Recent Evidence on the Health Effects of Ozone: The Pollutant of the Future

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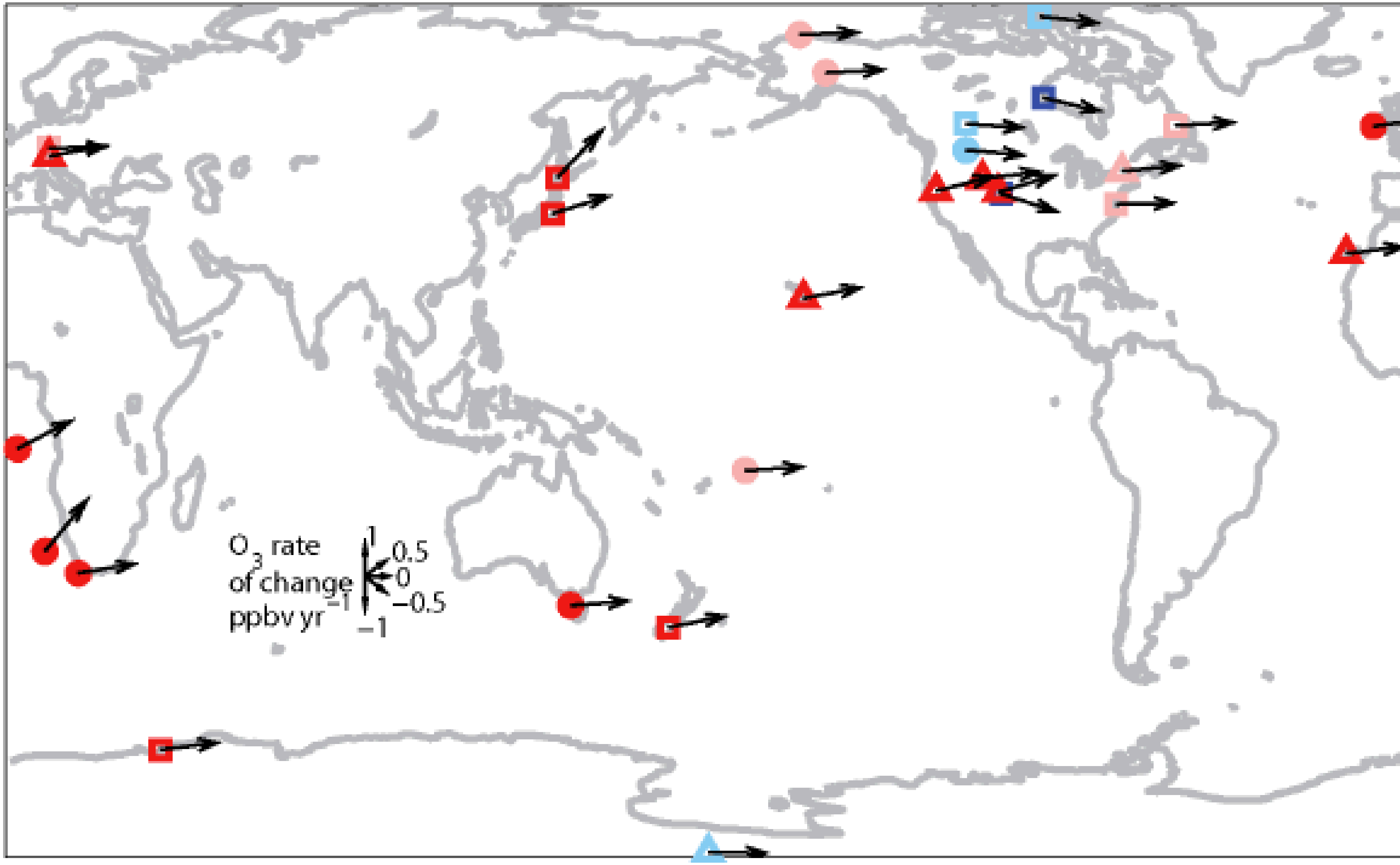
What Makes Ozone Important?

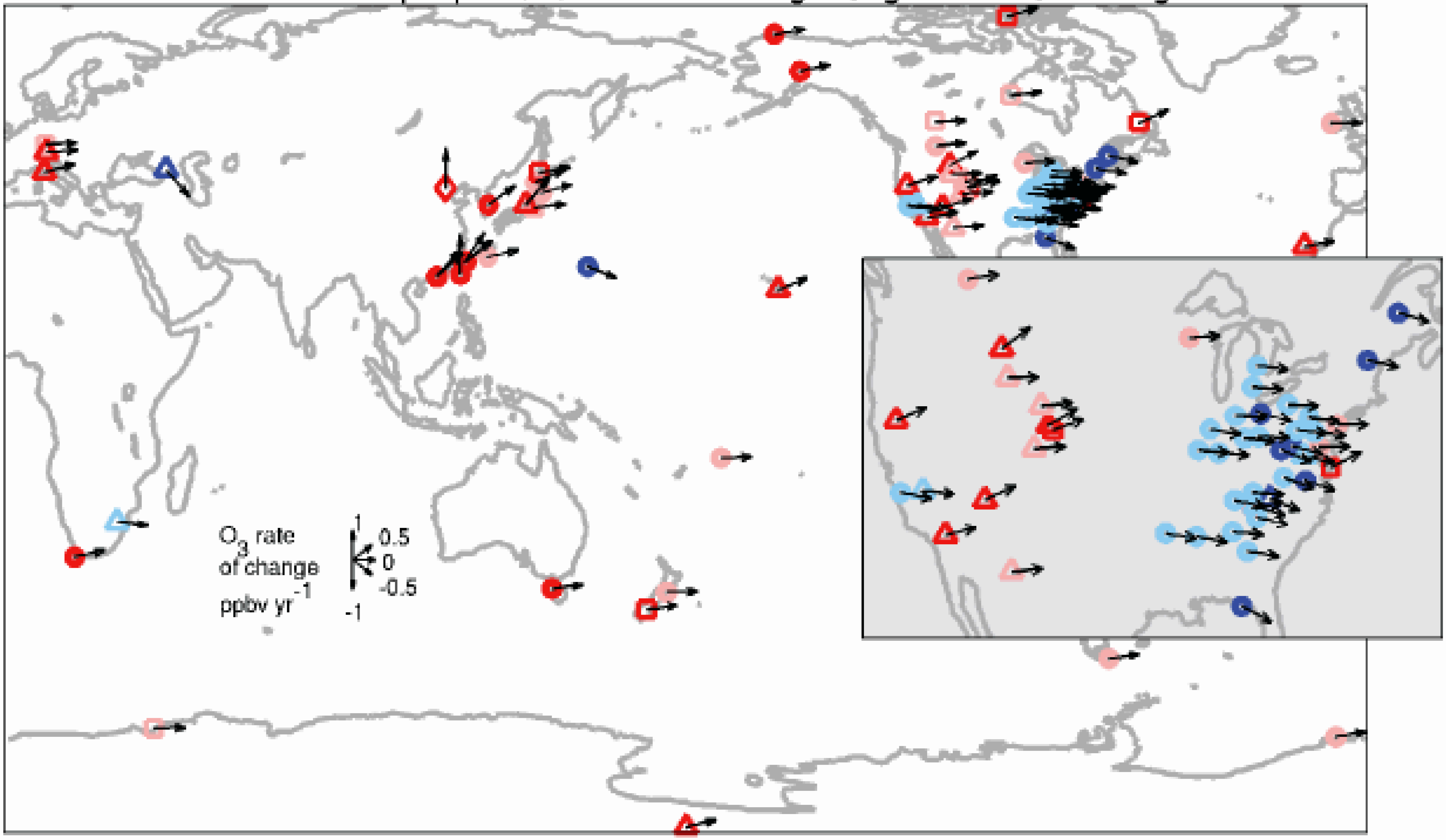
- Higher and worsening concentrations observed in densely-populated areas of South and East Asia (Parrish et al. 2012; Cooper et al. 2014)

Surface and lower tropospheric ozone trends beginning 1980-1989 through 2010



Source: Cooper et al. 2014

Surface and lower tropospheric ozone trends beginning 1990-1999 through 2010



Importance Cont’d

* Ozone has not seen nearly the same decreases as in other pollutants in many parts of the United States, particularly in more polluted areas such as Southern California (Gauderman et al. 2015)
* American Lung Association estimates 116,000,000 people live in areas exceeding the National Ambient Air Quality Standard for ozone (70 ppb)

Ozone Compared to Other Pollutants in Five Southern California Communities

(Source: Gauderman et al. 2015)

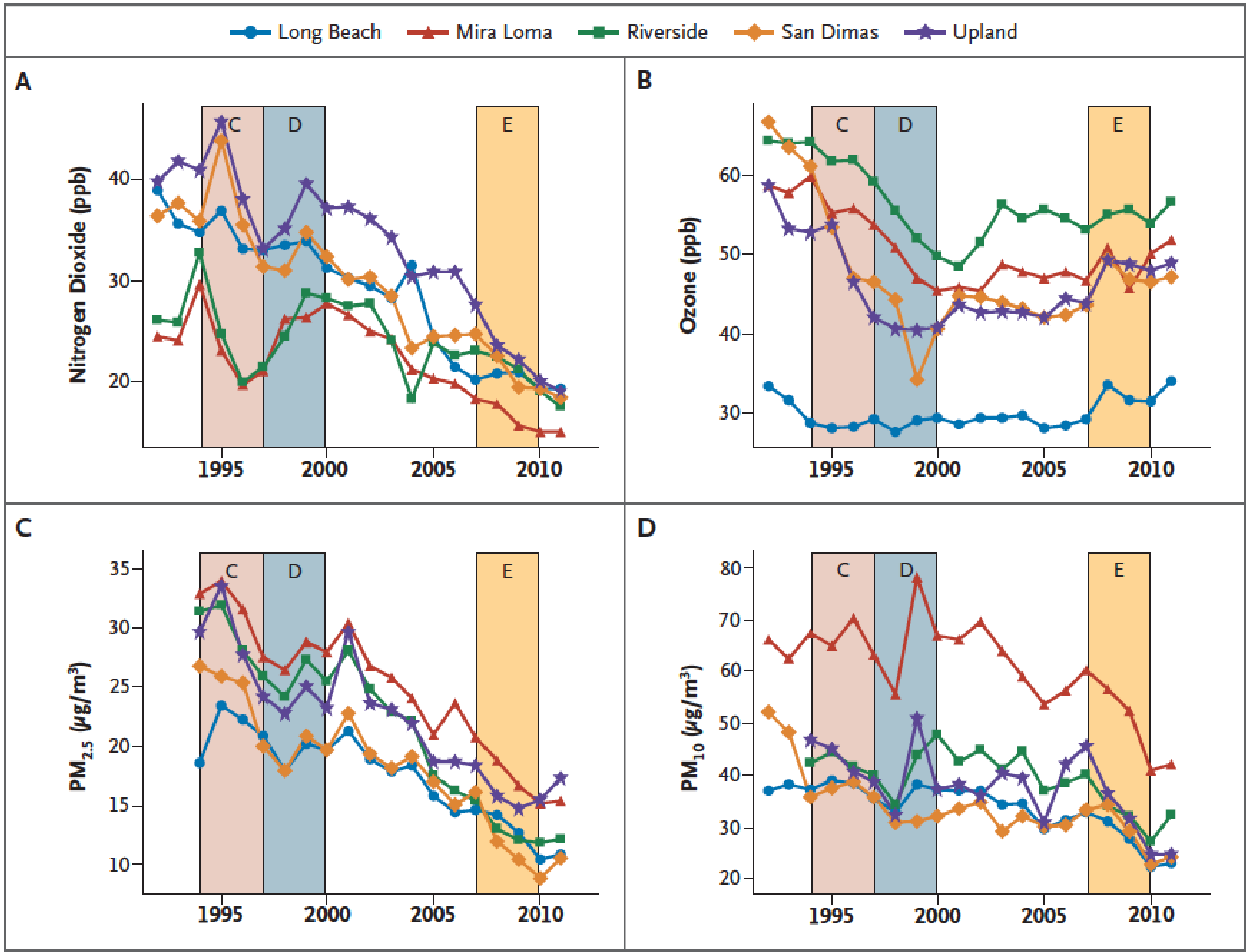


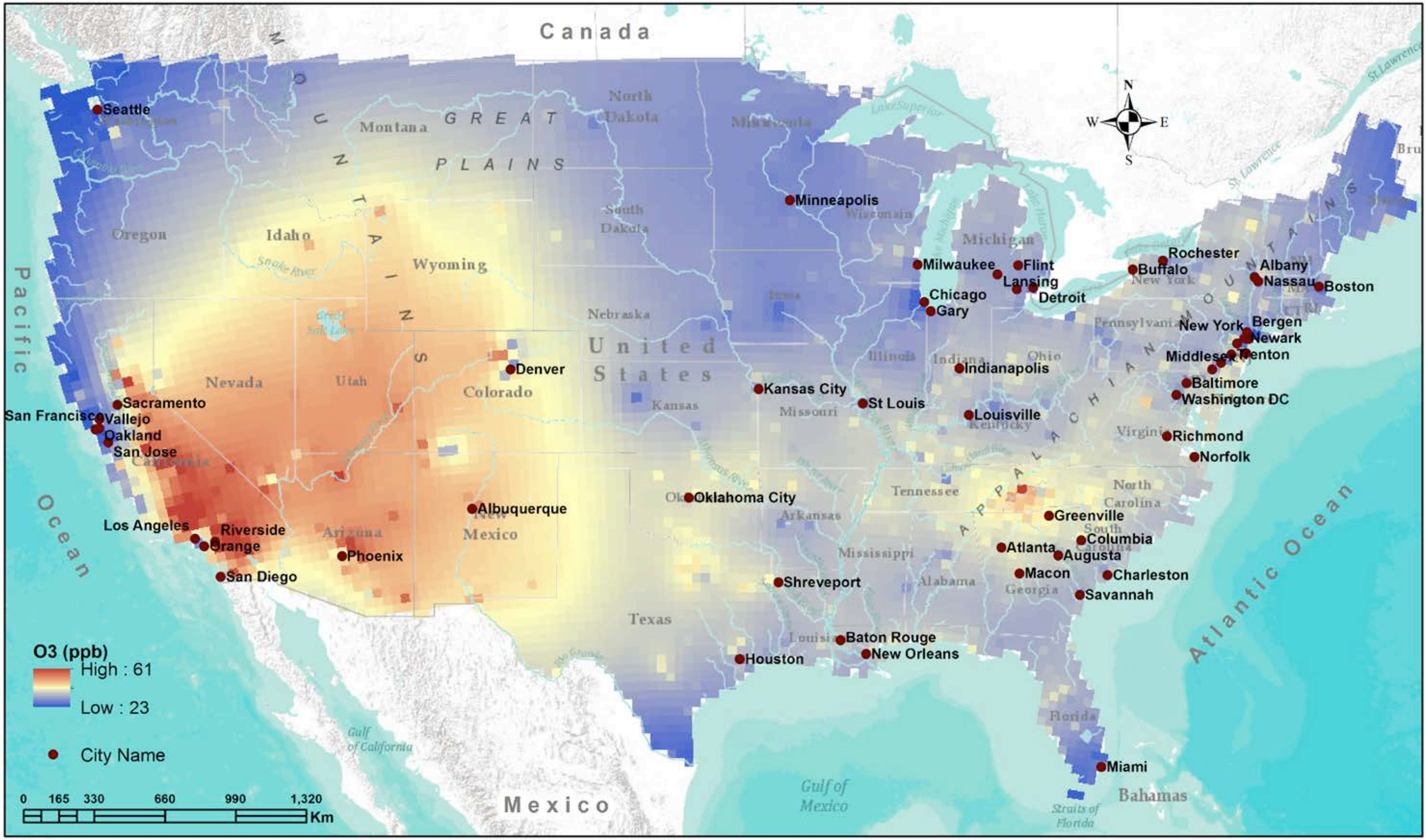
Figure 1. Levels of Four Air Pollutants from 1994 to 2011 in Five Southern California Communities.

What Makes Ozone Health Effects Hard to Study?

* Complex atmospheric chemistry that depends on sunlight creates complex spatiotemporal patterns that operate at meso (regional) and micro (within-city) scales

* Often follows a mirrored pattern with NO_2 which has many documented health effects at the micro scale

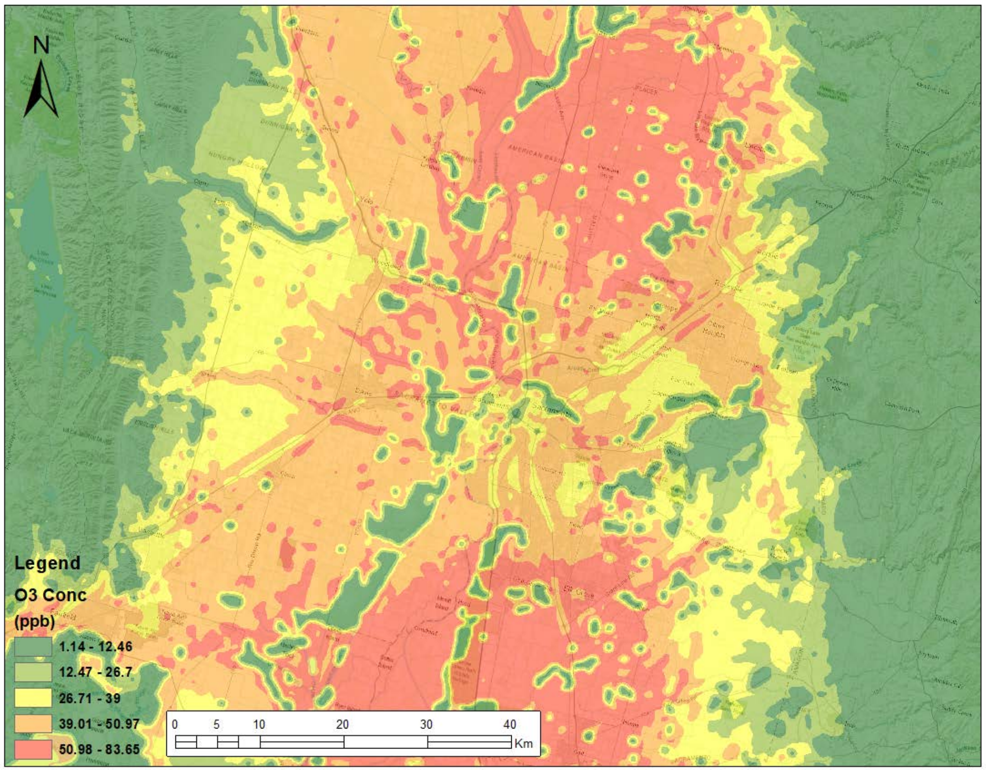
National Ozone Map 2008 EPA Downscaler Model: Large Area Regional Variations

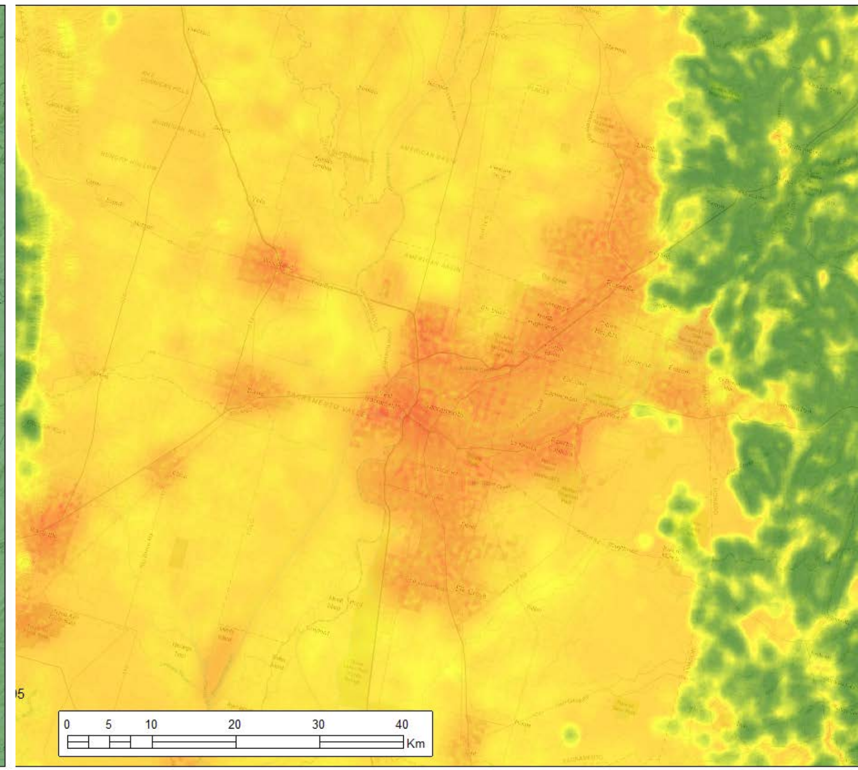


Inverse Association of Ozone with Nitrogen Dioxide Sacramento, CA

Preliminary Results Su, Jerrett, Ritz

R = -0.55





Hard to Study (Cont'd)

* Pattern of exposure different than most other pollutants in relation to possible social confounders, both individual and in neighborhoods
* Often higher in suburban areas and in green areas such as parks - areas with higher SES (Su, Jerrett et al. 2011)
* Ozone often competes against other variables that positively affect health (individual education, income, occupation, obesity or area green space or lower crime)

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Ambient ozone and incident diabetes: A prospective analysis in a large cohort of African American women

Michael Jerrett [a,*], Robert Brook [b], Laura F. White [h], Richard T. Burnett [d], Jeffrey Yu [c], Jason Su [e], Edmund Seto [f], Julian Marshall [g], Julie R. Palmer [c], Lynn Rosenberg [c], Patricia F. Coogan [c]

Black Woman's Health Study

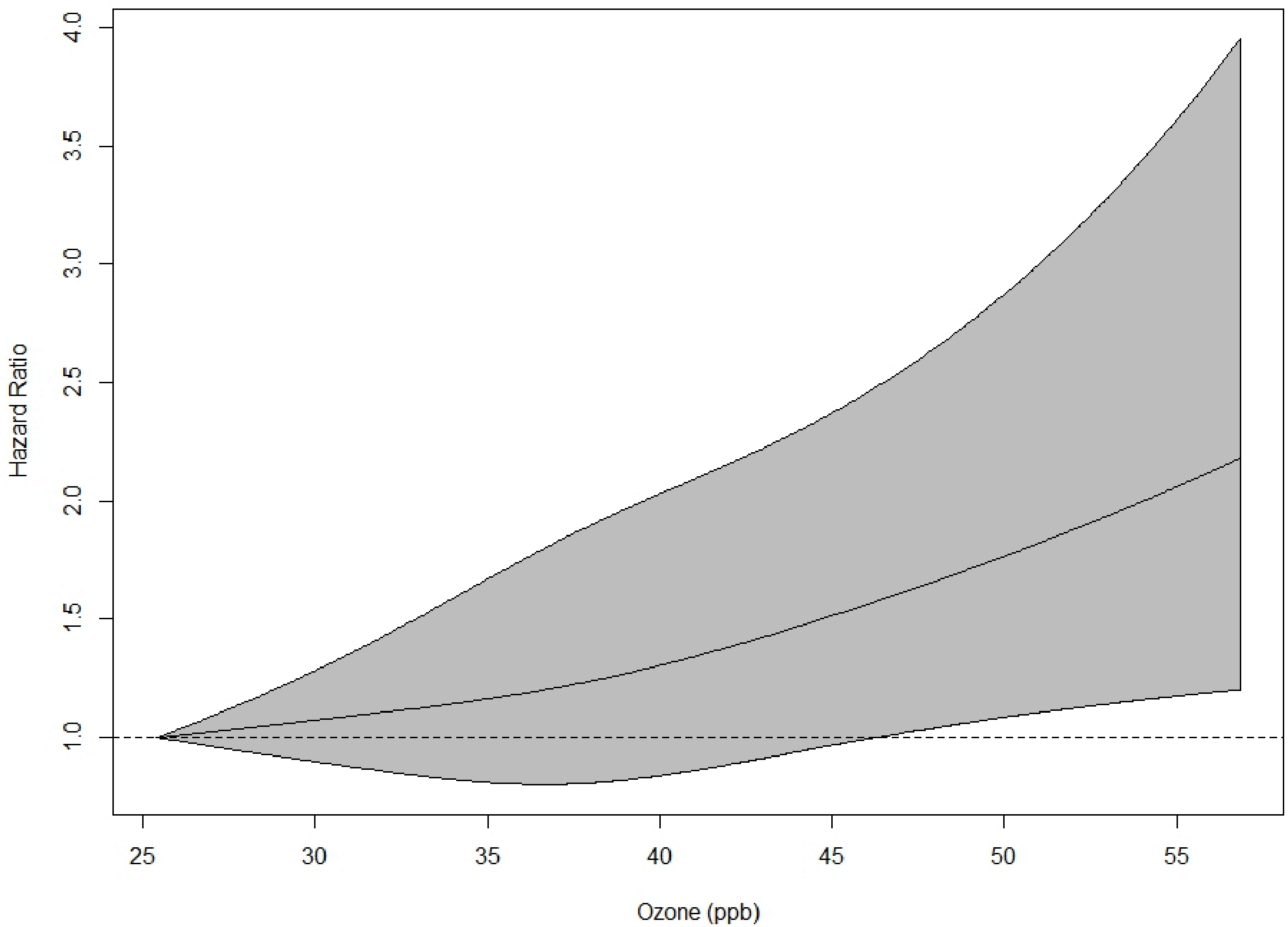
* Included 45,231 women who lived in any of 56 U.S. metropolitan areas who had complete BMI information at baseline (1995)
* Incident cases of type 2 diabetes were ascertained by self-report of doctor-diagnosed diabetes at age 30 or older during follow-up validated in sub-study of medical records till 2011
* Used EPA Downscaler ozone estimates 2007-2008
* Cox Proportional Hazards model

Effect of Individual Variables on HRs

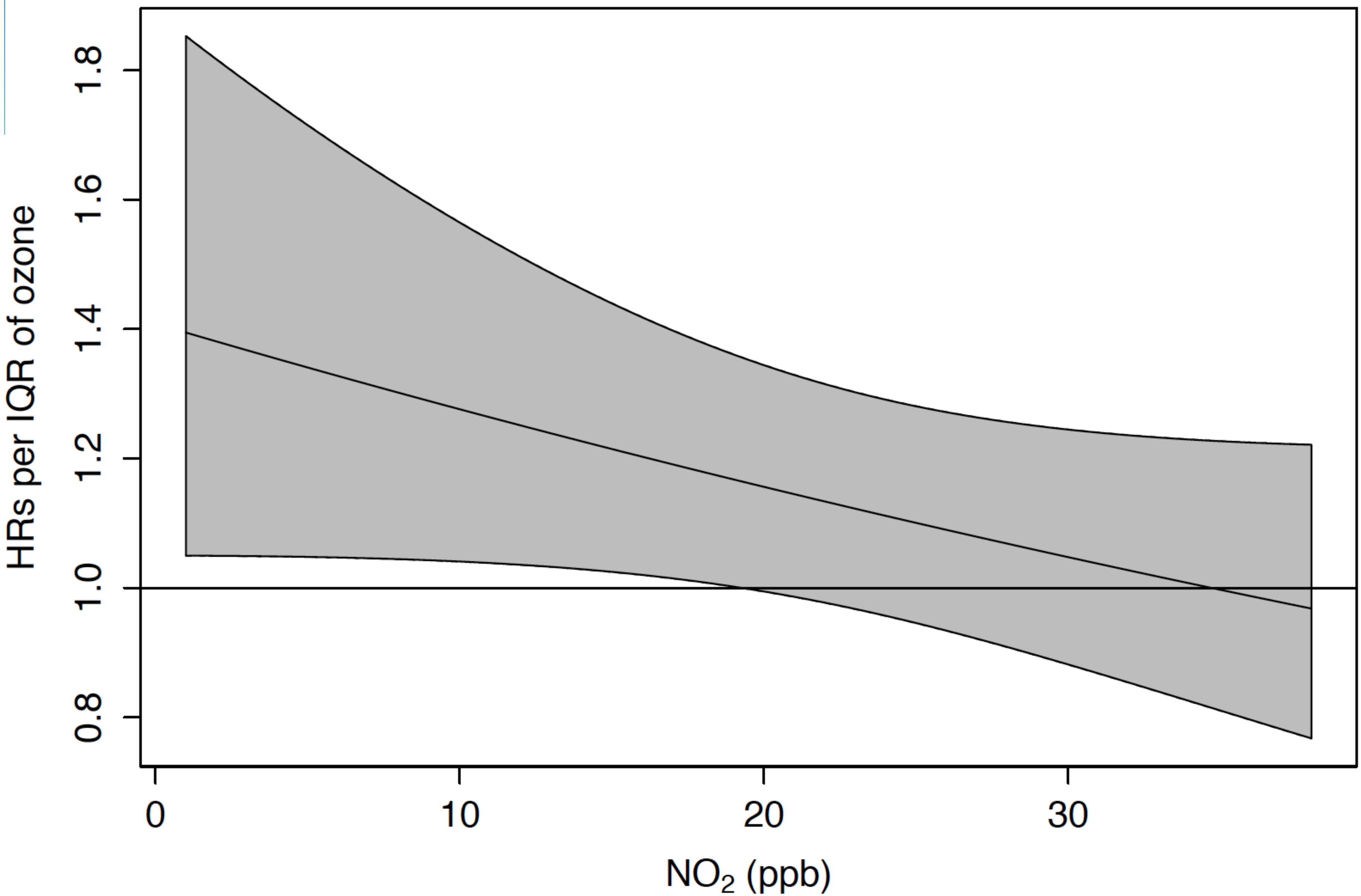
Model	Hazard Ratios (4,387 cases/453,221 p-yrs)
Basic model	1·00 (0·88, 1·13)
Basic model + BMI	1·07 (0·94, 1·21)
Basic model + SES	1·21 (1·07, 1·37)
Basic model + smoking	1·02 (0·90, 1·16)
Basic model + education	1·02 (0·91, 1·16)
Basic model + vig exercise	1·01 (0·89, 1·14)
Basic model + alcohol	1·00 (0·88, 1·13)
Basic model + parental hx DM	1·00 (0·88, 1·14)
Basic model + diet	1·02 (0·90, 1·16)

parental hx DM = parental history of diabetes; BMI = body mass index; HR = hazard ratio; SES = socioeconomic status

Concentration-Response Plot



Interaction Plot of O_3 by NO_2



Key Analytic Points

* Complex pattern of spatial confounding in the association between ozone and health
* Complex chemistry and interaction with NO2 has strong spatial component
* Substantive knowledge about spatial distributions of the pollutant, co-pollutants, and social variables critical to detect the association

Integrated Science Assessment

(Source: EPA 2013)

Table 1-1 Summary of O_3 causal determinations by exposure duration and health outcome.

Health Outcome[a]	Conclusions from 2006 O_3 AQCD	Conclusions from this ISA
Short-term Exposure to O_3		
Respiratory effects	The overall evidence supports a causal relationship between acute ambient O_3 exposures and increased respiratory morbidity outcomes.	Causal Relationship
Cardiovascular effects	The limited evidence is highly suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association.	Likely to be a Causal Relationship
Central nervous system effects	Toxicological studies report that acute exposures to O_3 are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
Total Mortality	The evidence is highly suggestive that O_3 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship

Long-term Effects

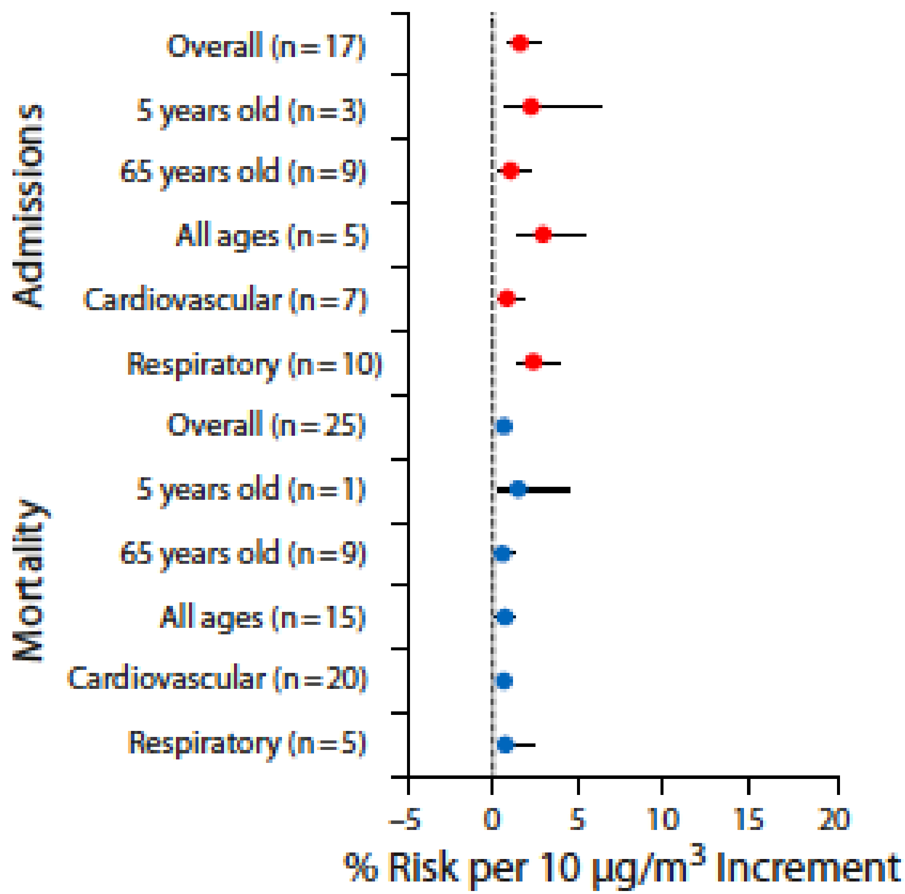
Respiratory effects	The current evidence is suggestive but inconclusive for respiratory health effects from long-term O_3 exposure.	Likely to be a Causal Relationship
Cardiovascular effects	No conclusions in the 2006 O_3 AQCD.	Suggestive of a Causal Relationship
Reproductive and developmental effects	Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O_3 effects.	Suggestive of a Causal Relationship
Central nervous system effects	Evidence regarding chronic exposure and neurobehavioral effects was not available.	Suggestive of a Causal Relationship
Cancer	Little evidence for a relationship between chronic O_3 exposure and increased risk of lung cancer.	Inadequate to Infer a Causal Relationship
Total Mortality	There is little evidence to suggest a causal relationship between chronic O_3 exposure and increased risk for mortality in humans	Suggestive of a Causal Relationship

Methods for Literature Review

* Searched PubMed database with keyword "ozone health effects" and "Air pollution health effects review"
* 602 entries scanned for relevance by title going back to 2016
* Selected relevant ones from those and did an abstract review (N =121)
* Contacted numerous colleagues involved in ozone health effects research
* Focused on newer evidence, but also evidence likely to influence causal determinations in the next Integrated Science Assessment conducted by EPA

Global Association of Air Pollution and Cardiorespiratory Diseases: A Systematic Review, Meta-Analysis, and Investigation of Modifier Variables

Weeberb J. Requia, PhD, Matthew D. Adams, PhD, Altaf Arain, PhD, Stefania Papatheodorou, PhD, Petros Koutrakis, PhD, and Moataz Mahmoud, PhD



Newell *et al. Environmental Health* (2018) 17:41
https://doi.org/10.1186/s12940-018-0380-3

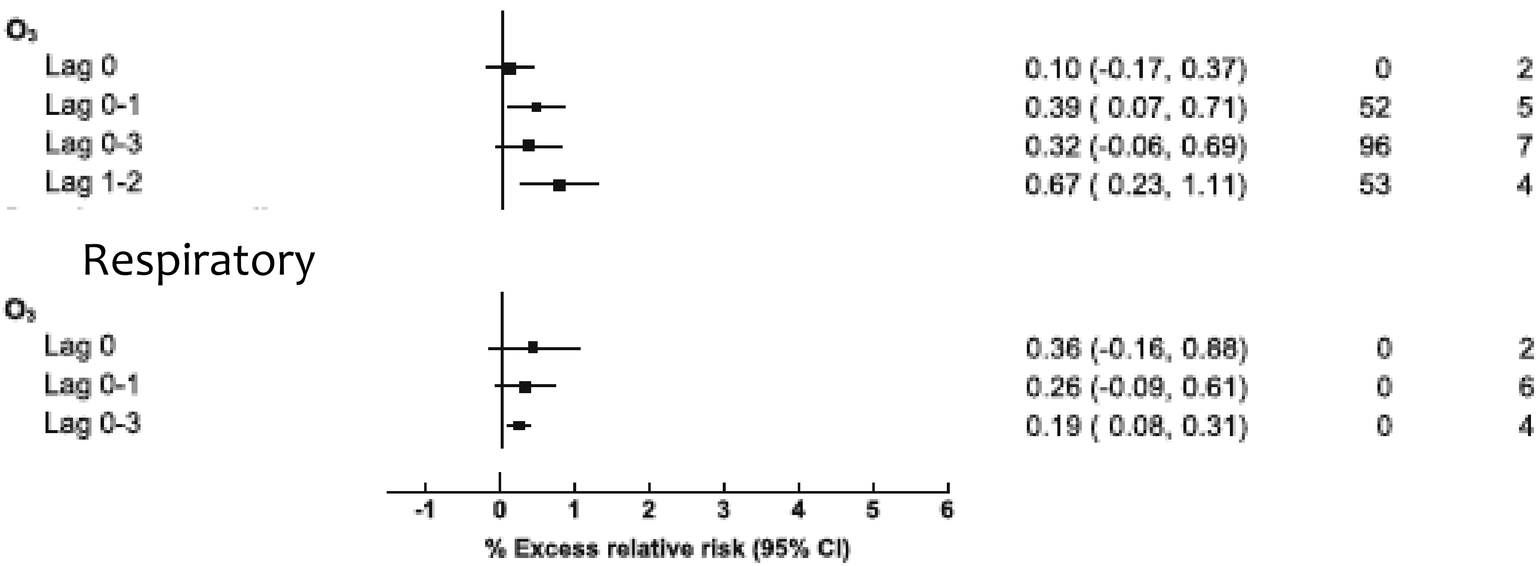
Environmental Health

RESEARCH Open Access

Cardiorespiratory health effects of gaseous ambient air pollution exposure in low and middle income countries: a systematic review and meta-analysis

Katherine Newell[1*], Christiana Kartsonaki[1,2], Kin Bong Hubert Lam[1] and Om Kurmi[1]

Cardiovascular



Respiratory Effects of OZone Exposure in Greek Children

- Panel study with 97 10-11 year old students of state elementary schools from Athens and from Thessaloniki, Greece (N = 176).
- Field work during the academic year 2013-14. Five intensive field work weeks: two in fall; one in winter; two in spring/summer period.
- Exposure: Weekly personal O_3 measurements for 5 weeks & Calibrated outdoor long-term exposure

Table 1. Weekly & long-term air pollution concentrations by city and area of high or low O_3 concentrations. Data are presented as mean (SD).

	Athens		Thessaloniki	
Environmental indicator	Low (n=37)	High (n=60)	Low (n=32)	High (n=57)
O_3 personal measurements (weekly; μg/m^3)	8.2 (6.7)	10.8 (7.8)	4.7 (4.8)	5.9 (6.6)
Calibrated outdoor long-term O_3 exposure (μg/m^3)	44.9 (19.7)	89.8 (35.7)	21.1 (10.7)	36.6 (28.3)
O_3 outdoor at schools (weekly; μg/m^3)	45.9 (14.7)	64.3 (20.1)	35.2 (20.7)	45.6 (19.4)
O_3 at fixed sites (weekly; μg/m^3)	24.6 (13.8)	63.8 (16.4)	36.3 (16.7)	41.3 (18.5)
PM_{10} at fixed sites (weekly; μg/m^3)	28.9 (7.4)	23.1 (7.1)	18.9 (3.8)	21.0 (9.3)

Short-term Effects

- Evidence base strengthened since last Integrated Science Assessment review
- Determination of a causal relationship between ozone and short-term respiratory effects unlikely to change
- Cardiovascular disease (CVD) effects may be upgraded to likely to be causal or causal depending on toxicology, chamber, quasi-experimental evidence

Evidence on Long-term Mortality

* Several major studies have appeared in the past 3 years on ozone and mortality
* American Cancer Society Cancer Prevention II study (ACS CPS II) with extended follow up and vastly improved exposure assignment
* Canadian Census Health and Environment Cohort (CanCHEC)
* Harvard Medicare Study

Key Characteristics

* Bigger sample sizes more than 60,000,000 in the Harvard study, more than 2,500,000 in CanCHEC and 670,000 in ACS
* Previous largest study was Jerrett et al. (2009) 440,000
* Improved exposure modeling with machine learning, remote sensing and ground data
* Better control for co-pollutants
* Worse control for individual confounders

Key Characteristics

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Long-Term Ozone Exposure and Mortality

Michael Jerrett, Ph.D., Richard T. Burnett, Ph.D., C. Arden Pope III, Ph.D.,
Kazuhiko Ito, Ph.D., George Thurston, Sc.D., Daniel Krewski, Ph.D.,
Yuanli Shi, M.D., Eugenia Calle, Ph.D., and Michael Thun, M.D.

- and
- 440,000
- Improved exposure modeling with machine learning, remote sensing and ground data
- Better control for co-pollutants
- Worse control for individual confounders

ACS CPS II New Findings

ORIGINAL ARTICLE

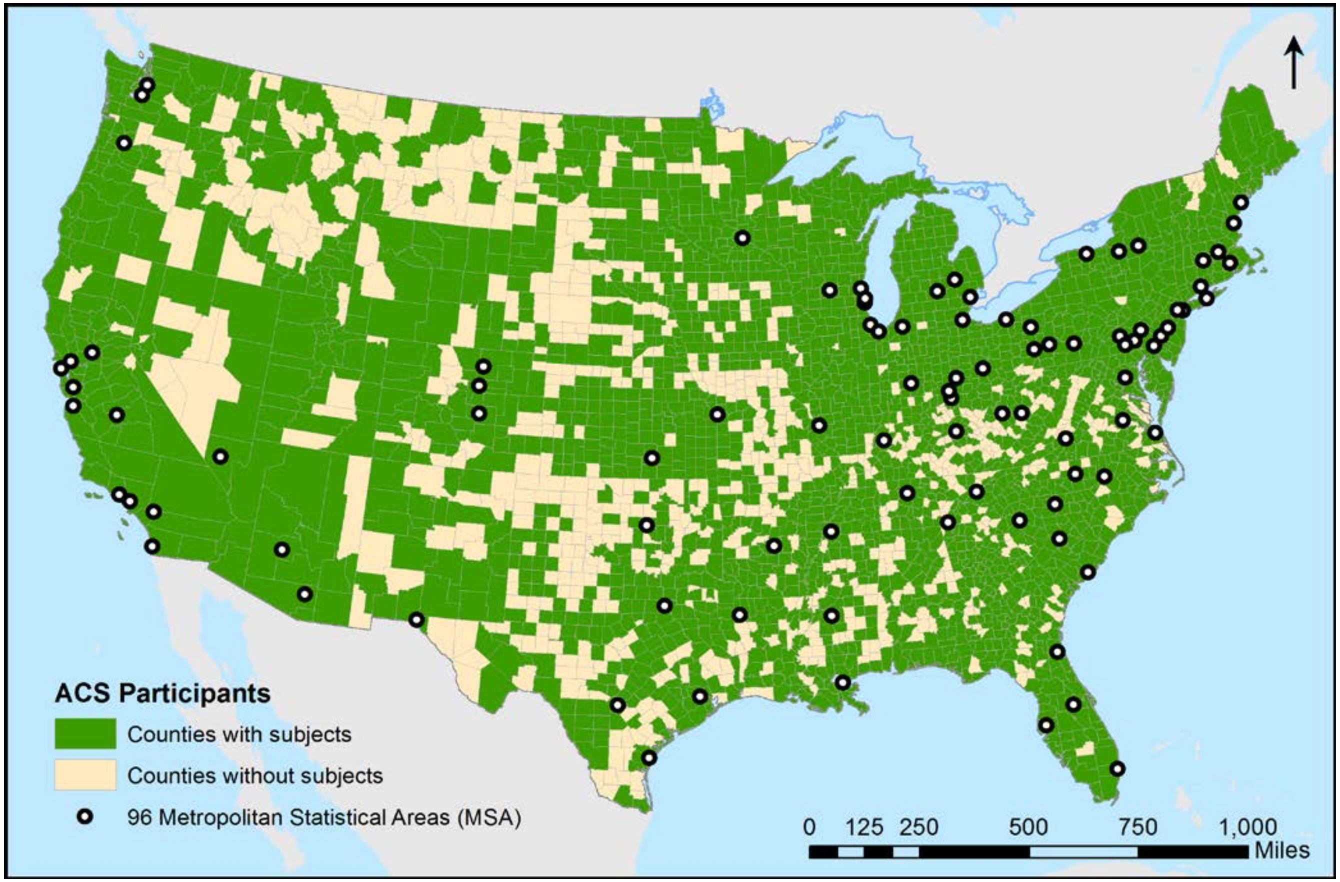
Long-Term Ozone Exposure and Mortality in a Large Prospective Study

Michelle C. Turner[1,2,3,4], Michael Jerrett[5], C. Arden Pope III[6], Daniel Krewski[1,7], Susan M. Gapstur[8], W. Ryan Diver[8], Bernardo S. Beckerman[5], Julian D. Marshall[9], Jason Su[5], Daniel L. Crouse[10], and Richard T. Burnett[11]

[1]McLaughlin Centre for Population Health Risk Assessment and [7]School of Epidemiology, Public Health and Disease Prevention, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [2]Centre for Research in Environmental Epidemiology, Barcelona, Spain; [3]Universitat Pompeu Fabra, Barcelona, Spain; [4]CIBER Epidemiología y Salud Pública, Madrid, Spain; [5]Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California; [6]Department of Economics, Brigham Young University, Provo, Utah; [8]Epidemiology Research Program, American Cancer Society, Atlanta, Georgia; [9]Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington; [10]Department of Sociology, University of New Brunswick, Fredericton, New Brunswick, Canada; and [11]Population Studies Division, Health Canada, Ottawa, Ontario, Canada

ACS CPS II Study Population

* 669,046 CPS-II participants
* 237,201 all-cause deaths (1982-2004)



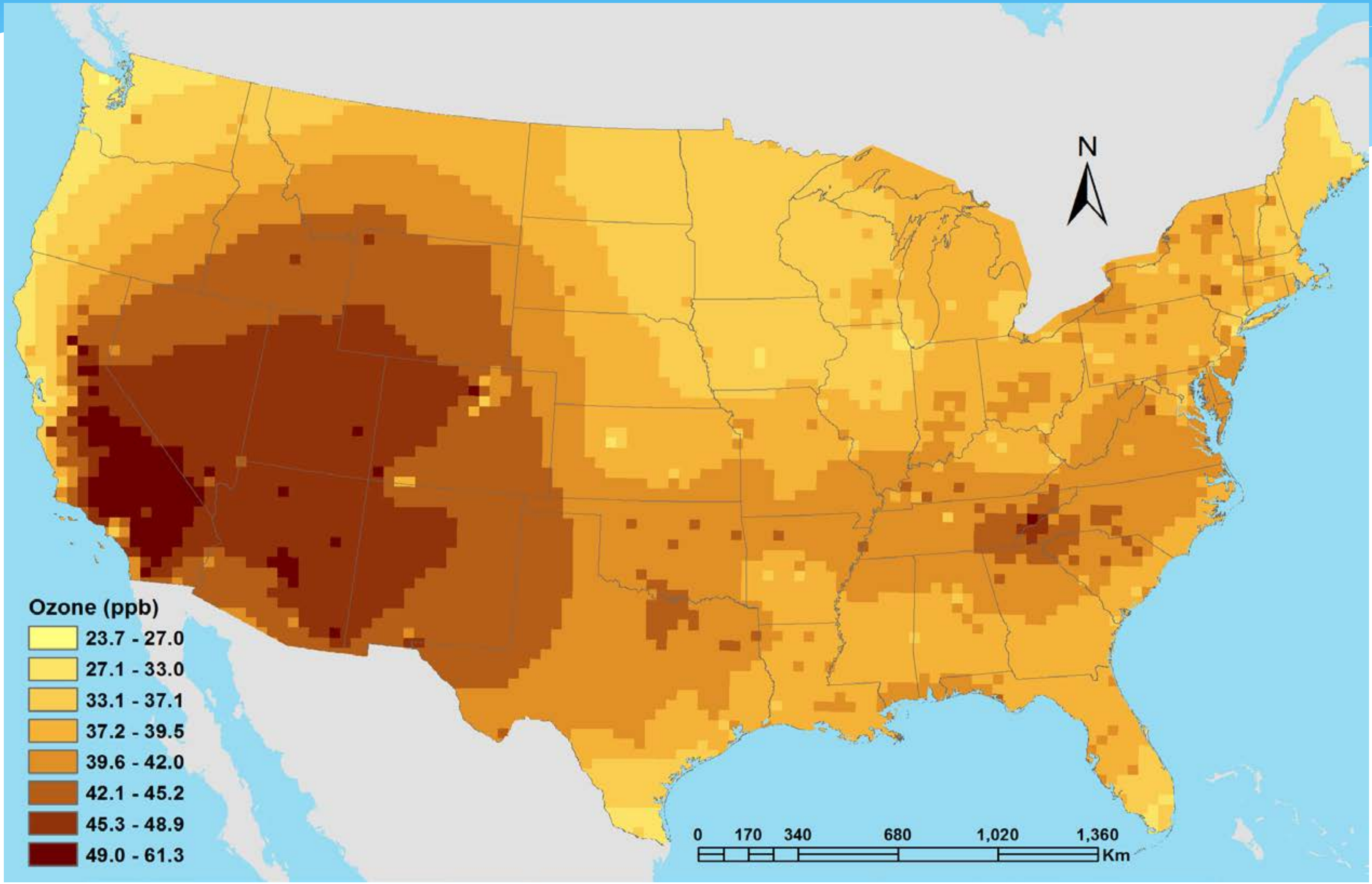
Methods

* O_3 concentrations
  * EPA Bayesian space-time hierarchical model (2002-2004)
    * Mean annual daily 8-hour maximum
    * 36 x 36 km grid level
* $PM_{2.5}$ concentrations
  * National-level hybrid land use regression (LUR) and Bayesian maximum entropy (BME) interpolation model (1999-2004) 50 m grid

* Statistical Analysis – Cox proportional hazards regression

* Control applied for 44 individual (e.g., smoking, occupation, education, nutrition) and 17 ecologic (e.g., unemployment, air conditioning, poverty, temperature) confounders in multilevel Cox models

Mean annual daily 8-hour maximum O_3 concentrations, Hierarchical Bayesian Space Time Modeling System, US, 2002-2004



Multi-Pollutant Models (per 10 units)

		O_3	$PM_{2.5}$ LURBME-LUR	$PM_{2.5}$ LUR
Cause of Death	No. of Deaths	Fully-adjusted HR (95% CI)[a]	Fully-adjusted HR (95% CI)[a]	Fully-adjusted HR (95% CI)[a]
All-cause	237,201	1.02 (1.01-1.04)	1.05 (1.03-1.06)	1.30 (1.24-1.37)
Circulatory	105,039	1.03 (1.01-1.05)	1.08 (1.06-1.11)	1.50 (1.39-1.62)
Cardiovascular	84,132	1.03 (1.01-1.05)	1.09 (1.06-1.12)	1.46 (1.34-1.59)
Ischemic heart disease	45,644	0.97 (0.95-1.00)	1.11 (1.07-1.15)	1.73 (1.54-1.94)
Respiratory	20,484	1.12 (1.08-1.16)	1.11 (1.05-1.17)	1.15 (0.98-1.36)

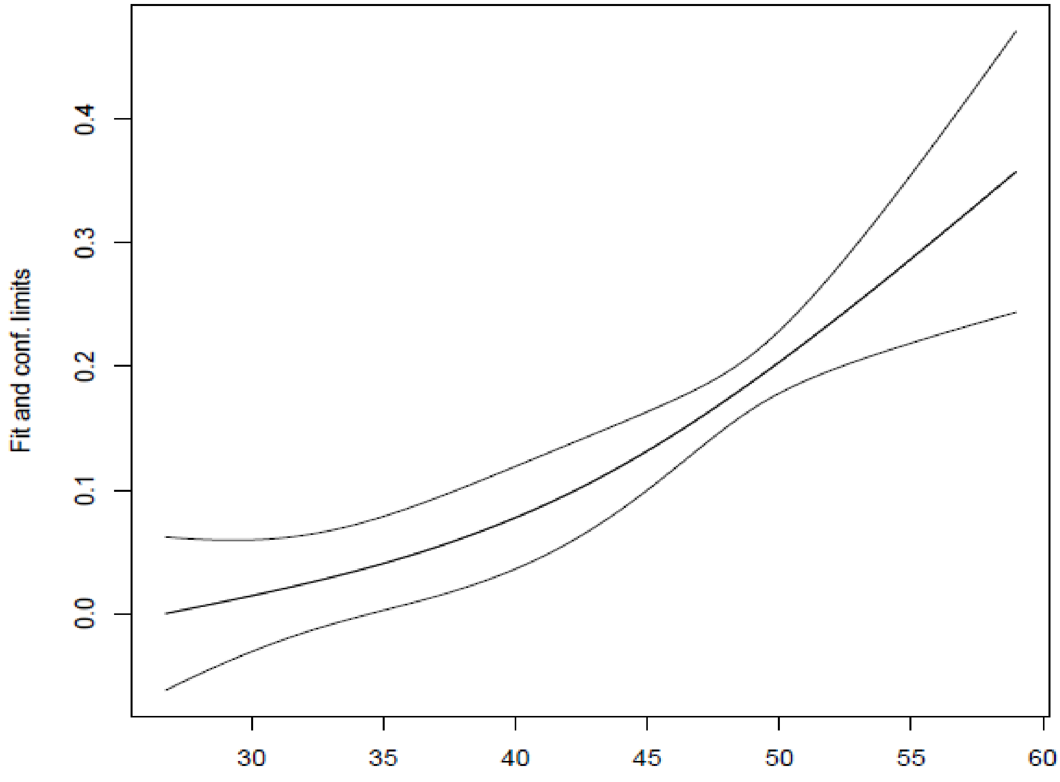
Key Points:

Now see ozone effects for all cause, circulatory and cardiovascular even with control for co-pollutants and 54 confounders

Respiratory effects are much larger than in Jerrett et al. (2009)

Threshold Present for Respiratory Mortality

* Respiratory mortality
  * 34-35 ppb annual O_3 (p = 0.002)



The NEW ENGLAND JOURNAL of MEDICINE

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Air Pollution and Mortality in the Medicare Population

Qian Di, M.S., Yan Wang, M.S., Antonella Zanobetti, Ph.D., Yun Wang, Ph.D., Petros Koutrakis, Ph.D., Christine Choirat, Ph.D., Francesca Dominici, Ph.D., and Joel D. Schwartz, Ph.D.

Methods Summary

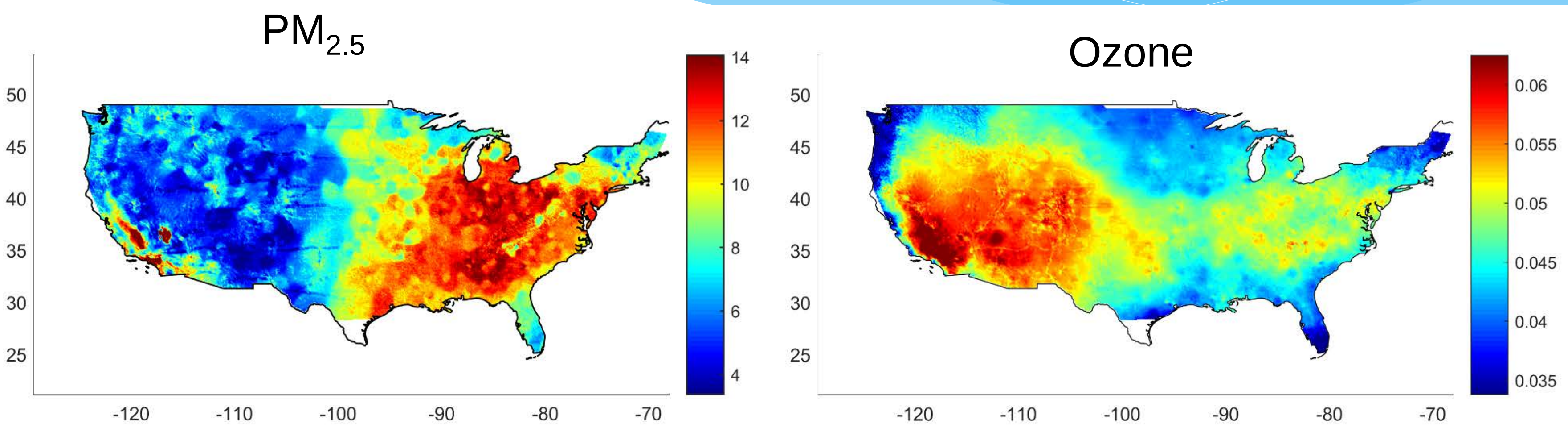
- All Medicare participants (n=67,682,479) in the continental United States from 2000 to 2012
- Outcome: all-cause mortality
- Cox proportional hazards model
- Covariates:
  - Date of death, age of entry, year of entry, sex, race, whether eligible for Medicaid (proxy for SES), and ZIP code of residence
  - Numerous ecological variables for SES, lifestyle, demography, and medical care

SES = socioeconomic status

Exposure assessment

Neural network:

satellite-based measurements, simulation outputs from a chemical transport model (CTM), land-use terms and other ancillary data



- Cross-validated correlation:
- R^2=0.84 for $PM_{2.5}$
- R^2=0.76 for ozone on held out monitors

Results

Table 2. Risk of Death Associated with an Increase of 10 μg per Cubic Meter in $PM_{2.5}$ or an Increase of 10 ppb in Ozone Concentration.*

Model	$PM_{2.5}$	Ozone
	hazard ratio (95% CI)	
Two-pollutant analysis		
Main analysis	1.073 (1.071–1.075)	1.011 (1.010–1.012)
Low-exposure analysis	1.136 (1.131–1.141)	1.010 (1.009–1.011)
Analysis based on data from nearest monitoring site (nearest-monitor analysis)†	1.061 (1.059–1.063)	1.001 (1.000–1.002)
Single-pollutant analysis‡	1.084 (1.081–1.086)	1.023 (1.022–1.024)

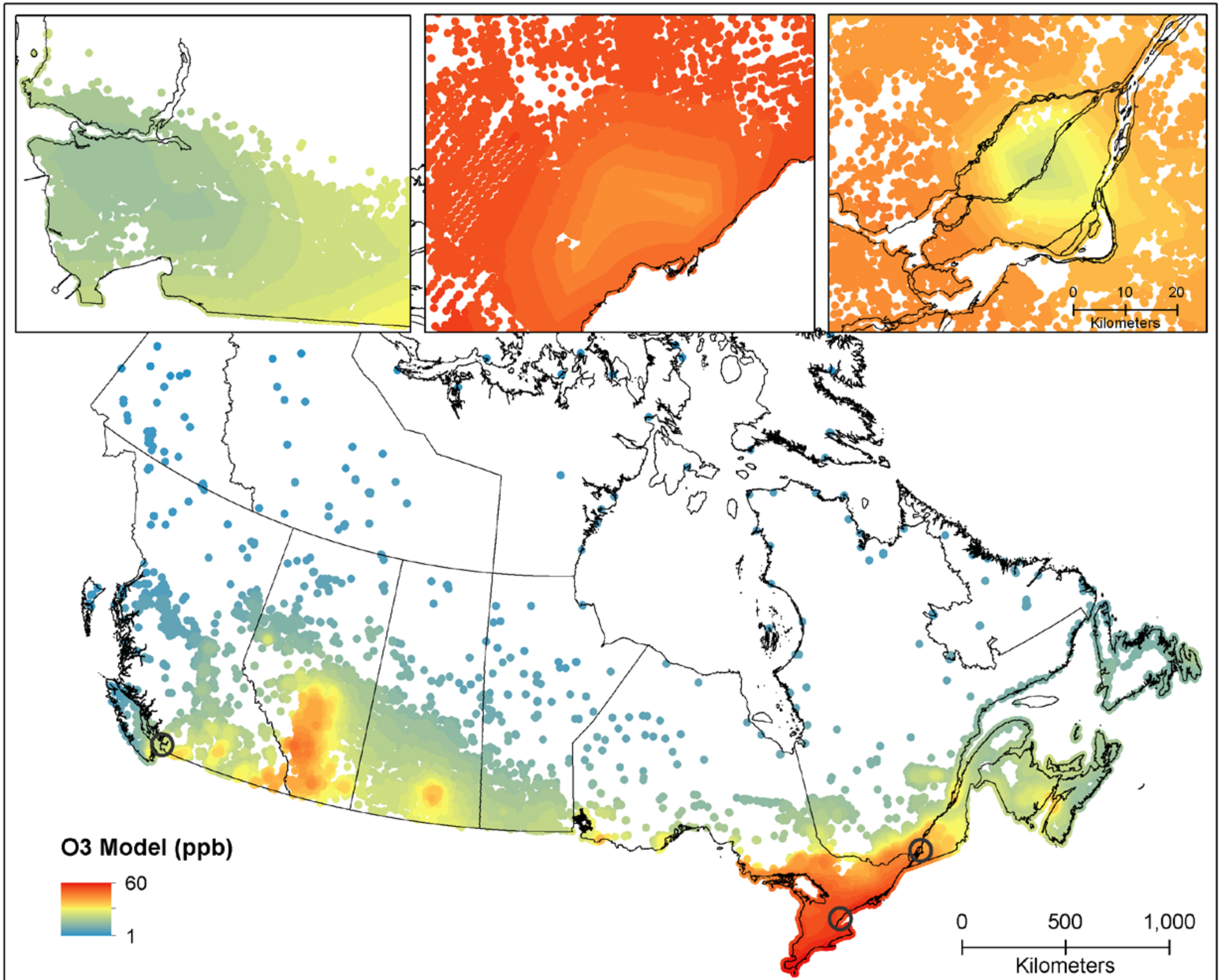
- 10 ppb increase in ozone ~ 1.1% increase in mortality
- 10 ppb increase in ozone ~ 1.0% increase in mortality below 50 ppb

Ambient $PM_{2.5}$, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC)

Dan L. Crouse,[1,2] Paul A. Peters,[2] Perry Hystad,[3] Jeffrey R. Brook,[4,5] Aaron van Donkelaar,[6] Randall V. Martin,[6] Paul J. Villeneuve,[7] Michael Jerrett,[8] Mark S. Goldberg,[9,10] C. Arden Pope III,[11] Michael Brauer,[12] Robert D. Brook,[13] Alain Robichaud,[14] Richard Menard,[14] and Richard T. Burnett[1]

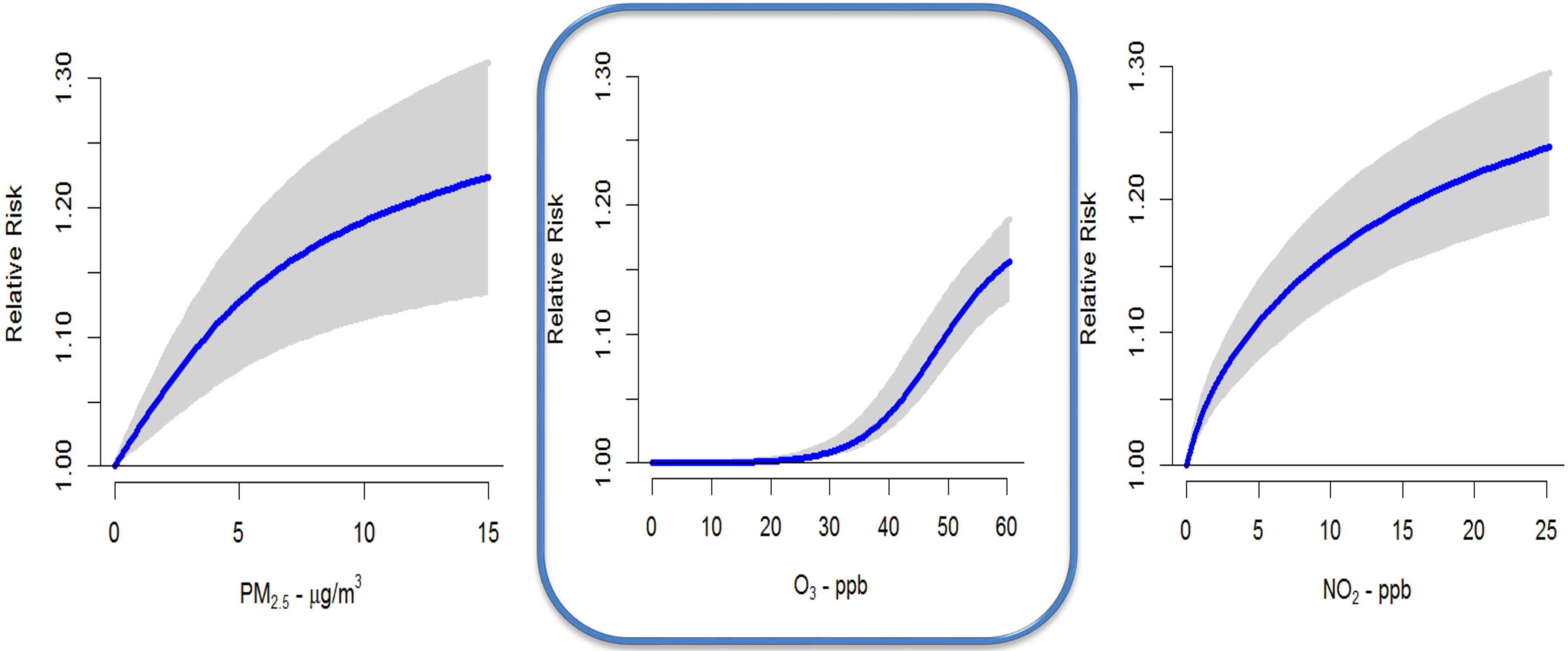
- Canadian Census Health and Environment Cohort
- N= 2,521,525
- 16 year follow up from 2001 onward
- Linked to mortality and tax files
- BUT no direct information on smoking, BMI, etc. so indirect adjustments made
- Ozone modeled with chemical transport model from Environment Canada
- Cox proportional hazards used for associative evaluation

BMI = body mass index



0
10
20
Kilometers
O3 Model (ppb)
60
1
0
500
1,000
Kilometers

Joint Non-Linear Three Pollutant Relative Risk Model (2001 CanCHEC Non-Accidental Mortality)



Source: Burnett personal communication

Synthesis of Results on Long-term Exposure and Mortality

* 3 very large cohorts all show ozone effects on total mortality, and some on CVD mortality, diabetes, and respiratory mortality

* Effects not confounded by co-pollutants of $PM_{2.5}$ and NO_2

CVD = cardiovascular disease

Overall Conclusions

* Huge increase in studies from Asia on short-term effects generally corroborating findings from earlier European and North American studies, with a few exceptions
* Strengthens overall evidence of short-term effects on cardiovascular and respiratory disease
* Substantial increase in long-term effects on mortality from large studies in areas of relatively low exposure
* Evidence of thresholds that are well below the current regulatory standard

Conclusion (Cont’d)

* Growing evidence of cardiometabolic effects (particularly diabetes and metabolic biomarkers), both short term and long term

* Stronger evidence of central nervous system and psychiatric effects

* Panel designs, quasi-experimental studies and long-term studies emphasize importance of high quality exposure assessment

* Some evidence of effect modification by age, gender, race, ethnicity, obesity, area deprivation, and weather patterns

Acknowledgements

- National Institute of Environmental Health Science
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- California Air Resources Board for assistance with ozone monitoring
- Rick Burnett, Francesca Dominici, Klea Katsouyanni Jason Su, and Michelle Turner for kindly sharing slides and preliminary results