The external exposome as a method for cumulative impact assessment

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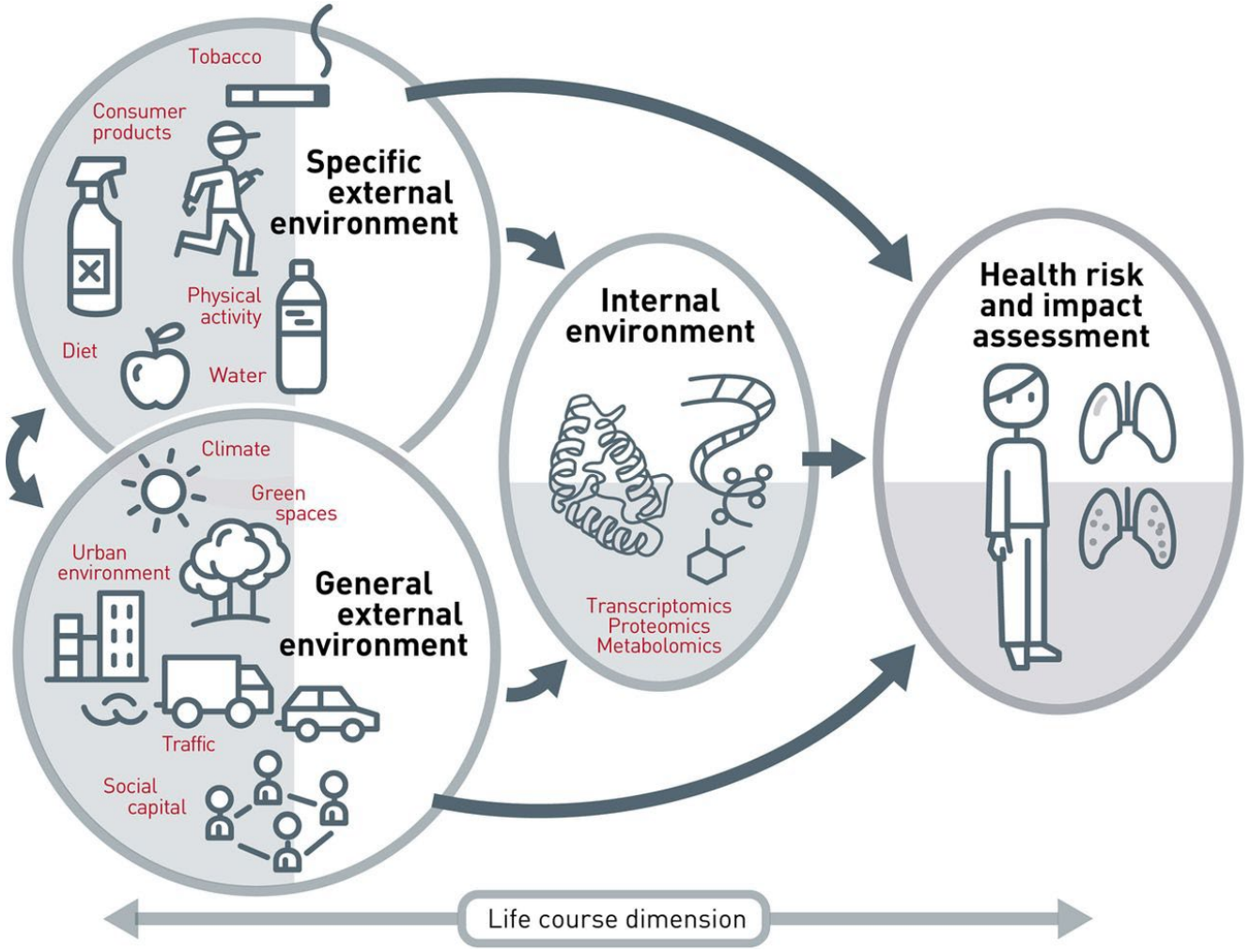
The exposome

- First conceptualized by Chris Wild in 2005 as the totality of human environmental (non genetic) exposure from conception onwards

- Requires accurate and reliable exposure assessment of many exposures over decades



Vrijheid et al. Thorax, 2014; 69:876-878

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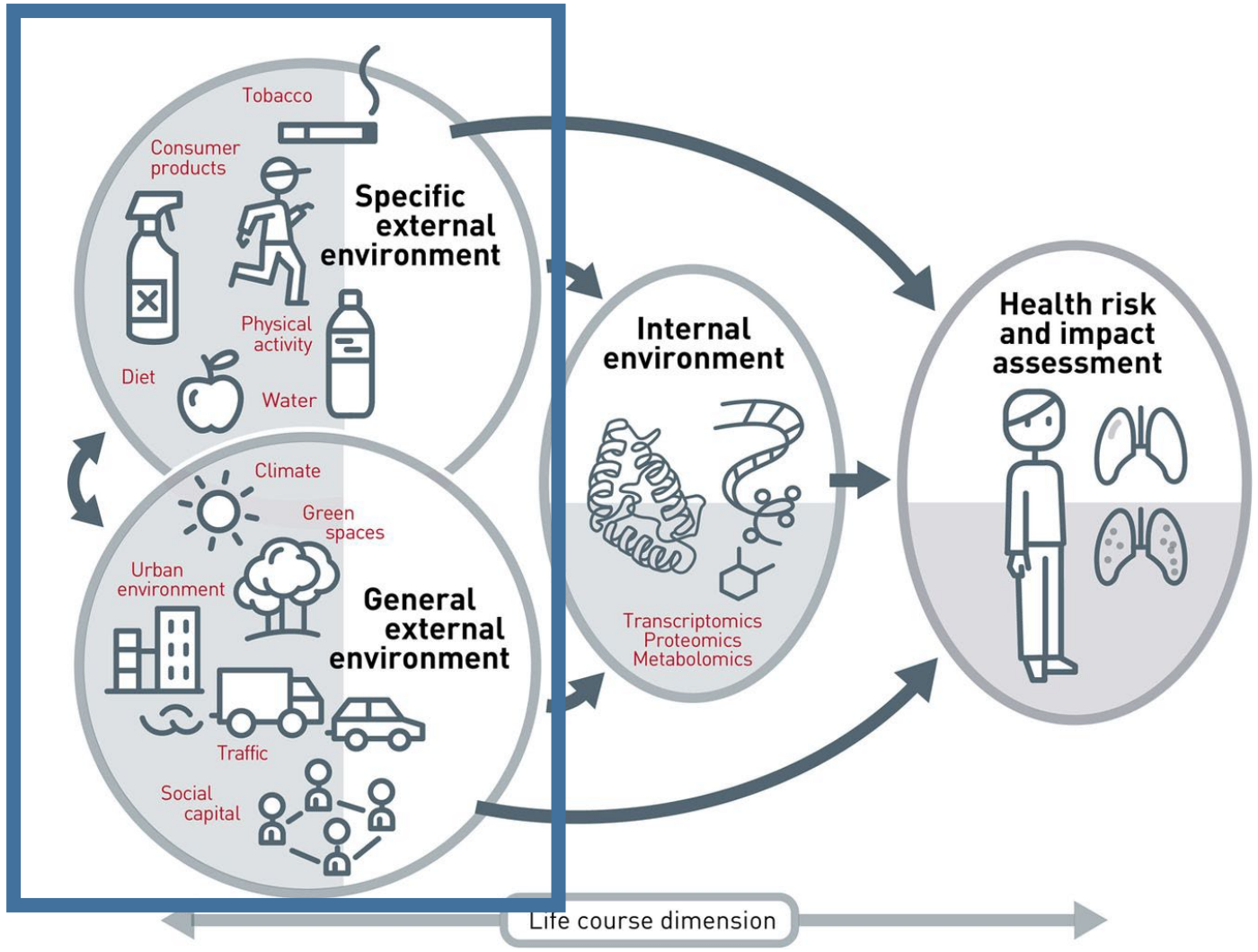

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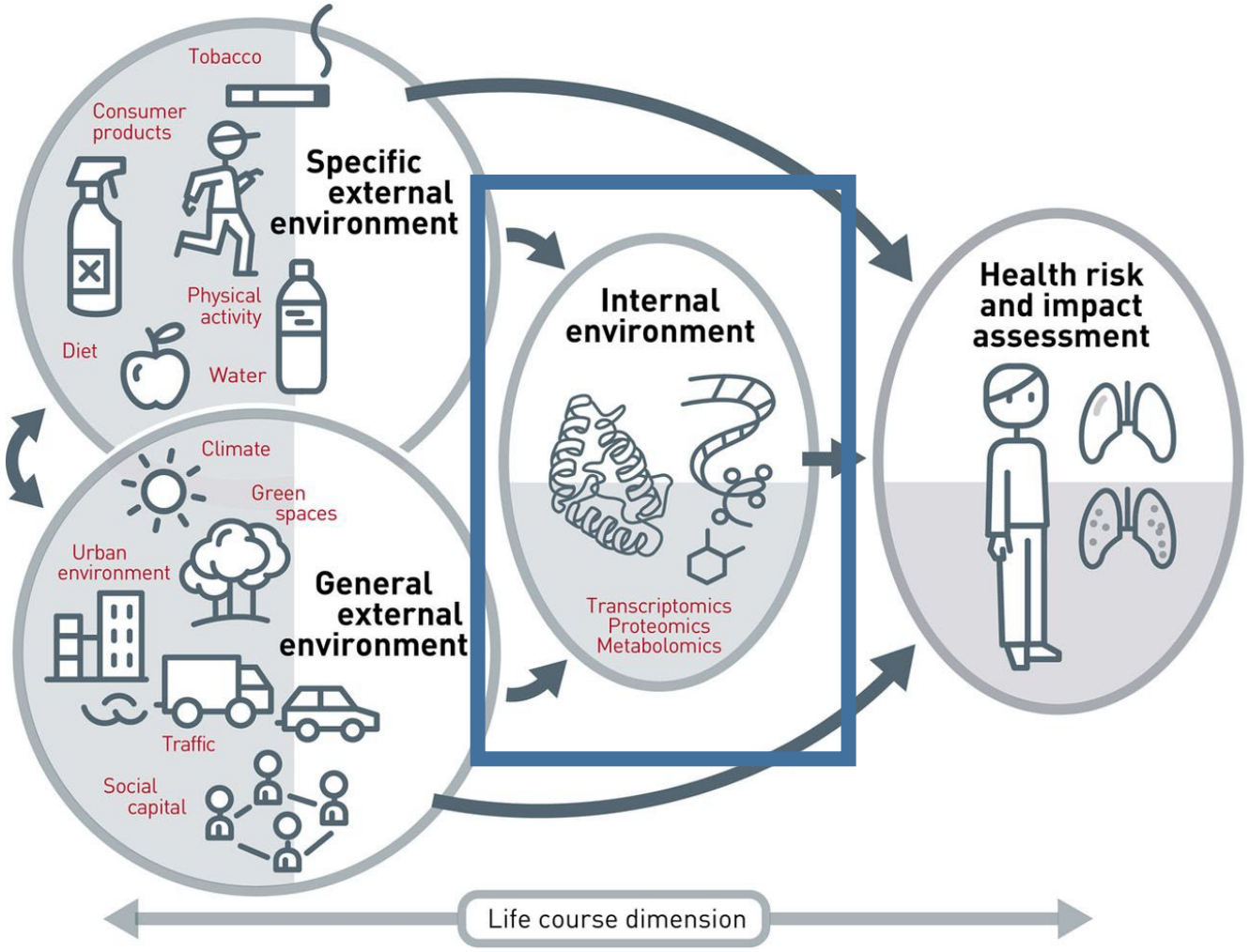

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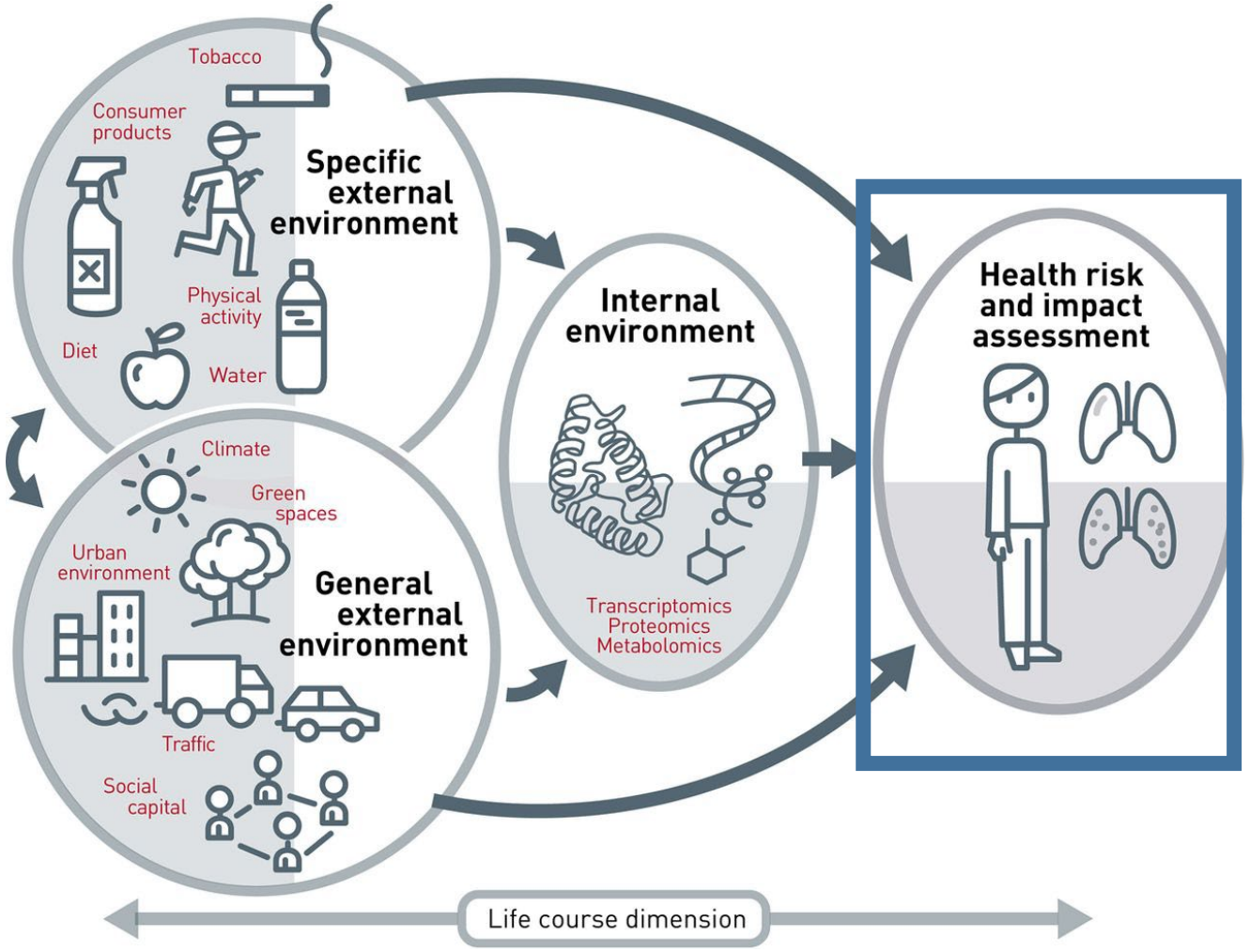

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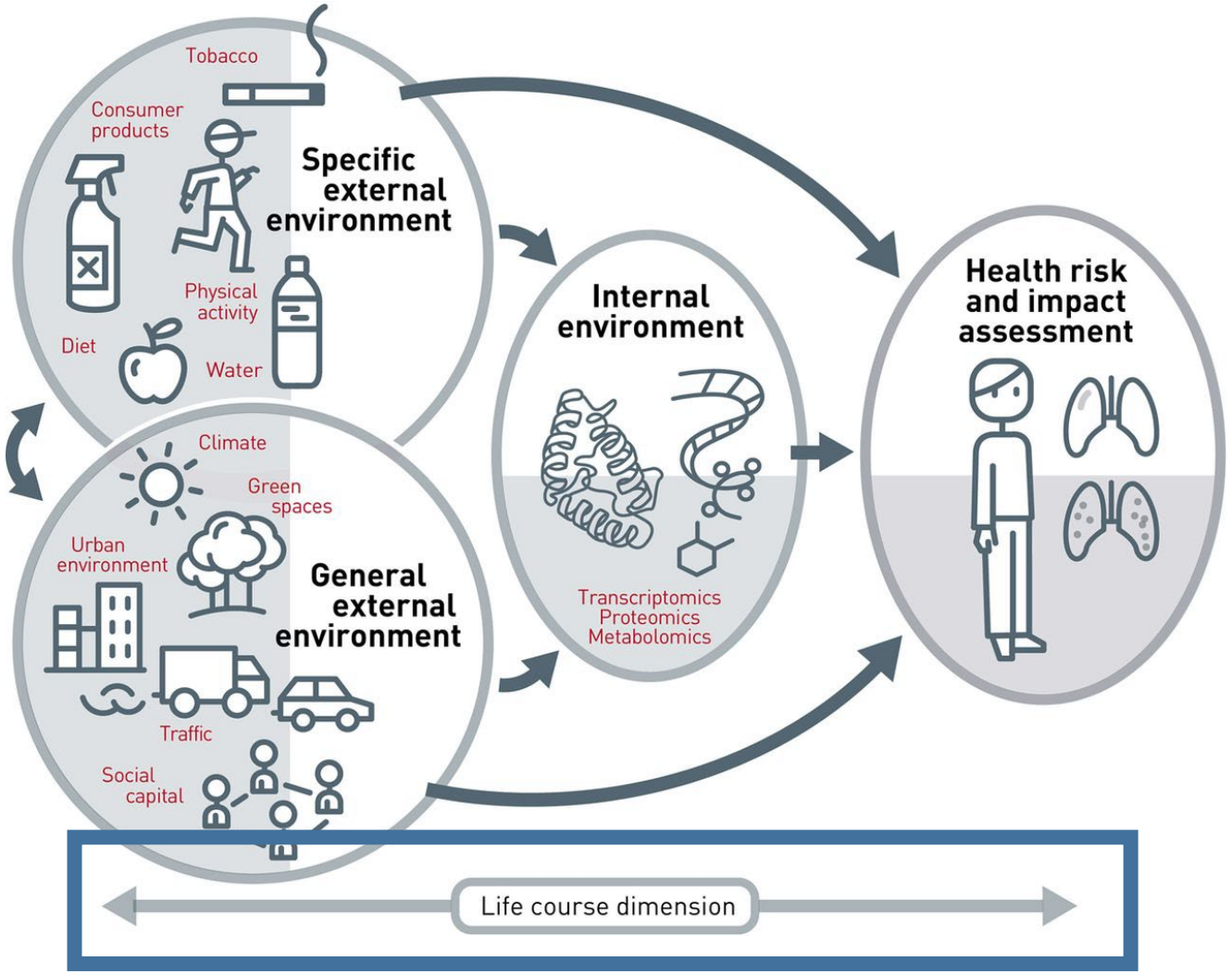

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Internal vs external exposome

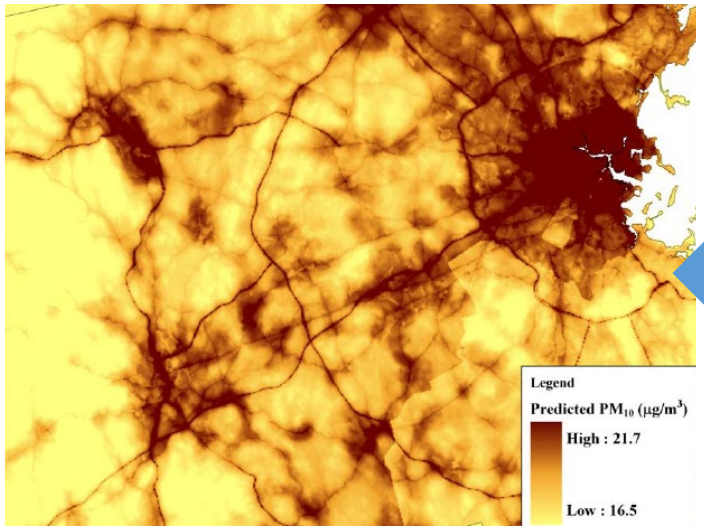
Internal

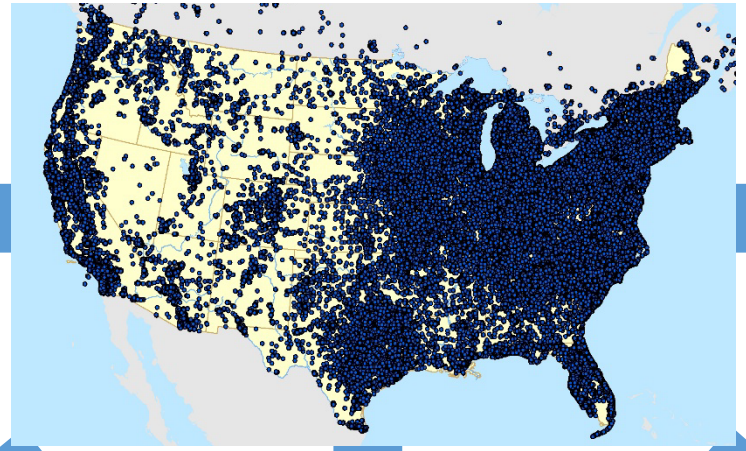
- Can integrate information on the impact of multiple sources of exposure
- Can be conducted on archived samples to give information on historical exposures
- Gives insights into biological processes impacted by exposures
- Can’t provide information on sources responsible for effects
- Can’t provide much information on timing of exposures

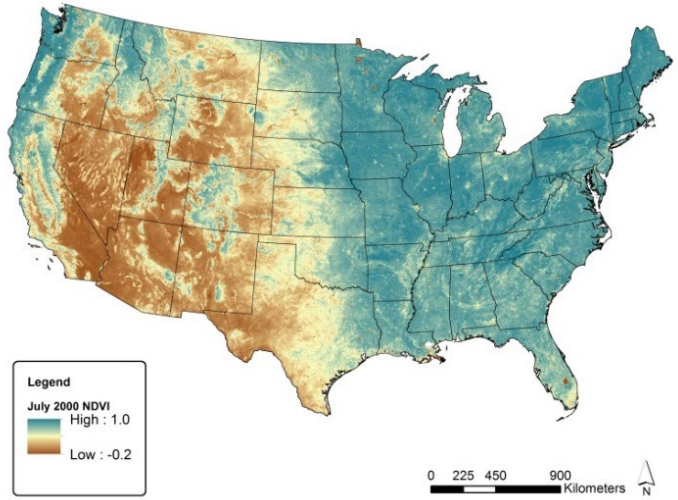
External

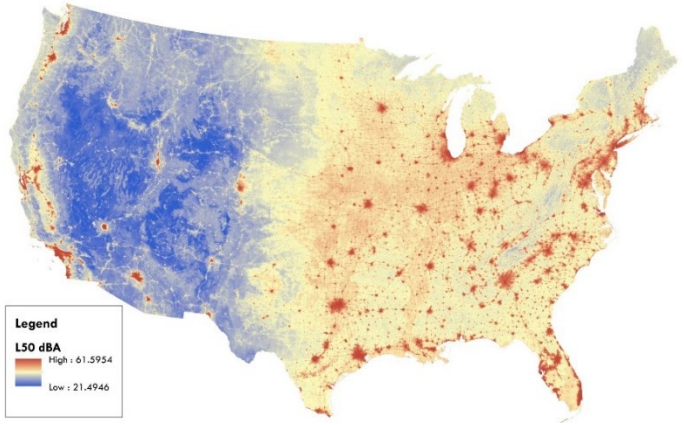
- Provides specific information on potential sources and source patterns
- Allows for assessment of interactions of sources or exposures on biological mechanisms and health outcomes
- Provides information that is more readily incorporated into current policy frameworks
- Requires information on each exposure source separately
- Is more challenging to do historically

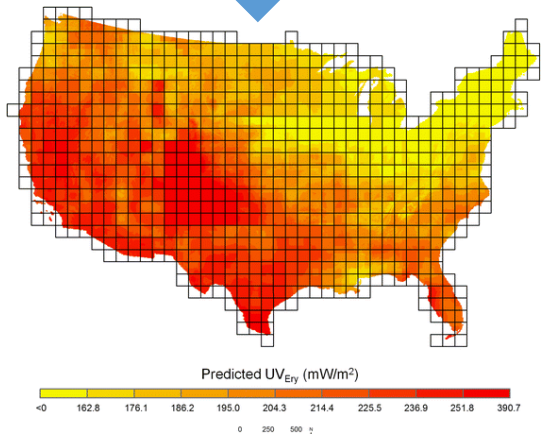
The external exposome in practice

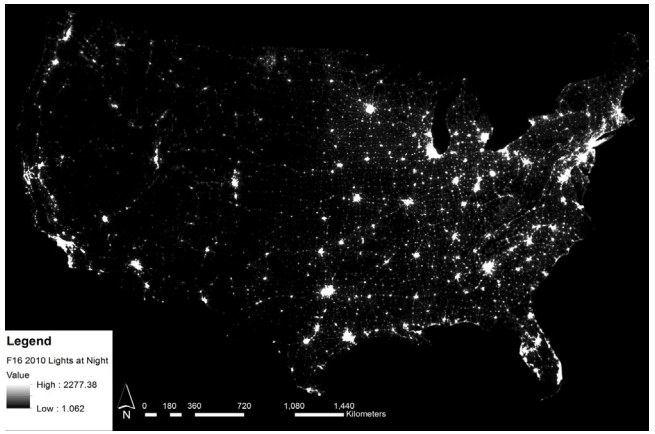








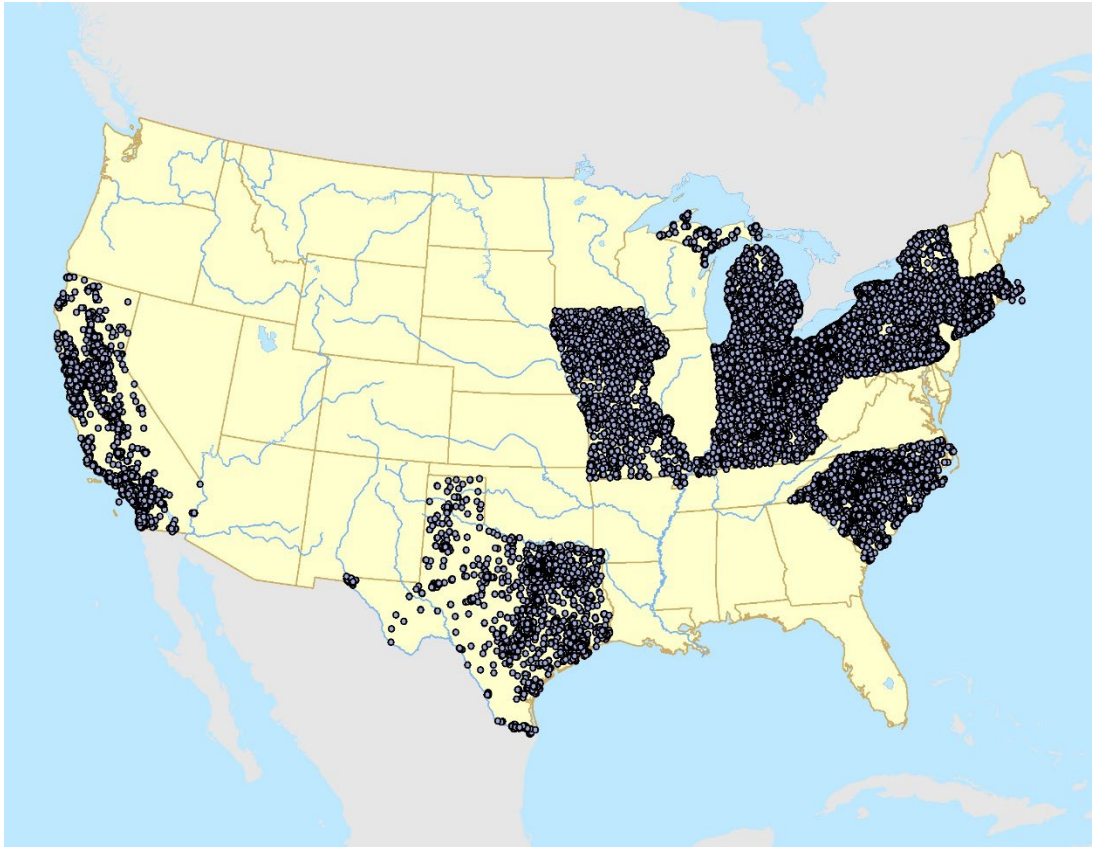


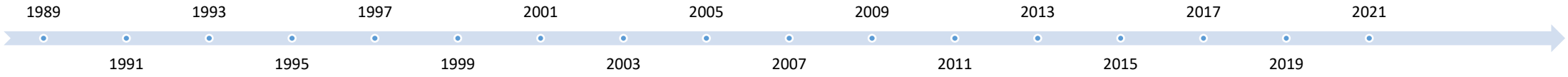


An example of this in practice

The Nurses' Health Study II (NHSII)

- Prospective cohort study
  - Started in 1989
  - 116,429 female nurses (RNs) aged 25-42 at baseline
  - Receive biennial questionnaires to collect information on health and lifestyle factors
- Questionnaire are mailed, providing a residential address history





Environmental exposures and anti-Müllerian hormone: a mixture analysis in NHSII

ORIGINAL ARTICLE

Environmental Exposures and Anti-Müllerian Hormone

A Mixture Analysis in the Nurses' Health Study II

Huichu Li,[a] Jaime E. Hart,[a,b] Shruthi Mahalingaiah,[a] Rachel C. Nethery,[c] Peter James,[a,d] Elizabeth Bertone-Johnson,[e,f] A. Heather Eliassen,[b,g] and Francine Laden[a,b,g]

Background: Previous studies have linked environmental exposures with anti-Müllerian hormone (AMH), a marker of ovarian reserve. However, associations with multiple environment factors has to our knowledge not been addressed.

Methods: We included a total of 2,447 premenopausal women in the Nurses' Health Study II (NHSII) who provided blood samples during 1996–1999. We selected environmental exposures linked previously with reproductive outcomes that had measurement data available in NHSII, including greenness, particulate matter, noise, outdoor light at night, ultraviolet radiation, and six hazardous air pollutants (1,3-butadiene, benzene, diesel particulate matter, formaldehyde, methylene chloride, and tetrachloroethylene). For these, we calculated cumulative averages from enrollment (1989) to blood draw and estimated associations with AMH in adjusted single-exposure models, principal component analysis (PCA), and hierarchical Bayesian kernel machine regression (BKMR).

Results: Single-exposure models showed negative associations of AMH with benzene (percentage reduction in AMH per interquartile range [IQR] increase = 5.5%, 95% confidence interval [CI] = 1.0, 9.8) and formaldehyde (6.1%, 95% CI = 1.6, 10). PCA identified four major exposure patterns but only one with high exposure to air pollutants and light at night was associated with lower AMH. Hierarchical BKMR pointed to benzene, formaldehyde, and greenness and suggested an inverse joint association with AMH (percentage reduction comparing all exposures at the 75th percentile to median = 8.2%, 95% CI = 0.7, 15.1). Observed associations were mainly among women above age 40.

Conclusions: We found exposure to benzene and formaldehyde to be consistently associated with lower AMH levels. The associations among older women are consistent with the hypothesis that environmental exposures accelerate reproductive aging.

Keywords: Anti-Müllerian hormone; Benzene; Formaldehyde; Hazardous air pollutants; Mixture; Reproductive aging

(*Epidemiology* 2023;34: 150–161)

Ovarian aging is characterized by the decline of oocyte quantity and fluctuations of hormones and is associated with cardiovascular, musculoskeletal, and cognitive health.[1–3] This process can be accelerated by both genetic and environmental factors, but to date, its associations with exposures in the ambient environment have been understudied.[1]

Produced by the granulosa cells in follicles, anti-Müllerian hormone (AMH) has been found to be correlated with other markers of ovarian reserve and menopausal age, and thus may be used as a reliable predictor of reproductive aging.[4–9] In addition, epidemiologic studies also suggested that women with low AMH had higher risks of cardiovascular and metabolic diseases.[10,11] Several environmental factors, including particulate air pollution, traffic, ultraviolet (UV) radiation, and greenspace, have been linked with AMH and age at menopause.[12–17] However, these studies only examined the association of single exposure, without considering the complex mixture of exposures that is truly experienced. Additionally, other studies have linked impaired fertility and menstrual disorders, which are common consequences of reproductive aging, with occupational exposure to organic compounds that are also present in the ambient atmosphere.[18–22] However, whether exposure to low levels of these compounds in the ambient environment can affect women's reproductive system remains unclear. Physical environmental factors such as light and noise have been suggested to disrupt neuroendocrine

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SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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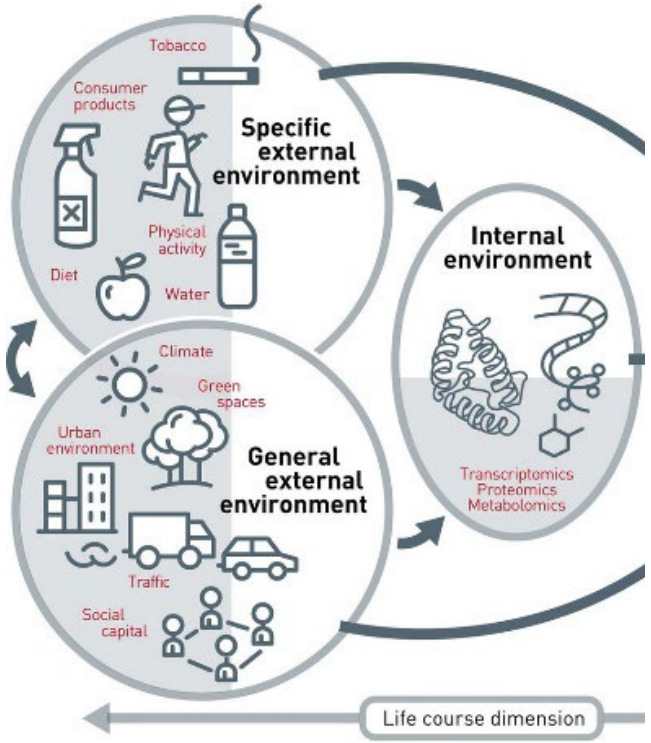

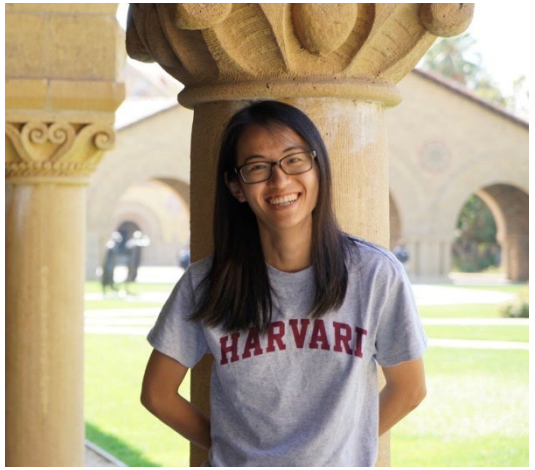

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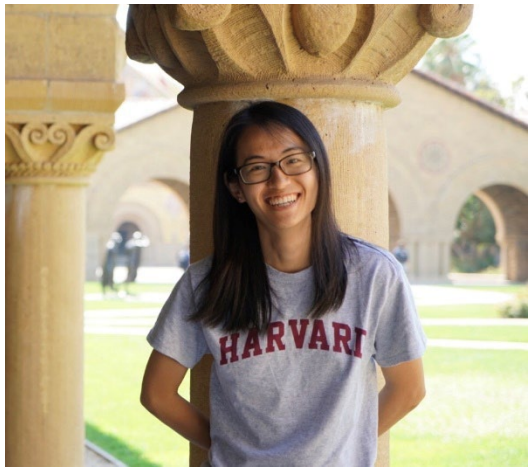
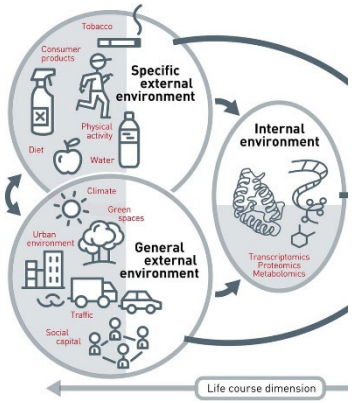
Environmental exposures and anti-Müllerian hormone: a mixture analysis in NHSII



- AMH measured from blood samples of 2,447 women
  - Measure of ovarian reserve
  - Data available from a series of case-control studies
    - All samples collected pre-disease
  - 39.8 years of age on average at blood draw
  - All participants premenopausal



- Cumulative average exposures until time of blood draw appended for
  - Greenness (NDVI)
  - Air pollution ($PM_{2.5}$ & $PM_{2.5-10}$)
  - Noise (daytime L_{50} dB & Nighttime L_{50} dB)
  - Light at night
  - UV
  - Hazardous air pollutants (HAPs)
    - 1,3-butadine, benzene, diesel particulate matter, formaldehyde, methylene chloride, and tetrachloroethylene

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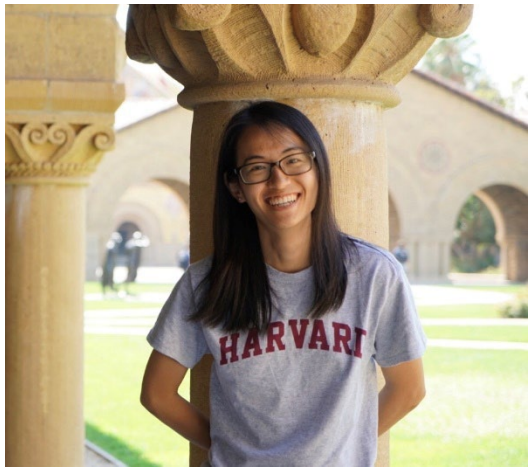
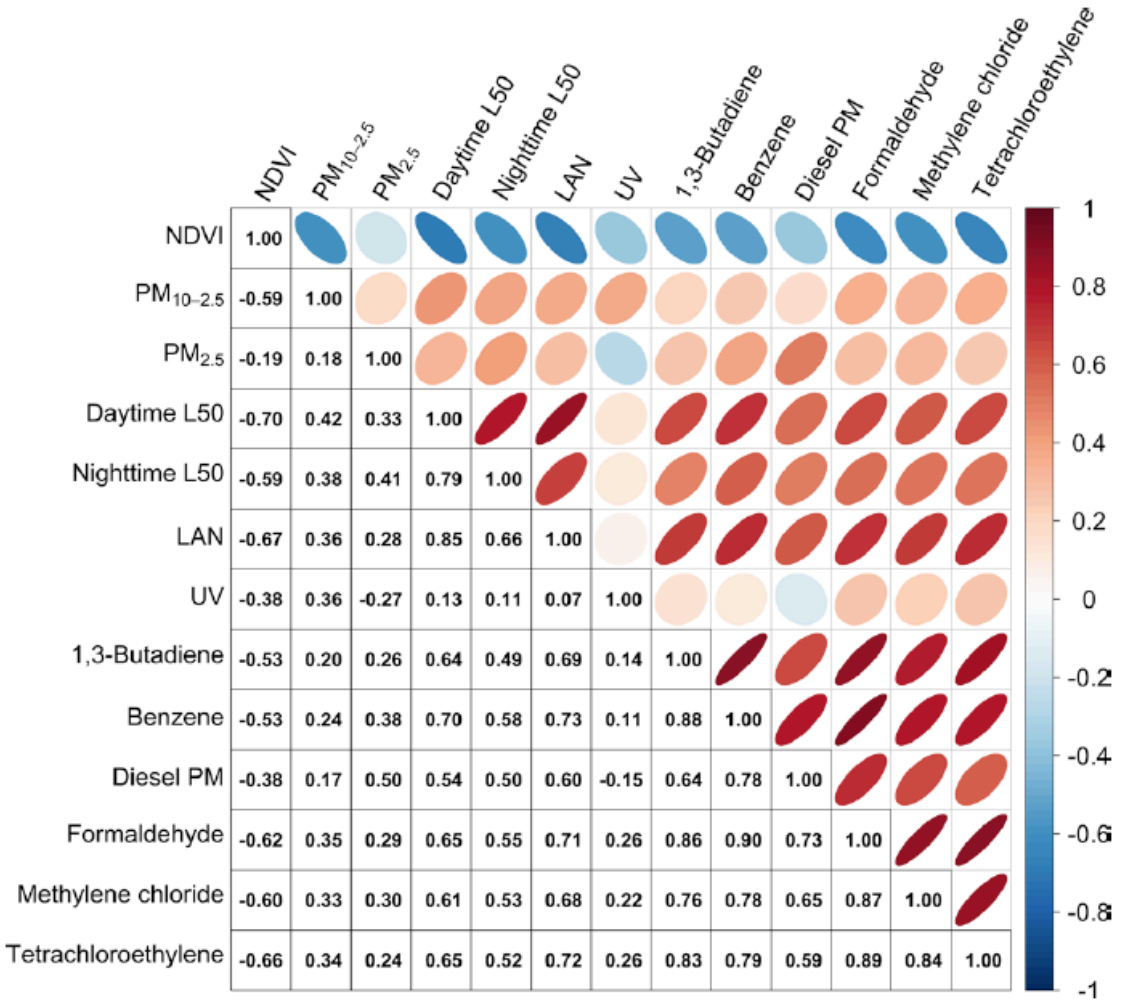


- Statistical Methods
  - Single exposure linear regression models
  - Multi-exposure linear regression models
  - Principle component analysis (PCA)
  - Hierarchical Bayesian kernel machine regression (BKMR)

- Potential confounders
  - age (in natural cubic spline with 3 degrees of freedom), body mass index, Census tract median income, batches, and smoking

Correlations between exposures



	NDVI	$PM_{10-2.5}$	$PM_{2.5}$	Daytime L50	Nighttime L50	LAN	UV	1,3-Butadiene	Benzene	Diesel PM	Formaldehyde	Methylene chloride	Tetrachloroethylene
NDVI	1.00												
$PM_{10-2.5}$	-0.59	1.00											
$PM_{2.5}$	-0.19	0.18	1.00										
Daytime L50	-0.70	0.42	0.33	1.00									
Nighttime L50	-0.59	0.38	0.41	0.79	1.00								
LAN	-0.67	0.36	0.28	0.85	0.66	1.00							
UV	-0.38	0.36	-0.27	0.13	0.11	0.07	1.00						
1,3-Butadiene	-0.53	0.20	0.26	0.64	0.49	0.69	0.14	1.00					
Benzene	-0.53	0.24	0.38	0.70	0.58	0.73	0.11	0.88	1.00				
Diesel PM	-0.38	0.17	0.50	0.54	0.50	0.60	-0.15	0.64	0.78	1.00			
Formaldehyde	-0.62	0.35	0.29	0.65	0.55	0.71	0.26	0.86	0.90	0.73	1.00		
Methylene chloride	-0.60	0.33	0.30	0.61	0.53	0.68	0.22	0.76	0.78	0.65	0.87	1.00	
Tetrachloroethylene	-0.66	0.34	0.24	0.65	0.52	0.72	0.26	0.83	0.79	0.59	0.89	0.84	1.00

FIGURE 1. Spearman correlation coefficients among measures of surrounding greenness, particulate air pollution, noise, LAN, UV, and HAPs. The shade of each ellipse on the upper panel indicates the absolute value of the correlation coefficient. When an ellipse is leaning towards the left, this suggests the correlation between two variables are negative; when an ellipse is leaning towards the right, this suggests the correlation between two variables are positive. HAPs indicates hazardous air pollutants; $PM_{10-2.5}$, particulate matter with an aerodynamic diameters between 10 and 2.5 microns. Figure is available in color online.

Exposure	IQR	Single exposure [a]	Multi-exposure [a]
NDVI	0.14	2.8 (-3.1, 9.0)	-5.2 (-15, 5.7)
$PM_{10-2.5}$ ($\mu g/m^3$)	5.2	-3.2 (-8.0, 1.8)	-5.6 (-12, 1.6)
$PM_{2.5}$ ($\mu g/m^3$)	4.2	1.4 (-4.9, 8.1)	9.6 (0.66, 19)
Daytime L50 (dB)	4.6	-2.2 (-7.2, 3.0)	-0.90 (-12, 12)
Nighttime L50 (dB)	3.5	-1.7 (-6.4, 3.3)	-0.8 (-9.8, 9.1)
LAN ($nW/cm^2/sr$)	34	-2.9 (-8.2, 2.6)	4.1 (-6.0, 15)
UV (nW/m^2)	33	-1.8 (-7.0, 3.6)	3.4 (-5.3, 12)
1,3-Butadine ($\mu g/m^3$)	0.10	-2.4 (-5.5, 0.92)	0.95 (-4.0, 6.2)
Benzene ($\mu g/m^3$)	0.67	-5.5 (-9.8, -1.0)	-1.0 (-14, 14)
Diesel PM ($\mu g/m^3$)	0.61	-2.6 (-5.4, 0.33)	-0.85 (-5.4, 3.9)
Formaldehyde ($\mu g/m^3$)	0.77	-6.1 (-10, -1.6)	-16 (-27, -2.1)
Methylene chloride ($\mu g/m^3$)	0.33	-0.85 (-3.7, 2.1)	1.7 (-2.0, 5.6)
Tetrachloroethylene($\mu g/m^3$)	0.20	-1.4 (-3.6, 0.94)	2.5 (-2.1, 7.4)

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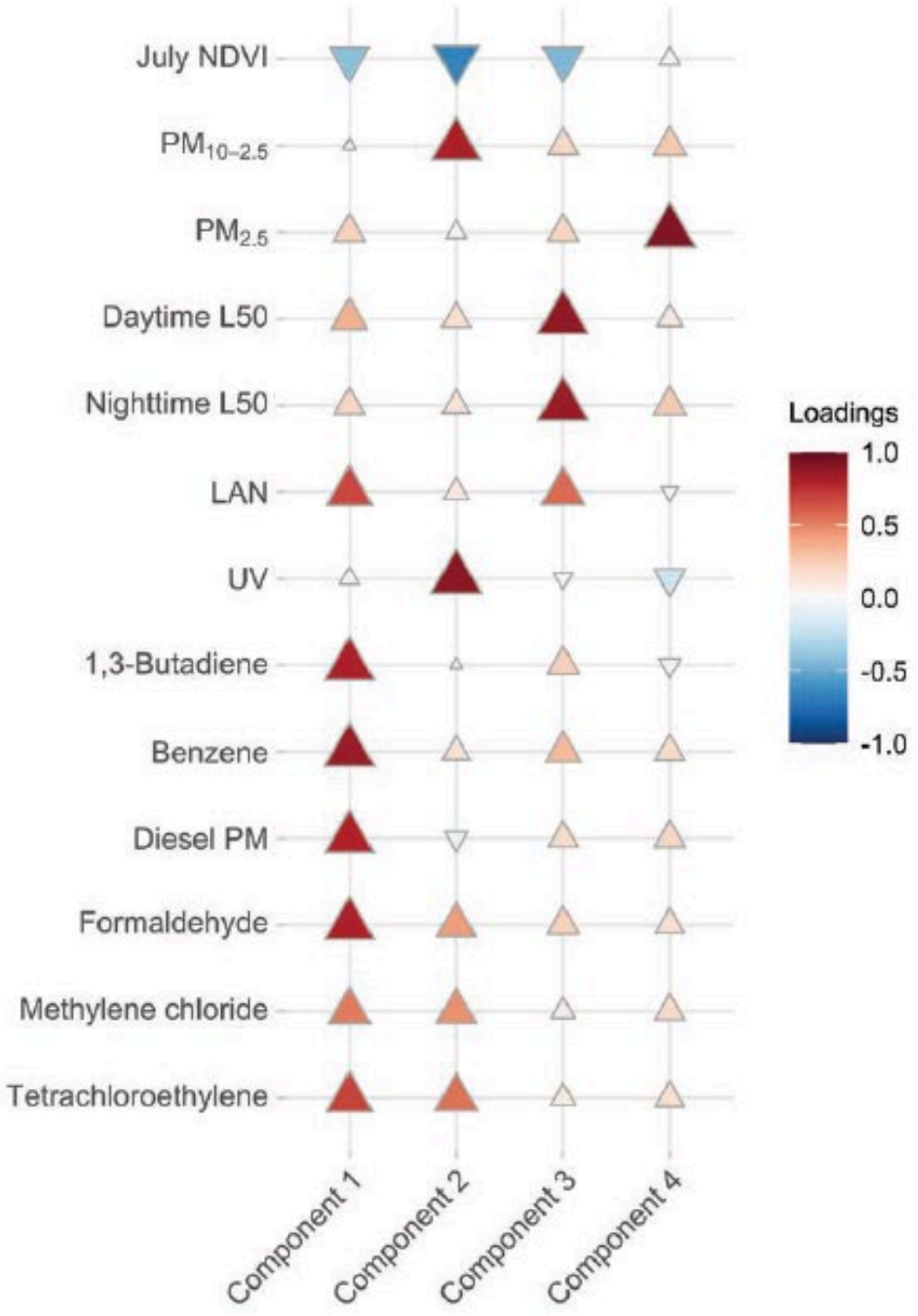
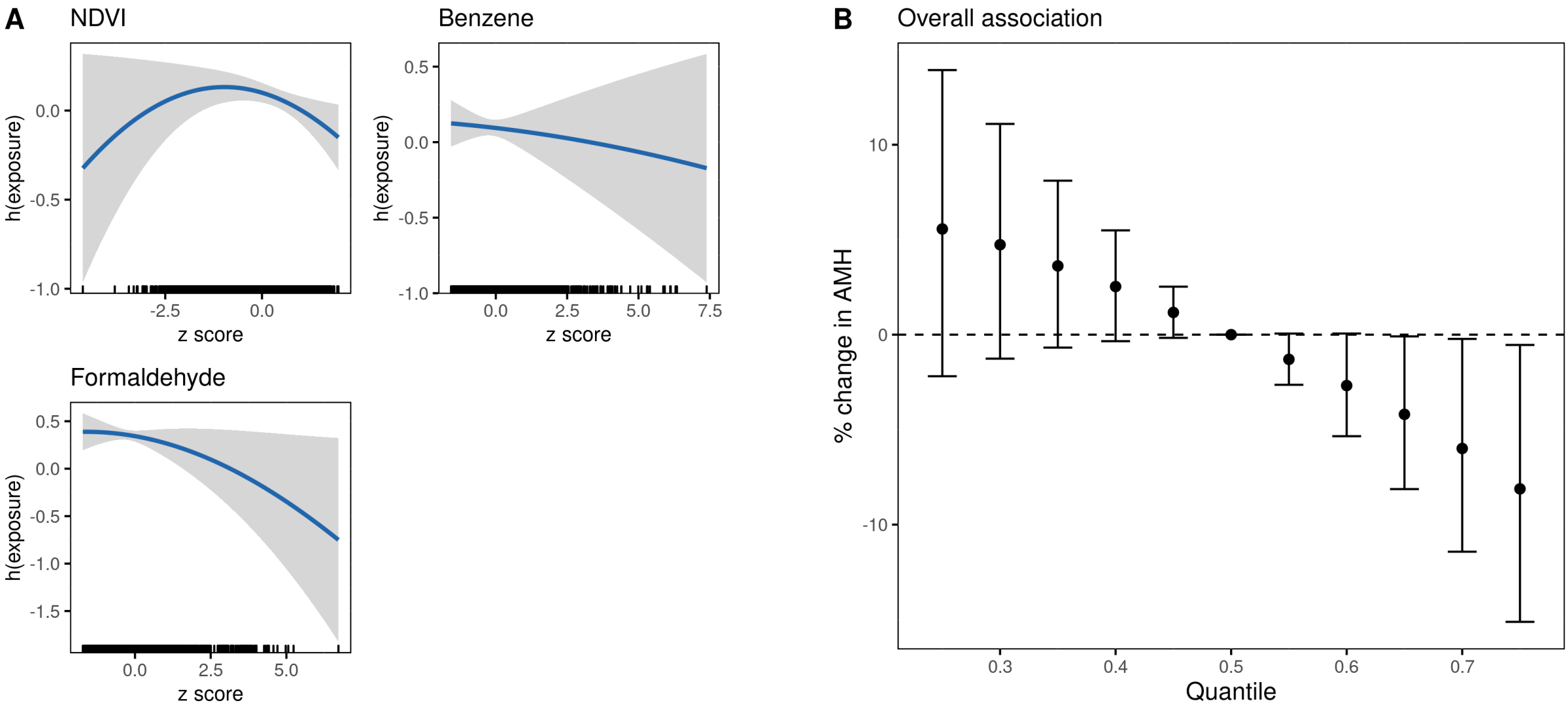


Component	High loading exposures	% change (95%CI) [a]
1	LAN, 1,3-butadine, benzene, diesel particulate matter, formaldehyde, methylene chloride, and tetrachloroethylene	-4.6 (-9.0, -0.08)
2	NDVI (negative), $PM_{10\text{-}2.5}$, and UV	-1.9 (-6.2, 2.6)
3	Daytime and nighttime L50	-0.76 (-5.1, 3.8)
4	$PM_{2.5}$	1.3 (-3.1, 5.8)


A
NDVI
h(exposure)
0.0
-0.5
-1.0
-2.5
0.0
z score
Benzene
h(exposure)
0.5
0.0
-0.5
-1.0
0.0
2.5
5.0
7.5
z score
Formaldehyde
h(exposure)
0.5
0.0
-0.5
-1.0
-1.5
0.0
2.5
5.0
z score
B
Overall association
% change in AMH
10
0
-10
0.3
0.4
0.5
0.6
0.7
Quantile

Ongoing work using a similar framework

- Intergenerational exposures and birth outcomes
- Multiple environmental exposures and untargeted metabolomics as a mediator of the effects of the environment on mental health
- Multiple exposures assigned by day/week/month/year long GPS locations with physical activity and sleep
- Multiple environmental exposures and risk of death after MI or stroke
- Multiple environmental exposures and prostate tumor histochemical markers

Conclusions

- The exposome is a useful framework for examining the impacts of multiple environmental exposures across decades on a myriad of health outcomes
  - Building on decades of single-exposure and single-outcome environmental epidemiology work

- Technological advances in many areas have been required to operationalize these studies
  - GIS and remote sensing
  - GPS and smartphone sensors and applications
  - Personal exposure methodologies
  - Data science and computing
  - Statistical methods

- More work is needed to make these studies useful for cumulative impact assessment

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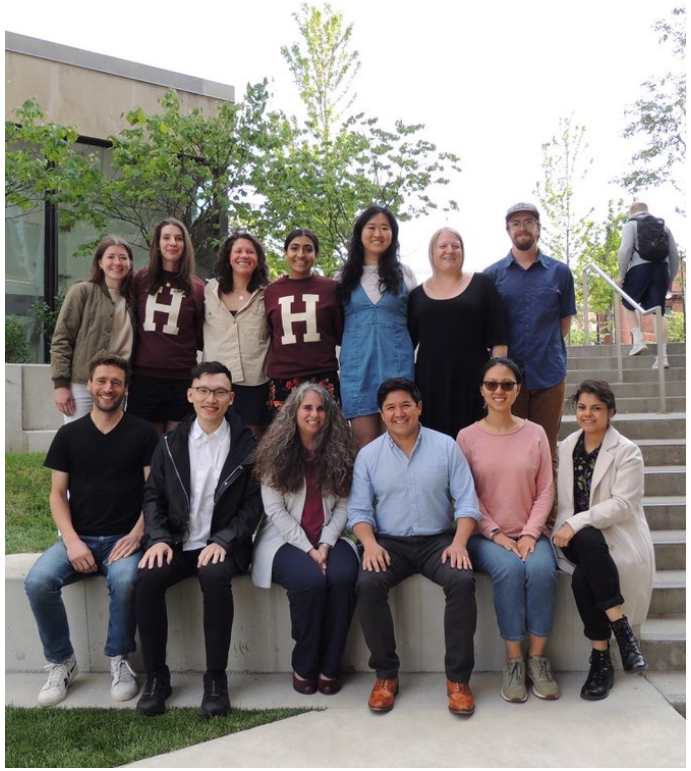

Happy to answer questions during the Q&A and in the chat

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