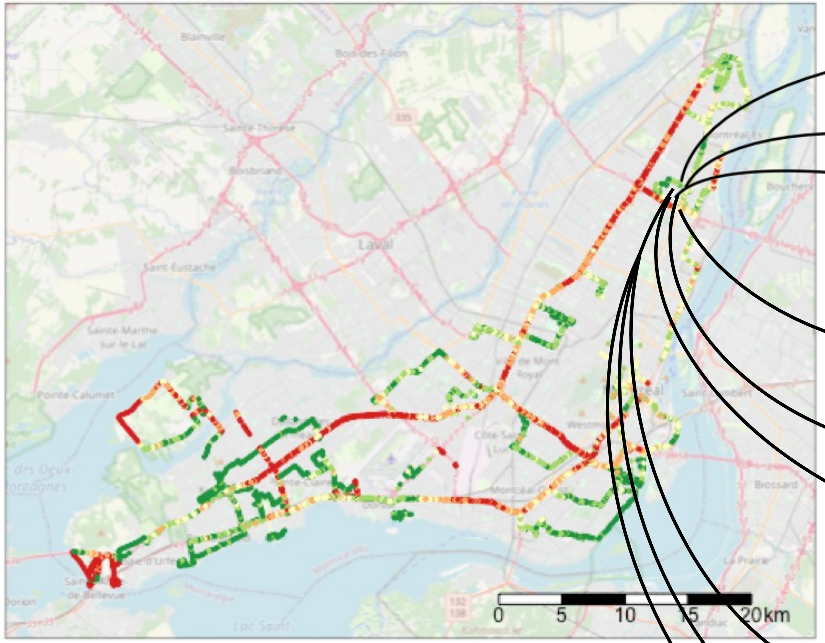
- Analytical cohort formed via linkage:
  - non-institutionalized respondents from the long-form Census (collected every 5-years on approximately 20% of households in Canada)
  - vital statistics (i.e., mortality records)
  - Canadian Cancer Registry (CCR – i.e., cancer incidence records)
  - postal codes from mailing addresses reported on annual income tax filings
- All participants were followed until 31st December 2015
  - except for residents of Montreal who were followed until 31st December 2010 due to lack of CCR data from Quebec
- ICD-10 codes for malignant neoplasms of the brain: C71·0–C71·9

# Methods
# – Detailed DAG



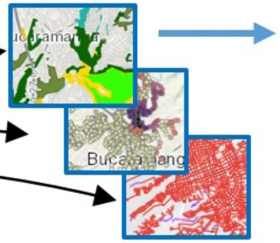
# Exposure Models from Mobile Monitoring

## 1. Measure




## 2. Model

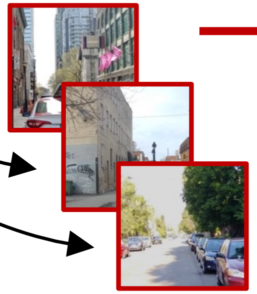
**Land Use Parameters**



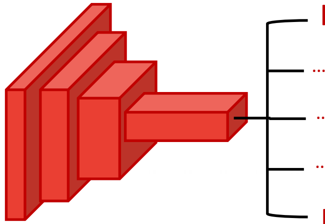
**Land Use Regression (LUR)**

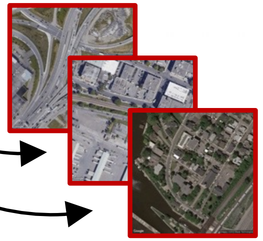
$$y = \beta_0 + \beta_1 x_1 + \ldots + \beta_j x_j$$

**Images**

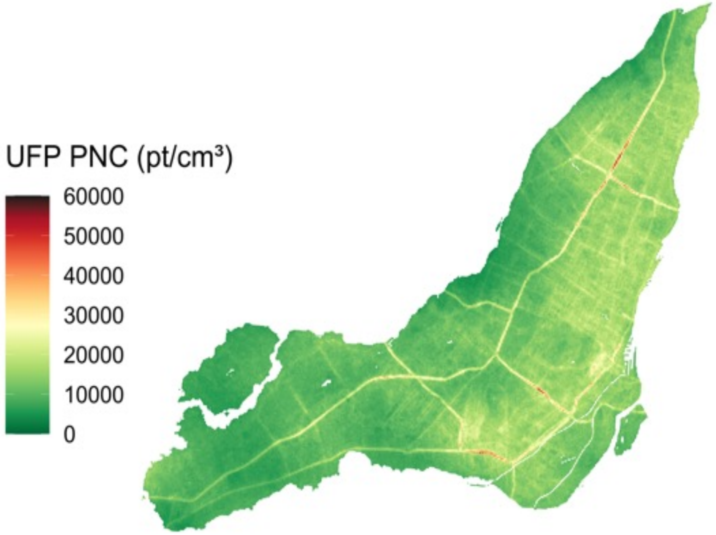


**Convolutional Neural Network (CNN)**

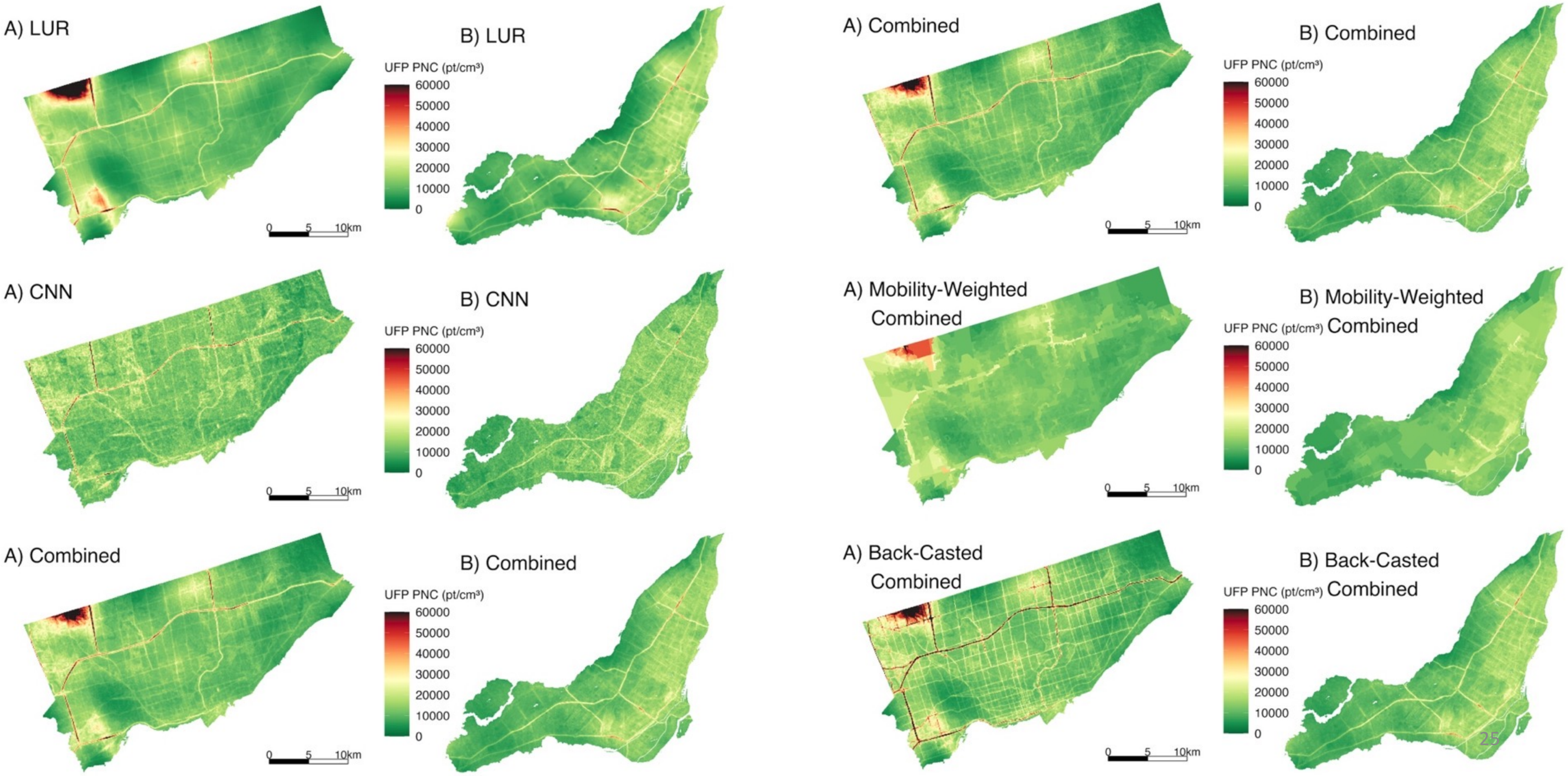


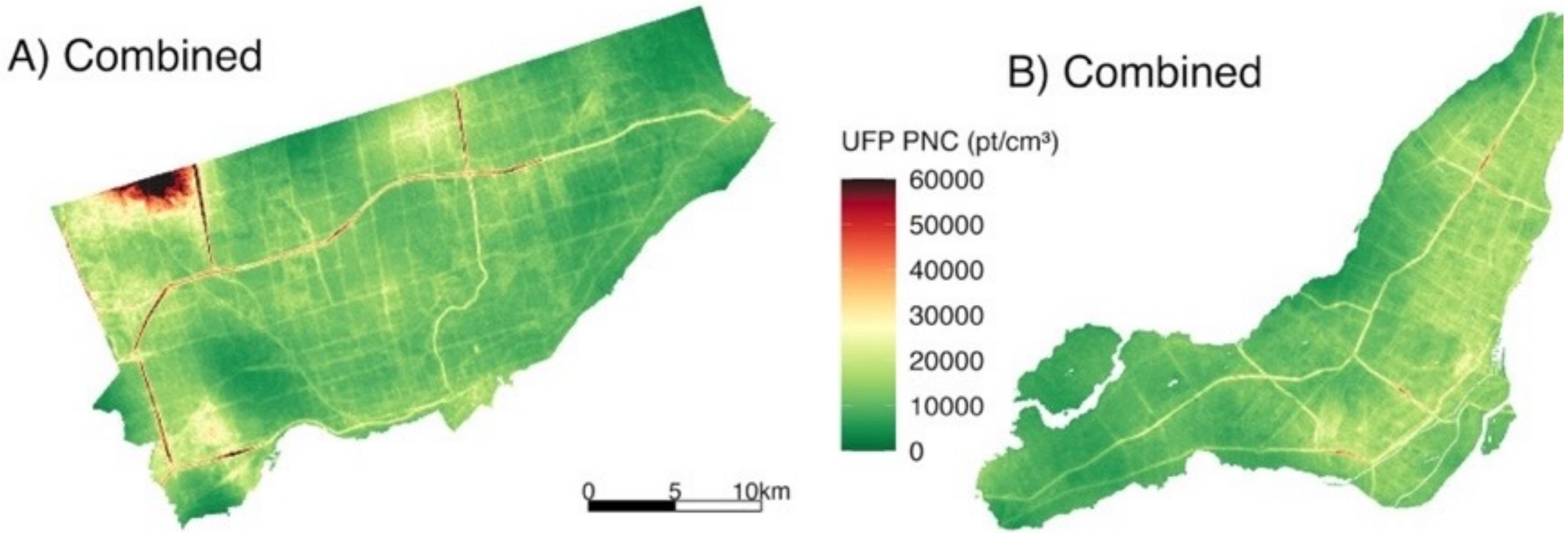
## 3. Predict



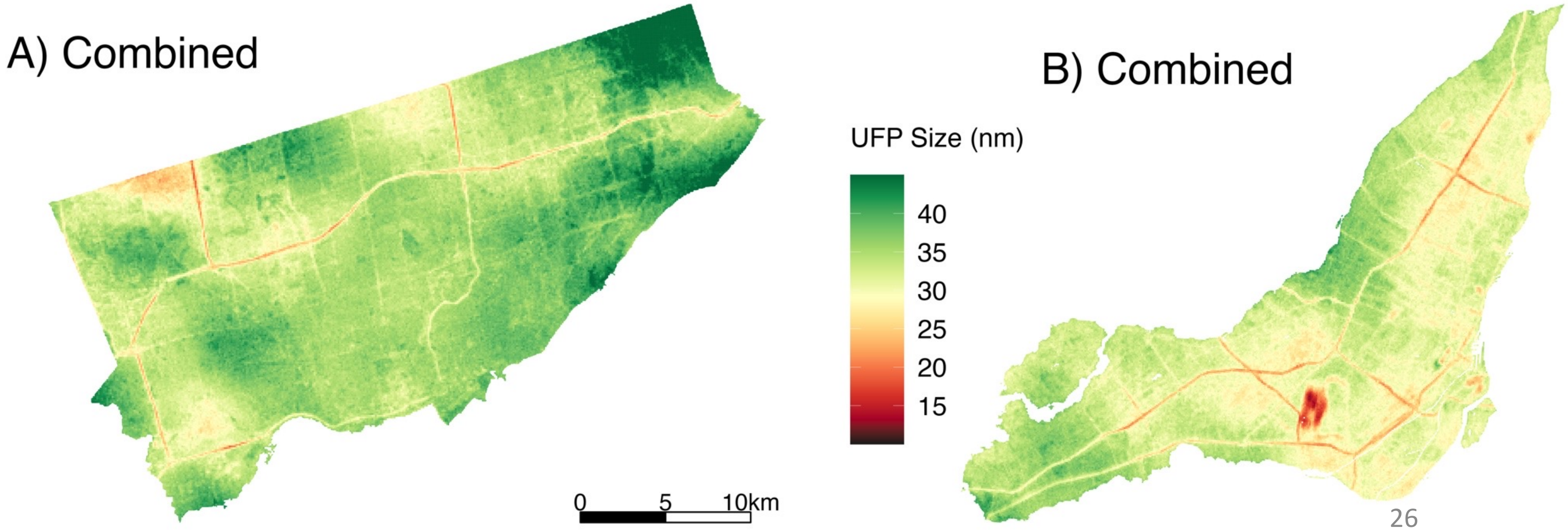
# Methods – Exposure Model Surfaces



UFP PNC




mean UFP size



# Results – Descriptive Statistics

| Statistic | UFP Number Concentration | Mean UFP size | BC Mass Concentration | Oxidant Gas Concentration | $PM_{2.5}$ Mass Concentration |
|---|---|---|---|---|---|
| Minimum | 3242 pt/cm$^3$ | 17.8 nm | 114 ng/m$^3$ | 10.0 ppb | 1.4 μg/m$^3$ |
| Maximum | 162,932 pt/cm$^3$ | 49.4 nm | 5264 ng/m$^3$ | 56.1 ppb | 18.4 μg/m$^3$ |
| Mean | 13,982 pt/cm$^3$ | 33.22 nm | 1109 ng/m$^3$ | 35.16 ppb | 10.16 μg/m$^3$ |
| SD | 6229 | 3.43 | 552 | 3.66 | 1.56 |
| **Correlation with:** | | | | | |
| UFP Number Concentration | *1* | *-0.54* | *0.38* | *0.17* | *0.10* |
| Mean UFP Size | *-0.54* | *1* | *0.09* | *0.22* | *0.17* |
| BC Mass Concentration | *0.38* | *0.09* | *1* | *0.57* | *0.42* |
| Oxidant Gases | *0.17* | *0.22* | *0.57* | *1* | *0.51* |
| $PM_{2.5}$ Mass Concentration | *0.10* | *0.17* | *0.42* | *0.51* | *1* |

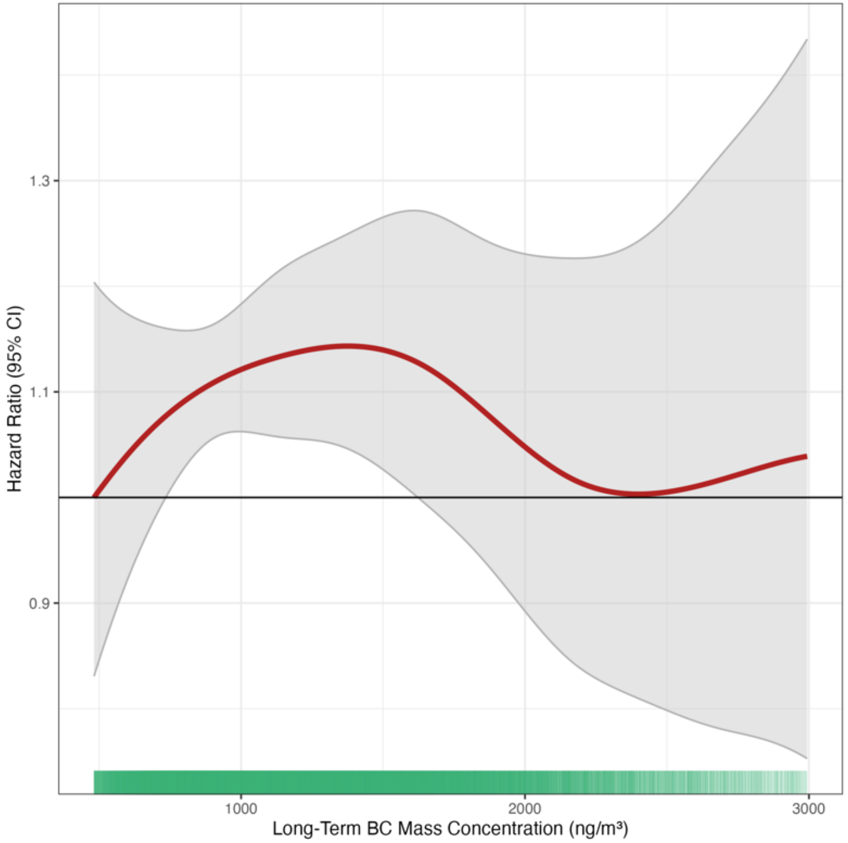
# Results – All Exposure Models

- Main analysis used back-cast combined exposure model with 3-year moving average exposure window (*italics in table*)
  - exposures updated for residential mobility
- Consistent associations between UFP exposure and brain tumour incidence
  - consistent across various exposure models and windows
- Models stratified by age, sex, immigrant status, and census cycle
- Models adjusted for education, occupation, income, marital status, visible minority status, and exposure to other pollutants ($PM_{2.5}$, UFP concentration, UFP size, BC, Ox)

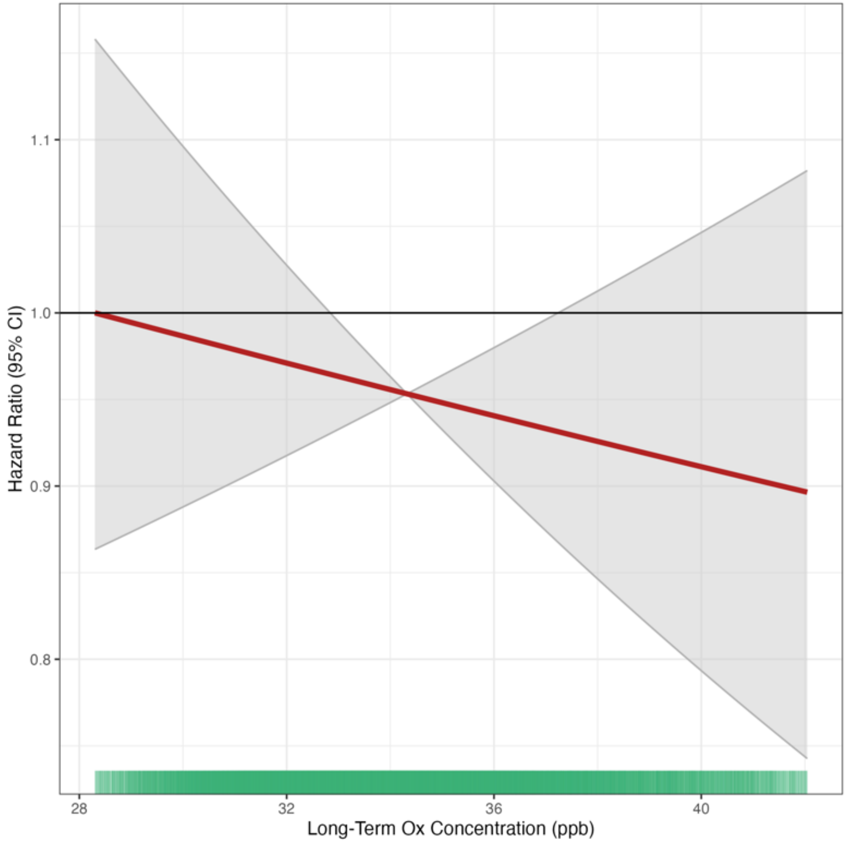
| Pollutant | 3 Year Exposure Window | | | | 10 Year Exposure Window | |
|---|---|---|---|---|---|---|
| | ***Back-cast Combined Model*** | **2020 Combined Model** | **2020 LUR Model** | **2020 CNN Model** | **Back-cast Combined Model** | **2020 Combined Model** |
| UFP (per 10,000pt/cm$^3$) | *1.105 (0.986, 1.240)* | 1.153 (1.004, 1.325) | 1.082 (0.998, 1.174) | 1.026 (0.851, 1.233) | 1.106 (0.966, 1.267) | 1.183 (1.000, 1.397) |
| BC (500 ng/m$^3$) | *0.988 (0.929, 1.052)* | 0.984 (0.901, 1.074) | 0.992 (0.920, 1.070) | 1.014 (0.918, 1.121) | 0.990 (0.916, 1.069) | 0.988 (0.883, 1.104) |
| Ox (5 ppb) | *0.972 (0.861, 1.098)* | 0.967 (0.856, 1.092) | NA | NA | 1.089 (0.927, 1.280) | 1.082 (0.920, 1.273) |

# Results – Additional Response Curves

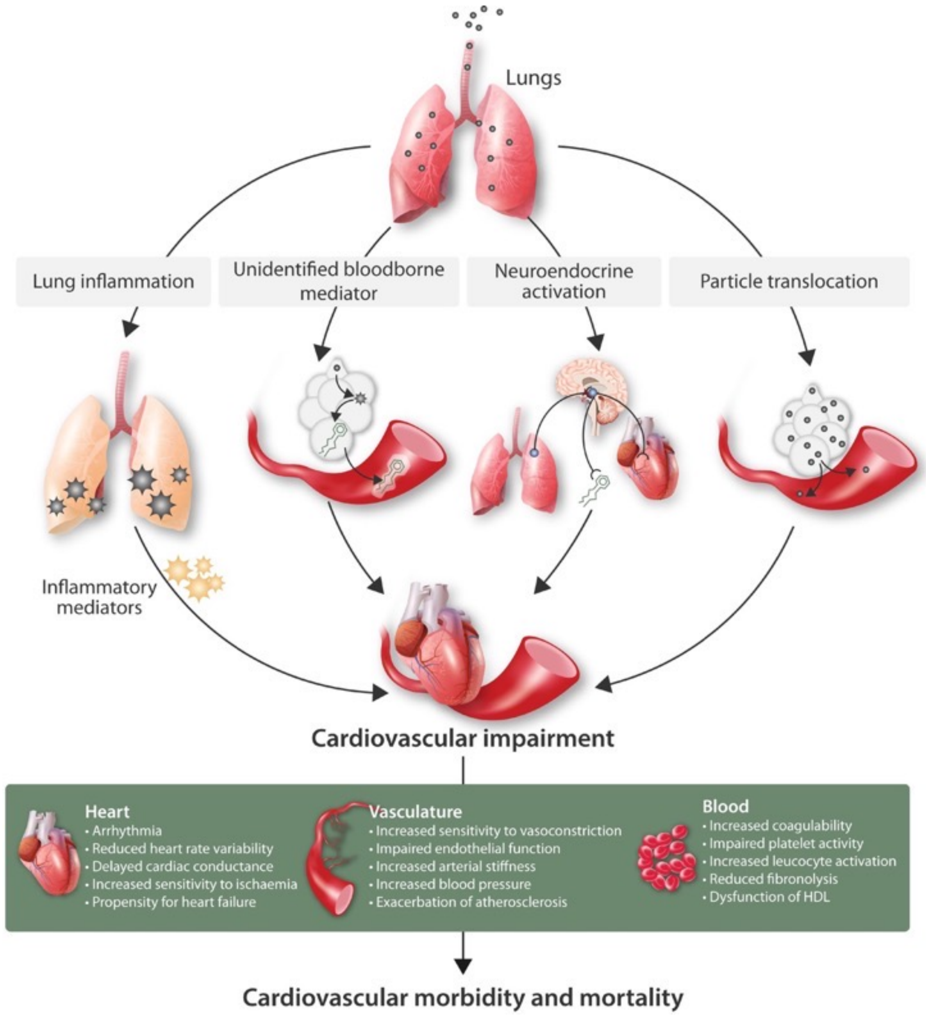
## Black Carbon

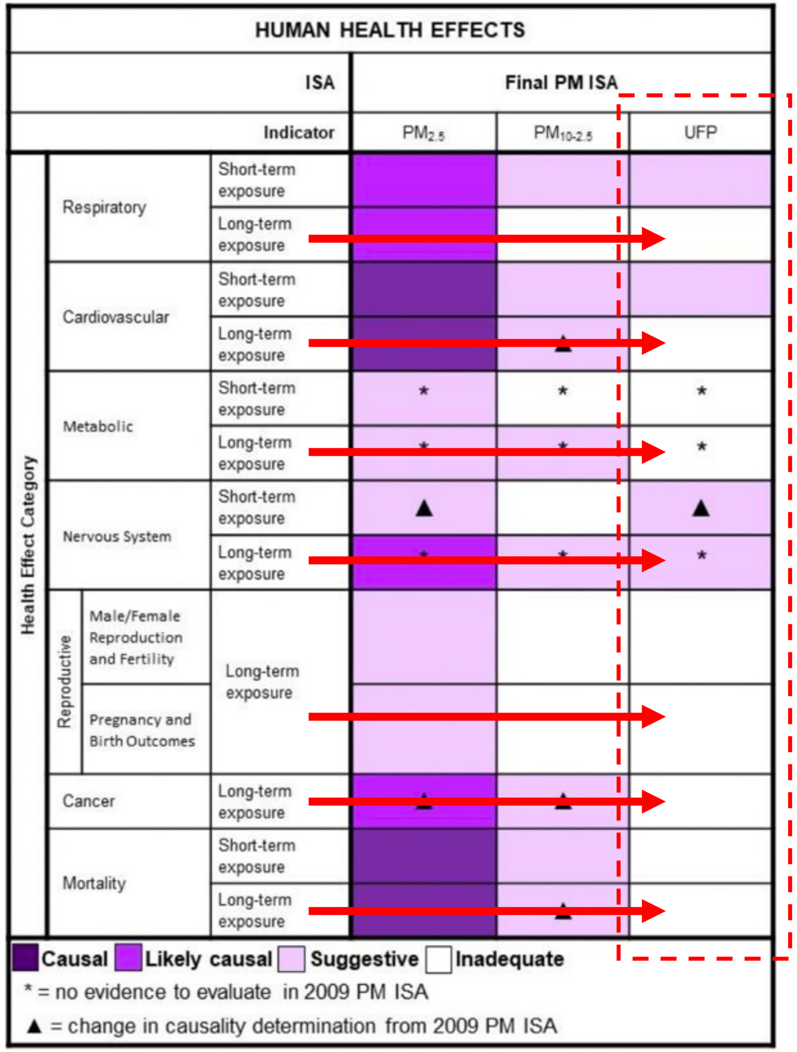



## Oxidant Gases



# UFPs and Health – Long-Term Exposure




*Mark R Miller, David E Newby, Air pollution and cardiovascular disease: car sick, Cardiovascular Research, Volume 116, Issue 2, 1 February 2020, Pages 279–294, https://doi.org/10.1093/cvr/cvz228*

*U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-19/188, 2019*

# Exposure Model Development

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ELSEVIER

Full length article

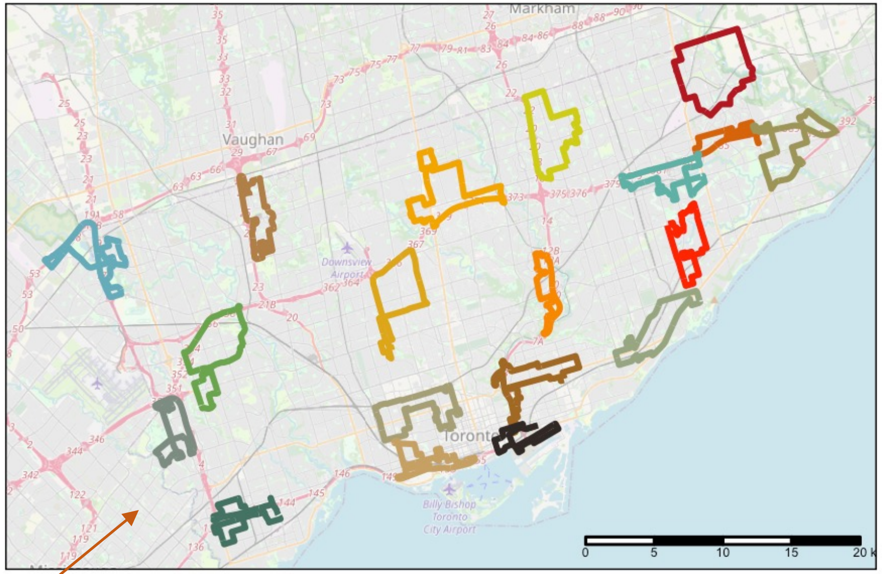
## Predicting spatial variations in annual average outdoor ultrafine particle concentrations in Montreal and Toronto, Canada: Integrating land use regression and deep learning models

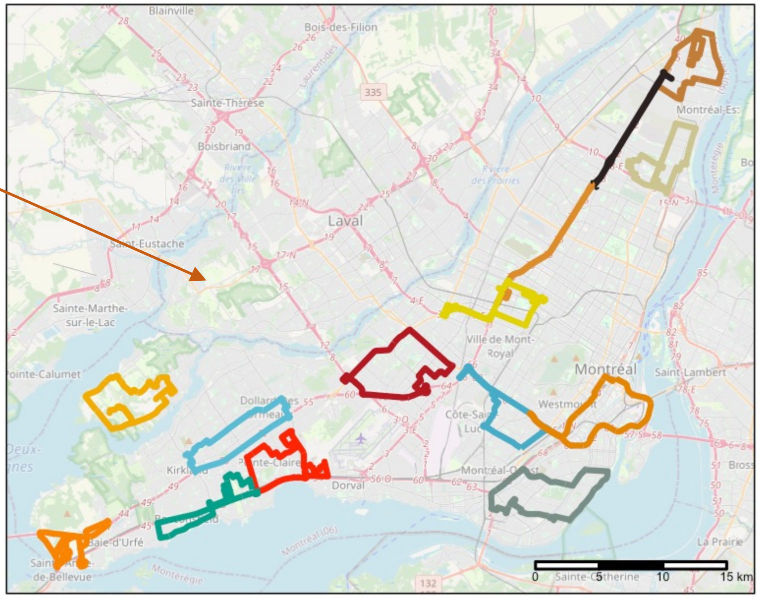
Marshall Lloyd [a], Arman Ganji [b], Junshi Xu [b], Alessya Venuta [a], Leora Simon [a], Mingqian Zhang [b], Milad Saeedi [b], Shoma Yamanouchi [b], Joshua Apte [c,d], Kris Hong [a], Marianne Hatzopoulou [b], Scott Weichenthal [a,*]

[a] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Québec H3A 1G1, Canada
[b] Department of Civil and Mineral Engineering, University of Toronto, Toronto, Ontario M5S 1A4, Canada
[c] Department of Civil and Environmental Engineering, University of California at Berkeley, Berkeley, CA 94720, United States
[d] School of Public Health, University of California, Berkeley, CA 94720, United States

# Data Sources and Measures

| | Outcome |
|---|---|
| Measure | ***-UFP number concentration***<br>***-mean UFP diameter (size)*** |
| Data Source | -Mobile Monitoring<br>(sample every 1s) |
| Details | -Representative sample of annual average<br>-All days of the week<br>-Between 7am and 11pm<br>-In all 4 seasons<br>-Through variety of land use |

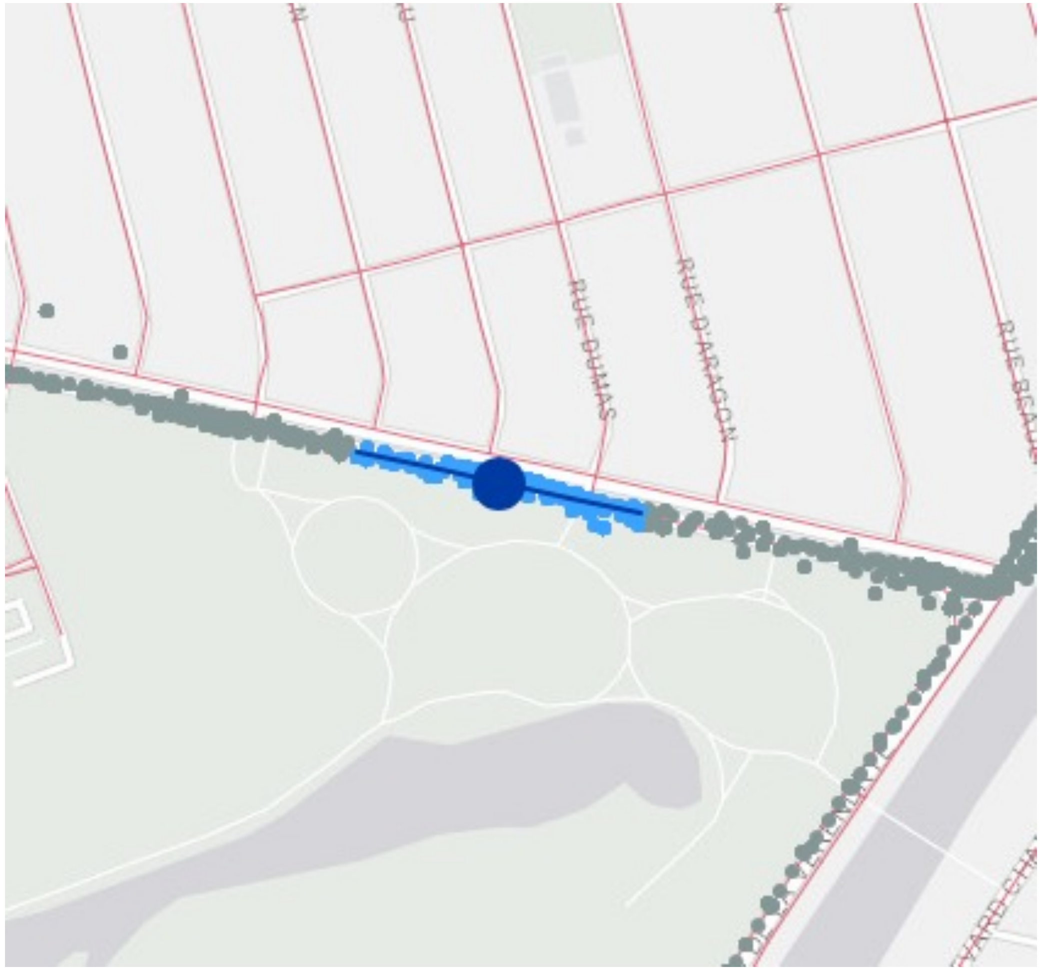



# Data Sources and Measures

| | Outcome |
|---|---|
| Measure | ***-UFP number concentration***<br>***-mean UFP diameter (size)*** |
| Data Source | -Mobile Monitoring<br>(sample every 1s) |
| Details | -Representative sample of annual average<br>-All days of the week<br>-Between 7am and 11pm<br>-In all 4 seasons<br>-Through variety of land use |

***Unit of Analysis = 100 m road segment***



# Data Sources and Measures

| | Outcome | Predictors |
|---|---|---|
| Measure | ***-UFP number concentration*** <br> ***-mean UFP diameter (size)*** | ***-Land use/traffic (LUR)*** <br><br> ***-Satellite view images (CNN)*** |
| Data Source | -Mobile Monitoring <br> (sample every 1s) | -Geographical Information Systems <br><br> -Google Maps satellite view |
| Details | -Representative sample of annual average <br> -All days of the week <br> -Between 7am and 11pm <br> -In all 4 seasons <br> -Through variety of land use | -land use/traffic examples: <br> -total length of roads within 100 m <br> -distance to airport <br> -mean $NO_x$ traffic emissions within 300 m <br><br> -2x satellite zooms |


# Data Sources and Measures

| | Outcome | Predictors | Other Covariates |
|---|---|---|---|
| Measure | ***-UFP number concentration***<br>***-mean UFP diameter (size)*** | ***-Land use/traffic (LUR)***<br><br>***-Satellite view images (CNN)*** | ***Outdoor weather***<br><br>***Position (latitude, longitude)*** |
| Data Source | -Mobile monitoring<br>(sample every 1s) | -Geographical Information Systems<br><br>-Google Maps satellite view | -Airport Automated Surface Observing System<br><br>-Mobile monitoring (GPS) |
| Details | -Representative sample of annual average<br>-All days of the week<br>-Between 7am and 11pm<br>-In all 4 seasons<br>-Through variety of land use | -land use/traffic examples:<br>-total length of roads within 100 m<br>-distance to airport<br>-mean $NO_x$ traffic emissions within 300 m<br><br>-2x satellite zooms | Weather:<br>-temperature<br>-relative humidity<br>-wind speed |

# Model Development

## A. Land Use Regression

A1. Select candidate variables ($\beta_k$ 95% CI excludes null)

$$y_i = \beta_0 + \beta_k x_{ki} + \beta_T x_{Ti} + \beta_H x_{Hi} + \beta_W x_{Wi} + \epsilon_i$$

A2. Remove variable from pairs of highly correlated candidate variables (cor > 0.7)

A3. Train Generalized Additive Model (GAM) using selected variables (Restricted Maximum Likelihood)

$$\boldsymbol{y_i = \beta_0 + \sum_j f_j(x_{ji}) + f_{j+1}(x_{LATi}, x_{LONi}) + \epsilon_i}$$

**Model remaining spatial dependencies**

where:

$\epsilon_i \sim N(0, \sigma^2)$

$f_j$ are thin plate splines (tps) on selected variables and weather (max 3 basis functions)

$f_{j+1}$ is tensor product of marginal tps on latitude and longitude (max 50 basis functions each)

A4. Generate predictions and evaluate model in test data (15%)

# Model Development

## A. Land Use Regression

$$y_i = \beta_0 + \sum_j f_j(x_{ji}) + f_{j+1}(x_{LATi}, x_{LONi}) + \epsilon_i$$

## B. Convolutional Neural Network

B1i. Train *satellite* CNN model on *satellite* view images

B2. Select CNN model weights based on MSE

B3. Combine CNN prediction with temporal adjustment in test data (15%)

$$\boldsymbol{y_i = \beta_0 + \beta_1 x_{CNN.SATi} + \beta_T x_{Ti} + \beta_H x_{Hi} + \beta_W x_{Wi} + \epsilon_i}$$

where:

$\epsilon_i \sim N(0, \sigma^2)$

B4. Generate predictions and evaluate model in test data (15%)

# Model Development

## A. Land Use Regression

$$y_i = \beta_0 + \sum_j f_j(x_{ji}) + f_{j+1}(x_{LATi}, x_{LONi}) + \epsilon_i$$

## B. Convolutional Neural Network

$$y_i = \beta_0 + \beta_1 x_{CNN.SATi} + \beta_2 x_{CNN.STRi} + \beta_T x_{Ti} + \beta_H x_{Hi} + \beta_W x_{Wi} + \epsilon_i$$

## C. Final Combined Model (for use in Obj 2 and 3)

C1. Combine predictions from LUR and CNN in validation data

$$\boldsymbol{y_i = \beta_0 + \beta_1 x_{LURi} + \beta_2 x_{CNNi} + \epsilon_i}$$

where:

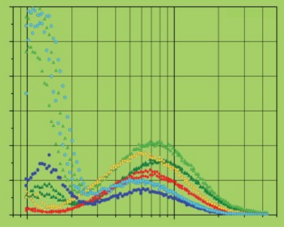
$$\epsilon_i \sim N(0, \sigma^2)$$

C2. Evaluate in test set

C3. Generate predictions throughout Montreal and Toronto

C4. Apply back-casting and mobility weighting

# Oxidant Gases



Exposure to oxidant gases (i.e., the combined oxidant capacity of $NO_2$ and $O_3$) was calculated using weights based on their approximate redox potential:

$$O_x = \frac{(1.07 * NO_2) + (2.075 * O_3)}{3.145}$$

# Results – Mortality

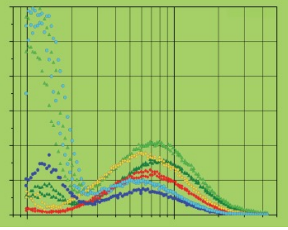
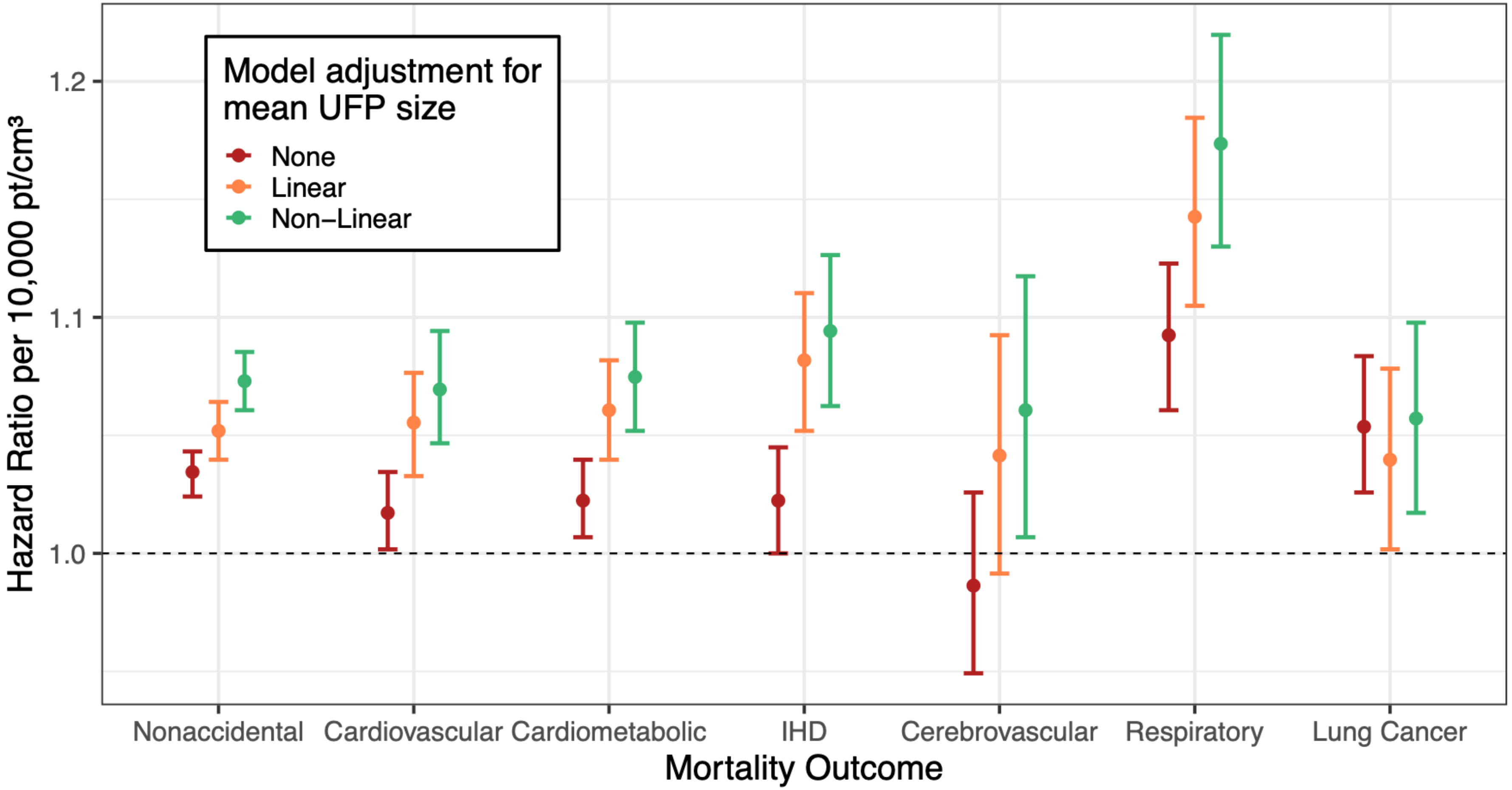
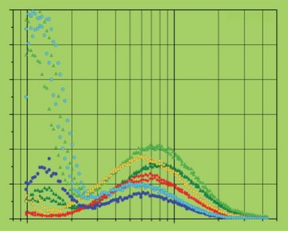
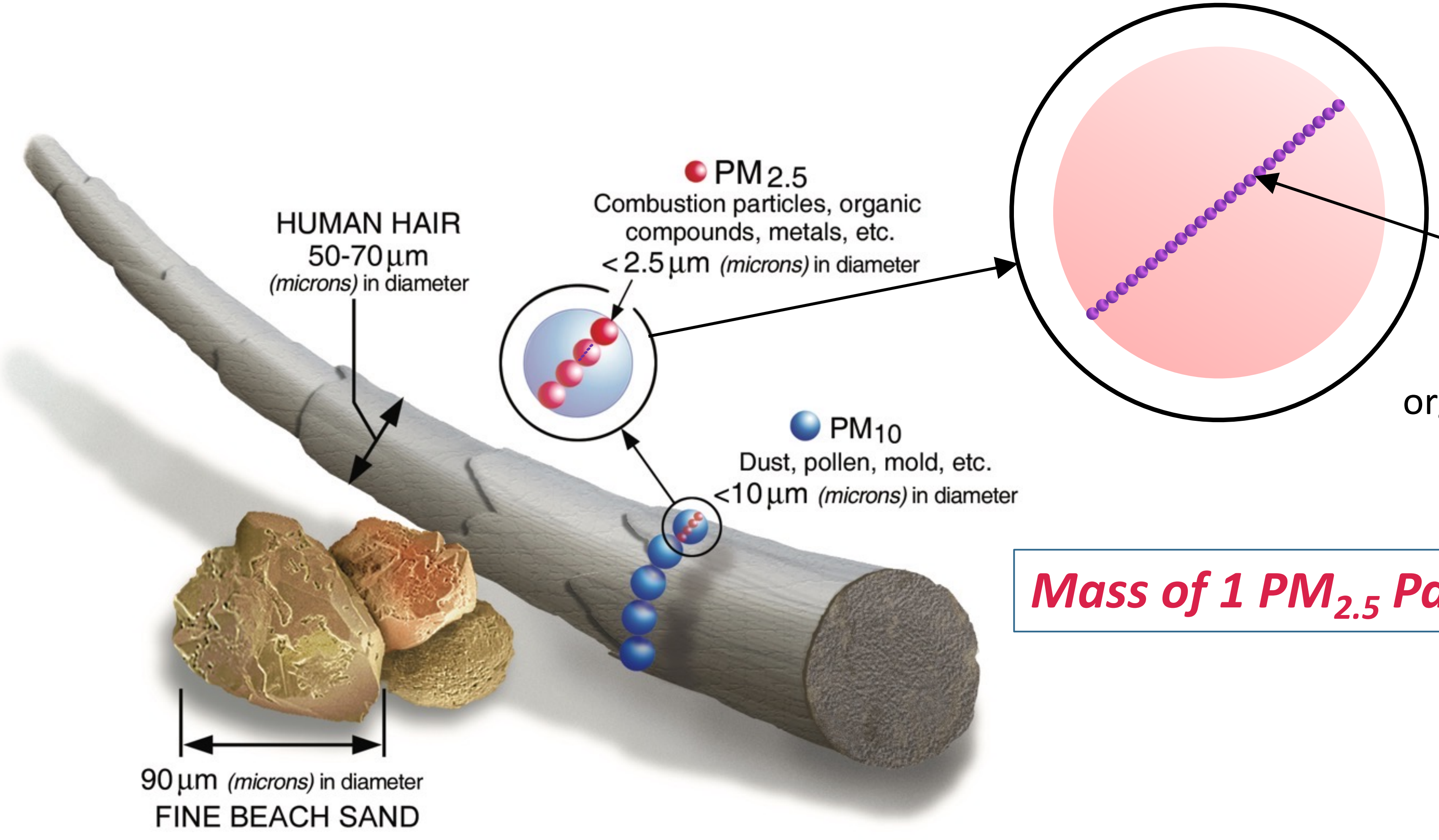


**Figure 2.** Hazard ratios (95% CI) for a 10,000 particle/cm[3] increase in long-term average outdoor UFP number concentration and mortality with and without adjustment for mean UFP size. All models are adjusted for socio-demographic variables, mass concentrations of $PM_{2.5}$ and black carbon, and $O_x$.



# Outdoor Ultrafine Particles (UFPs)






UFP (aka $PM_{0.1}$, nanoparticles)

Combustion particles (liquid and solid), organic compounds, metals, nucleation, etc.

< 0.1 µm in diameter (100 nm)

***Mass of 1 $PM_{2.5}$ Particle ≈ Mass of 15,000 UFPs***

*U.S. EPA (https://www.epa.gov/pm-pollution/particulate-matter-pm-basics)*