RESEARCH REPORT

HEALTH EFFECTS INSTITUTE

Number 206
July 2021

Social Susceptibility to Multiple Air Pollutants in Cardiovascular Disease

Jane E. Clougherty, Jamie L. Humphrey, Ellen J. Kinnee, Lucy F. Robinson, Leslie A. McClure, Laura D. Kubzansky, and Colleen E. Reid

ISSN 1041-5505 (print)
ISSN 2688-6855 (online)

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with a Critique by the HEI Review Committee

Research Report 206

Health Effects Institute

Boston, Massachusetts

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Publishing history: This document was posted at *www.healtheffects.org* in July 2021.

Citation for document:

Clougherty JE, Humphrey JL, Kinnee EJ, Robinson LF, McClure LA, Kubzansky LD, Reid CE. 2021. Social Susceptibility to Multiple Air Pollutants in Cardiovascular Disease. Research Report 206. Boston, MA:Health Effects Institute.

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

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All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 206, *Social Susceptibility to Multiple Air Pollutants in Cardiovascular Disease,* presents a research project funded by the Health Effects Institute and conducted by Dr. Jane E. Clougherty of Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania, and her colleagues. The report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The Investigators' Report, prepared by Clougherty and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Critique, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Critique reflects the information provided in the final version of the report.

HEI STATEMENT
Synopsis of Research Report 206

Susceptibility to Multiple Air Pollutants from Social Stressors in Patients with Cardiovascular Disease

INTRODUCTION

There is ample epidemiological and toxicological evidence that short- and long-term exposures to ambient air pollutants are associated with CVD events such as heart attacks and stroke. At the same time, evidence also indicates that the likelihood of CVD events is associated with social and economic disadvantage factors.

In the United States, population subgroups with lower socioeconomic status, which are primarily non-White, and which encounter other adverse social and community-based stressors, experience disproportionately higher levels of air pollution compared with other population subgroups. Because of the interplay between air pollution exposures, social stressors, and CVD outcomes, disentangling the role of social stressors as modifiers or confounders of the associations between air pollution and CVD is imperative to identify potentially vulnerable populations and to provide the additional scientific evidence needed to support mitigation measures.

In the current study, Dr. Jane Clougherty and colleagues sought to quantify the combined effects of exposures to multiple pollutants and stressors (e.g., violence and chronic stress) on CVD events and to identify which social stressors influence susceptibility to the health effects of air pollution, using data for 1.1 million people living in New York City (NYC).

APPROACH

Clougherty and colleagues pursued three specific aims. The first aim was to assess whether social stressors confound or modify the relationships between CVD events and air pollutant exposures. It

What This Study Adds

- This study examined whether the associations between community- and individual-level cardiovascular disease (CVD) events and ambient air pollutant concentrations vary with social stress.
- Unique datasets included data on CVD events in all New York City hospitals, citywide levels of fine particulate matter, nitrogen dioxide, sulfur dioxide, and ozone, community-level social stressors, and noise disturbance.
- The study demonstrated that variations in the social stressors in NYC were associated with CVD events, reinforcing the importance of considering such stressors in air pollution health analyses.
- At the same time, the study found that associations between the pollutants and CVD were attenuated when adjusting for social stressors.
- Given the several limitations in the analysis, the HEI Review Committee disagreed with the investigators' interpretation of Aim 3 results that associations between air pollution and CVD were stronger in communities with higher stressor levels.
- Future studies attempting to disentangle social stressor from air pollution effects on CVD events should build on the steps taken here by further investigating important social stressor confounders and modifiers.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Jane E. Clougherty at Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania, and colleagues. Research Report 206 contains both the detailed Investigators' Report and a Critique of the study prepared by the Institute's Review Committee.

also assessed the separate and combined associations of stressors and air pollutants with CVD events, all estimated at the same spatial (census-tract) resolution and annual timescale. The second aim was to examine the association between daily average exposures to individual pollutants and copollutants and the short-term individual-level risk of CVD events, evaluating exposures during multiple days before the CVD event. The third aim was to examine effect modification by community-level social stressors on the relationship between the short-term air pollution exposures and CVD events assessed in Aim 2.

The investigators used existing datasets for the health outcome analyses to construct air pollution exposure estimates and to characterize multiple social stressors. They obtained data on in- and outpatient CVD events between 2005 and 2011 from all NYC hospitals (1,113,185 events). Data on concentrations of fine particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone were obtained from the NYC Community Air Survey (NYCCAS). The data were collected between 2008 and 2010 over a 2-week period during each season from 155 sites across NYC, and provided information about spatial variability. To obtain information on temporal variability in air pollutant concentrations, the investigators used daily air pollution data from the U.S. Environmental Protection Agency (EPA)'s Air Quality System (AQS).

A unique aspect of this study was the use of many different datasets to obtain data on community-level social stressors (e.g., poverty metrics, violent crime rates, a socioeconomic deprivation index [SDI], and racial and economic segregation) and noise. The investigators then used statistical techniques to create social stressor indices that combined the many stressor variables into groups. These included the SDI, which represented material hardship; a variable representing racial and economic segregation; and three indices representing (1) violence and physical disorder, (2) crowding and poor resource access, and (3) noise and air pollution complaints collected from several datasets (U.S. Census, NYC Housing and Vacancy Survey, NYC Police Department, and NYC School Districts).

For Aim 1, Clougherty and colleagues applied 100 × 100–m concentration surfaces of each pollutant across the study area that NYCCAS had previously developed using a land use regression model combined with spatial smoothing. Associations of annual average pollutant concentrations and social-stressor exposures with annual CVD in- and outpatient hospitalizations at the census-tract level were analyzed using negative binomial regression models. The investigators conducted analyses using several mutually adjusted models (i.e., one pollutant and one stressor in the same model) and fully adjusted models (i.e., multiple pollutants and selected social stressors). They tested the sensitivity of their results to spatial autocorrelation and spatial scale and by running all main models with ischemic heart disease events (their most prevalent CVD subdiagnosis) as the health outcome.

For Aims 2 and 3, the investigators performed analyses at the individual level, including daily data for in-patient CVD events only (837,523) occurring over the study period (2005–2011). To adjust for non-time-varying covariates (e.g., age, race, and sex), the investigators implemented a case-crossover approach in which individuals with a CVD event served as their own control during a time when they did not have an event. Control days were selected using time-stratified sampling. The investigators assigned annual average NYCCAS pollutant concentrations to each geocoded residence, which they combined with daily citywide average AQS data to estimate exposures at each residence for up to 6 days preceding the event and referent dates.

For Aim 2, they used conditional logistical regression to examine associations between multiple pollutants on the day of the event and up to 6 days before and all CVD events and CVD subdiagnoses. They performed copollutant (i.e., multiple pollutants in one model) adjustments using penalized splines.

For Aim 3, the investigators evaluated effect modification in their same-day copollutant exposure models from Aim 2 by including interaction terms between each pollutant and the social stressor data subdivided into quintiles or into two groups divided by the median. The investigators also ran several sensitivity analyses.

KEY RESULTS

In Aim 1 models testing each pollutant independently against census-tract-level CVD events, the investigators reported positive associations with NO_2 and SO_2 concentrations and inverse associations with O_3 exposure. In the investigators'

assessment of confounding, results were attenuated in models including one pollutant and one stressor in the same model and in fully adjusted models. When they evaluated effect modification, the investigators reported stronger associations between SO_2 and CVD across quintiles of increasing poverty. They also reported that associations between NO_2, $PM_{2.5}$, or SO_2 and CVD were higher across quintiles of increasing felony assault and violent crime rates, based on using the *P* value for trend and *P* values for associations between air pollutants and CVD within strata of the stressors. There were no differences in the magnitude of associations between pollutants and CVD by quintiles of SDI, income, or ICE I&R.

When the investigators ran case-crossover models at the individual level to examine associations between copollutant exposures and CVD event (Aim 2), they reported an increase in CVD event risk per 10-unit increase in NO_2 (ppb) and $PM_{2.5}$ ($\mu g/m^3$) exposure and a decreased risk with O_3 (ppb) exposure on the day of the event (lag day 0). Associations reported between CVD events and NO_2 or $PM_{2.5}$ exposures across all other lag days (1 to 6 days before the event), and for any associations between CVD and wintertime SO_2 levels, were generally consistent with the null.

In their evaluation of social stressor effect modification at the individual level (Aim 3), the investigators did not report consistent increases in CVD risk with any of the pollutants across social stressor quintiles (e.g., a consistent increase in CVD events across communities with higher violent crime rates). They reported that NO_2 was positively associated with CVD in the highest quintile of community violence and SDI, which they supported with the *P* values for associations between air pollutants and CVD within individual stressor strata. Tests of interaction were consistent with the null for the UHF-level factor scores and noise.

REVIEW COMMITTEE EVALUATION

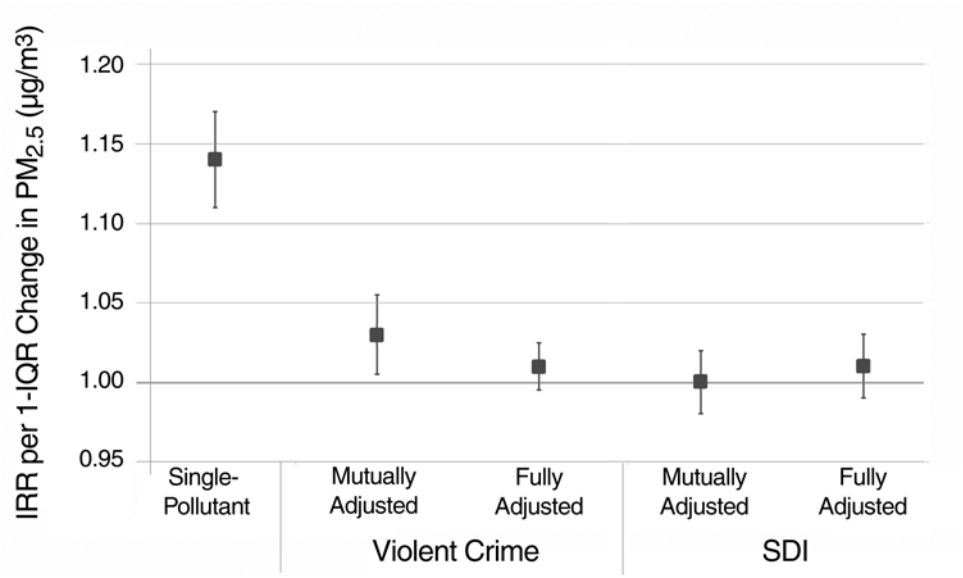
In its independent review of the study, the HEI Review Committee found that Clougherty and colleagues used several rich and well-validated data sources to address important questions about the role of social stressors as possible confounders or effect modifiers in investigations of the relationships between air pollutants and CVD events. The Committee appreciated the use of a case-crossover design to control for non-time-varying confounders in Aims 2 and 3. They also commended the investigators for their inclusion of noise as a potential stressor as well as their extensive sensitivity analyses to test and assess alternative approaches to the exposure assessments, stressor categorizations, and inclusion of copollutants in the models.

The Committee thought that a limitation of the study was the potential for temporal mismatch among the CVD data, exposure data, and stressor data because it was not always clear when temporal mismatches occurred or the potential implications for the results. They thought that exposure assessment could have been improved with a dataset incorporating day-to-day variations in spatial patterns of pollutant concentrations to fully capture the spatial and temporal variability.

The Committee also thought that the investigators could have improved their interpretation and presentation of social stressor confounding results in Aim 1 by comparing results from their three types of models: (1) single-pollutant models, (2) mutually adjusted models, and (3) fully adjusted models. This would have allowed them to identify and discuss the presence and magnitude of confounding for specific stressors more fully. The Statement Figure, for example, illustrates confounding by violent crime and the SDI for $PM_{2.5}$ using the results presented in the report, but displayed in a manner that allows for the reader to draw conclusions about the presence and magnitude of confounding. In this example, the investigators reported a positive association between $PM_{2.5}$ and CVD event rates. However, the results were attenuated when these stressors were added to the models.

In addition, the investigators' main conclusion for Aim 1 was that the associations between the social stressors and CVD events were stronger than those between the air pollutants and CVD events. There is an important caveat to this interpretation, which the investigators discussed in their report: the social stressors had large variability in this study and relatively large magnitudes of association with CVD, while the pollutants had relatively small variability across the study population and thus small magnitudes of association. Overall, the Committee thought that the investigators missed an opportunity to specify which stressors were important modifiers or confounders of the associations in Aim 1.

The Committee also disagreed with investigators' approach to interpreting and conclusions about effect



Statement Figure. Attenuation of the association between $PM_{2.5}$ and CVD event rates (Aim 1) when social stressors (violent crime or the SDI) were added to the models. Data are shown as the incidence rate ratio (IRR) with 95% confidence intervals per interquartile range (IQR) for $PM_{2.5}$ (1.37 µg/m³).

modification results. To support the conclusion that there was evidence of stronger associations in communities with worse stressor characteristics, the investigators used *P* values for associations within individual strata of the census-level stressors and tests for trend. The Committee thought that the more appropriate evidence to support conclusions about effect modification would have involved statistical tests of interaction, as discussed above, as well as discussion of differences among the IRRs between strata. The Committee's interpretation of the results in Aim 3 is that magnitude and direction of the associations varied greatly among the stressor categories.

CONCLUSIONS

The study helps highlight the importance of considering the role of distinct social stressors as risk factors for health outcomes such as CVD events. At the same time, the study added to the existing epidemiology literature on associations between air pollutant exposures and CVD events, while also examining the role of those social stressors on the relationships. It also added to the limited body of evidence exploring copollutant exposures and CVD.

There is a need for future studies to continue disentangling social stressor effects and build on the steps taken in this study. In particular, future studies should ensure systematic assessment of confounding and effect modification. They should also identify specific social stressors that act as confounders, identify the degree of potential confounding, and identify social stressor modifiers to help understand disproportionate susceptibility to pollution.

INVESTIGATORS' REPORT

Social Susceptibility to Multiple Air Pollutants in Cardiovascular Disease

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ABSTRACT

INTRODUCTION

Cardiovascular disease (CVD*) is the leading cause of death in the United States, and substantial research has linked ambient air pollution to elevated rates of CVD etiology and events. Much of this research identified increased effects of air pollution in lower socioeconomic position (SEP) communities, where pollution exposures are also often higher. The complex spatial confounding between air pollution and SEP makes it very challenging, however, to disentangle the impacts of these very different exposure types and to accurately assess their interactions.

The specific causal components (i.e., specific social stressors) underlying this SEP-related susceptibility remain unknown, because there are myriad pathways through which poverty and/or lower-SEP conditions may influence pollution susceptibility — including diet, smoking, co-exposures in the home and occupational environments, health behaviors, and healthcare access. Growing evidence suggests that a substantial portion of SEP-related susceptibility may be due to chronic psychosocial stress — given the known wide-ranging impacts of chronic stress on immune, endocrine, and metabolic function — and to a higher prevalence of unpredictable chronic stressors in many lower-SEP communities, including violence, job insecurity, and housing instability. As such, elucidating susceptibility to pollution in the etiology of CVD, and in the risk of CVD events, has been identified as a research priority.

This interplay among social and environmental conditions may be particularly relevant for CVD, because pollution and chronic stress both impact inflammation, metabolic function, oxidative stress, hypertension, atherosclerosis, and other processes relevant to CVD etiology. Because pollution exposures are often spatially patterned by SEP, disentangling their effects — and quantifying any interplay — is especially challenging. Doing so, however, would help to improve our ability to identify and characterize susceptible populations and to improve our understanding of how community stressors may alter responses to multiple air pollutants. More clearly characterizing susceptible populations will improve our ability to design and target interventions more effectively (and cost-effectively) and may reveal greater benefits of pollution reduction in susceptible communities, strengthening cost–benefit and accountability analyses, ultimately reducing the disproportionate burden of CVD and reducing health disparities.

This Investigators' Report is one part of Health Effects Institute Research Report 206, which also includes a Critique by the Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Jane E. Clougherty, 3215 Market Street, Room 616, Philadelphia, PA 19104; e-mail: *jec373@drexel.edu*. No potential conflict of interest was reported by the authors.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83467701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred. The authors report that this publication was produced from raw data purchased from or provided by the New York State Department of Health (NYSDOH). However, the conclusions derived, and views expressed herein are those of the author(s) and do not reflect the conclusions or views of NYSDOH. NYSDOH, its employees, officers, and agents make no representation, warranty or guarantee as to the accuracy, completeness, currency, or suitability of the information provided here.

* A list of abbreviations and other terms appears at the end of this volume.

METHODS

In the current study, we aimed to quantify combined effects of multiple pollutants and stressor exposures on CVD events, using a number of unique datasets we have compiled and verified, including the following:

1. Poverty metrics, violent crime rates, a composite socioeconomic deprivation index (SDI), an index of racial and economic segregation, noise disturbance metrics, and three composite spatial factors produced from a factor analysis of 27 community stressors. All indicators have citywide coverage and were verified against individual reports of stress and stressor exposure, in citywide focus groups and surveys.
2. Spatial surfaces for multiple pollutants from the New York City (NYC) Community Air Survey (NYCCAS), which monitored multiple pollutants year-round at 150 sites and used land use regression (LUR) modeling to estimate fine-scale (100-m) intra-urban spatial variance in fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3).
3. Daily data and time-trends derived from all U.S. Environmental Protection Agency (EPA) Air Quality System (AQS) monitors in NYC for 2005–2011, which we combined with NYCCAS surfaces to create residence- and day-specific spatiotemporal exposure estimates.
4. Complete data on in- and out-patient unscheduled CVD events presented in NYC hospitals for 2005–2011 (n = 1,113,185) from the New York State (NYS) Department of Health's Statewide Planning and Research Cooperative System (SPARCS).

In the study, we quantified relationships between multiple pollutant exposures and both community CVD event rates and individual risk of CVD events in NYC and tested whether pollution–CVD associations varied by community SEP and social stressor exposures. We hypothesized (1) that greater chronic community-level SEP, stressor, and pollution exposures would be associated with higher community CVD rates; (2) that spatiotemporal variations in multiple pollutants would be associated with excess risk of CVD events; and (3) that pollution–CVD associations would be stronger in communities of lower SEP or higher stressor exposures.

RESULTS

To first understand the separate and combined associations with CVD for both stressors and pollutants measured *at the same spatial and temporal scale of resolution*, we used ecological cross-sectional models to examine spatial relationships between multiple chronic pollutant and stressor exposures and age-adjusted community CVD rates. Using census-tract-level annual averages (n = 2,167), we compared associations with CVD rates for multiple pollutant concentrations and social stressors. We found that associations with community CVD rates were consistently stronger for social stressors than for pollutants, in terms of both magnitude and significance. We note, however, that this result may be driven by the relatively greater variation (on a proportional basis) for stressors than for pollutants in NYC. We also tested effect modification of pollutant–CVD associations by each social stressor and found evidence of stronger associations for NO_2, $PM_{2.5}$, and wintertime SO_2 with CVD rates, particularly across quintiles of increasing community violence or assault rates (P trend < 0.0001).

To examine individual-level associations between spatiotemporal exposures to multiple pollutants and the risk of CVD events, across multiple lag days, we examined the combined effects of multiple pollutant exposures, using spatiotemporal (day- and residence-specific) pollution exposure estimates and hospital data on individual CVD events in case-crossover models, which inherently adjust for non-time-varying individual confounders (e.g., sex and race) and comorbidities. We found consistent significant relationships only for *same-day* pollutant exposures and the risk of CVD events, suggesting very acute impacts of pollution on CVD risk. Associations with CVD were positive for NO_2, $PM_{2.5}$, and SO_2, as hypothesized, and we found inverse associations for O_3 (a secondary pollutant chemically decreased ["scavenged"] by fresh emissions that, in NYC, displays spatial and temporal patterns opposite those of NO_2).

Finally, to test effect modification by chronic community social stressors on the relationships between spatiotemporal pollution measures and the risk of CVD events, we used individual-level case-crossover models, adding interaction terms with categorical versions of each social stressor. We found that associations between NO_2 and the risk of CVD events were significantly elevated only in communities with the highest exposures to social stressors (i.e., in the highest quintiles of poverty, socioeconomic deprivation, violence, or assault). The largest positive associations for $PM_{2.5}$ and winter SO_2 were generally found in the highest-stressor communities but were not significant in any quintile. We again found inverse associations for O_3, which were likewise stronger for individuals living in communities with greater stressor exposures.

CONCLUSIONS

In ecological models, we found stronger relationships with community CVD rates for social stressors than for pollutant exposures. In case-crossover analyses, higher exposures to NO_2, $PM_{2.5}$, and SO_2 were associated with greater excess risk of CVD events but only on the case day (there were no consistent significant lagged-day effects).

In effect-modification analyses at both the community and individual level, we found evidence of stronger pollution–CVD associations in communities with higher stressor exposures. Given substantial spatial confounding across multiple social stressors, further research is needed to disentangle these effects in order to identify the predominant social stressors driving this observed differential susceptibility.

INTRODUCTION

CVD is the leading cause of death in the United States, and substantial research has linked ambient air pollution to elevated rates of CVD etiology and increased risk of CVD events (Franklin et al. 2015; Kaufman et al. 2016a; Pope et al. 2004). Research has identified increased effects of pollution in lower-SEP communities (Jerrett et al. 2004; Jones et al. 2014; Kravitz-Wirtz et al. 2016; Krewski et al. 2003, Morello-Frosch et al. 2011; Villeneuve et al. 2003). The specific social stressors underlying SEP-related susceptibility, however, remain unidentified (Gallo and Matthews 2003; Matthews and Gallo 2011); as a result, better characterization of this SEP-related susceptibility to pollution, particularly as it relates to CVD risk, has been identified as a research priority (Brook et al. 2004, 2010; Brook and Rajagopalan 2017).

Growing evidence suggests that chronic social stressors (e.g., violence and job insecurity) may play an important role in explaining SEP-related susceptibility to pollution, given substantial evidence that chronic stress strongly impacts immune, endocrine, and metabolic function (McEwen 1998a, 1998b, 2012, 2017; McEwen and Seeman 1999; McEwen and Tucker 2011; Snyder-Mackler et al. 2016). Combined effects of pollutant and stressor exposures may be particularly relevant for CVD (Hajat et al. 2013; Hicken et al. 2013, 2014, 2016), because both impact inflammation, metabolic function, oxidative stress, hypertension, atherosclerosis, and systemic function (Bartoli et al. 2009a,b; Brook et al. 2010; Du et al. 2016; Everson-Rose et al. 2015; Franklin et al. 2015; Godleski 2006; Kaufman et al. 2016b; Kubzansky et al. 1997, 2007; Kubzansky and Kawachi 2000).

Because pollution is often spatially patterned by SEP (Jones et al. 2014), disentangling the effects — and quantifying any potential interplay — is especially challenging. Doing so, however, will help to more precisely identify and characterize susceptible populations as well as to target interventions more effectively (and cost-effectively) and may reveal greater benefits of pollution reduction in key communities, strengthening cost–benefit and accountability analyses.

BACKGROUND

AIR POLLUTION AND CARDIOVASCULAR DISEASE

Epidemiological evidence has consistently linked urban air pollution to CVD (Franklin et al. 2015; Kaufman et al. 2016a), the leading cause of death in the United States and worldwide (Kochanek et al. 2019). Urban $PM_{2.5}$ has been linked with higher risk of myocardial infarction (MI) (Miller et al. 2007) and cardiovascular mortality (Gehring et al. 2006; Thurston et al. 2016) and to intermediate endpoints, including increased blood plasma viscosity (Peters et al. 1997), lowered heart rate variability (Park et al. 2008), systemic inflammation (Calderon-Garciduenas et al. 2007; Hoffmann et al. 2009), hypertension (Adar et al. 2018; Harrabi et al. 2006), and atherosclerosis (Kunzli et al. 2010). Animal studies have linked air pollution to higher blood pressure (Bartoli et al. 2009a,b; Godleski 2006; Godleski et al. 2000; Lamoureux et al. 2012) and to CVD through a number of pathways (Fiordelisi et al. 2017), including inflammation (Zeka et al. 2006), autonomic imbalance (Sanidas et al. 2017), vasoconstriction and structural alterations (Bhatnagar 2017), oxidative stress (Kelly and Fussell 2017; Nel et al. 2001), electrophysiologial changes (Ghelfi et al. 2008), and vascular impacts of circulating $PM_{2.5}$ constituents (Diaz et al. 2012; Godleski et al. 2000).

SOCIOECONOMIC POSITION AND CARDIOVASCULAR DISEASE

A vast literature has linked lower SEP to increased prevalence and severity of CVD (Diez Roux et al. 2016; Pickering 1999; Rose and Marmot 1981; Schultz et al. 2018). CVD is disproportionately prevalent in lower-SEP communities (James et al. 2006; Lee et al. 2001; Thurston et al. 2005), which may be due in part to heightened air pollution exposures (Bhatnagar 2017; Fuller et al. 2017), which are often concentrated in lower-SEP communities (Clark et al. 2014), and also to a host of other chemical and nonchemical risk factors for CVD often clustered by SEP (Barber et al. 2016; Evans and Kim 2010; Hazlehurst et al. 2018; Rider et al. 2014; Schulz et al. 2008; Sharma et al. 2004).

Substantial evidence has linked chronic stress to the etiology and exacerbation of CVD (Everson-Rose et al. 2015, Hagstrom et al. 2018; Vale 2005) and risk factors, including hypertension (Dimsdale 2008; Spruill 2010). In fact, chronic stress is hypothesized to explain much of the impact of SEP on CVD risk (Pickering 1999; Steptoe and Kivimäki 2012), given consistent evidence of a role for stress responsivity in the etiology of CVD (Kivimäki 2018;

Steptoe et al. 2002) and evidence linking negative affect to subsequent risk of CVD (Kubzansky et al. 1997, 1998, 2007; Kubzansky and Kawachi 2000). Much of this research has linked CVD to specific stressors, including exposures to violence (Ford and Browning 2014), neighborhood disorder (Daniel et al. 2008; Diez Roux et al. 2016; Kubzansky et al. 2005), intimate partner violence (Wright et al. 2019), and workplace stressors (Chandola et al. 2008; Clougherty et al. 2009, 2010; Eller et al. 2009; Kivimäki et al. 2006).

Recent studies, including the Multi-Ethnic Study of Atherosclerosis (MESA), have provided insight into the role of air pollution in preclinical cardiovascular risk (Kaufman et al. 2016), with specific attention to community SEP and chronic stressor exposures, both independently and in combination with air pollution exposures (Chi et al. 2016; Hajat et al. 2013; Hicken et al. 2016). MESA has documented variations in cardiovascular responses to air pollution by race (i.e., elevated left ventricular mass index and left ventricular ejection fraction with $PM_{2.5}$ and nitrogen oxides [NO_x] among Blacks compared with other races) (Everson-Rose et al. 2015) and has examined the role of neighborhood segregation and discrimination in shaping cardiovascular risk (Jones et al. 2014, Kershaw et al. 2015).

DIFFERENTIAL SUSCEPTIBILITY TO AIR POLLUTION BY SOCIOECONOMIC POSITION AND CHRONIC STRESSORS IN CARDIOVASCULAR RISK

The potential synergy between chronic stress and pollution is particularly relevant for CVD, because both stress and pollution have been linked to relevant pathways, including hypertension, inflammation, impaired metabolic function, low heart rate variability, and atherosclerosis (Hazlehurst et al. 2018; Spruill 2010), as well as to CVD diagnosis (Fuller et al. 2017; Hazlehurst et al. 2018; Hicken et al. 2016). Evidence has suggested that SEP-related susceptibility to pollution may be explained in part through chronic stress (Clougherty and Kubzansky 2009; Clougherty et al. 2014). Chronic stress and air pollution impact many common physiological systems (Cory-Slechta et al. 2013; Erickson and Arbour 2014; Li et al. 2017; Sass et al. 2017; Virgolini et al. 2005), including immune and endocrine function (Segerstrom and Miller 2004), catecholamine production (i.e., epinephrine, norepinephrine, and growth hormone) (Glaser and Kiecolt-Glaser 2005), cytokine (e.g., interleukin 6 and immunoglobulin E production) (Miller et al. 2002), and oxidative stress (Bhattacharya et al. 2001). More recent evidence has identified epigenetic effects of stress (especially early life stress) that may influence pollution susceptibility (Madrigano et al. 2012) through DNA methylation, particularly at the NR3C1 gene, which is key to hypothalamic-pituitary-adrenal axis response to stress (Mulligan 2016; Turecki and Meaney 2016). Finally, some recent evidence has suggested that stress–pollution synergies may be bidirectional, in that pollution may directly impact cognitive and emotional well-being, hypothalamic-pituitary-adrenal axis function, and stress responsivity (Brook and Rajagopalan 2017; Kristiansson et al. 2015; Li et al. 2017; Oudin et al. 2018; Sass et al. 2017).

Despite the plausibility of stress–pollution interactions in CVD, evidence to date has not been conclusive. The MESA study, for example, found mixed evidence of social–environmental interactions (Hicken et al. 2013), in part due to higher pollution exposures in higher-SEP communities in some cities. We have built on this framework, using a larger dataset that represents the full population-at-risk in NYC, and have attempted to "unpack" SEP by examining specific stressors that may drive SEP-related pollutant susceptibility.

LITERATURE GAPS

The current study primarily aims to address a key gap in the literature — specifically, the fact that, although many studies have observed SEP altering observed health effects of air pollution, relatively few have aimed to unpack the SEP construct itself by testing which of the many potential stressors underlying SEP-related stressors may actually modify air pollution's health effects.

In addition, relatively few studies have been able to examine multiple pollutants (with co-pollutant adjustment), across multiple lag days, at very fine spatial and temporal scales, on a large number of CVD subdiagnoses, using exhaustive emergency department data for the region of interest — or have considered such a broad a range of social susceptibility factors.

Finally, confounding between air pollutants and social factors remains an important and unresolved issue in the literature. Our ecological analysis, which compares air pollution and social stressors on the same spatial and temporal scales of resolution, is designed to help address this gap, as is our focus on NYC, which has relatively high air pollution exposures in both high- and low-SEP neighborhoods.

In the current study, we quantified relationships between multiple pollutant exposures and CVD in NYC and tested whether pollution–CVD associations varied by community SEP and stressor exposures. We hypothesized the following: (1) that chronic community-level SEP, stressor, and pollution exposures would be associated with community CVD rates; (2) that spatiotemporal variation in multiple

pollutants would be associated with increased individual-level risk of CVD events; and (3) that pollution–CVD associations would be stronger in communities with lower-SEP or higher-stressor exposures.

SPECIFIC AIMS

We aimed to examine multiple pollutant exposures and susceptibility related to SEP in the large, highly diverse population of NYC, a city of eight million persons widely varying in SEP characteristics and pollution exposures. We did so by leveraging several existing datasets and methods, including the following:

1. A large existing geodatabase of community SEP and stressor indicators, which we previously verified against citywide focus-group and survey data (n = 1,589) on perceived community stressors and chronic stress;
2. Existing surfaces for fine-scale spatial variation in multiple pollutants from NYCCAS (Clougherty et al. 2013, Matte et al. 2013);
3. Daily data from all EPA AQS monitors in NYC for 2005–2011, which we combined with NYCCAS surfaces to create spatiotemporal exposure estimates;
4. Complete data on in- and out-patient unscheduled cardiovascular event visits (ICD-9 codes 390–459) in NYC hospitals for 2005–2011 from SPARCS (n = 1,113,185); and
5. Previously developed methods for case-crossover analyses with spatial interactions, allowing for spatiotemporal variation in pollution, spatial variation in community susceptibility, and co-pollutant analyses across multiple lag days.

Our study addressed the following aims.

Aim 1 To understand the separate and combined associations of CVD with both stressors and pollutants measured *at the same spatial and temporal scale of resolution*, we used ecological cross-sectional models to examine spatial relationships between multiple chronic pollutant and stressor exposures and age-adjusted community CVD rates (using in- and out-patient data). We tested cross-sectional ecological associations between annual-average pollutant exposures and social stressors — separately and in combination — against age-adjusted community CVD event rates, using data reported by census tract (n = 2,167) or United Hospital Fund (UHF) area (n = 34). (UHF areas are conglomerates of zip codes used for administrative purposes by the NYC Department of Health and Mental Hygiene [DOHMH].) We also used negative binomial models with and without adjustment for copollutants and other community stressors and tested for confounding and modification in pollutant–CVD associations by community SEP and social stressor indicators.

Aim 2 To examine spatiotemporal associations between each pollutant and individual-level risk of CVD event, we used spatiotemporal (day- and residence-specific) pollution exposure estimates and individual-level hospital data in case-crossover models, which inherently adjust for individual confounders and comorbidities, with and without adjustment for copollutants, temperature, and relative humidity (RH). We used case-level data on 837,523 in-patient (admitted) CVD events presented in emergency departments at NYC hospitals in 2005–2011, in case-crossover models.

Aim 3 To test effect modification by community-level SEP and/or social stressor exposures on the relationship between spatiotemporal pollution measures and individual-level CVD risk, we used the case-crossover models developed in Aim 2, adding interactions to test whether pollutant–CVD relationships differed by community SEP and/or social stressor indicators.

METHODS AND STUDY DESIGN

DATASETS

Our study leveraged a number of existing, previously validated datasets, detailed below, including (1) NYCCAS spatial data (surfaces) capturing fine-scale (100-m resolution) estimates of spatial variance in multiple pollutants; (2) daily EPA regulatory air pollution data from NYC monitoring stations for 2005–2011; (3) complete emergency department data on CVD events (ICD-9 codes 390–459 and specific diagnoses therein) in NYC hospitals for 2005–2011 from SPARCS; and (4) a number of geographic information system (GIS)–based citywide community socioeconomic and susceptibility indicators (stressors), previously verified against perceived stress measures in citywide focus groups and surveys.

New York City Hospitals' Cardiovascular Disease Data

We obtained complete data on in- and out-patient unscheduled cardiovascular events (ICD-9 codes 390–459) presented in NYC hospitals for 2005–2011 (n = 1,113,185) from SPARCS, a comprehensive data reporting system established as a cooperation between the healthcare industry and government. The system collects patient-level detail on patient characteristics, diagnoses and treatments,

services, and charges for each in-patient hospital stay, out-patient visit (ambulatory surgery, emergency department, and out-patient services), and visit to a hospital extension clinic licensed to provide ambulatory surgery services. All NYC hospitals are required to report data into SPARCS, with no known differential missingness by hospital; as such, our analysis represents the full population-at-risk for acute CVD events in NYC over the study period.

For purposes of our study, a "CVD event" was a new case presenting at a NYC hospital on the admission date listed. The case could be either "in-patient" (admitted to overnight stay in the hospital) or "out-patient" (discharged same day). To focus on acute events, we limited our analysis to cases listed under either of two admission types — "emergent" and "urgent" — both indicating events requiring immediate medical attention; the vast bulk of our cases were patients who were admitted through the emergency department.

Notably, by virtue of using hospital data on urgent and emergency encounters for CVD, we were not evaluating disease etiology per se, but rather testing associations between space–time patterns in pollution and the likelihood of acute CVD events. Accordingly, to further reduce misclassification in the outcome variable, we restricted individual-level analyses (Aims 2 and 3) to in-patient CVD visits (n = 837,523) to eliminate unverified or less severe cardiovascular events presenting at emergency departments (e.g., chest pain or tachycardia) that were unlikely to result in hospital admission. This restriction retained 75.2% of all CVD cases but 91.3%–95.9% of verified cases in each of our severe subdiagnosis categories (i.e., ischemic heart disease [IHD], heart failure [HF], stroke, ischemic stroke, and acute myocardial infarction).

Citywide Air Pollution Data

NYCCAS is one of the largest studies to date of intra-urban variation in multiple pollutants within one city. It was established by the DOHMH to inform local policy and air quality initiatives. The study's overall sampling design and quality control–quality assurance measures were detailed by Matte and colleagues (2013), and its modeling methods were detailed by Clougherty and colleagues (2013). Briefly, spatial saturation monitoring was performed year-round at 155 sites across all NYC communities for 2 years, from December 2008 to November 2010. The sites were selected via stratified random sampling to capture variations in the density of key sources (i.e., traffic and buildings) and their combinations and to provide spatial coverage across the communities. Two-week samples were collected on a randomized basis across sites; the sites were sampled for one 2-week session per season. Five additional reference sites (one per borough, generally in city parks and away from local sources) were sampled every session to account for temporal variance and long-term trends. All samples were collected at a height of 10–12 feet on light poles for consistency across sites.

Pollutants were selected to capture key local sources that were potentially amenable to policy intervention (i.e., SO_2 was examined due to its relatively high concentrations in the city and its specificity to residual oil-burning, which is used for heat and hot water in many large NYC buildings) and were previously associated with health in the peer-reviewed literature.

In the current study, we examined $PM_{2.5}$ — collected using Harvard Impactors (Air Diagnostics and Engineering, Harrison, ME) at 4 l/min for 15 min per hour over 2 weeks — and NO_2, SO_2, and O_3, all collected using Ogawa badges (Ogawa USA, Pompano Beach, FL) and analyzed at RTI International (Research Triangle Park, NC). O_3 was monitored only in summer, and SO_2 only in winter, when concentrations of each are elevated.

Intra-urban spatial variation in each pollutant was modeled using LUR methods, and final spatial surfaces (maps) were derived for a 100 × 100-m grid using kriging with external drift, which combines LUR model output with spatial smoothing (Clougherty et al. 2013). Prior work has established that the spatial variation captured by the spatial surfaces is highly stable across seasons and years – that is, locations remain consistently high, or consistently low, relative to the rest of the city, over time (New York City Department of Health and Mental Hygiene, 2015). These final spatial surfaces were used to create exposure estimates for all SPARCS CVD cases in the study, using the mean concentration at 100-m NYCCAS grid centroids within 300 m of each SPARCS residence, as shown in Figure 1.

Daily U.S. EPA Regulatory Air Pollution Data

To construct a time series for spatiotemporal pollutant exposure estimates, we retrieved hourly data from the EPA AQS regulatory monitoring stations in NYC for 2005–2011. We examined data coverage for each monitor and imputed missing values (based on long-term relationships among the monitors) to reduce potential spatial bias induced by any systematic missingness. We then calculated daily averages at each monitor and averaged them into one mean time trend for the city, as in Sheffield and colleagues (2015). We combined this final citywide time series from the monitors with NYCCAS spatial pollution surfaces to create day- and location-specific (our spatiotemporal) exposure estimates, as detailed below and in earlier publications (Ross et al. 2013; Shmool et al. 2015a).

Geographic Information System–Based Community Susceptibility Indicators

We examined effects of community-level susceptibility to air pollution using a range of community susceptibility

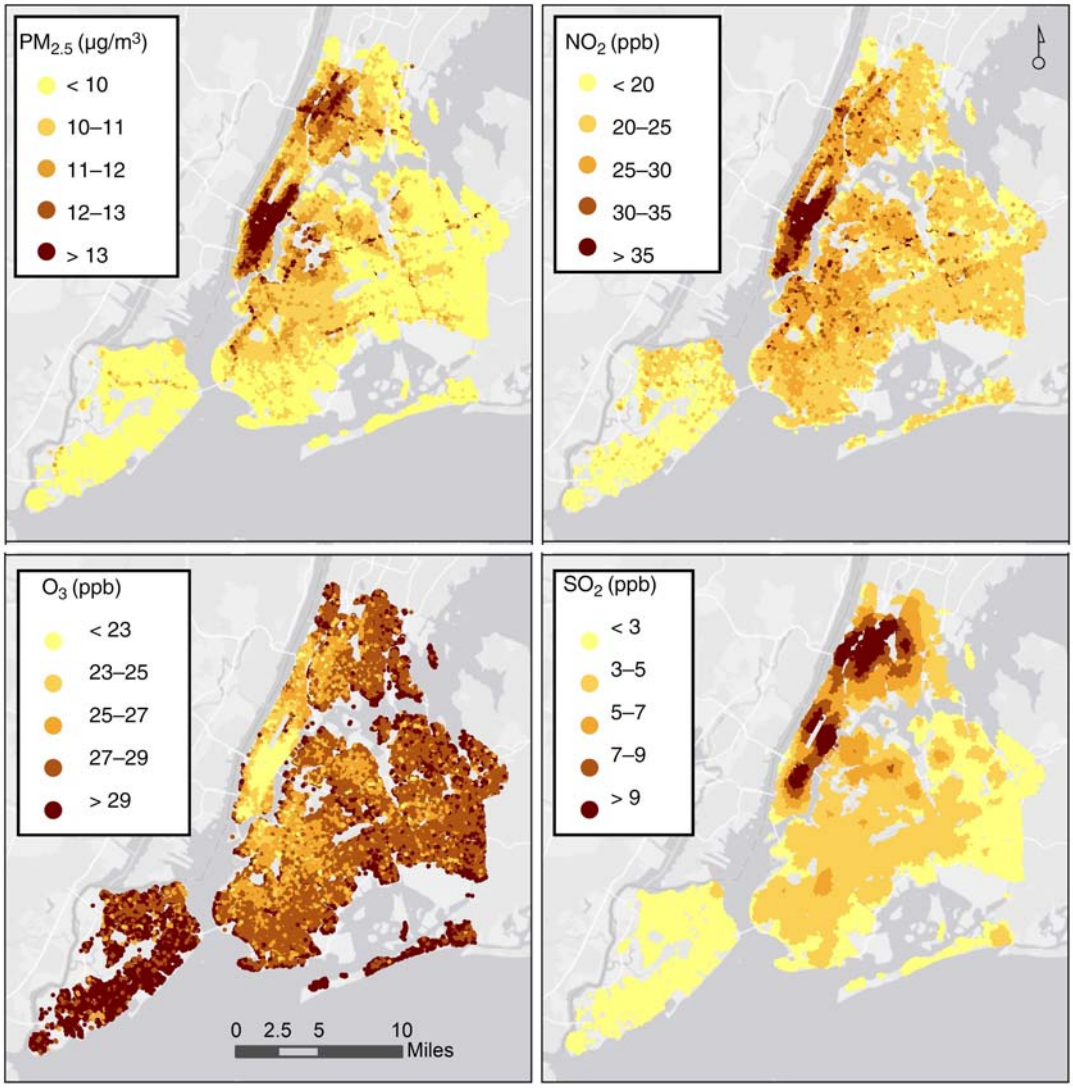


Figure 1. Spatial air pollution exposure estimates for all SPARCS CVD cases (n = 1,113,185), based on NYCCAS air pollution concentration surfaces.

indicators, including (1) our SDI, designed to capture relative material deprivation across communities (at the census-tract level); (b) three sets of spatially correlated community stressors derived from factor analysis of 27 stressor indicators (at the UHF level); and (c) two key community stressor indicators — violent crime rates and percentage of households below 200% of federal poverty line — that emerged as the strongest predictors of individual perceived stress in our earlier research (see Appendix 3, available on the HEI website). In addition, we included census-based indicators for median household income and an index of race-based economic segregation, and we greatly improved the spatial resolution in our crime analyses by obtaining and processing point-level New York Police Department (NYPD) data.

Importantly, we originally planned to perform all ecological analyses at the UHF level (n = 34), because the three stressor factors we analyze here, previously derived via factor analysis (Shmool et al. 2014), were built at this level (given the limited spatial resolution available in some included variables). We were able, however, to obtain point-level crime data (described below) and thus were able to perform most ecological analyses at the much finer census-tract level

(n = 2,167 census tracts, using year 2010 boundaries) and re-derived indices to this level (i.e., SDI, described below). Only analyses of noise and factor scores (described below) were restricted to UHF-level analysis. Further detail on earlier focus-group and survey-based verification of social stressor indicators, and spatial analysis of relationships among and between the social stressor indicators and pollutant concentrations, is provided in Appendix 3.

Socioeconomic Deprivation Index To examine effects of material deprivation, we updated our previously published citywide SDI (Shmool et al. 2015a), following the spatially stratified principal components analysis (PCA) method we adapted from Messer and colleagues (2010), as detailed in Appendix 3. Briefly, we used 25 indicators representing multiple dimensions of SEP (e.g., income, wealth, education, employment–occupation, housing, language, and racial–ethnic composition), using American Community Survey 2007–2011 data at the census-tract level (year 2010 boundaries), excluding tracts with populations of <20 persons. To identify spatial strata that maximized internal and minimized external correlation, we used local indicators of spatial association to quantify each observation's contributions to the global (overall) pattern and to identify significant clusters and outliers (Anselin 1995).

After implementing a citywide PCA, we repeated the PCA process within each borough separately. There were no variables that loaded > ± 0.40 in two or more borough-specific PCAs; as such, the initial citywide solution was retained as the final SDI solution, which included eight American Community Survey variables: median household income, percentage of households living below 200% of the poverty level, percentage receiving public assistance income, percentage receiving food stamps and/or Supplemental Nutrition Assistance Program (SNAP) benefits, percentage families with annual income <$35,000, percentage renter or owner housing costs in excess of 30% of household income, percentage households with annual income >$50,000, and percentage residents with less than a high school diploma. The first component of the final PCA explained 53.43% of the overall variance. We operationalized the measure as an interquartile range (IQR)–standardized score, with higher scores indicating greater tract-level socioeconomic deprivation. The final SDI is shown in Figure 2.

Spatially Correlated Suites of Community Stressors from Factor Analysis To identify suites of spatially correlated stressors, we previously used unconstrained factor analysis with and without adjustment for spatial autocorrelation (Shmool et al. 2014). We aggregated, reformulated, and examined 27 administrative stressor indicators across six domains (SEP, violence and crime, healthcare access, physical disorder, noise and pollution, and school-related stressors) from multiple data sources (U.S. census, NYC Housing and Vacancy Survey, NYC Community Health Survey, NYPD, and NYC school districts). In selecting indicators, we required citywide coverage and conceptual comparability with verified measures from our earlier

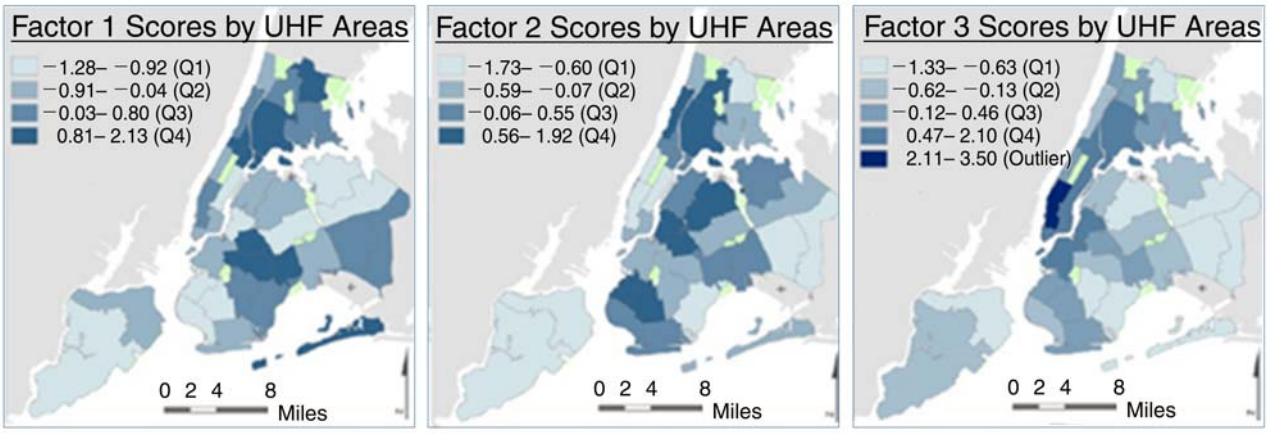


Figure 2. Three spatial factors derived from unconstrained factor analysis of 27 community stressor indicators. Factor 1 is characterized by indicators of violence and physical disorder, Factor 2 by crowding and poor resource access, and Factor 3 by noise and air pollution complaints. Factor scores are by quartile. Darker blue colors are "worse" for each factor. High positive scores indicate high concentrations of the stressors associated with the latent variable of interest. Negative scores indicate very low concentrations. Green-shaded areas represent parks.

citywide stress survey (e.g., Perceived Neighborhood Disorder [Ross and Mirowsky 2001]) and excluded indicators systematically underreported or with strong reporting bias (i.e., felony rape). We used orthogonal (varimax) rotation, selecting the optimal number of factors using scree plots, covariance eigenvalues, and interpretability. We sensitivity-tested results using two to five factors and removing redundant indicators (Pearson $r \geq 0.70$). We found three distinct factors (as shown in Figure 2) explaining 92.7% of overall variance. Factor 1 included indicators of violence and physical disorder. Factor 2 included crowding and poor resource access. Factor 3 included noise and air pollution complaints. The factors explained 51.5%, 25.7% and 15.5% of overall variance, respectively.

Key Census-Tract-Level Susceptibility Indicators: Poverty and Violence In verifying community stressor indicators against focus group and survey data on perceived stress and perceived stressor exposures, we found that these two stressors (especially violence) were most strongly reported by residents and were statistically associated with perceived neighborhood disorder and mental health problems (chronic stress, anxiety, and depression) among residents. For this reason, we examined these as separate effect modifiers.

Poverty Rate and Median Household Income

We defined poverty rate as the percentage of households living below 200% of the federal poverty level (a threshold often used in NYC statistics, because of the higher cost of living compared with that of the rest of the country). Given strong observed influences of poverty, we also wanted to examine a more resolved (continuous) indicator of household economic resources and thus chose to examine census-tract median household income. Both indicators were derived from the American Community Survey 2007–2011 data at the census-tract level (using year 2010 boundaries).

New York Police Department Point-Level Violence Data: Assault Rate and Total Violent Crime Rate

Given the great importance placed on neighborhood crime as a chronic stressor by participants in our earlier NYC focus groups and survey (Appendix 3), we sought to improve the spatial resolution of crime analyses beyond the police precinct level ($n = 72$) to better match our spatial resolution in crime data to that of our pollution data. We thus obtained point-level date- and time-stamped data on all violent offenses (murder and non-negligent manslaughter, aggravated assault, and robbery) in NYC during 2009 from NYC OpenData (*https://opendata.cityofnewyork.us/*). Rape was excluded, because these crimes are not geocoded. We followed the FBI's Uniform Crime Reporting definition for comparability with other studies (*https://ucr.fbi.gov/crime- in-the-u.s/2017/crime-in-the-u.s.-2017/topic-pages/violent- crime*) and coded crimes as felony assault or violent crime according to the FBI definitions. Crimes were spatially joined to census tracts and summed to obtain counts per tract, and rates per 10,000 population were calculated using the census-tract residential population, obtained from the American Community Survey 2007–2011 5-year estimates. We sensitivity-tested our selection of 2009 as an index year by comparing annual census-tract rates for each year from 2009 to 2012, finding Spearman correlations consistently >0.95.

Racialized Economic Segregation

Because there is known strong spatial clustering in community stressors by race (i.e., racialized economic segregation), researchers have developed indices to quantify the composite clustered disadvantage experienced by individuals and communities on the basis of race and/or economic standing. To explore susceptibility due to the combined effects of poverty and race in NYC, we calculated an Index of Concentration at the Extremes: Income and Race–Ethnicity (ICE I&R) (Krieger et al. 2017; Massey et al. 2009; Massey and Brodmann 2014), using the census variables described above. This index was designed to empirically capture racialized patterns in poverty, in which low-income Black and high-income White people live in different areas (Massey and Brodmann 2014). The index quantifies the extent to which an area's residents are disproportionately at either extreme of the socioeconomic scale. A value of 1 means that 100% of the population is concentrated in the most privileged (highest-SEP) group; a value of −1 means that 100% of the population is concentrated in the most deprived (lowest-SEP) group. The spatial variation in all census-tract-level social covariates is shown in Figure 3.

Noise Disruption at the United Hospital Fund Level

We used noise disturbance data from the DOHMH's Community Health Survey, detailed at *https://www1.nyc.gov /assets/doh/downloads/pdf/episrv/ chs2009survey.pdf*. These data are pre-aggregated at the level of the much larger UHF areas ($n = 34$ versus 2,167 census tracts). The dataset provides summarized data from a large annual representative survey, powered for comparison across communities at the UHF level. Though delivered annually (surveys are implemented March through December), the Community Health Survey collected only in-depth information on noise in 2009 and included inquiries on whether respondents were disturbed by noise more than three times per week (i.e., "3+ Noise Disruptions") and the percentage of respondents reporting frequent disruption by key noise sources — including traffic, construction, sirens, street noise, or subway noise — over the prior 3 months.

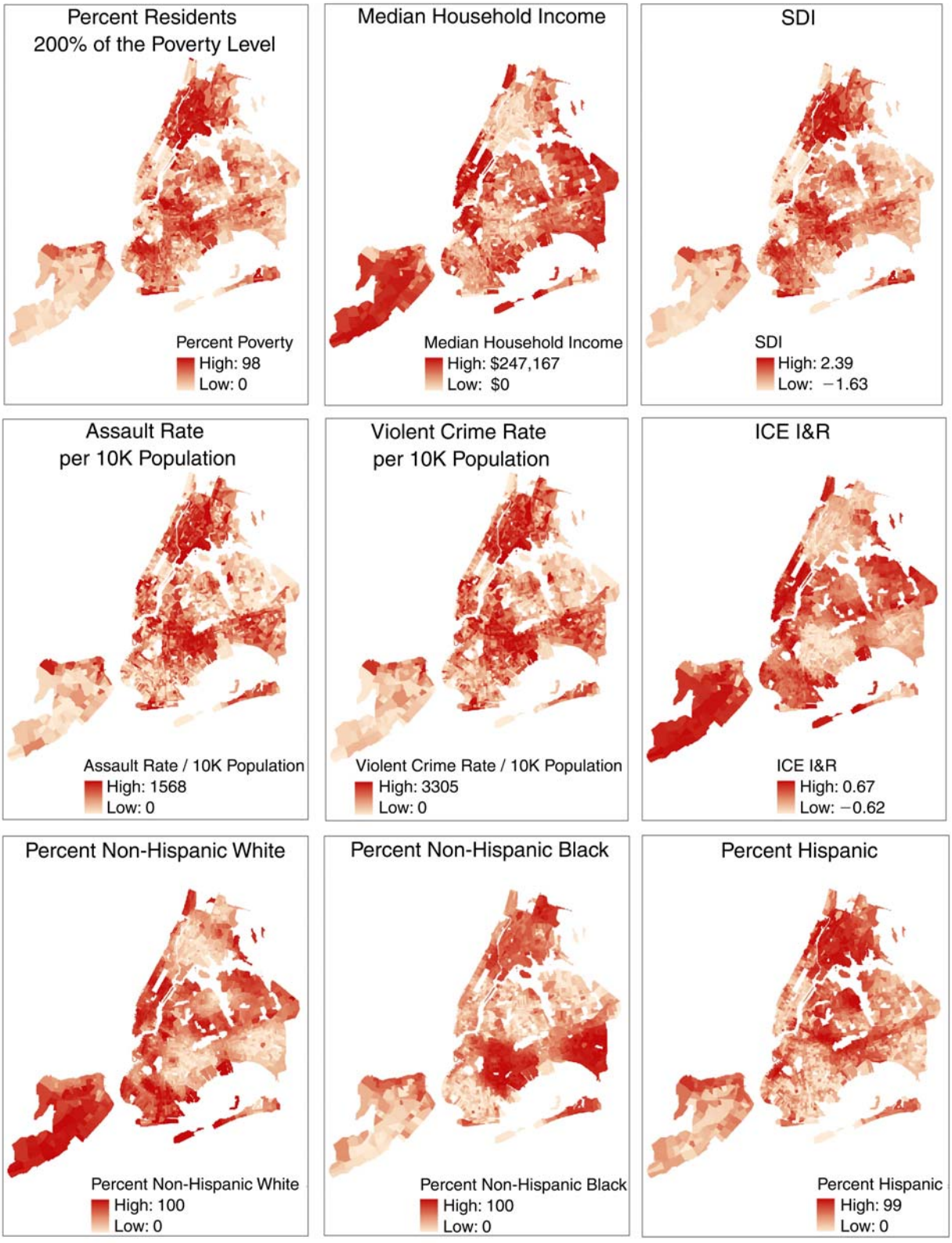


Figure 3. Spatial distribution of census-tract-level social covariates across NYC. Higher ICE I&R values indicate greater privilege (i.e., whiter, wealthier neighborhoods). Higher SDI values indicate greater material deprivation. Source: Humphrey et al. 2019. Licensed under CC BY 4.0.

GEOCODING AND SPATIAL–SPATIOTEMPORAL EXPOSURE ASSIGNMENTS

Geocoding processes rely on address locators, which rely in turn on available reference data and lead to tradeoffs between maximizing match rates (and thus analytic power) and positional accuracy (exposure misclassification). Street locators are the most commonly used method in public health but can induce positional errors of up to several hundred meters (Jacquemin et al. 2013; Zandbergen 2011) and systematic exposure misclassification in dense or heterogeneous areas (e.g., urban versus rural or by variation in street network complexity). We developed a multistep process to filter and standardize addresses, using an off-line composite address locator with three sets of reference data to maximize positional accuracy, as possible, without sacrificing match rate. We excluded P.O. boxes, non-NYC addresses, incomplete address records, and those of homeless patients (coded 999, Homeless or Undomiciled). Because hospitals record addresses differently, we standardized to U.S. Postal Service specifications, including address cleaning processes (e.g., standardizing abbreviations, such as BLVD for Boulevard) in SAS version 9.4 statistical software (SAS Institute) and gVim 7.4, an open source PC version of the Unix vi editor. We then used U.S. Postal Service reference databases, in ZP4 software (Semaphore Corporation, Monterey, CA). Without these steps, we would have had systematic missingness by area (e.g., Queens addresses have a distinct hyphenated format), inducing spatial bias. Finally, our three-level composite locator matched each address using the most accurate reference data possible, running addresses through each level sequentially, starting with the most accurate. Level one uses address point reference data (postal delivery points), sufficiently precise to assign latitude and longitude to building footprint centroids. Level two uses a tax-parcel layer in GIS, assigning the latitude and longitude of the parcel centroid. Level three, a street network locator, matches addresses to street segments and interpolates to the address number along the segment. Because interpolated addresses are not validated against real address data or parcels, we used ZP4 software to validate that these address parcels exist and are eligible for mail delivery.

Citywide Time Series

To construct a citywide time series of $PM_{2.5}$, NO_2, SO_2, and O_3 concentrations, hourly or daily $PM_{2.5}$ monitoring data were retrieved from the EPA AQS regulatory monitoring stations in NYC for the years 2005–2011. We considered the spatial distribution of, and data density within, these regulatory monitors to minimize bias in the citywide time trend toward parts of the city with a higher number of AQS monitors or due to systematic missingness. Because two monitors in the Bronx were deployed at the same location and covered complementary years, these were combined and treated as one monitor. For each pollutant, we identified and used only the monitoring stations that provided data for at least 80% of the year for each of the 7 years in the study period. This resulted in the use of eight monitors for $PM_{2.5}$ (at least one monitor in each borough), two monitors for NO_2 (one in the Bronx, one in Queens), one monitor for SO_2 (in the Bronx), and three monitors for O_3 (one in the Bronx, one in Queens, and one in Staten Island). To evaluate and interpolate missing values to create a citywide time series, we assessed the proportion of missing values for each monitor in order to identify the monitor with the fewest missing values (i.e., our reference monitor). Once the reference monitor was identified, we interpolated the missing values at the other monitors by calculating the ratio of the daily average across all remaining monitors to the daily average for the reference monitor, which we then multiplied by the average daily concentration at the remaining monitors. In this way, the relative relationship between the reference monitor and other monitors remained constant but was increased or decreased by daily pollutant concentrations. After missing values in the reference monitor were interpolated, we used the same method to interpolate missing values at the remaining monitors.

The final citywide daily average trends for $PM_{2.5}$, NO_2, SO_2, and O_3 were computed by averaging the daily values across all monitors. Because the measures from monitors in the same borough were highly correlated, their daily values were averaged to avoid overweighting (biasing) the citywide average by that borough. For each pollutant, the time series was computed on an annual basis. To be consistent with the NYCCAS spatial surface and pollution source, additional season-specific time series were computed for SO_2 (winter only) and O_3 (summer only). For sensitivity analyses, a summertime EPA AQS daily time series was provided by the DOHMH. The correlation between the time series from the DOHMH and the citywide daily time series we created ranged from $r = 0.96$ to $r = 0.98$ across all pollutants.

Spatiotemporal Pollution Exposure Assignment

We estimated short-term near-residence exposures to $PM_{2.5}$, NO_2, SO_2, and O_3 for the date of the CVD event and 0–6 days prior for each case by integrating temporally and spatially refined data sources. We first applied the multistep address validation and geocoding process described above, then estimated near-residence annual-average exposures for each pollutant from NYCCAS spatial

surfaces. Residence-specific annual averages were quantified as mean concentrations, using all grid-cell centroids of a 100 × 100–m grid that fell within a 300-m radial buffer around each subject's residential location, following earlier work validating this approach using NYCCAS surfaces. Exposure estimates and epidemiological results were not sensitive to the choice of buffer size (Ross et al. 2013). Spatial data consisted of fine-scale annual average NO_2 and $PM_{2.5}$, summertime O_3, and wintertime SO_2, derived from 2 years of NYCCAS monitoring data (methods have been detailed elsewhere [Clougherty et al. 2013; Matte et al. 2013; and *https://www1.nyc.gov/assets/doh/downloads/pdf/environmental/comm-air-survey-08-10.pdf*]).

To generate spatiotemporal exposure estimates across lag days 0–6, we multiplied the daily EPA AQS citywide time-series concentration by the ratio of the near-residence (300 m) concentration to the mean NYCCAS concentration at the AQS monitoring sites for each pollutant. Because the spatial surfaces for SO_2 and O_3 are season-specific and we did not have data verifying that these surfaces accurately capture spatial variance in other seasons, we opted to restrict case-crossover analyses for SO_2 and O_3 in Aims 2 and 3 to winter (November–March) and summer (May–September), respectively.

Spatiotemporal Exposure Assignments for Temperature

Because of substantial spatial and temporal confounding between ambient O_3 and temperature, all epidemiological analyses of O_3 were adjusted for spatiotemporal temperature exposures, using measures we previously developed. Because physiological recovery from daytime heat can be impaired when nighttime temperatures remain elevated, and because we observed more spatial variation in daily minimum temperature (Tmin) than maximum temperature, we created a spatial surface for fine-scale spatial variation in Tmin, using the same LUR methods as for NYCCAS pollutant models (Clougherty et al. 2013). Data on daily temperature, RH, and dew point were collected from the four meteorological stations in the NYC area (JFK International Airport, LaGuardia International Airport, Central Park, and Newark International Airport) and retrieved from the National Oceanic and Atmospheric Administration (NOAA) National Climatic Data Center. Daily Tmin, average temperature, and maximum temperature were highly correlated across the four stations and were therefore averaged after imputing missing data, as described above. To create spatiotemporal temperature estimates, we adjusted the daily temperature time series using the spatial ratio (i.e., the near-residence [300 m] daily Tmin to the citywide NYCCAS average daily Tmin for each case) across lag days 0–6. RH and dew point were not measured in the NYCCAS fine-scale spatial surface and were therefore strictly temporal covariates.

STATISTICAL METHODS AND DATA ANALYSIS

We first examined the relative contributions of air pollution and social stressors on CVD rates with exposures measured at the same spatial and temporal scale (Aim 1). Then, to use more precise residence- and date-specific spatiotemporal pollution exposure estimates, allowing for daily variation in pollution exposures, we implemented case-crossover models including multiple pollutants across multiple lag days (0–6 days prior) (Aim 2). Finally, to identify community stressors that may modify pollutant effects — and to quantify the magnitude of this modification — we incorporated spatial interactions into the case-crossover models described, using previously verified metrics of community SEP and stressor exposures. We tested for effect modification by our SDI, our three spatially correlated stressor factors, community violent crime and assault rates, percentage of households below 200% of federal poverty level, median household income, and our ICE I&R in relationships between spatiotemporal pollutant exposures and CVD events.

All statistical models were implemented in SAS version 9.4 (SAS Institute). Spatial modeling (e.g., Moran's *I*, simultaneous autoregressive models, and conditional autoregressive models) and plots were implemented in R version 3.6.1. Spatial analyses were performed in ArcMap version 10.4 (Esri, Redlands, CA). Analyses were implemented under the oversight of the Drexel University Institutional Review Board Protocol #1702005173R002.

Methods for Ecological Analyses (Aim 1)

To first understand the separate and combined associations with CVD for chronic stressors and pollutant exposures *measured at the same spatial and temporal scale*, we performed an ecological analysis that included all inpatient emergency department visits or hospitalizations for CVD (ICD-9 code 390–459) in NYC from 2005 to 2011 (n = 1,113,185). Cases younger than age 18 or older than 95 were excluded from the analysis (1% of cases). A multistep address validation and geocoding process was used (Shmool et al. 2016), and cases were assigned to residential census tracts (n = 2,167). The 100-m-resolution NYCCAS pollutant concentration surfaces were averaged by census tract to estimate chronic exposures.

We calculated age-adjusted community-level CVD event rates per 100,000 population using the SPARCS hospital data and 2000 U.S. standard population. Census tracts

with no residents (n = 42) and populations with fewer than 200 residents (n = 21) were excluded from analysis, leaving n = 2,104 census tracts. We then excluded outlier tracts for air pollution and social stressors, identified as ± 3 standard deviations from the mean, and performed listwise deletion to account for missing data across census tracts (n = 123). The final sample included n = 1,981 census tracts. All pollutants and social stressors were IQR-standardized. All census-tract-level analyses included adjustment for false discovery rates (FDRs) to adjust for multiple comparisons; statistical power did not allow for FDR adjustment in UHF-level analyses (noise and factor scores) (n = 34).

We quantified correlations among age-adjusted CVD event rates, average NO_2, $PM_{2.5}$, SO_2, and O_3, and social stressors using Pearson correlation coefficients. The Poisson distribution assumes the variance and expected value are equal, which was not the case in these data, as determined by the Pearson chi-square dispersion. Because the data were overdispersed (i.e., the variance was greater than the mean), we used negative binomial regression (Ismail and Jemain 2007) to model CVD event rates as a function of each air pollutant separately, with adjustment for, and modification by, each social stressor. We first modeled each social stressor in combination with each pollutant, then tested each social stressor as an effect modifier of each pollutant–CVD relationship. Each "mutually adjusted" model includes only one pollutant and one social stressor.

"Fully Adjusted" Models Because community social stressors are very highly collinear, it is often not possible to adjust for all relevant social covariates in the same model (e.g., adjustment for poverty rates could nullify effects of the SDI and vice versa). Thus, we needed to selectively adjust for other types of social stressors in our "fully adjusted" models. To develop a reasonable adjustment approach, we first recognized that our social stressors generally describe three concepts: (1) economic deprivation (i.e., SDI and percentage living below 200% of the FPL), (2) exposure to crime (violent crime rate and assault rate), and (3) minority racial–ethnic composition (i.e., census-tract percentage non-Hispanic White, percentage non-Hispanic Black, and percentage Hispanic population). Our "fully adjusted" models, for the effect of each stressor of interest, were adjusted for the strongest predictor of CVD from each of the other two categories; SDI was the strongest predictor of CVD among the economic deprivation variables and thus was used as the adjustment variable. Violent crime was the strongest crime covariate. Percentage non-Hispanic Black was the strongest race–ethnicity variable.

Methods for Sensitivity Analyses of Ecological Models (Aim 1)

Sensitivity analyses were conducted to evaluate the consistency and stability of observed associations between areal measures of social stressors and pollutants with CVD rates.

Sensitivity to Impacts of Spatial Autocorrelation We examined the impacts of spatial autocorrelation on measures of association using Moran's I (to quantify spatial autocorrelation in census-tract CVD rates not accounted for by the pollutants and social variables tested) and spatial filtering to assess and remove spatial autocorrelation from the residuals of negative binomial regression and negative binomial generalized linear models. Spatial filtering was performed using Queens's first-order neighborhood matrix, incidence rate ratios (IRRs) and confidence intervals (CIs) compared between models, and models compared by Akaike-information-criterion fit.

Sensitivity to Scale of Measurement In addition to the census-tract-level analyses, we examined the influence of spatial autocorrelation using the same methods at the UHF-area scale (n = 34) and tested the effect of excluding two outlier UHFs.

Variation by Subdiagnosis Finally, because CVD is a very broad category and the mechanisms linking pollutants and stressors are many and varied, the associations reported here may differ by subdiagnosis. As a sensitivity test, therefore, we also ran these models for IHD, the most prevalent subdiagnosis in our dataset.

Methods for Case-Crossover Analyses of Pollutant–Cardiovascular Disease Associations (Aim 2)

We used conditional logistic regression, with time-stratified referent sampling in the case-crossover design, to estimate percentage excess risk for 10-unit (μg/m^3 or ppb) increments in pollutants, across lag days 0 to 6, to capture associations between multiple pollutant exposures and risk of acute CVD events. We used a time-stratified design for referent sampling, examined multiple CVD subdiagnoses, and adjusted for effects of same-day residence-specific temperature, RH, and co-pollutant exposures.

The key outcomes we examined in SPARCS in-patient data were as follows: All CVD (ICD-9 390–459; n = 837,523), IHD (ICD-9 410–414; n = 232,61 0), HF (ICD-9 428; n = 165,505), stroke (ICD-9 430–438, n = 120,163), ischemic stroke (ICD-9 433, 434, and 436; n = 62,307), and acute myocardial infarction (ICD-9 410, n = 78,187).

We leveraged a key advantage of the case-crossover design in using day- and location-specific exposure estimates. We estimated spatial variation in pollution using

the ratio of the mean NYCCAS concentration within 300 m of the participant's home to the mean at the AQS monitoring locations, multiplied by the daily mean concentration from all EPA AQS monitors in NYC (Ross et al. 2013). We defined the case day as the day of emergency department visit and matched it with referent (control) days from the same day of the week in the same calendar month and year (Janes et al. 2005a; Lumley and Levy 2000), inherently controlling for covariates that do not vary within the 1-month timeframe (e.g., sex, race, and age), day of week, or season. We further adjusted using same-day Tmin (3 degrees of freedom [df]), and RH (3 df).

Co-Pollutant Adjustment We adjusted for copollutants using penalized splines of case-day concentration estimates at the residential location. Models for NO_2, SO_2, and O_3 were adjusted only for $PM_{2.5}$. $PM_{2.5}$ models were adjusted only for O_3. Before adjusting for any copollutants, we examined relationships among the pollutants and developed models adjusting solely for temperature and RH. We examined multicollinearity and variance inflation factors with additional inclusion of any co-pollutant.

The $PM_{2.5}$ models were not adjusted for SO_2, because they share a predominant local source in NYC (i.e., oil burning) and have very similar spatial and temporal patterns (Clougherty et al. 2013), thereby potentially overadjusting. Because the spatial surfaces for SO_2 and O_3 are season-specific (the SO_2 surface was derived using only winter data, the O_3 using only summer data), these surfaces represent maximum (peak-season) spatial variance in each pollutant, which we determined may not be appropriate for use in adjusting year-round associations between other pollutants and health outcomes. Similarly, NO_2 and O_3 were not mutually adjusted, given the strong inverse relationship between these two pollutants in NYC (Clougherty et al. 2013). Finally, adjusting any other pollutant for the effects of NO_2 nullified or reversed directionality in the association between any other pollutant and CVD and greatly increased variance inflation factors, which we interpreted to underscore a stronger association with CVD for NO_2 than for any other pollutant.

Referent Selection A key issue in the case-crossover design is selection of a referent time period, and multiple strategies have been proposed, including unidirectional selection (using only reference days prior to case event) (Boutin-Forzano et al. 2004), symmetric bidirectional selection (using reference days equally distributed before and after event day) (Lin et al. 2002), and time-stratified selection (using referent times within a given period, such as same-month) (Villeneuve et al. 2006). A systematic review of case-crossover analyses showed that only 7.7% used unidirectional design and the remainder used bidirectional, most using symmetric or time-stratified bidirectional designs (91.1% combined) (Carracedo-Martinez et al. 2010). Bidirectional time-stratified methods commonly select referent days to include non-case days on the same day of the week, month, and year as the event, which can control for seasonal trends and day of week (Bateson and Schwartz 1999; 2001).

We used a time-stratified approach to select referent days of the same day of week, month, and year as the case day (e.g., the other Mondays in June). This approach The time-stratified design inherently controls for season and day of week, because (Janes et al. 2005a). It also provides unbiased conditional logistic regression estimates and avoids biased results from temporal trends in air pollution exposure, because referent days in the time-stratified approach do not change daily with the index time and have a consistent pattern in the placement of referents relative to the index time.

Subpopulation Analyses We compared the pollutant–CVD associations observed in these models in various subpopulations. In the appendices, we have included subanalyses stratified by age, sex, and individual-level race–ethnicity.

Multiple Comparisons To reduce the likelihood of false positives arising from the large number of models tested, we made efforts to hone the number of models explored at each stage of the analytic process and adjusted the significance level for all models using the FDR. We opted to adjust using the FDR via the Benjamini-Hochberg procedure (Benjamini and Hochberg 1995) rather than Bonferroni correction, because the Bonferroni method is known to be overly conservative (hence, statisticians are increasingly adjusting for multiple comparisons using the FDR rather than the Bonferroni method). More important, the FDR is less sensitive to how a "family of tests" is defined; that is, the Bonferroni method controls the familywise error rate by setting a new critical *P* value by dividing 0.05 by the number of tests. In our case, the correction can be run either by pollutant or by social stressor, and the number of tests and resultant critical *P* value varied greatly depending on which family–direction we chose to adjust. Using the FDR, given that the distribution of *P* values is relatively consistent, increasing the number of tests does not significantly alter the proportion of significant results. As such, the FDR method proved much more stable and interpretable than the Bonferroni method while still providing appropriate adjustment for multiple comparisons.

All case-crossover analyses were performed in SAS version 9.4 (SAS Institute).

Methods for Case-Crossover Analyses with Effect Modification by Social Stressors (Aim 3)

Using the same case-crossover modeling approach described in Aim 2, we examined variation in observed associations between all spatiotemporal pollutant exposures (NO_2, $PM_{2.5}$, SO_2, and O_3) and risk of CVD event (all in-patient CVD events [ICD-9 codes 390–459] as well as key subdiagnoses [IHD, HF, stroke, ischemic stroke, and acute myocardial infarction]). We again used a time-stratified design for referent sampling; adjusted for effects of same-day, residence-specific temperature, RH, and co-pollutant exposures; and tested for effect modification by key community-level social stressors (SDI, percentage of households below 200% of federal poverty level, and the three stressor factors: violent crime rate, assault rate, and noise disturbance by source). Each social stressor modifier was tested separately, in combination with each pollutant, as an interaction term between a categorical stressor term and the continuous pollutant exposure metrics.

Because of concerns about spatial clustering of social stressors by race and ethnicity in NYC (i.e., nonrandom assignment into tracts), we adjusted year-round models (NO_2 and $PM_{2.5}$) for modification by percentage non-Hispanic Black and Hispanic by census tract; season-specific SO_2 and O_3 were underpowered for this adjustment.

To limit multiple-comparison issues, we focused this analysis on same-day associations rather than on lag days 0–6, because we observed more significant associations with each pollutant on the case day, for all subdiagnoses. Using poverty and violent crime rates, we assessed modification across all lag days.

We examined the efficacy of using various cut points for categorical effect modifiers (e.g., median-dichotomized [binary], tertiles, and quartiles) and opted to present results here in quintiles (representing very low, low, medium, high, and very high social stressors) to depict highly resolved effect modification for census-tract-level stressors, given n = 2,167 census tracts in NYC. For social variables at the UHF level (n = 34), the much smaller number of areas limited our ability to categorize the modifier, and thus we used median dichotomization to preserve statistical power. We adjusted for the FDR, as described above.

Methods for Sensitivity Analyses of Case-Crossover Models (Aims 2 and 3)

We sensitivity-tested all methods — spatiotemporal exposure estimation, geocoding and exposure assignment, stressor validations, and epidemiological analysis — for robustness to variation in analytic methods and quantified attributable variation in exposure assignments and epidemiological associations.

Sensitivity of Exposure Assignment and Epidemiological Results to Geocoding Method We geocoded using a tri-level geolocator that leverages three positional locators (address point, parcel, and street segment) and selected, for each address, the method that achieved the highest positional accuracy (Shmool et al. 2016). We quantified both directional and distance errors and, using pollution exposure estimates derived using each method, quantified resultant uncertainty in exposure estimates (Kinnee et al. 2020).

Sensitivity to Spatial Exposure Assignment We examined variation in exposure assignments and epidemiological effect estimates using three radial distances from residence (address point, 300 m, and 800 m).

Sensitivity to Use of Spatiotemporal (Versus Temporal-Only) Exposure Estimates To assess the influence of potential exposure misclassification in spatial exposure assignments and of improvements attributable to the use of the 100-m NYCCAS spatial surface, we examined Pearson correlations between temporal and spatiotemporal exposure estimates for the full SPARCS cohort.

Sensitivity of Effect Estimates for O_3 to Adjustment for Temperature Because of high correlations between temperature and O_3, we tested for sensitivity to adjustment for spatiotemporal same-day Tmin and RH. NYCCAS data for O_3 were collected only during summer, and for SO_2 only during winter.

Sensitivity of O_3 Effect Estimates to Adjustment for NO_2 Because NO_2 is a precursor in ground-level O_3 formation — and because NO_x reacts with ambient O_3, scavenging it in dense urban areas — treating NO_2 as a confounder of O_3 may overadjust in urban epidemiology. In NYC, where major roadways lie in deep street canyons, this scavenging effect is so strong that NO_2 (with a negative coefficient) is the strongest covariate in the NYCCAS O_3 LUR model (*https://www1.nyc.gov/assets/doh/down loads/pdf/environmental/nyccas-report-summer09.pdf*). This strong inverse association between O_3 and combustion emissions — combined with strong inverse temporal correlations between O_3 and NO_2 in the regulatory data — likely underlies the inverse associations observed for O_3 in this study. We compared epidemiological models for O_3, with and without adjustment for NO_2.

Sensitivity to Adjustment for Copollutants To assess the influence of co-pollutant adjustment on observed associations between the pollutant of interest and CVD, we also

implemented single-pollutant case-crossover models, not adjusted for copollutants.

Sensitivity to Assumption of Linearity in Pollutant–Cardiovascular Disease Associations To assess linearity in NO_2–CVD associations, we performed exploratory analyses using spatiotemporal measures of NO_2 and copollutants, both as cubic splines with $n = 5$ knot points, to estimate relative risk of CVD events.

Sensitivity to Covariate Formulation and Multicollinearity To conserve power, we adjusted for co-pollutant exposures using penalized splines, selecting df based on the shape of the nonlinear fit between pollutant concentrations and likelihood of event. To sensitivity-test epidemiological models to df selection, we refit all models with 4-df, 5-df, and 7-day-average co-pollutant exposures. The functional form of model covariates was determined using likelihood ratio tests to compare fit across models of increasing complexity (i.e., linear form, natural spline [ns] with defined df, or penalized spline with unlimited df), one variable at a time.

Sensitivity to Cut Points in Effect Modifiers We assessed ed the robustness of observed effect modification by testing various categorizations of effect modifiers. Main results are presented in quintiles — our most highly resolved categorization. In sensitivity analyses, we present effect modification results for the NO_2–CVD association, using two key modifiers (violent crime and the SDI) as median-dichotomized (binary), for all CVD across lag days 0–6.

Sensitivity to Modeling Lag Days Independently As an alternative to estimating associations between pollutant exposures and risk of CVD events at multiple lag days using a separate model for each lag, we considered a distributed lag nonlinear model (Gasparrini et al. 2010) to incorporate lags 0–6 in a single model. The distributed lag model allows for estimation of lag-specific effects after adjustment for the effects at other lags, assuming a smooth nonlinear form for the variation across lags in the magnitude of the association.

RESULTS

SUMMARY STATISTICS AND BIVARIATE ASSOCIATIONS

Summary Statistics for Census-Tract-Level Exposures and Cardiovascular Disease Rates

Over the period January 1, 2005, to December 31, 2011, there were a total of 1,113,185 in-patient and out-patient acute CVD events presented at hospitals in NYC, in the SPARCS data. To examine this data by census tract, after geocoding, we created age-adjusted community CVD event rates (per 100,000 population) for the full 7 years of the study period (2005–2011), using 2010 census-tract boundaries (n = 2,167) and census residential population as the denominator. (In separate sensitivity analyses, not shown in this report, we explored adjustment by daytime population and area and found that violence rates per 10,000 residential population was most strongly correlated with perceived stress in survey data and in area CVD rates). We excluded 42 census tracts with zero residents and 21 with fewer than 200 residents. After removing statistical outliers for pollution and stressors (outside of mean ± 3 × standard deviation [SD]) and performing listwise deletion to account for missing data across tracts, the final sample included n = 1,981 census tracts.

Table 1 presents summary statistics for age-adjusted CVD event rates, average pollutant concentrations, and social stressors by census tract. Census-tract CVD event rates averaged 14,387 per 100,000 population (range = 1,293–58,500). Census-tract mean concentrations of annual-average NO_2 and $PM_{2.5}$, wintertime SO_2, and summertime O_3 concentrations averaged 24.4 (SD = 3.4) ppb, 10.4 (SD = 1.0) μg/m^3, 4.5 (SD = 2.0) ppb, and 27.2 (SD = 1.5) ppb, respectively.

In subsequent sections of this report, we examine and compare associations with CVD on a one-IQR basis, because the units among the pollutants differ (i.e., ppb for NO_2, SO_2, and O_3 and μg/m^3 for $PM_{2.5}$), and are very different from the units for social variables, which differ greatly among themselves (e.g., number of crimes/10,000 population, percentage Hispanic, median household income [in dollars], and index values range from −1 to 1).

We note that, on a proportional basis, there was greater variance in some of the social stressors than in the pollution exposures. For NO_2, for example, the 75th percentile exposure (26.4 ppb) was 17% higher than the 25th percentile exposure (22.5 ppb). For $PM_{2.5}$, SO_2, and O_3, the IQRs represent increases of 17.3%, 14.3%, and 6.1%, respectively. For the social stressors, however, the IQR represents

Table 1. Summary Statistics for Census-Tract-Level CVD Rates, NYCCAS Air Pollutants, and Social Stressors

							Percentile		
	N	Min	Mean	Max	SD	Median	25	75	IQR
Age-adjusted CVD/ 100,000	1,981	1,293	14,387	58,500	6,316	13,046	9,947	17,618	7,671
Air Pollutants (average)									
NO_2 (ppb)	1,981	12.7	24.4	38.0	3.38	24.4	22.5	26.4	3.89
$PM_{2.5}$ (μg/m^3)	1,981	8.47	10.4	14.4	1.01	10.2	9.60	11.0	1.37
SO_2 (ppb)	1,981	1.43	4.45	11.7	1.98	3.84	3.09	5.17	2.08
O_3 (ppb)	1,981	21.1	27.2	32.9	1.48	27.4	26.5	28.1	1.61
Social Stressors									
SDI[a]	1,981	−1.27	0.08	1.86	0.66	0.01	−0.42	0.53	0.95
ICE I&R[a]	1,981	−0.57	0.03	0.60	0.21	0.03	−0.12	0.17	0.28
200% of the federal poverty line (%)	1,981	0.0	0.38	0.85	0.18	0.36	0.23	0.51	0.28
Median household income (U.S. $)	1,981	9,662	54,344	136,053	22,903	51,786	37,380	68,059	30,679
Violent crime rate[b]	1,981	0	44.2	323.3	39.0	33.8	16.5	60.8	44.3
Assault rate[b]	1,981	0	20.3	175.1	20.4	14.2	5.8	29.3	23.5
Non-Hispanic White (%)	1,981	0.0	32.9	100.0	30.8	21.2	4.1	60.7	56.6
Non-Hispanic Black (%)	1,981	0.0	25.5	98.5	30.8	9.3	1.3	44.4	43.2
Hispanic (%)	1,981	0.0	26.1	92.9	22.2	18.2	9.0	38.5	29.6

[a] SDI and ICE I&R are composite variables.

[b] Events per 10,000 persons, residential population.

CVD = cardiovascular disease; IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SD = standard deviation; SO_2 = sulfur dioxide.

increases of 121% in poverty, 405% in assault rate, and 268% in overall violent crime. Notably, these large increases in the IQR ranges do not even include the high outlier tracts for violence (where assault rates are 30+ times those in the 25th-percentile tracts). These vast differences in the ranges of social versus pollution exposures in NYC should be accounted for in interpreting our results.

Summary Statistics for United Hospital Fund–Level Exposures and Cardiovascular Disease Rates

The SPARCS CVD rates, NYCCAS air pollution concentrations averaged to UHF level, and UHF-level noise metrics are summarized in Table 2. On average, across UHF areas, 20.4% of respondents reported that their normal activities were disrupted by noise at least three times per week (SD = 5.3 times). The most frequently reported source of disruptive noise was traffic (mean = 21.3%; SD = 5.6%), followed by siren noise and street noise.

Joint Associations Among Social Stressors and Air Pollutants

Before fitting epidemiological models, we investigated the joint associations (i.e., spatial correlations) among chronic stressors and air pollution exposures. These relationships are particularly complicated in NYC, where — unlike many other areas of the United States — there are high-income neighborhoods with high pollution exposures (notably the Upper East Side of Manhattan) and many lower-income neighborhoods with lower pollution exposures.

These unusual patterns among social stressors and pollution exposures makes NYC, in many respects, an ideal

Table 2. Summary Statistics for UHF-Level CVD Rates, NYCCAS Air Pollutants, and Reported Disturbance by Multiple Noise Sources from the DOHMH Community Health Survey, and Spatially Correlated Factors

							Percentile		
	N	Min	Mean	Max	SD	Median	25	75	IQR
Age-adjusted CVD/100,000	34	868	1,670	3,013	556	1,641	1,229	1,882	653
Air Pollutants									
NO_2 (ppb)	34	15.8	24.0	37.5	4.73	23.5	21.1	26.0	4.91
$PM_{2.5}$ (μg/m^3)	34	8.84	10.4	13.7	1.17	10.2	9.58	10.9	1.35
SO_2 (ppb)	34	1.77	4.55	9.49	2.05	4.13	3.01	5.26	2.25
O_3 (ppb)	34	21.1	27.3	30.8	2.08	27.7	26.7	28.4	1.72
Noise Disturbance[a]									
3+ Noise disruptions/week	34	12.0	20.4	30.3	5.30	20.2	16.3	24.6	8.25
Traffic noise	34	11.1	21.3	35.8	5.56	21.5	17.3	24.3	7.03
Construction noise	34	4.70	14.4	30.9	6.57	13.3	9.69	16.8	7.11
Siren noise	34	8.91	18.9	30.4	5.76	18.8	14.1	22.2	8.17
Street noise	34	8.44	17.4	27.7	5.70	16.3	14.2	23.6	9.41
Subway noise	34	0.00	3.63	10.9	2.63	3.26	1.32	5.56	4.24
Spatially Correlated Factors									
Factor 1: "Violence & Physical Disorder"	34	−0.65	0.08	1.30	0.58	0.00	−0.46	0.54	1.00
Factor 2: "Crowding/Poor Resource Access"	34	−1.34	0.06	1.75	0.85	0.00	−0.51	0.49	1.00
Factor 3: "Noise & Air Pollution Complaints"	34	−0.77	0.31	4.56	1.05	0.00	−0.31	0.69	1.00

[a] Percentage of population reporting disturbance.

CVD = cardiovascular disease; IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SD = standard deviation; SO_2 = sulfur dioxide.

setting for analyses attempting to separate their combined and synergistic effects, because it offers contrasts in exposures that are intractably confounded in other settings. These complex joint distributions, however, also complicate the interpretability of some results.

In the example shown in Figure 4, NO_2 is notably higher, and more varying, in more privileged tracts (i.e., lower-SDI or lower-poverty tracts). This greater variance in exposures in the more privileged communities may point to greater exposure misclassification in those communities or to the risk that co-occurring assets (e.g., better healthcare), not directly accounted for in the current analysis, may confound some results.

This nonlinearity was not apparent for violence or assault, where very modest increases in NO_2 were observed, on average, with increasing community violent crimes. The variation in NO_2 across communities, however, was substantial, again underscoring the lack of a strong correlation among these exposures in NYC and the potential for exposure misclassification or co-occurring stressors (or assets) to confound some results or to complicate interpretations.

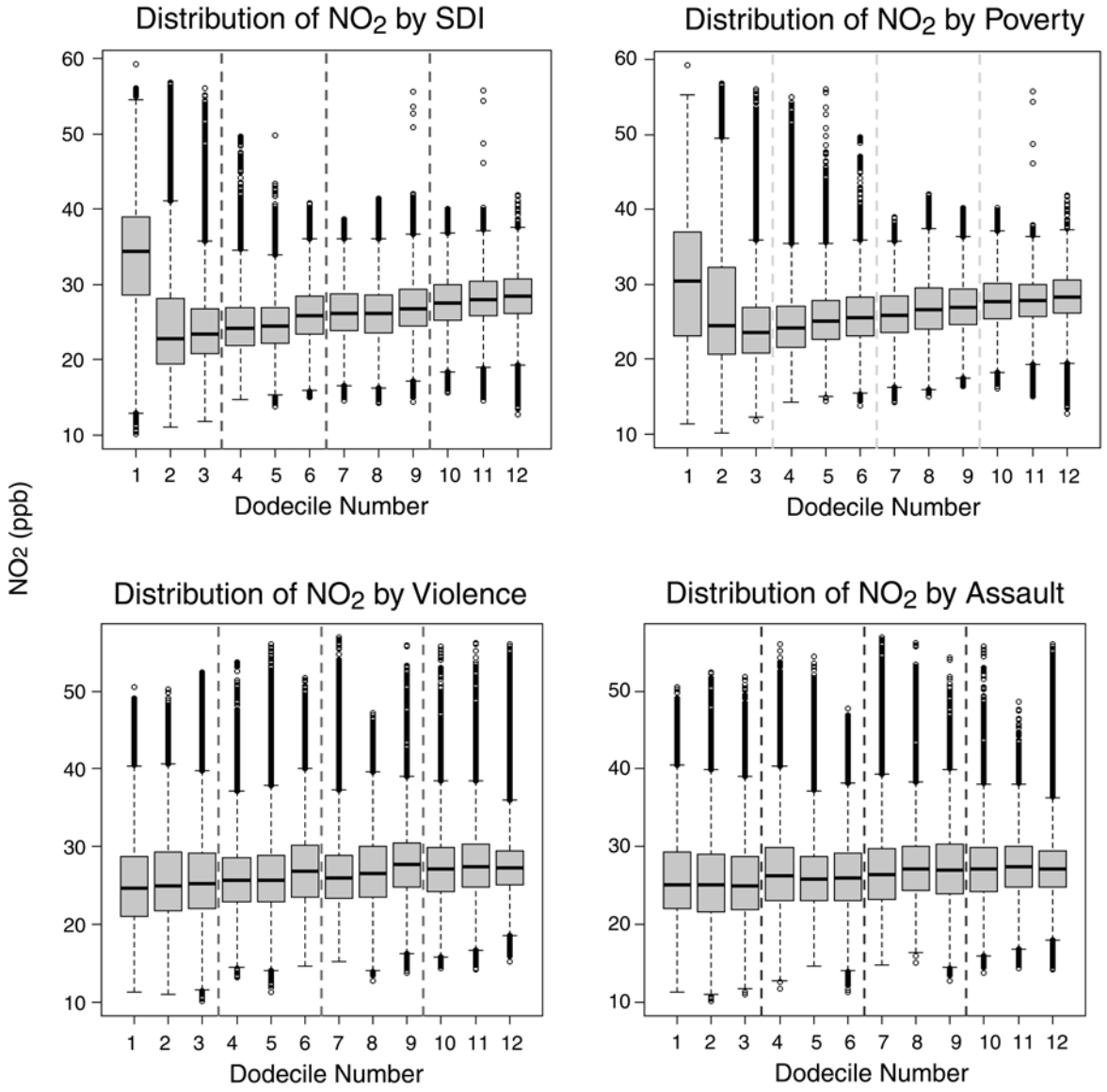


Figure 4. Distribution of estimated NO_2 exposures by refined ranked categories of key chronic social stressors. Dotted vertical lines indicate cut-points for quartiles.

Bivariate Correlations with Cardiovascular Disease

Census-Tract-Level Exposures and Cardiovascular Disease Rates Age-adjusted CVD event rates were not significantly correlated with any annual average air pollutant concentration (see Table 3). CVD rates were positively correlated with all social stressors in the hypothesized direction; all were positively correlated with CVD, except for median household income, percentage non-Hispanic White residents, and the ICE I&R — each of which was negatively correlated with CVD rates. As expected, NO_2, $PM_{2.5}$, and SO_2 were very highly correlated with one another and negatively correlated with O_3 (a secondary pollutant). Social stressors were not strongly correlated with the pollutants.

Table 3. Pearson Correlations Among Census-Tract-Level CVD Rates, Air Pollutant Concentrations, and Social Stressors

												Percentage		
	CVD	NO_2	$PM_{2.5}$	SO_2	O_3	SDI	ICE I&R	Poverty	Median Income	Violent Crime	Assault Rate	Non-Hispanic White	Non-Hispanic Black	Hispanic
Mean age-adjusted CVD/100,000	1.00													
NO_2 (average)	0.16	1.00												
$PM_{2.5}$ (average)	0.21	**0.83**	1.00											
SO_2 (average)	0.15	0.57	**0.76**	1.00										
O_3 (average)	−0.12	**−0.92**	**−0.80**	−0.57	1.00									
SDI[a]	**0.60**	0.24	0.33	0.33	−0.16	1.00								
ICE I&R[a]	**−0.64**	−0.10	−0.12	−0.15	0.04	**−0.70**	1.00							
200% of federal poverty line (%)	0.57	0.29	0.37	0.34	−0.20	**0.95**	**−0.63**	1.00						
Median household income	−0.51	−0.19	−0.24	−0.27	0.10	**−0.90**	**0.72**	**−0.86**	1.00					
Violent crime rate	0.56	0.28	0.28	0.19	−0.19	0.46	−0.53	0.44	−0.39	1.00				
Assault rate	0.57	0.25	0.26	0.18	−0.17	0.51	−0.56	0.48	−0.43	**0.89**	1.00			
Non-Hispanic White (%)	−0.51	−0.12	−0.15	−0.19	0.06	−0.54	**0.84**	−0.48	0.49	−0.49	−0.50	1.00		
Non-Hispanic Black (%)	0.47	−0.02	−0.07	−0.04	0.02	0.17	−0.72	0.10	−0.18	0.40	0.42	**−0.65**	1.00	
Hispanic (%)	0.34	0.18	0.37	0.43	−0.11	0.59	−0.31	0.57	−0.48	0.28	0.30	−0.46	−0.18	1.00

[a] SDI and ICE I&R are composite variables.

Bold values indicate stronger correlations, with absolute value >0.60.

CVD = cardiovascular disease; ICE I&R = index of concentration at the extremes: income and race; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SDI = social deprivation index; SO_2 = sulfur dioxide.

United Hospital Fund–Level Stressors, Pollution, and Cardiovascular Disease Rates At the UHF-level, as shown in Table 4, only Factor 1 (characterized by violent crime) was strongly positively correlated with CVD rates. Factor 3 (characterized by noise and air pollution complaints) was strongly correlated with noise disruption from traffic, construction, and sirens.

No noise metrics were significantly correlated with CVD at the UHF level, though several noise metrics were correlated with pollutant concentrations. For example, traffic, construction, and siren noise were all strongly positively correlated with NO_2 and $PM_{2.5}$ and negatively correlated with O_3, as expected. These associations are corroborated by scatterplots of the joint distribution between NO_2 and each noise metric (Appendix 2, available on the HEI website); strong linear associations were apparent between NO_2 and reports of traffic, construction, and siren noise; weaker positive associations were observed with other noise metrics.

RESULTS OF ECOLOGICAL ANALYSES (AIM 1)

Ecological Models for Census-Tract-Level Stressors and Pollution

In unadjusted negative binomial models, we tested each pollutant and social stressor separately against census-tract CVD event rates. NO_2, $PM_{2.5}$, and SO_2 were significantly positively associated with CVD rates; O_3 was inversely associated with CVD (Appendix Table A1-1, available on the HEI website). All social stressors were significantly positively associated with CVD, except for median household income and the ICE I&R, which were significantly negatively associated (i.e., operating in the hypothesized

Table 4. Pearson Correlations Among Age-Adjusted CVD Rates (per 100,000 Population), Air Pollutant Concentrations, UHF-Level Noises Sources, and Spatially Correlated Factors

	CVD	NO_2	$PM_{2.5}$	SO_2	O_3	3+ Noise	Traffic Noise	Construction Noise	Siren Noise	Street Noise	Subway Noise	Factor 1	Factor 2	Factor 3
Age-adjusted CVD/100,000	1.00													
NO_2 (average)	−0.09	1.00												
$PM_{2.5}$ (average)	−0.07	**0.93**	1.00											
SO_2 (average)	0.02	**0.63**	0.76	1.00										
O_3 (average)	0.14	**−0.97**	**−0.94**	**−0.70**	1.00									
3+ Noise disruptions	0.33	0.52	0.54	0.56	−0.47	1.00								
Traffic noise	0.01	**0.70**	**0.65**	0.48	**−0.68**	**0.74**	1.00							
Construction noise	−0.19	**0.78**	**0.77**	0.57	**−0.80**	0.53	0.79	1.00						
Siren noise	0.14	**0.75**	**0.72**	0.61	**−0.74**	**0.80**	0.89	**0.80**	1.00					
Street noise	0.46	0.48	0.52	0.50	−0.43	**0.87**	0.67	0.50	**0.73**	1.00				
Subway noise	0.50	0.07	0.15	0.41	−0.04	**0.72**	0.40	0.13	0.41	**0.67**	1.00			
Factor 1	**0.80**	−0.05	−0.06	0.11	0.09	0.30	−0.05	−0.15	0.14	0.43	0.41	1.00		
Factor 2	0.36	−0.02	0.07	0.15	0.08	0.57	0.22	−0.03	0.25	0.52	**0.60**	0.01	1.00	
Factor 3	−0.02	**0.78**	**0.78**	0.42	**−0.75**	**0.60**	**0.73**	**0.79**	**0.74**	0.56	0.18	0.02	−0.01	1.00

Bold values indicate stronger correlations, with absolute value >0.60.

CVD = cardiovascular disease; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SO_2 = sulfur dioxide.

directions). The magnitude of association for each social stressor was much larger than for the air pollutants. For example, a one-IQR increase in NO_2 was associated with a 9% increase in CVD cases per 100,000 population (IRR = 1.09, 95% CI = 1.07–1.12); in contrast, a one-IQR increase in the SDI was associated with a 43% increase in CVD cases (IRR = 1.43, 95% CI = 1.40–1.46), an increase five times greater. In interpreting these results, however, it is important to bear in mind that, as discussed in the previous section, the variation in many of these social stressors across NYC is much greater than the relative variation in pollution concentrations.

Mutually Adjusted Negative Binomial Ecological Models In mutually adjusted models (each model containing one pollutant and one stressor; see Figure 5 and Appendix Table A1-2), testing each pollutant–stressor combination against census-tract CVD rate, the social stressors consistently retained significance, in the original (hypothesized) direction. All were positively associated with CVD except for percentage non-Hispanic White, median household income, and the ICE I&R, which all had inverse associations with CVD, as hypothesized.

In most cases, in models including SDI, poverty, or violence variables, air pollution–CVD associations became null. NO_2 and $PM_{2.5}$ retained significance with adjustment for median household income, the ICE I&R, and race–ethnic composition. In a few cases, SO_2–CVD associations reversed direction with adjustment for SDI or poverty. All associations between O_3 and CVD rate were null, except for an adverse association where adjusting for median household income, racial–ethnic composition, or the ICE I&R.

Fully Adjusted Negative Binomial Ecological Models

In fully adjusted models for each pollutant–social stressor combination (see Figure 6 and Appendix Table A1-3), adjusted for SDI, percentage non-Hispanic Black residents, and violent crime rate (the strongest predictor of CVD rate from each of three broad conceptual stressor categories), associations between each pollutant and census-tract CVD rate were generally null.

All associations between NO_2 and CVD rate were null, except for a significant inverse association in models also testing percentage non-Hispanic White or Hispanic.

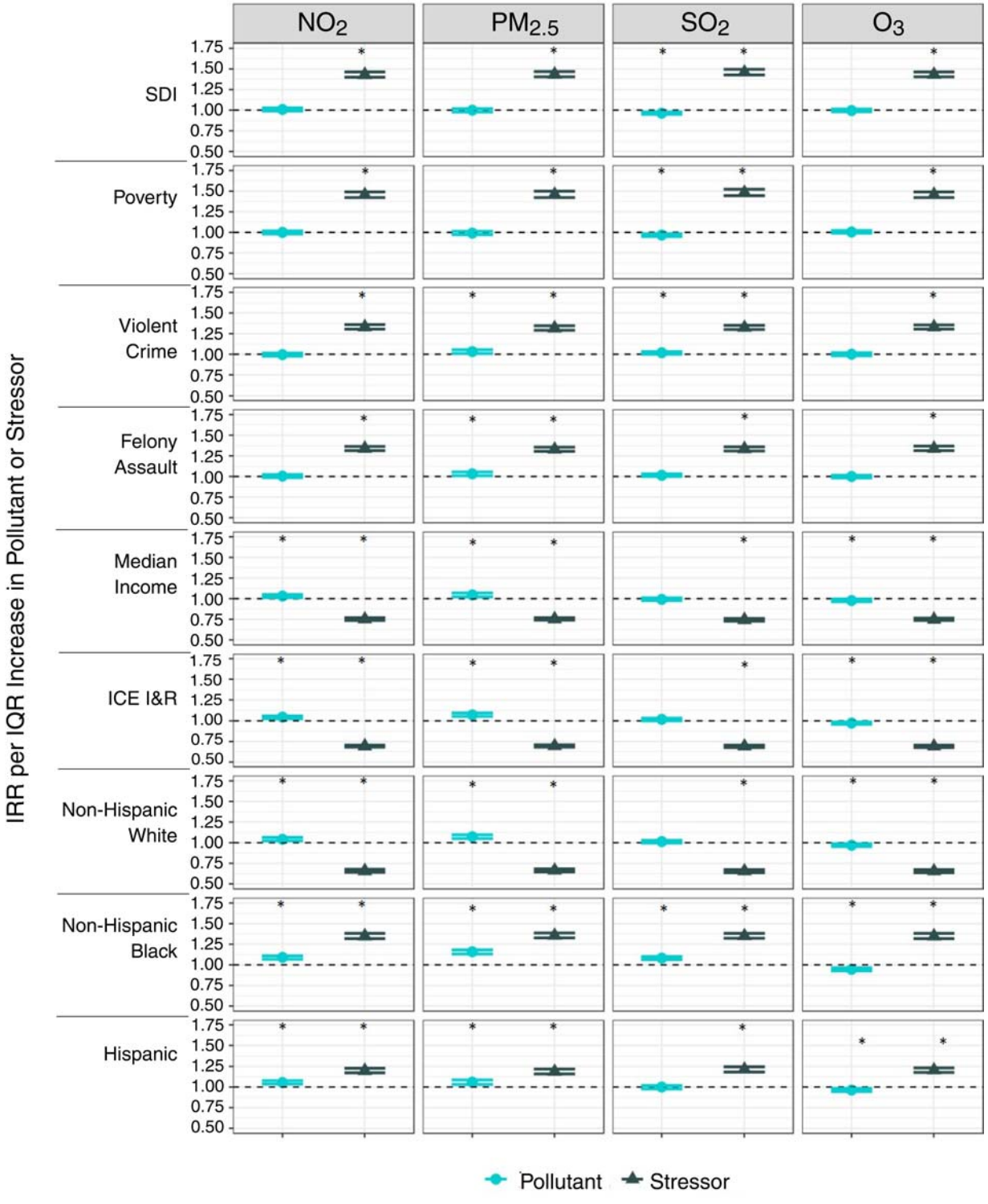


Figure 5. Mutually adjusted negative binomial ecological models for each pollutant–stressor combination versus census-tract CVD rate (*n* = 1,981). Each model includes one pollutant and one social stressor. IRRs represent the change in community CVD event rates per 1-IQR change in each covariate, shown with 95% confidence intervals. Asterisks indicate statistical significance after adjusting for FDRs.

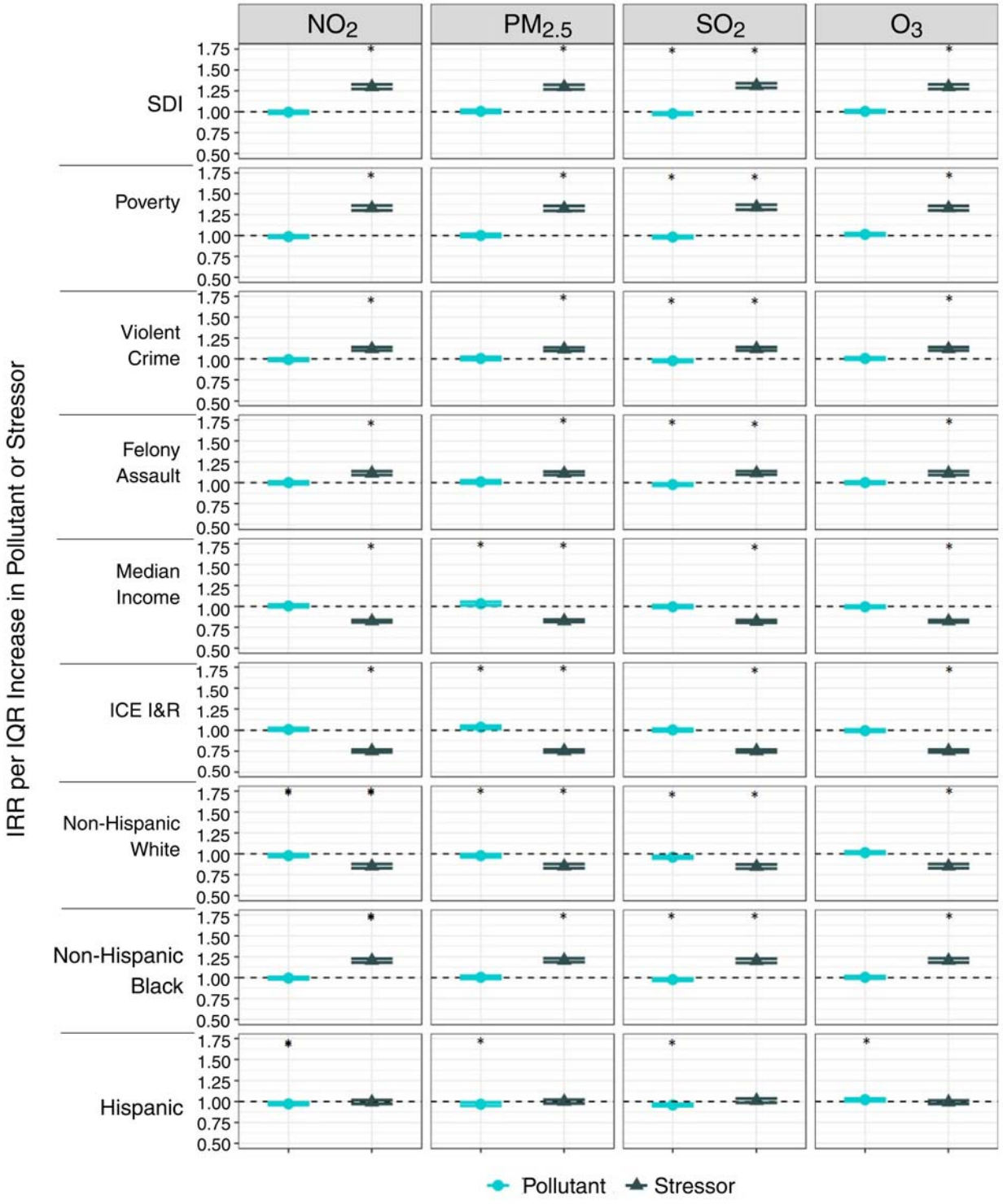


Figure 6. Fully adjusted negative binomial ecological models for each pollutant–social stressor combination versus census-tract CVD rate (n = 1,981), adjusted for SDI, percentage non-Hispanic Black residents, and violent crime (the strongest predictor from each of three broad conceptual categories). IRRs represent the change in community CVD event rates per 1-IQR change in each covariate, shown with 95% confidence intervals. Asterisks indicate statistical significance after adjusting for FDRs.

Associations between $PM_{2.5}$ and CVD rate were nonsignificant, except for adverse associations in models adjusted for median income or the ICE I&R and, similar to NO_2, inverse associations in models testing percentage non-Hispanic White or Hispanic.

SO_2 was inversely associated with CVD, except for null associations, where adjusting for median income or the ICE I&R. All associations between O_3 and CVD rate were null, except for an inverse association where adjusting for percentage Hispanic.

In all cases, all social stressors retained significance in the hypothesized direction, and IRRs for a one-IQR change in any social stressor were larger than for the pollutants.

Compared with the mutually adjusted models (Figure 5), associations between social stressors and CVD rate were attenuated in fully adjusted models (Figure 6).

Negative Binomial Models for United Hospital Fund–Level Noise Disturbance and Pollution on Community Cardiovascular Disease Rates

In ecological analyses for the combined (mutually adjusted) associations between pollutants and noise sources versus UHF-level CVD rates (see Figure 7 and Appendix Table A1-4), we found that self-reported noise disruption more than three times per week and disturbance by street noise or subway noise were significantly positively associated with UHF-level age-adjusted CVD rates.

After adjustment for disturbance by street noise, both NO_2 and $PM_{2.5}$ were inversely associated with CVD rates (i.e., IRRs below 1.0). After adjusting for disturbance by street noise, siren noise, or noise disturbance more than three times per week, O_3 was positively associated with UHF-level CVD rates.

Negative Binomial Models for Community Cardiovascular Disease Rates, Using Spatially Correlated Factor Scores (United Hospital Fund–Level) and Pollution Concentrations

We also examined mutually adjusted pollutant–stressor negative binomial ecological models (one pollutant, one stressor) and effect modification using the three spatial factor scores we previously derived from an unconstrained factor analysis of 27 community stressor indicators (shown in Figure 1 in Methods section). Factor 1 was characterized by indicators of violence and physical disorder; Factor 2 by crowding and poor resource access; Factor 3 by noise and air pollution complaints. Because of limited statistical power (n = 34 UHF areas), we tested only binary (median-dichotomized) cut points for these variables.

Adjusting each air pollutant for each factor score, pollution–CVD associations were null (see Figure 8 and Appendix Table A1-5). Most associations between factor scores and community CVD event rates remained significant after adjusting for NO_2, and the magnitude of association with CVD rate for each social factor score was higher than for NO_2. These results were in keeping with our census-tract-level analyses. Likewise, for $PM_{2.5}$, SO_2, and O_3, results using these UHF-level factors were in keeping with results using census-tract-level stressor indicators.

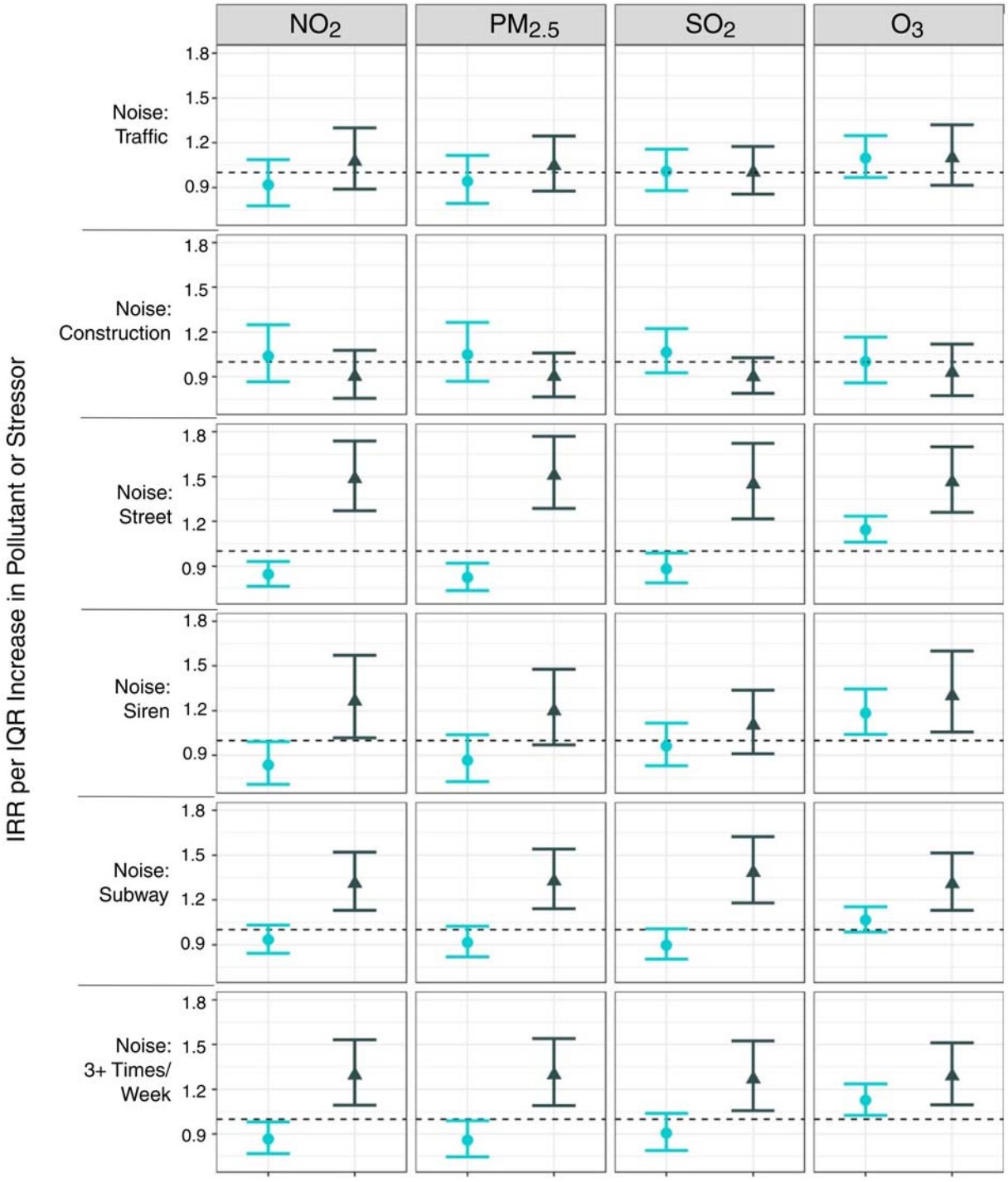


Figure 7. Mutually adjusted negative binomial ecological models for UHF-level noise and pollution versus CVD rate (n = 34). Each model includes one pollutant and one social stressor. IRRs represent the change in community CVD event rates per 1-IQR change in each covariate, shown with 95% confidence intervals.

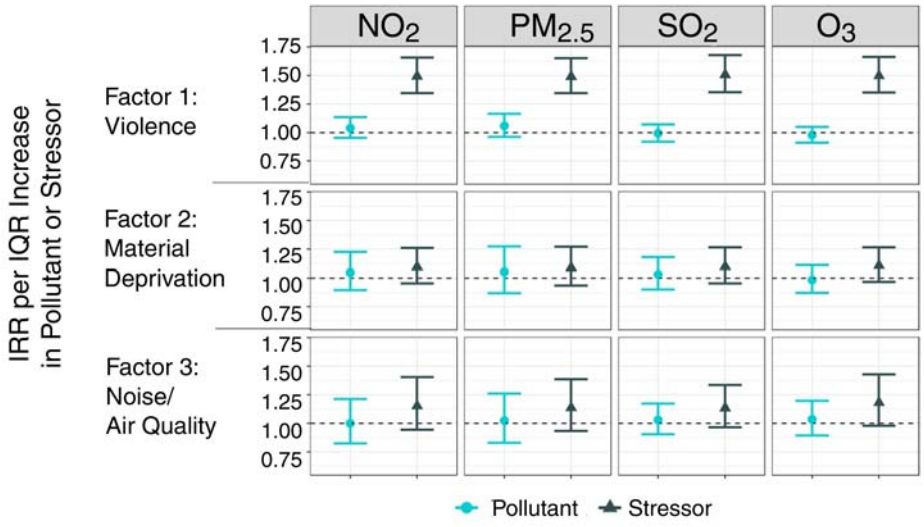


Figure 8. Mutually adjusted negative binomial ecological models for UHF-level stressor factor scores and pollution versus UHF-level CVD rate (*n* = 32; two statistical outliers removed). Each model includes one pollutant and one social stressor. IRRs represent the change in community CVD event rates per 1-IQR change in each covariate, shown with 95% confidence intervals.

Ecological Models for Effect Modification of Pollution–Cardiovascular Disease Associations by Social Stressors

Effect Modification by Census-Tract-Level Social Stressors In negative binomial ecological models for associations between each pollutant and census-tract CVD rate (see Figure 9), we generally found stronger pollutant–CVD associations in communities with elevated stressor exposures.

Specifically, we found evidence of significantly stronger associations for the primary pollutants (NO_2, $PM_{2.5}$, or SO_2) across quintiles of increasing poverty, community violence, or assault rates (P trend < 0.0001).

For those social factors coded in the opposite direction (i.e., for which higher values may reflect less chronic stress, higher median household incomes, or increasing ICE I&R), the trends across quintiles were less distinct.

Only O_3 — which has spatial and temporal patterns opposite those of combustion-related pollutants in NYC and inverse associations with CVD — showed a somewhat different pattern. O_3–CVD associations were stronger (more negative) in communities with higher deprivation, poverty, violence, or assault. As expected, associations were in the opposite direction (more positive) in communities ranked by higher median household incomes or increasing ICE I&R.

Effect Modification by United Hospital Fund–Level Noise In ecological analyses of modification in pollutant–CVD associations by noise (see Figure 10), we found significantly higher positive associations between NO_2 or $PM_{2.5}$ and CVD rates in communities with below-median noise from traffic, construction, or sirens and below-median self-reported noise disturbance (3+ times per week).

SO_2–CVD associations were significantly stronger in communities with above-median subway noise. For O_3, we found significantly greater positive associations with CVD rates in communities with above-median traffic and construction noise (P value for interactions = 0.01 and 0.03, respectively).

Effect Modification by United Hospital Fund–Level Stressor Factors After excluding two statistical outliers, we observed significant positive associations between concentrations of NO_2 or $PM_{2.5}$ and UHF-level CVD rates only in communities with above-median Factor 1 (violence and physical disorder) scores (P value for interaction = 0.01 in both cases).

We observed nonsignificantly greater positive associations between SO_2 and CVD rates in communities with above-median Factor 1 scores (P = 0.07).

For O_3, we observed associations with CVD rates that were significantly greater in communities with below-median (versus above-median) Factor 1 scores (P value for interaction = 0.03) (see Figure 11).

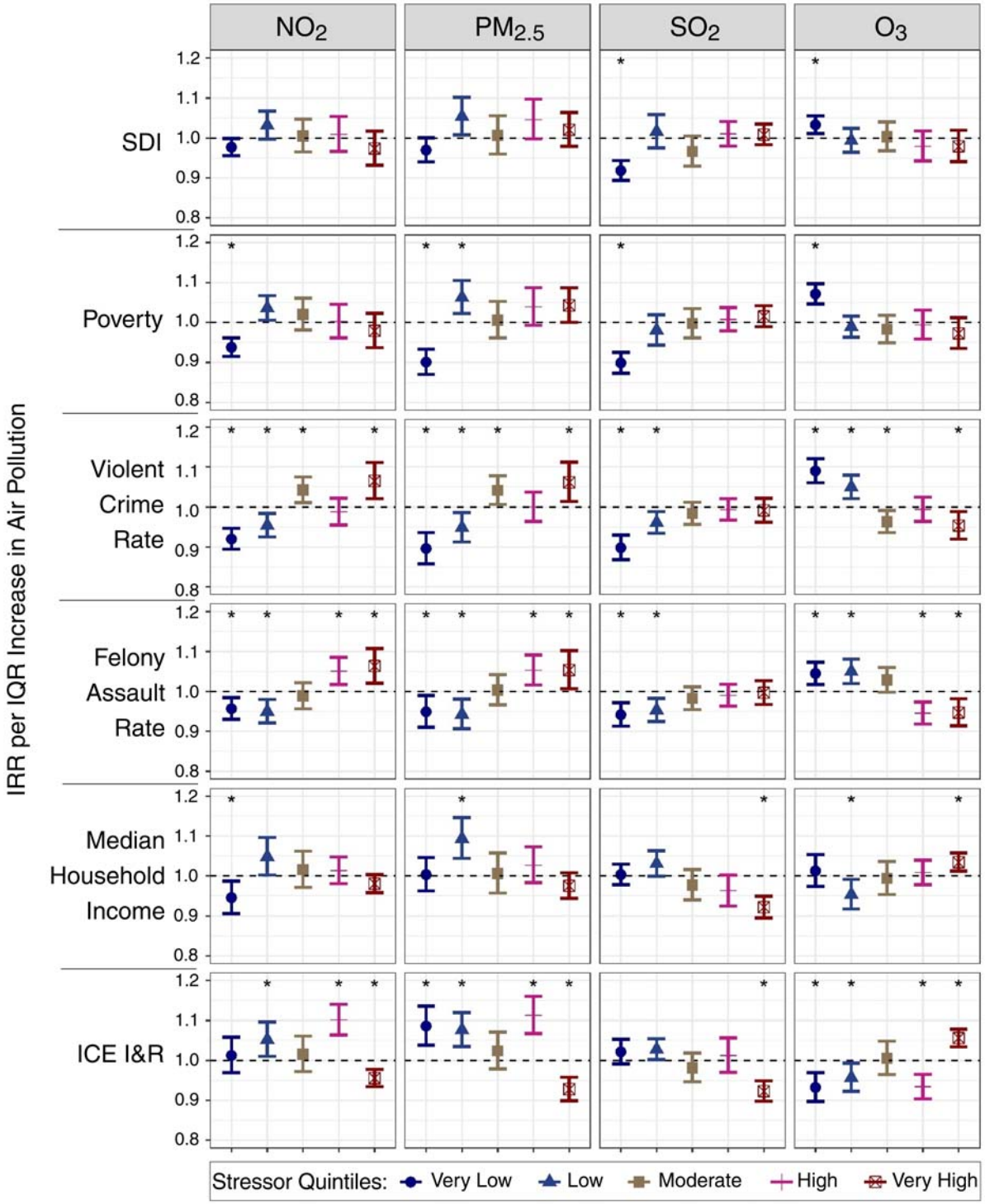


Figure 9. Effect modification by social stressors in census-tract-level negative binomial ecological models for pollutant–CVD associations (n = 1,981). IRRs represent the change in community CVD event rates per 1-IQR change in the pollutant, shown with 95% confidence intervals. Asterisks indicate statistical significance after adjusting for FDRs.

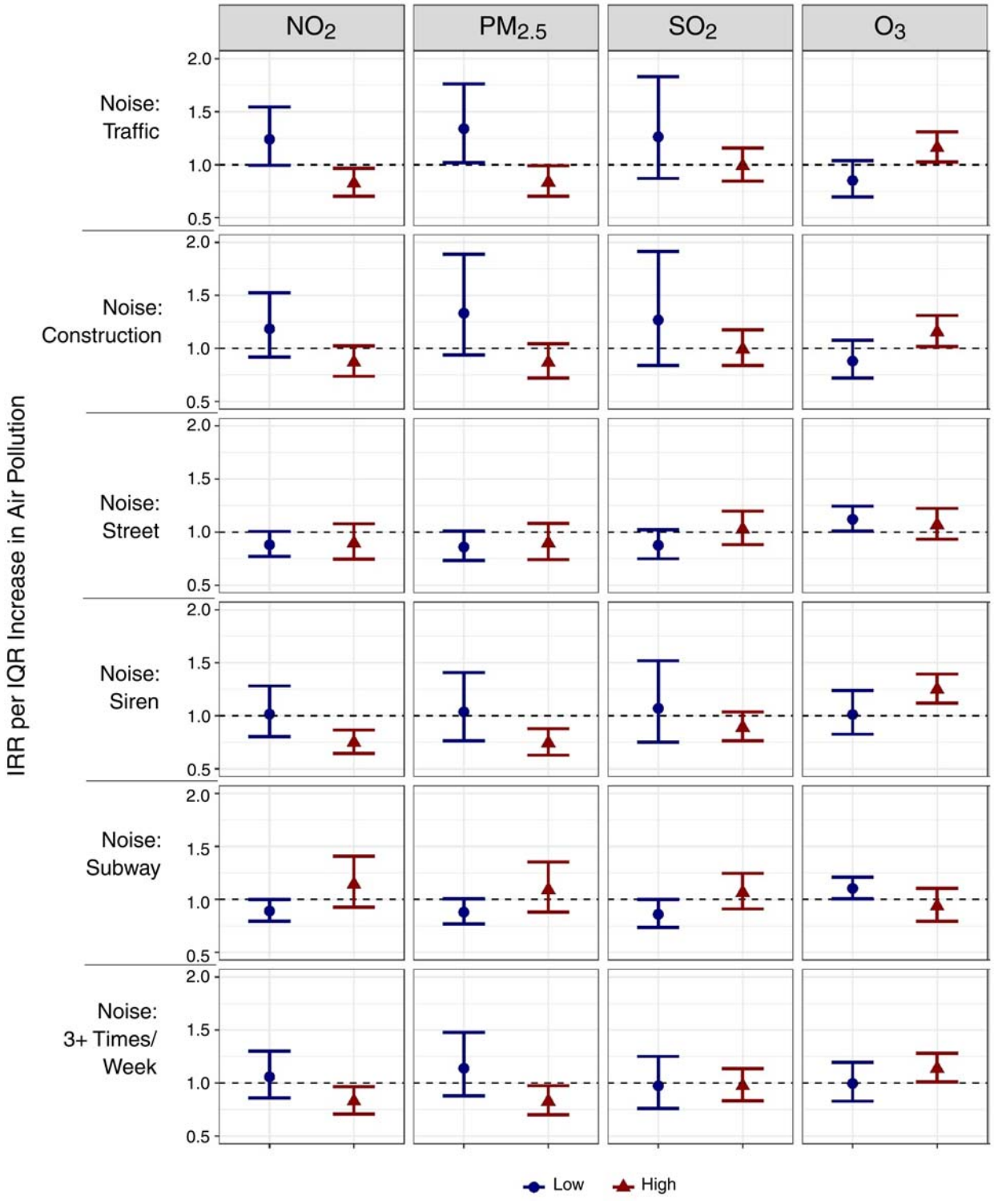


Figure 10. Effect modification by noise sources in ecological associations between air pollutants and UHF-level CVD rates (n = 34). Associations were estimated using negative binomial regression models. IRRs represent the change in community-level CVD event rates per 1-IQR change in the pollutant, shown with 95% confidence intervals.

RESULTS OF SENSITIVITY ANALYSES FOR ECOLOGICAL MODELS (AIM 1)

Because CVD is a very broad category and the mechanisms linking pollutants and stressors are many and varied, the associations reported here may differ by subdiagnosis; as a sensitivity test, therefore, we also ran these models for IHD, the most prevalent subdiagnosis in our dataset. Results were generally consistent with those for total CVD and are detailed in Appendix A1-13.

Sensitivity to Spatial Correlation and Autocorrelation

Most ecological models presented in Aim 1 had significant Moran's *I* values in residuals, indicating significant spatial autocorrelation in census-tract CVD rates not accounted for by the pollutants and social variables tested. We examined the impacts of this spatial autocorrelation on measures of association using Moran's *I* and spatial filtering methods to assess and remove spatial autocorrelation from the residuals of negative binomial regression and negative binomial generalized linear models. Spatial filtering did not meaningfully alter results, and thus we opted to present the simpler models as our primary results. Spatially adjusted and unadjusted results for census-tract-level ecological models are presented for each pollutant separately, in Appendix Tables A1-10 to A1-12, and for UHF-level models (noise and factor scores; $n = 34$) in Appendix Table A1-13.

Scale of Variation and Observed Associations with Cardiovascular Disease

As noted previously, we needed to examine and compare associations with CVD on a one-IQR basis, because the measuring units used for the pollutants differ among themselves — and differ greatly from those used for the social variables. There is, however, greater variance in some social stressors than in pollution exposures across NYC, on a proportional basis (e.g., a one-IQR increase in NO_2 represents a 17% increase in exposures versus 121% for poverty or 405% for the assault rate). Though these differences in variation do not lend themselves to a sensitivity analysis per se, we note them here as a caution in the interpretation of results and note the potential for a lack of generalizability to other areas, where pollution may vary more than do social stressors.

RESULTS OF CASE-CROSSOVER ANALYSES OF POLLUTANT–CARDIOVASCULAR DISEASE ASSOCIATIONS, WITHOUT EFFECT MODIFICATION (AIM 2)

The cohort examined in case-crossover models (Aims 2 and 3) is detailed in Table 5. In the SPARCS dataset, 837,523 in-patient CVD cases had geocodeable residential address information and event dates, enabling the assignment of spatiotemporal pollutant exposure estimates and UHF- and census-tract-level social stressor indicators.

The most prevalent subdiagnosis in our dataset was IHD, which accounted for 27.8% of cases, followed by HF (19.8%) and stroke (14.4%). Ischemic stroke (7.4%) and acute myocardial infarction (9.3%) were less prevalent, potentially limiting the interpretability of analyses for these subdiagnoses in case-crossover analyses.

Cases were roughly balanced between females (50.3%) and males (49.7%), with slightly more non-Hispanic Whites (36.3%) than non-Hispanic Blacks (29.0%). The average age at CVD was 67.2 (SD = 15.3) years, although, as detailed in Appendix 4.3, age at CVD was substantially younger for non-Hispanic Blacks than for non-Hispanic Whites. Final case-crossover model results (see Figure 12a and 12b and Appendix Table A1-15) were broadly consistent with the

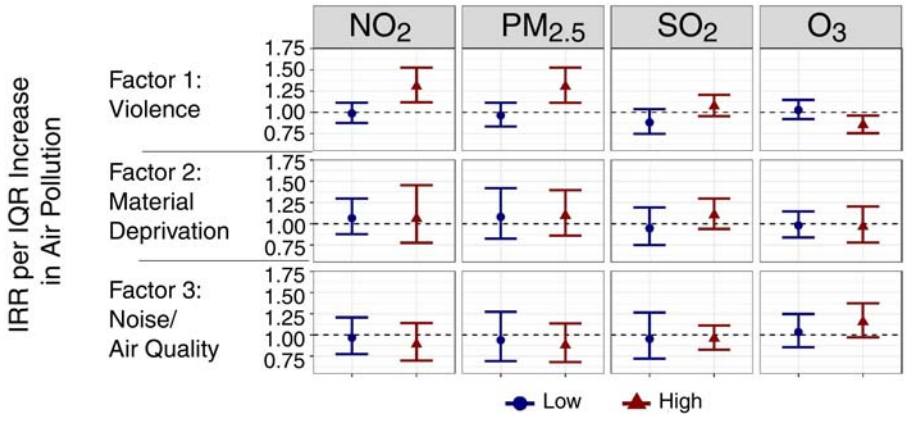


Figure 11. Effect modification by factor scores at the UHF level.

Table 5. Descriptive Statistics for Case-Crossover Dataset[a]

							Percentile		
	N	Min	Mean	Max	SD	Median	25	75	IQR
Spatiotemporal									
NO_2	837,523	2.47	26.97	136.14	11.38	25.06	18.83	33.01	14.17
$PM_{2.5}$	837,523	1.57	12.64	75.46	7.8	10.52	6.87	16.28	9.41
SO_2 (winter-only)	347,218	0.3	14.1	164.06	11.48	10.82	6.67	17.73	11.06
O_3 (summer-only)	347,386	3.43	27.45	70.36	9.39	26.61	20.67	33.64	12.97
Age	837,523	18	67.22	95	15.26	69	57	79	22
Census Tract									
SDI[b]	837,523	−1.63	0.22	2.39	0.73	0.18	−0.36	0.75	1.11
200% of the federal poverty line (%)	837,523	0	0.41	0.97	0.19	0.4	0.25	0.56	0.31
Violent crime rate[c]	837,523	0	46.03	2,262.3	40.56	36.53	18.01	63.25	45.24
Assault rate[c]	837,523	0	21.97	1,344.26	22.56	15.75	6.63	31.59	24.97
UHF: Noise disruption/sources[d]									
3+ Noise disruptions	837,523	11.97	20.51	30.29	5.28	19.44	16.74	24.59	7.85
Traffic noise	837,523	11.11	21.08	35.83	5.17	21.53	16.74	24.2	7.46
Construction noise	837,523	20.25	34.61	61.26	10.53	31.39	27.27	41.46	14.19
Siren noise	837,523	33.67	48.57	66.22	7.56	48.18	43.18	53.03	9.85
Street noise	837,523	25.64	45.45	62.03	9.09	44.55	38.13	54.41	16.28
Subway noise	837,523	0	9.74	25.23	6.49	8.76	3.85	15.19	11.34
UHF: Spatially correlated factors									
Factor 1: "Violence & Physical Disorder"	837,523	−0.65	0.17	1.3	0.62	0.08	−0.45	0.58	1.03
Factor 2: "Crowding & Poor Resource Access"	837,523	−1.34	0.11	1.75	0.82	0.02	−0.44	0.95	1.39
Factor 3: "Noise & Air Pollution Complaints"	837,523	−0.77	0.24	4.56	0.89	0	−0.26	0.69	0.95

Table continues next page

[a] Spatiotemporal exposures, summarized for the case-crossover dataset; predicted pollution exposures within 300 m of each residence, on the case day. Spatial surfaces and case-crossover models include only winter months for SO_2 and summer months for O_3.

[b] SDI is a composite variable.

[c] Events per 10,000 persons, residential population.

[d] Percentage of population reporting disturbance.

CVD = cardiovascular disease; IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SDI = socioeconomic deprivation index; SD = standard deviation; SO_2 = sulfur dioxide.

Summer = May, June, July, August, September; Winter = January, February, March, November, December.

larger air pollution–CVD literature we found significant same-day associations between NO_2 and risk of any CVD event, IHD, and HF that were robust to adjustment for multiple comparisons using FDRs. For example, a 10-ppb increase in NO_2 conferred a 1.51% excess risk of any CVD event (CI = 1.22 − 1.80%). These associations remained significant with any form of co-pollutant adjustment (e.g., penalized splines). Likewise, associations for $PM_{2.5}$ on all CVD and HF were robust to adjustment for copollutants and multiple comparisons.

No significant associations were observed for winter-time SO_2, and we found an inverse association between

Table 5 (*Continued*). Descriptive Statistics for Case-Crossover Dataset

	All-Year		Winter-Only		Summer-Only	
	N	%	*N*	%	*N*	%
All CVD	837,523	100	347,218	100	347,386	100
IHD	232,610	27.77	96,600	27.82	96,592	27.81
HF	165,505	19.76	71,638	20.63	65,024	18.72
Stroke	120,163	14.35	49,153	14.16	50,681	14.59
Ischemic stroke	62,307	7.44	25,541	7.36	26,256	7.56
Acute myocardial infarction	78,187	9.34	33,087	9.53	31,717	9.13
Women	421,621	50.34	174,227	50.18	175,207	50.44
Men	415,899	49.66	172,990	49.82	172,178	49.56
Non-Hispanic White	297,754	36.27	123,439	36.27	123,503	36.28
Non-Hispanic Black	237,527	29.02	97,744	28.8	99,030	29.17
Hispanic	142,875	18.17	58,769	18.04	59,971	18.38
Non-Hispanic other	100,815	12.88	42,853	13.22	40,644	12.52
Hospital admission						
January	70,732	8.45	70,732	20.37	—	—
February	66,771	7.97	66,771	19.23	—	—
March	75,642	9.03	75,642	21.79	—	—
April	71,069	8.49	—	—	—	—
May	73,702	8.8	—	—	73,702	21.22
June	69,035	8.24	—	—	69,035	19.87
July	68,722	8.21	—	—	68,722	19.78
August	68,638	8.2	—	—	68,638	19.76
September	67,289	8.03	—	—	67,289	19.37
October	71,850	8.58	—	—	—	—
November	67,757	8.09	67,757	19.51	—	—
December	66,316	7.92	66,316	19.1	—	—
Sunday	82,536	9.85	34,194	9.85	33,970	9.78
Monday	140,794	16.81	58,239	16.77	57,985	16.69
Tuesday	139,737	16.68	58,189	16.76	58,547	16.85
Wednesday	134,670	16.08	55,977	16.12	56,127	16.16
Thursday	129,972	15.52	53,830	15.5	54,223	15.61
Friday	124,030	14.81	50,979	14.68	51,384	14.79
Saturday	85,784	10.24	35,810	10.31	35,150	10.12

[a] Spatiotemporal exposures, summarized for the case-crossover dataset; predicted pollution exposures within 300 m of each residence, on the case day. Spatial surfaces and case-crossover models include only winter months for SO_2 and summer months for O_3.

[b] SDI is a composite variable.

[c] Events per 10,000 persons, residential population.

[d] Percentage of population reporting disturbance.

CVD = cardiovascular disease; HF = heart failure; IHD = ischemic heart disease; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; SD = standard deviation; SDI = socioeconomic deprivation index; SO_2 = sulfur dioxide.

Summer = May, June, July, August, September; Winter = January, February, March, November, December.

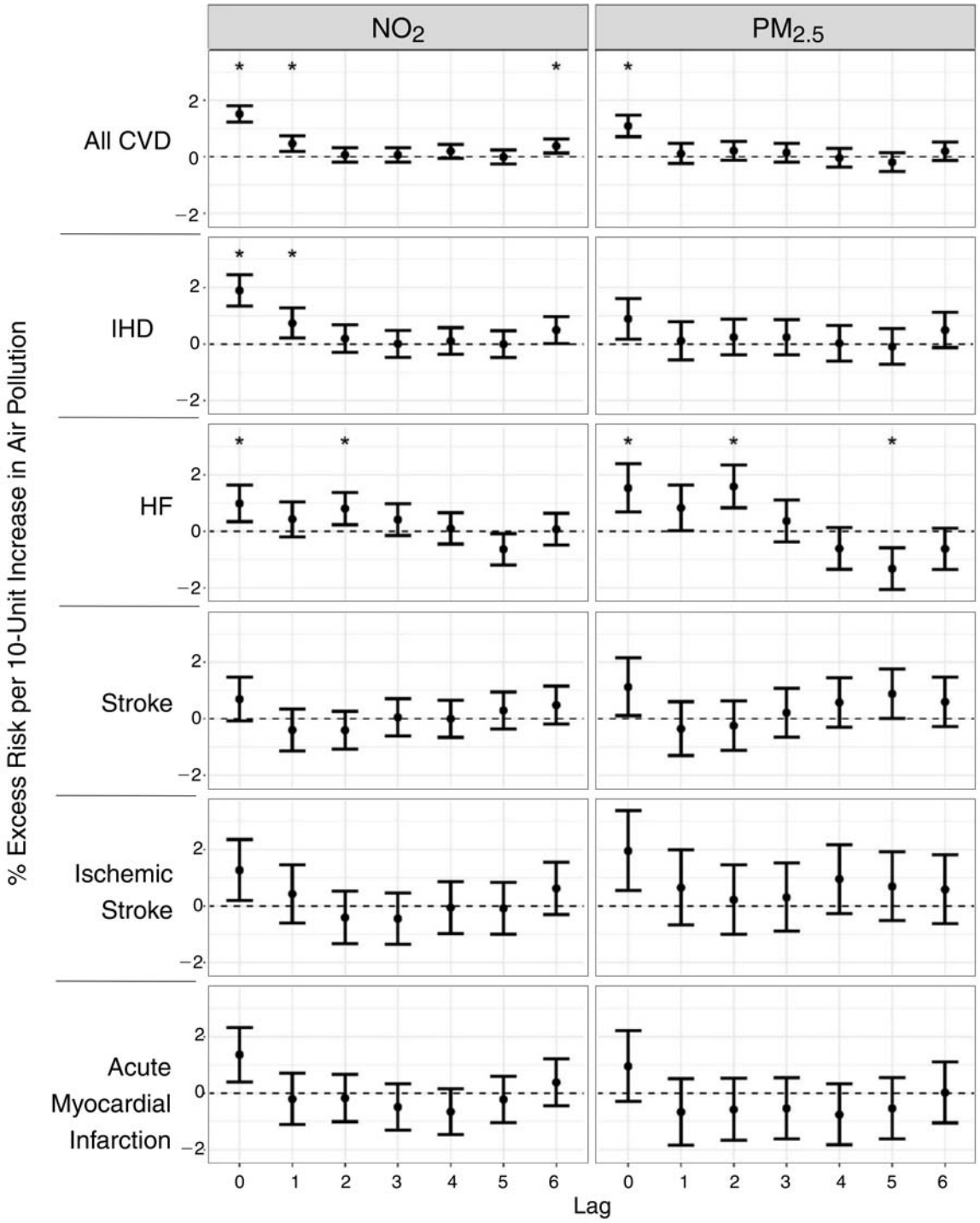


Figure 12a. Percentage excess risk of CVD event per 10-unit change in NO_2 and $PM_{2.5}$ from case-crossover analysis of year-round spatiotemporal pollution versus CVD by subdiagnosis, across lag days 0–6 (*n* = 837,523). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), spatiotemporal same-day copollutants (penalized spline), and modification by percentage non-Hispanic Black and Hispanic by census tract. Asterisks indicate statistical significance after adjusting for FDRs.

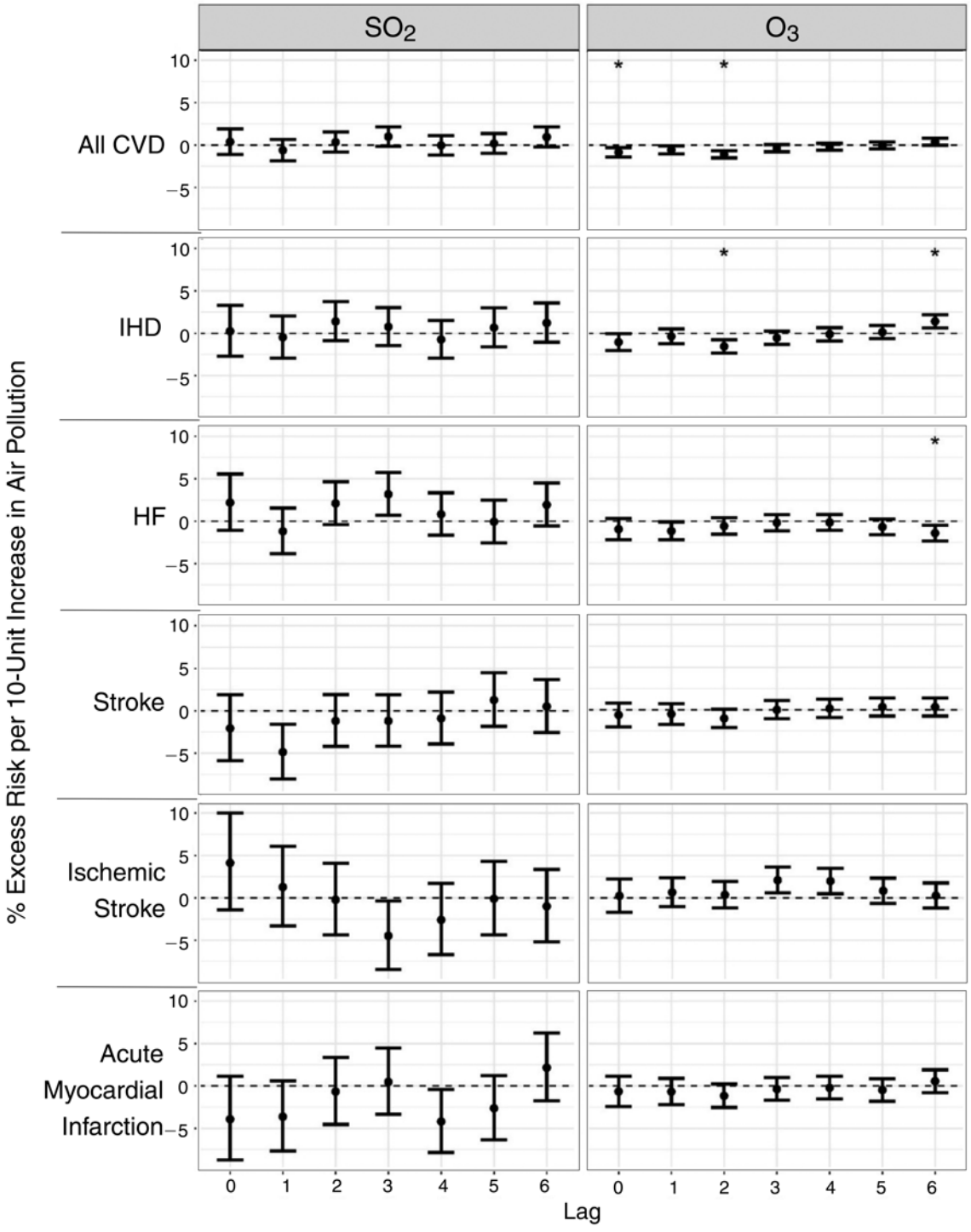


Figure 12b. Percentage excess risk of CVD event per 10-unit change in wintertime SO_2 and summertime O_3 from case-crossover analysis of pollution versus CVD by subdiagnosis, across lag days 0–6 (*n* = 837,523). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), and spatiotemporal same-day copollutants (penalized spline). Asterisks indicate statistical significance after adjusting for FDRs.

summertime O_3 and all CVD events, as expected, given that O_3 and NO_2 are spatial and temporal inverses of one another in NYC (*https://www1.nyc.gov/assets/doh/downloads/pdf/environmental/nyccas-report-summer09.pdf*).

RESULTS OF CASE-CROSSOVER ANALYSES WITH EFFECT MODIFICATION BY SOCIAL STRESSORS (AIM 3)

We examined effect modification by each social stressor separately on the relationship between each spatiotemporal pollutant exposure and percentage excess risk of CVD event, using case-crossover models and examining exposures across lag days 0–6.

In case-crossover models without effect modification (Aim 2), we consistently found the strongest associations on the case day (day 0) for all pollutants, so we expected to focus effect modification analyses on lag day 0. Figure 13 shows effect modification results for NO_2 across all lag days 0–6, using two key effect modifiers — the violent crime rate and the material SDI, examined separately. We generally found stronger associations between NO_2 and excess risk of a CVD event in communities with elevated violent crime, compared with communities in the lowest quintile (reference) for lag days 1–3. However, it is only on lag day 0 for violent crime and SDI that we consistently observed significant overall risks of CVD events with elevated NO_2 across most communities. Thus, for a conservative approach, we focused all our subsequent analyses on lag day 0. These results are also reported in tabular form in Appendix Table A1-16, where significant associations were evident only on lag day 0 and only in the very high violence ($P = 0.03$) and very high SDI tracts ($P = 0.04$).

Effect Modification by Census-Tract-Level Social Stressors

In effect modification results for census-tract-level social stressors (see Figure 14a and 14b and Appendix Table A1-17), using only results for lag day 0, we observed that NO_2 was generally positively associated with the likelihood of a CVD event. Although there is no significant trend across stressor categories, NO_2 is associated with significantly elevated risks only in communities in the highest quintile of violence, assault, SDI, or poverty. For example, a 10-ppb increase in NO_2 conferred a 1.07% excess risk of any CVD event (CI = 0.12–2.04%) in communities in the highest quintile of violent crime ($P = 0.03$), compared to only 0.52% (CI = −0.86–1.92%) in the lowest-violence quintile ($P = 0.46$).

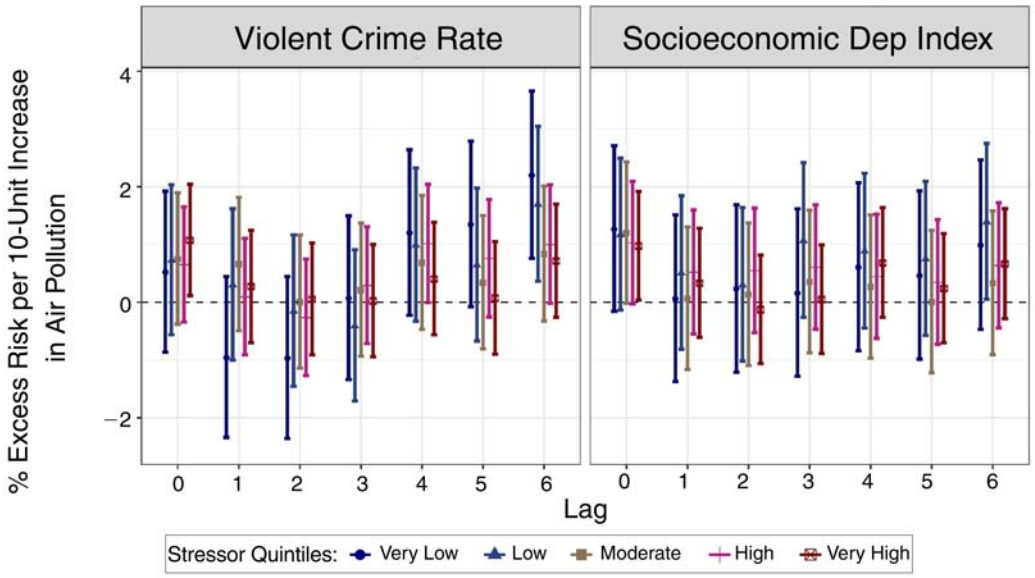


Figure 13. Effect modification by violent crime and the SDI in case-crossover analyses of NO_2 versus CVD, across lag days 0–6 (n = 837,523). Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), spatiotemporal same-day copollutants (penalized spline), and modification by census tract-level racial–ethnic composition. Percentage excess risk represents the change in risk of CVD event per 10-unit change in NO_2, shown with 95% confidence intervals.

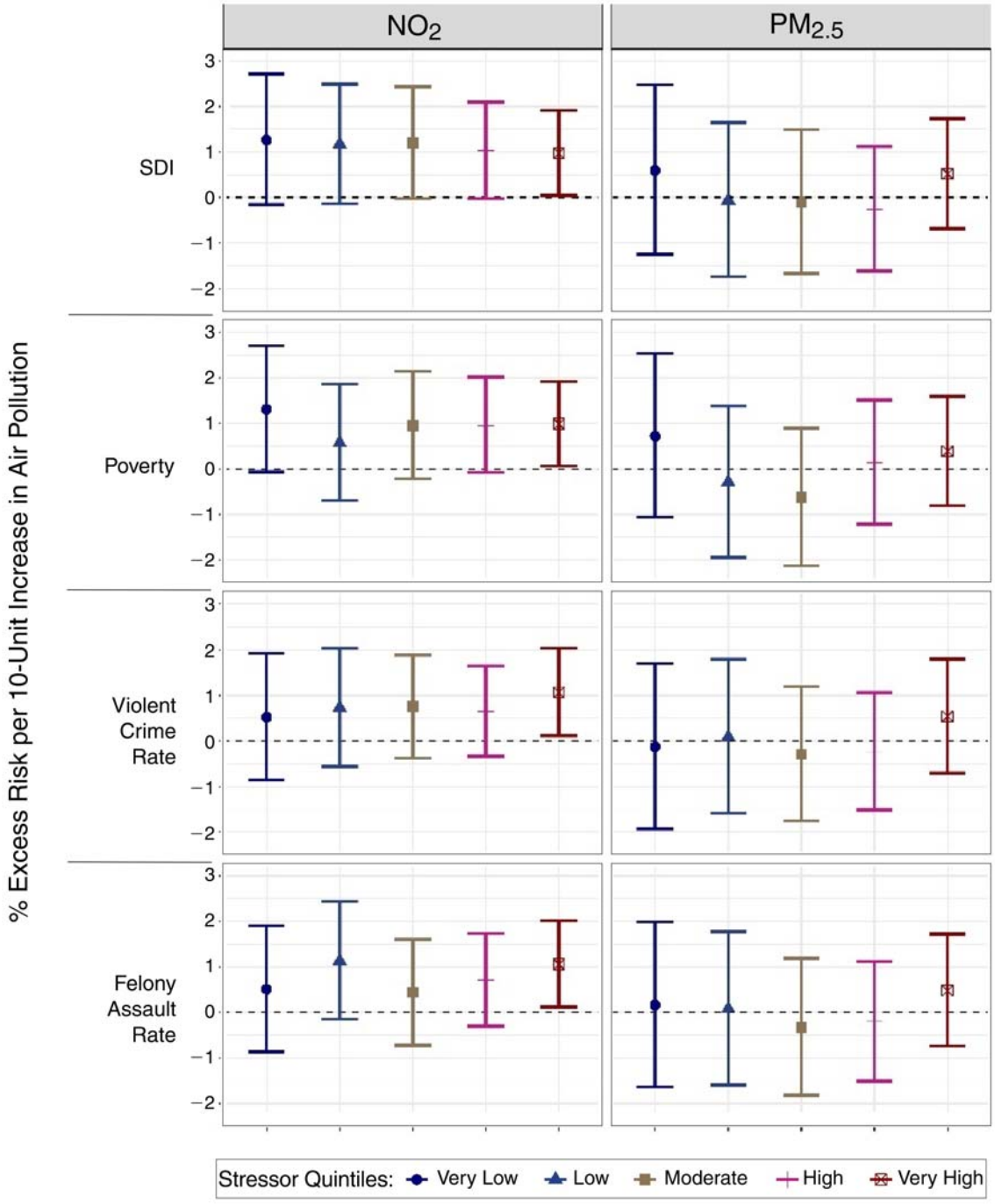


Figure 14a. Effect modification by census-tract-level social stressors in case-crossover analyses of year-round spatiotemporal NO_2 and $PM_{2.5}$ versus excess risk of CVD event, on lag day 0 (*n* = 837,523). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), spatiotemporal same-day copollutants (penalized spline), and modification by census tract percentage non-Hispanic Black and Hispanic. No statistical significance was observed after adjusting for false discovery rate.

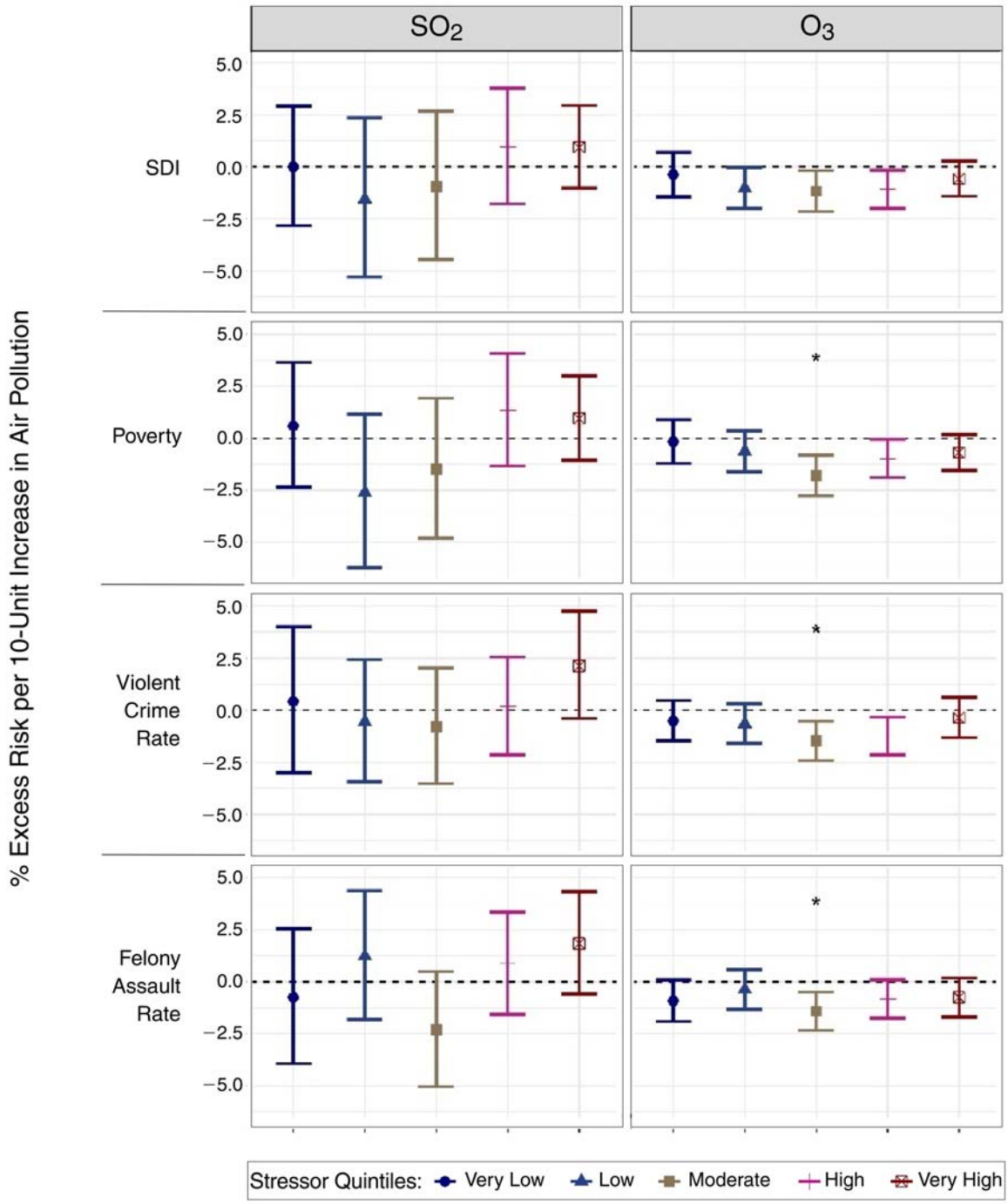


Figure 14b. Effect modification by census-tract-level social stressors in case-crossover analyses of spatiotemporal wintertime SO_2 and summertime O_3 versus excess risk of CVD event, on lag day 0 (n = 837,523). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Models are adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), spatiotemporal same-day copollutants (penalized spline), and modification by percentage non-Hispanic Black and Hispanic by census tract. Asterisks indicate statistical significance after adjusting for FDRs.

For both $PM_{2.5}$ and wintertime SO_2, associations with CVD were nonsignificant within each quintile, but consistently positive only among communities in the highest-stressor quintiles. For summertime O_3, we generally observed negative associations with CVD in all quintiles. In interpreting these results, however, it is important to bear in mind that, as discussed in a previous section, the joint associations among chronic stressors and pollution exposures in NYC are particularly complicated and nonlinear, with greater NO_2 variation in low-poverty, low-SDI neighborhoods.

Effect Modification by United Hospital Fund–Level Noise Disturbance

As shown in Figure 15 and Appendix Table A1-18, median-dichotomized noise, at the UHF level, did not significantly modify results. We found statistically significant associations for both NO_2 and $PM_{2.5}$ on CVD on lag day 0, in both high- and low-noise tracts, even after adjustment for FDRs.

For wintertime SO_2, pollutant–CVD associations were nonsignificant, regardless of noise exposures. We observed inverse associations for summertime O_3, which were not significantly altered by noise.

Effect Modification by United Hospital Fund–Level Stressor Factors

Considering the dichotomized UHF-level effect modifiers (Factors 1, 2, and 3), we observed that pollutant–CVD associations did not significantly differ by UHF-level factor scores.

NO_2 and $PM_{2.5}$ were associated with elevated risk of CVD on lag day 0, regardless of factor score. SO_2–CVD associations were nonsignificant. For O_3, we observed inverse associations with CVD, regardless of factor score. Results are shown in Figure 16 and Appendix Table A1-19.

RESULTS OF SENSITIVITY ANALYSES FOR CASE-CROSSOVER MODELS

We sensitivity-tested all methods — spatiotemporal exposure estimation, geocoding and exposure assignment, stressor validations, and epidemiological analyses — for robustness to variation in analytic methods and quantified attributable variation in exposure assignments and epidemiological associations.

Sensitivity of Exposure Assignments and Epidemiological Results to Geocoding Method We geocoded using a tri-level geolocator that leveraged three positional locators (address point, parcel, and street segment) and assigned the final geocode for each address as the one that produced the highest positional accuracy. We have previously quantified distance and directional error for this method and, using pollution exposure estimates derived using each method, quantified resultant uncertainty in exposure estimates (Kinnee et al. 2020).

Sensitivity of Exposure Assignments and Epidemiological Results to Spatial Exposure Assignment Using the 100 × 100-m NYCCAS spatial surfaces, residence-specific annual average exposures were quantified as mean pollutant concentrations for all grid cell centroids within 300 m of each geocoded residence. We examined variation in exposure assignment for each pollutant and in epidemiological effect estimates, using three radial distances from the residence (address point, 300 m, and 800 m). As in earlier exposure validations using NYCCAS data, we found very high correlations across estimates and no impact on epidemiological analyses (Ross et al. 2013).

Sensitivity to Use of Spatiotemporal (Versus Temporal-Only) Exposure Estimates To assess potential exposure misclassification attributable to the use of the 100-m NYCCAS spatial surface, we examined Pearson correlations between temporal and spatiotemporal exposure estimates for the full SPARCS cohort. Correlations were generally very high — near 1.0 (0.97 and 0.98) for $PM_{2.5}$ and O_3, respectively, which was relatively unsurprising, because temporal (versus spatial) variation comprises the majority of the total variation in these pollutants in NYC. NO_2 and SO_2, on the other hand, showed somewhat weaker correlations (0.87 and 0.79, respectively), because spatial variation comprises a greater portion of the total variation in these pollutants and because, for SO_2, the only available AQS monitors were located in very source-intensive areas of the city, potentially misrepresenting temporal trends in other areas.

Sensitivity to Adjustment for Copollutants To assess the influence of co-pollutant adjustment on observed associations between pollutants of interest and CVD, we implemented single-pollutant case-crossover models (Appendix Table A1-19). In the case of NO_2, the single-pollutant models did not differ substantially from the final models; NO_2–CVD associations were robust to adjustment by any co-pollutant. For the other pollutants, associations observed in single-variable models were somewhat stronger than in models with co-pollutant adjustment, as expected.

Sensitivity of Effect Estimates for Summer O_3 to Adjustment for Temperature Because of high correlations between temperature and O_3, we tested for sensitivity to adjustment for spatiotemporal same-day Tmin and RH. Previously, we found no differences in case-crossover results adjusting for temperature, RH, or dew point (Sheffield et al. 2015). In this case, we found weaker inverse associations

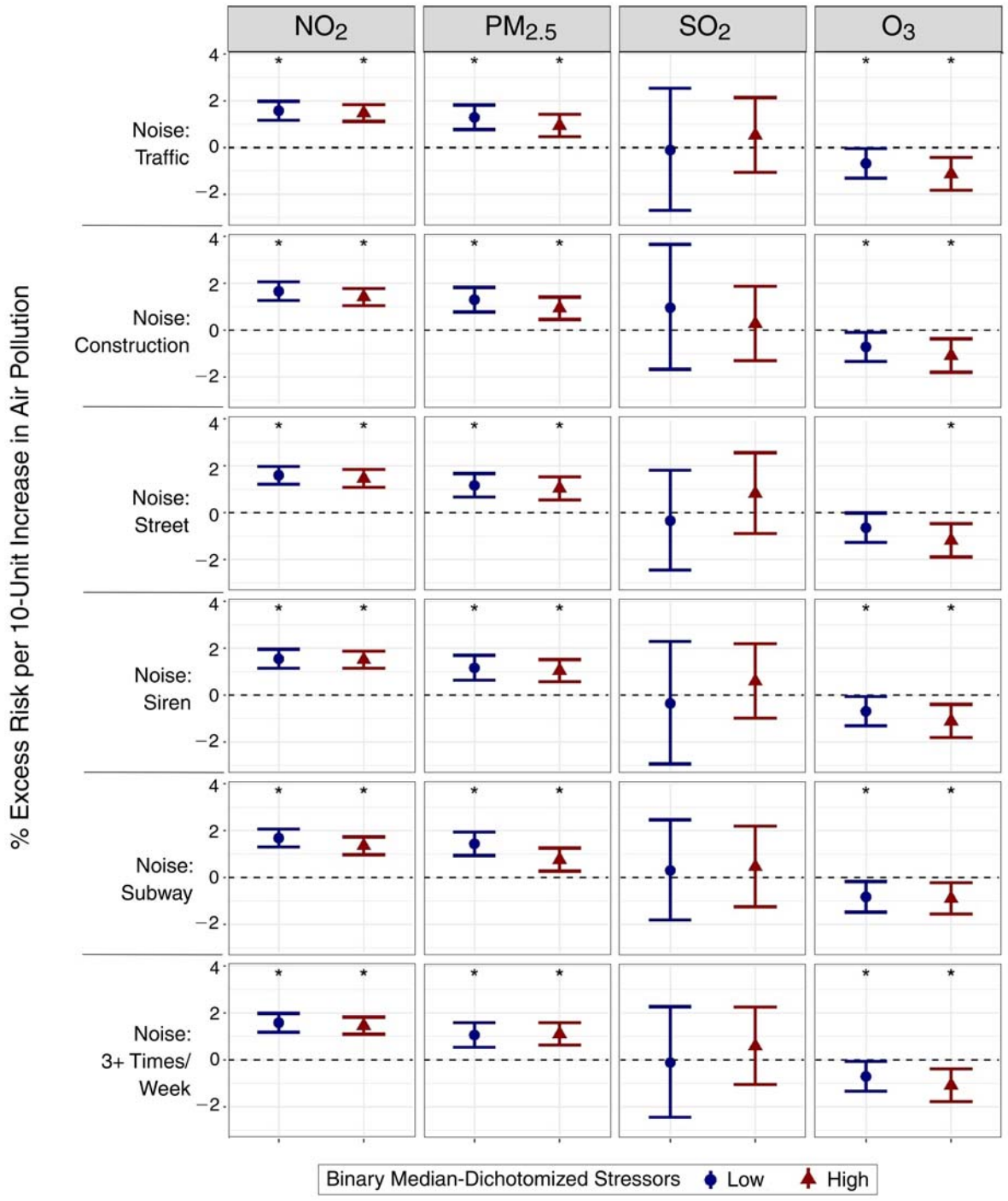


Figure 15. Effect modification by census-tract-level noise disturbance in case-crossover analyses of spatiotemporal pollution exposures versus excess risk of CVD event, on lag day 0 (*n* = 837,523). Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), and spatiotemporal same-day copollutants (penalized spline). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Asterisks indicate statistical significance after adjusting for FDRs.

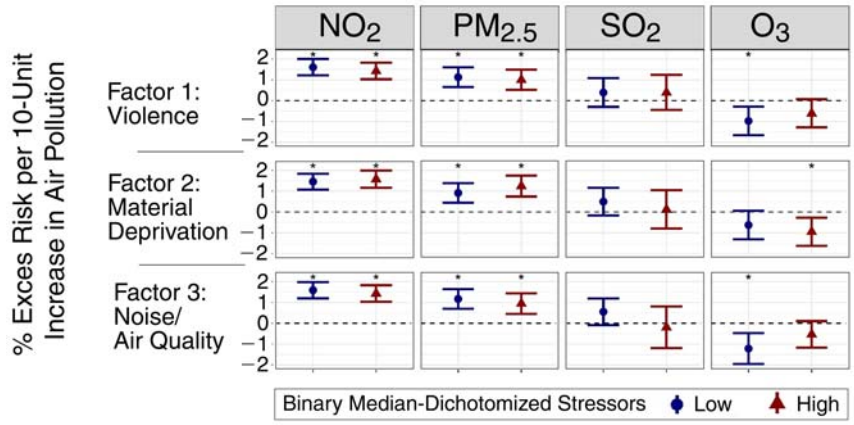


Figure 16. Effect modification by UHF-level stressor factors in case-crossover analyses of spatiotemporal pollution exposures versus excess risk of CVD event, on lag day 0 (*n* = 837,523). Models were adjusted for spatiotemporal same-day Tmin (ns, df = 3), RH (ns, df = 3), and spatiotemporal same-day copollutants (penalized spline). Percentage excess risk represents the change in risk of CVD event per 10-unit change in the pollutant, shown with 95% confidence intervals. Asterisks indicate statistical significance after adjusting for FDRs.

between summer O_3 and CVD after adjusting for temperature and RH; before adjustment, a 10-ppb increase in summer O_3 conferred a same-day excess risk of −1.09% (95% CI = −1.54% to −0.64%), which decreased to −0.86% (95% CI = −1.39% to −0.33%) after adjustment ($P = 0.0016$ and $P < 0.0001$, respectively) (Appendix Table A1-20).

Season-Specific Pollutant Models Because NYCCAS data for O_3 were collected only during summer, and for SO_2 only during winter, we opted to present season-specific case-crossover models as the main results for these pollutants. We found, in both cases, that the observed associations were slightly more conservative in season-specific models. For example, a 10-ppb increase in O_3 conferred a same-day excess risk of −1.53% (95% CI = −1.87% to −1.19%) in year-round models but of only −0.86% (95% CI = −1.39% to −0.33%) in summer-only models ($P < 0.0001$ and $P = 0.0016$, respectively), likely due in part to reduced sample size and statistical power in summer-only models, despite the reduction in exposure misclassification (Appendix Table A1-20).

For SO_2, we found a same-day excess risk of 2.47% (95% CI = 1.26% to 3.69%) in year-round models ($P = 0.0001$) but of only 0.38% (95% CI = −1.10% to 1.89%) ($P = 0.62$) in winter-only models, again likely due in part to reduced sample size in season-specific models, despite the reduction in exposure misclassification (Appendix Table A1-21).

Sensitivity to Assumption of Linearity in Pollutant–Cardiovascular Disease Associations To assess linearity in NO_2–CVD associations, we performed exploratory analyses using spatiotemporal measures of NO_2 and copollutants, both as cubic splines with $n = 5$ knot points, to estimate the relative risk of CVD events. Results indicated that NO_2–CVD associations were generally linear, even with nonlinear adjustment for copollutants. As such, we reported linear models but retained nonlinear co-pollutant adjustments, because allowing a more flexible fit in potential confounders should provide for a more conservative analysis of the main pollutants of interest.

Sensitivity of O_3 Effect Estimates to Adjustment for NO_2 A particularly complicated co-pollutant adjustment was presented by the relationship between O_3 and NO_2 because NO_2 is a precursor in ground-level O_3 formation, and NO_x reacts with ambient O_3, scavenging it in dense urban areas. This strong inverse association between O_3 and combustion emissions — combined with strong negative (inverse) temporal correlations between O_3 and NO_2 in regulatory data — likely underlies the apparent inverse associations that we observed for O_3. We compared models for O_3 with and without adjustment for NO_2. Adjustment for spatiotemporal NO_2 substantially attenuated O_3 effect estimates but did not fully attenuate results; without NO_2 adjustment, a 10-ppb increase in summer O_3 conferred a same-day excess risk of −0.86% (95% CI = −1.39% to

−0.33%), which decreased to −0.74% (95% CI = −1.22% to −0.25%) after adjustment (P = 0.0016 and 0.003, respectively) (Appendix Table A1-20).

Sensitivity to Covariate Formulation and Multicollinearity To conserve power, we adjusted for co-pollutant exposures using penalized splines, selecting df based on the shape of the nonlinear fit between pollutant concentrations and likelihood of event. To sensitivity-test epidemiological models to df selection, we refitted all models with 4 df, 5 df, and 7-day-average co-pollutant exposures. The functional form of model covariates was determined using likelihood ratio tests to compare fit across models of increasing complexity (i.e., linear form, ns with defined df, or penalized spline with unlimited df), one variable at a time. To sensitivity-test our case-crossover methods, we controlled for temperature, RH, and a smooth function of time to control for long-term trends and day of week (Sheffield et al. 2015). As in earlier analyses, we found no significant impact of this variation on our main associations of interest.

Sensitivity to Cut Points in Effect Modifier Categorization Though we opted to present effect modifications in quintiles for the main analyses — our most resolved categorization supported only by the large number of census tracts — we examined various other categorizations of the stressor modifiers. We also present results for two key modifiers (violent crime and SDI) as median-dichotomized census-tract-level modifiers (Appendix Table A1-22), for all CVD across lag days 0–6. In all cases, as in the main analyses, we found significant associations between the pollutant and CVD on lag day 0 (case day), though NO_2–CVD associations were significantly elevated in communities with both above- and below-median stressor exposures. These models are limited in several ways, however, including both the large number and variety of neighborhoods within each group (because of using a coarse binary dichotomization) and not adjusting for modification by spatially co-occurring stressors.

Sensitivity to Modeling Lag Days Independently Based on the results of the lag-specific models for the associations between pollutants and CVD event risk, with associations largely limited to lag day 0, we determined that distributed lag nonlinear models would not yield additional useful information. For pollutants other than NO_2, associations at non-zero lags were indistinguishable from the null even in models unadjusted for other lags. For NO_2 exposure, there was some evidence for association at lag one, but interpretability of this effect would not be meaningfully improved by increasing model complexity.

DISCUSSION AND CONCLUSION

In this study, we quantified relationships between chronic and acute exposures to multiple pollutant exposures in NYC and tested whether pollution–CVD associations varied by community SEP and stressor exposures. We hypothesized that (1) chronic community-level SEP, stressor, and pollution exposures would be associated with higher community CVD event rates; (2) that spatiotemporal variation in multiple pollutants would be associated with increased excess risk of CVD events; and (3) that pollution–CVD associations would be stronger in communities of lower-SEP, higher-stressor exposures.

Broadly, we found evidence of social susceptibility to pollution, in the hypothesized direction, with stronger pollution–CVD associations in communities of lower-SEP, higher-chronic-stressor exposures. Associations with CVD were strongest for same-day pollutant exposures, notably for NO_2. In keeping with other results in the literature, we observed inverse associations for O_3, likely due to strong inverse (negative) spatial and temporal associations between NO_2 (and other primary combustion-related, traffic-related pollutants) and O_3 in NYC. Further investigation is needed to elucidate causal stressors underlying this SEP-related susceptibility, to separate community- from individual-level susceptibility, and to examine differences in susceptibility by age, particularly with regard to race (noting that the median age at CVD event was 14 years younger for Black than for White New Yorkers).

To first understand the separate and combined associations with CVD for stressors and pollution measured at the same spatial and temporal scale of resolution, we used ecological cross-sectional models to examine *spatial* relationships between multiple "chronic" pollutant and stressor exposures and age-adjusted community CVD event rates. Using the same spatial and temporal scales (i.e., census-tract annual averages, n = 1,981), we compared associations with CVD event rates for multiple pollutant concentrations and social stressors (e.g., poverty metrics, violent crime rates, a composite SDI, the ICE I&R, and three spatial factors produced from a factor analysis of 27 community stressors). We found that, after accounting for social stressors, most pollutant–CVD associations became nonsignificant; in contrast, most social stressors retained significance, and the magnitude of the association was much larger for a one-IQR difference in social stressors than for pollutant concentrations. Although substantial questions remain about the most appropriate, *meaningful* scales for the measurement and evaluation of air pollutants and social stressors, our results indicated that — when offered equal spatial and temporal resolution

— associations between social stressors and CVD were much stronger than pollutant–CVD associations. Importantly, however, we note that — although we needed to compare exposures on a one-IQR basis for comparability — on a proportional basis, there is much greater variance in some social stressors than in pollution exposures across NYC, and thus one should not assume these results would be generalizable to locations where pollution varies more than do social stressors.

We also tested effect modification of ecological pollutant–CVD associations by each social stressor, finding consistent evidence of stronger associations for NO_2, $PM_{2.5}$, and wintertime SO_2 with CVD rates in higher-stressor communities. These trends were particularly strong across quintiles of increasing community violence or assault rates (P trend < 0.0001).

To examine associations between multiple pollutant exposures and individual-level excess risk of CVD event across multiple lag days, we tested spatiotemporal (day- and residence-specific) exposure estimates against case-level hospital data in case-crossover models, which inherently adjust for individual-level confounders that do not vary on short timescales (e.g., sex, race, age) and comorbidities. For these models, we focused on in-patient data (to reduce misclassification in patient-level outcomes) and found consistent significant relationships only for *same-day* pollutant exposures and excess risk of CVD event; associations with CVD were positive for NO_2, $PM_{2.5}$, and winter SO_2, as hypothesized. Wintertime O_3 (a secondary pollutant chemically scavenged by fresh emissions) was inversely associated with CVD risk. Results were in keeping with findings elsewhere in the literature emphasizing the short-term (i.e., same-day) effects of acute air pollution on CVD.

Finally, we tested whether community-level SEP and stressor exposures modified individual-level relationships between spatiotemporal pollutant exposures and excess risk of CVD event. We generally found, as hypothesized, stronger and more significant associations between the primary pollutants (NO_2, $PM_{2.5}$, and SO_2) and CVD among individuals living in communities with higher exposures to most social stressors. O_3 was inversely associated with CVD but was likewise stronger for individuals living in communities with higher stressor exposures.

Broadly, our results show the complexity of accounting for multiple clustered social stressors and pollutants operating simultaneously in urban communities. These stressors are neither independently, nor randomly, distributed, pointing to the need for richer methods to account for the social and economic forces that sort individuals into neighborhoods based on individual attributes (most notably race and income) and to account for multiple community susceptibilities operating simultaneously (e.g., violence, poverty, and low-quality housing). As such, future investigations should refine our attempt to investigate effect modification attributable to multiple social stressors simultaneously (i.e., multiple-modifier models) and to investigate cross-level interactions among individual-level characteristics (e.g., race and sex) and community-level stressors (e.g., violence and poverty), which together may influence pollution susceptibility (e.g., three-way multilevel interactions). Because of profound race-based residential segregation and strong sorting into neighborhoods by income in NYC, it will remain a challenge to disaggregate the strong spatial confounding between these individual- and community-level characteristics.

The complex joint distributions among stressors (e.g., higher noise in wealthier Manhattan communities) and between stressors and pollution in NYC (e.g., higher and more varying NO_2 in wealthy Upper East Side communities) may contribute to the nonlinearity we observed in some analyses (e.g., pollution-associated risks do not necessarily increase linearly across quintiles of a community stressor).

In addition, each stressor had a very different statistical distribution (e.g., there were several very high outliers for community violence, though most tracts had relatively low violence; in contrast, poverty was more normally distributed). As such, there was no common means of categorizing the stressors that was equally accurate or informative for all stressor types. We opted here to present our most refined (quintile) models; other methods may have been more accurate for each stressor but would have lost interpretability across stressors.

Finally, our results point to the need to investigate longer timescales in the social processes underlying pollution susceptibility. We observed a 14-year difference in median age at CVD between White and Black New Yorkers — suggesting that the processes underlying social susceptibility likely operate on the order of years or decades rather than in the day-to-day changes that case-crossover methods isolate and emphasize.

CHALLENGES AND LIMITATIONS

Inverse Associations for O_3

We observed inverse associations between O_3 and CVD, as has been noted elsewhere, including in national-scale studies where O_3 was shown to have inverse associations with cardiovascular and cardiopulmonary death after adjustment for $PM_{2.5}$ (Jerrett et al. 2009). Concentrations of O_3, a secondary pollutant, are often higher in less densely

urbanized areas — which, in the context of many U.S. cities, may be wealthier suburbs — and hence their inverse associations with health may be attributable to residual confounding by SEP and/or co-pollutant adjustment. In our setting, some of the wealthiest NYC communities happen to be located in very dense areas with substantial primary pollution (e.g., the Upper East Side) and, consequently, lower O_3 concentrations. Such conflicting results have led to a call for more mechanistically oriented studies and a more rigorous consideration of the chemical nature of O_3, both in the atmosphere and as related to biological pathways and health (Srebot et al. 2009), as well as for a stronger consideration of climatic zones (Cakmak et al. 2016) and physiological interactions with copollutants. In our study, results were likely influenced by strong chemical scavenging of O_3 by fresh emissions in a dense urban environment, producing an inverse spatial and temporal relationship between NO_x and O_3 — in fact, NO_2 (with a negative coefficient) is the strongest spatial predictor of O_3 concentrations in the NYCCAS models ($r = -.93$; *https://www1.nyc.gov/assets/doh/downloads/pdf/environmental/nyccas-report-summer09.pdf*). As a result, the inverse associations for O_3 may in fact indicate a detrimental impact of fresh combustion emissions on CVD.

Residual Confounding

As in all epidemiological studies of administrative data, there are several important potential confounders for which we lacked data, including individual smoking status, diet, and other health behaviors. These covariates, to the extent that they vary between communities, may confound the negative binomial (ecological) model results and, to the extent that they vary within communities, may contribute to misclassification, likely dampening our ability to observe any true effect modifications. Our case-crossover design, however, inherently controls for non-time-varying covariates within the stratified period (1 month). As such, we should expect no confounding of results by age, race–ethnicity, sex, or smoking status, although these variables may plausibly modify pollutant impacts on CVD.

In addition, our social stressors data were annual-average percentages and rates, aggregated to area-level (census tract or UHF area); in contrast, our air pollution exposures were estimated at the individual's residential address on the day of a CVD event and for each of 6 days prior. This tremendous difference in the accuracy and resolution of stressor versus pollution data was the impetus for our Aim 1 ecological analyses, putting social and environmental factors on the same spatial and temporal scale. Likewise, we removed census tracts with very low populations (i.e., <200 persons) to reduce the influence of unstable population rates in our analysis. Further research is needed to understand the role of misclassification in studies combining exposures of very different types, measured at very different scale of resolution, and to assess how misclassification in effect modifiers (i.e., community-level stressor indicators) may influence observed effect modifications.

Generalizability

As a large, dense, and highly varied city, generalizing results from NYC to other areas should be done with some caution. Notably, the specific stressors (e.g., violence) and specific pollutants of interest (e.g., SO_2) in this city may not be directly relevant to other areas. But our methods — which included identifying locally meaningful chronic stressors reported by residents and capturing fine-scale spatiotemporal variation in pollutants relevant to local sources — are generalizable. Likewise, our findings of very acute pollution impacts on CVD (i.e., same-day effects) and of greater apparent susceptibility in lower-SEP, higher-stressor communities are likely generalizable to populations in very different settings.

Confounding Between Community Stressors and Individual-Level Race

As in most U.S. cities, the distribution of neighborhood social stressor exposures in NYC is tightly intertwined with racial and economic segregation. The area-level social variables we examined capture only a very limited aspect of the complexities of urban social and sociodemographic patterning. In addition, when examining effect modifiers as categorical variables, the "high" or "low" quintile often disproportionately comprises members of one racial–ethnic group, leading to challenges of off-support inference as well as confounding. Future studies will require deeper investigation into the patterns of persistent racial segregation and related processes that lead to clustering in social and economic disadvantage, and stressor exposures, by race. There is also a need for richer methods to capture cross-level interactions between very highly correlated individual- and neighborhood-level characteristics, with the potential for effect modification of air pollution exposures at both levels.

Misclassification in Effect Modifiers

Misclassification in the measurement of potential effect modifiers generally dampens the ability to observe any true effect modification — regardless of whether the error is classical or Berkson-type. In the case of social stressor indicators, misclassification is a substantial concern

because we must often rely on community-level indicators — such as neighborhood poverty or crime rates — as proxies for individual-level experience. In most cases, this error can be assumed to be Berkson-type (in which many individuals in the same neighborhood are assigned the same poverty rate), though we cannot always assume that the interindividual variation around the true neighborhood mean is entirely random. For this reason, as possible, all models were adjusted for individual-level covariates, including those potentially associated with chronic stressor exposures (e.g., sex and race), and we have, in earlier studies, gone to substantial lengths — including performing focus groups and surveys across NYC, as detailed in the Appendix — to verify that the indicators we use reasonably capture intercommunity variation in individual-level stress experience.

Given that all chronic stressors we examined in this study are community-level, and hence that substantial (nondifferential) individual-level exposure misclassification must be assumed, the consistent effect modification that we did observe, in the hypothesized direction, may reasonably be interpreted as a conservative estimate of true effect modification by social stressors.

STRENGTHS

Our study had a number of notable strengths. First, our population-at-risk was the entire adult population of NYC, from 2005 to 2011, providing a study population with substantial variation in exposures to multiple pollutants (ranging from dense, highly polluted Manhattan to suburban Staten Island) and in individual- and community-level stressors that may underlie susceptibility. Given the large population, wide range in exposures, and widely varying susceptibility characteristics, we benefited from the statistical power both to detect meaningful interactions and to examine dose–response relationships across the full range of pollutant concentrations normally encountered in ambient urban environments, with covariation by community stressors, underscoring our ability to observed true interactions. A great advantage in examining combined effects of stressors and pollution in NYC was the presence of many high-income neighborhoods in dense areas with high pollution concentrations, as well as low-income neighborhoods with low pollution concentrations. These "off-diagonal" communities helped to ameliorate the challenges associated with persistent spatial confounding between pollution and social stressors in many settings, allowing us to examine independent and interaction effects with lesser risk of bias caused by persistent confounding or off-support inference.

In addition to our very large sample size and complete hospital records covering the entire city over several years, our exposure measures included fine-scale data on multiple pollutants (100-m resolution) and citywide coverage in key social variables derived from extensive earlier work examining spatial correlations among a wider array of social stressors (Shmool et al. 2014); we also verified relationships between community stressors and resident perceptions (Shmool et al. 2015b). Although the list of census-tract-level social variables we were able to examine here was reasonably long and well curated, they did capture only a very limited portion of the depth and complexity of the social processes that influence population susceptibility.

We were able to use extremely fine-scale (100-m) spatial air pollution surfaces to construct day- and location-specific exposure estimates. In addition, because census tracts are very small in much of NYC (n = 2,167), the social data derived at this scale is more refined than in many other locations. We were thus able to examine relationships among pollutants, social stressors, and health with excellent spatial resolution and to test these relationships at multiple spatial scales (e.g., UHF area) to establish consistency in results.

IMPLICATIONS OF FINDINGS

RELEVANT INSIGHTS PROVIDED BY THIS STUDY

This study detailed patterns of susceptibility to air pollution as they relate to the risk of cardiovascular events in one large U.S. city. By more clearly elucidating aspects of community susceptibility, the study points to opportunities to more effectively target pollution-reduction interventions in communities where pollution health effects are magnified and may point to opportunities to increase community resilience and reduce health disparities.

Given our large population-at-risk (all adults among the eight million residents of NYC) and fine-scale multipollutant data, we had adequate statistical power and appropriate methods to deliver quantitative insights on population susceptibility to pollution. We improved scientific knowledge by incorporating social information on communities to gain insight into the differential impacts of multiple pollutants on the risk of CVD events, thereby pointing to modifiable opportunities for intervention. We were able to break through several earlier barriers in research on this topic because (1) we had already developed and verified locally relevant indicators of chronic stress, using citywide focus-group and survey data, (2) we had fine-scale spatiotemporal data on multiple pollutants

and the statistical power to examine associations for multiple pollutants, separately and together, on CVD risk and to test modification in each pollutant by SEP–stressor exposures, and (3) we had high-quality, complete CVD hospital event data, reducing error and improving efficiency in epidemiological models of independent and interaction effects.

IMPORTANCE OF THE RESEARCH

Because CVD remains the leading cause of death in the United States and worldwide, any excess risk is meaningful in terms of total morbidity and years of life lost, regardless of statistical significance. CVD disproportionately impacts lower-SEP urban communities, with higher rates of hypertension and cardiovascular death as well as several key comorbidities, including diabetes and obesity.

Further, the world population is rapidly urbanizing, and, particularly under climate change scenarios, urban exposures to O_3 and other pollutants will likely rise. These exposures to complex mixtures — including multiple pollutants and spatially correlated social factors — will therefore be increasingly important determinants of health and health disparities. Given complex spatial patterning between SEP and pollution sources (Jones et al. 2014), disentangling their effects — and elucidating their potential synergies — is particularly challenging and increasingly important.

Few populations offer the sample size, variation in multiple-pollutant exposures, and diversity in SEP and sociocultural mix as does NYC. This wide variation in exposures and exposure combinations is needed to quantify interactions among multiple pollutants — and among social stressor and physical environmental exposures — and to compare dose–response curves. Because of the small size of NYC census tracts, we were able to examine social effect modifiers at a much finer scale than is often possible — at scales closer to "individual" exposures. Moreover, NYC includes both low- and high-SEP communities exposed to both relatively low and high pollution — providing the critical "off-diagonal" groups needed for epidemiological comparisons and assessment of interactions.

REGULATORY SIGNIFICANCE

Given the complexity of multiple exposures converging to influence the risk of CVD events in urban communities — and the importance to public health of alleviating the disproportionate CVD burden in lower-SEP communities — there is an urgent need to better understand *susceptibility* to pollution in CVD risk, pointing toward modifiable interventions. Our study helps to quantify associations between multiple air pollutants and CVD events in a large urban population and to build the critical evidence base needed to support targeted pollution exposure reductions.

Because our study examined multiple air pollutants — with fine spatiotemporal resolution and multiple lag days — we could observe and compare pollutant impacts in communities of varying susceptibility. By identifying susceptible populations and quantifying the extent to which air pollution–CVD associations vary by population characteristics, we have contributed toward identifying opportunities to more effectively (and cost-effectively) target pollution-reduction interventions. By better quantifying potential benefits of focusing interventions on susceptible communities, we may find *greater* benefits to exposure reductions than some of those that have previously been made for the general population.

FUTURE DIRECTIONS

Multiple-Modifier and Mediated-Modifier Models

Given substantial spatial correlation among urban stressors, there is a great need to develop methods to examine multiple simultaneous (and potentially interacting) modifiers, to compare the strength of effect modifications by multiple stressors, and to identify the predominant social stressors driving observed susceptibilities. Relatedly, there is a need for methods to more formally test the role of specific social stressors in explaining (i.e., mediating) observed susceptibility by SEP. Structural equation models may be an important methodological approach to help answer these questions, insofar as they may enable examination of multiple effect modifiers in nonlinear and continuous forms (rather than categorical) and enable examination of multiple modifiers and pollutants simultaneously, with interactions.

Temporal Autocorrelation Across Multiple Lag Days

We found that impacts of pollution on CVD were largely restricted to same-day (day 0) effects and thus that model structures better accounting for multiday exposures (i.e., distributed-lag models) may be of limited use in this context. There were, however, possible day-of-week trends in our data (i.e., CVD events were more prevalent on Monday and Tuesdays), within-week trends in exposures (e.g., weekdays versus weekends), and possible day-of-week trends in stressor and traffic exposures (i.e., commuting and work activities) that may influence relationships among pollution, stress, and CVD. These within-week patterns may lead to challenges in interpreting case-crossover results; we observed, for example, that effects on lag days 1 and 6 were often more similar to the case day than were lag

days 2–5, following from temporal autocorrelation (i.e., that, when day 0 is a weekend, so is either day 1 or day 6 as well), producing some commonality in exposures among the case day, day 1, and day 6. Such patterns may merit further investigation, though we have no reason to believe that an alternative method (i.e., distributed lag models) would alter the results reported here.

Improvements in Fine-Scale Stressor Exposure Data

As previously described, as in many large epidemiological studies, we needed to rely on area-level administrative data as a proxy for social stressor exposures, in contrast to the fine-scale spatiotemporal models for air pollution exposures used here and elsewhere in air pollution epidemiology. As a result, there is a great need for improvement in social stressor exposure assessment, to better match the resolution of environmental exposure data, to avoid biasing results, and to avoid artificially dampening observed effects of social stressors. We have taken steps to improve the geographic resolution of our stressor data (i.e., by obtaining and aggregating NYPD point-level crime data to census tracts [n = 2,167] rather than relying on the much larger police precinct area rates [n = 72]), and by verifying our stressor indicators as proxies for stress by comparing them with focus-group and survey data on perceived stress and perceived neighborhood stressor exposures. Nonetheless, there remains much work to do in developing and validating more refined metrics of SEP and social stressor exposures appropriate for use in environmental epidemiology studies.

Age at Cardiovascular Disease Event by Race–Ethnicity

The median age at CVD is much younger for non-Hispanic Black (60 years) than for non-Hispanic White New Yorkers (74 years) ($P < 0.0001$). These vast differences are obscured in case-crossover models, which focus on day-to-day changes in pollution and inherently adjust for confounders that do not vary on short timescales (i.e., race, sex, and age). It is highly likely that the social processes underlying SEP-related impacts on health and susceptibility operate on the order of decades rather than days. We noted that individual-level race–ethnicity and community social stressor exposures are deeply spatially confounded in NYC, as in other U.S. cities, complicating the interpretability of observed effect modification. There is a great need for future research aimed at disentangling entrenched confounding between individual-level characteristics and neighborhood exposures. In the case of the SPARCS data, there are documented challenges in the interpretation of the hospital-based race–ethnicity variables (*https://www.health.ny.gov/statistics/sparcs/reports/race_eth/*) that will require some effort to identify those hospitals and years for which the data are reliable. This issue is in keeping with the growing emphasis on methods to verify electronic health records data. In addition, we note the need for survival analysis and related methods to examine the substantial differences in age at CVD by race, toward elucidating underlying causes and opportunities to reduce population health disparities.

CONCLUSIONS

In ecological and case-crossover analyses, we found consistent evidence of heightened risk of CVD events for all CVD subtypes, with elevated same-day-only exposures to NO_2, $PM_{2.5}$, and SO_2 in NYC. Consistent with our hypotheses, pollution–CVD associations were stronger in communities with elevated exposures to social stressors. Given substantial spatial confounding among social stressors, further research is needed to identify the predominant social stressors driving this differential susceptibility; such research may include the development of methods for multiple-modifier and mediated-modifier analyses to better understand the role of specific social stressors in mediating socioeconomic susceptibility to pollution. In addition, further research is needed to elucidate the longer-term processes underlying population susceptibility to pollution, given the substantially younger median age at CVD event for Black than for White New Yorkers.

ACKNOWLEDGMENTS

The research described in this report was developed under Health Effects Institute (HEI) 15-2: Social Susceptibility to Multiple Air Pollutants in CVD (Clougherty). Geocoding methods were developed under National Institutes of Health (NIH) 1R01HL114536-01: Validating GIS-based Methods to Address Spatial Uncertainty in Clinical Trials (Clougherty and Holguin). Administrative data on social stressors was compiled and analyzed under EPA-G2009-STAR-E-2: Community Stressors and Susceptibility to Air Pollution in Urban Asthma (Clougherty) and NIH 5 R01 ES19955-3: Air Pollution and Pregnancy Outcomes in NYC (Savitz). Case-crossover methods applied here were developed under NIH 1 R21 ES021429-01: Children's Health and Vulnerability to Heat and Ozone in New York City (Sheffield and Clougherty). Hospital CVD data were provided by SPARCS. Citywide spatial surfaces for $PM_{2.5}$ and elemental constituents, NO_2, summertime O_3, and wintertime SO_2 were provided by the DOHMH. Daily air pollution data were obtained from the EPA AQS.

REFERENCES

Adar SD, Chen YH, D'Souza JC, O'Neill MS, Szpiro AA, Auchincloss AH, et al. 2018. Longitudinal analysis of long-term air pollution levels and blood pressure: A cautionary tale from the Multi-Ethnic Study of Atherosclerosis. Environ Health Perspect 126(10):107003.

Anselin L. 1995. Local Indicators of Spatial Association — LISA. Geograp Anal 27(2):93–115.

Barber S, Hickson DA, Kawachi I, Subramanian SV, Earls F. 2016. Double-jeopardy: The joint impact of neighborhood disadvantage and low social cohesion on cumulative risk of disease among African American men and women in the Jackson Heart Study. Soc Sci Med 153:107–115.

Bartoli CR, Wellenius GA, Coull BA, Akiyama I, Diaz EA, Lawrence J, et al. 2009a. Concentrated ambient particles alter myocardial blood flow during acute ischemia in conscious canines. Environ Health Perspect 117(3):333–337.

Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, et al. 2009b. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. Environ Health Perspect 117(3):361–366.

Bateson TF, Schwartz J. 1999. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. Epidemiology 10(5):539–544.

Bateson TF, Schwartz J. 2001. Selection bias and confounding in case-crossover analyses of environmental time-series data. Epidemiology 12(6):654–661.

Benjamini Y, Hochberg Y. 1995. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J Royal Stat Soc, Series B 57:289–300.

Bhatnagar A. 2017. Environmental determinants of cardiovascular disease. Circ Res 121(2):162–180.

Bhattacharya A, Ghosal S, Bhattacharya SK. 2001. Antioxidant effect of Withania somnifera glycowithanolides in chronic footshock stress-induced perturbations of oxidative free radical scavenging enzymes and lipid peroxidation in rat frontal cortex and striatum. J Ethnopharmacol 74:1–6.

Boutin-Forzano S, Adel N, Gratecos L, Jullian H, Garnier JM, Ramadour M, et al. 2004. Visits to the emergency room for asthma attacks and short-term variations in air pollution: A case-crossover study. Respiration 71:134–137.

Brook R, Franklin DB, Cascio W, Hong Y, Howard G, Lipsett M, et al. 2004. Air pollution and cardiovascular disease: A statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109(21):2655–2671.

Brook RD, Rajagopalan S. 2017. "Stressed" about air pollution: Time for personal action. Circulation 136(7):628–631.

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121(21):2331–2378.

Cakmak S, Hebbern C, Vanos J, Crouse DL, Burnett R. 2016. Ozone exposure and cardiovascular-related mortality in the Canadian Census Health and Environment Cohort (CANCHEC) by spatial synoptic classification zone. Environ Pollut 214:589–599.

Calderon-Garciduenas L, Franco-Lira M, Torres-Jardon R, Henriquez-Roldan C, Barragan-Mejia G, Valencia-Salazar G, et al. 2007. Pediatric respiratory and systemic effects of chronic air pollution exposure: Nose, lung, heart, and brain pathology. Toxicol Pathol 35(1):154–162.

Carracedo-Martinez E, Taracido M, Tobias A, Saez M, Figueiras A. 2010. Case-crossover analysis of air pollution health effects: A systematic review of methodology and application. Environ Health Perspect 118(8):1173–1182.

Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. 2008. Work stress and coronary heart disease: What are the mechanisms? Eur Heart J 29(5):640–648.

Chi GC, Hajat A, Bird CE, Cullen MR, Griffin BA, Miller KA, et al. 2016. Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. Environ Health Perspect 124(12):1840–1847.

Clark LP, Millet DB, Marshall JD. 2014. National patterns in environmental injustice and inequality: Outdoor NO_2 air pollution in the United States. PLoS One 9(4):e94431.

Clougherty JE, Eisen EA, Slade MD, Kawachi I, Cullen MR. 2009. Workplace status and risk of hypertension among hourly and salaried aluminum manufacturing employees. Soc Sci Med 68(2):304–313.

Clougherty JE, Kheirbek I, Eisl HM, Ross Z, Pezeshki G, Gorczynski JE, et al. 2013. Intra-urban spatial variability in wintertime street-level concentrations of multiple combustion-related air pollutants: The New York City

Community Air Survey (NYCCAS). J Expo Sci Environ Epidemiol 23(3):232–240.

Clougherty JE, Kubzansky LD. 2009. A framework for examining social stress and susceptibility to air pollution in respiratory health. Environ Health Perspect 117(9):1351–1358.

Clougherty JE, Shmool JLC, Kubzansky LD. 2014. The role of non-chemical stressors in mediating socioeconomic susceptibility to environmental chemicals. Curr Environ Health Rep 1(4):302–313.

Clougherty JE, Souza K, Cullen MR. 2010. Work and its role in shaping the social gradient in health. Ann NY Acad Sci 1186:102–124.

Cory-Slechta DA, Merchant-Borna K, Allen JL, Liu S, Weston D, Conrad K. 2013. Variations in the nature of behavioral experience can differentially alter the consequences of developmental exposures to lead, prenatal stress, and the combination. Toxicol Sci 131(1):194–205.

Daniel M, Moore S, Kestens Y. 2008. Framing the biosocial pathways underlying associations between place and cardiometabolic disease. Health Place 14(2):117–132.

Diaz EA, Chung Y, Lamoureux DP, Papapostolou V, Lawrence J, Long MS, et al. 2012. Effects of fresh and aged traffic-related particles on breathing pattern, cellular responses, and oxidative stress. Air Quality Atmos Health 6(2):431–444.

Diez Roux AV, Mujahid MS, Hirsch JA, Moore K, Moore LV. 2016. The impact of neighborhoods on CVD risk. Glob Heart 11(3):353–363.

Dimsdale JE. 2008. Psychological stress and cardiovascular disease. J Am Coll Cardiol 51(13):1237–1246.

Du Y, Xu X, Chu M, Guo Y, Wang J. 2016. Air particulate matter and cardiovascular disease: The epidemiological, biomedical and clinical evidence. J Thorac Dis 8(1):E8–E19.

Eller NH, Netterstrom B, Gyntelberg F, Kristensen TS, Nielsen F, Steptoe A, et al. 2009. Work-related psychosocial factors and the development of ischemic heart disease: A systematic review. Cardiol Rev 17(2):83–97.

Erickson AC, Arbour L. 2014. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. J Environ Public Health 2014:901017.

Evans GW, Kim P. 2010. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status-health gradient. Ann NY Acad Sci 1186:174–189.

Everson-Rose SA, Lutsey PL, Roetker NS, Lewis TT, Kershaw KN, Alonso A, et al. 2015. Perceived discrimination and incident cardiovascular events: The Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 182(3):225–234.

Fiordelisi A, Piscitelli P, Trimarco B, Coscioni E, Iaccarino G, Sorriento D. 2017. The mechanisms of air pollution and particulate matter in cardiovascular diseases. Heart Fail Rev 22(3):337–347.

Ford JL, Browning CR. 2014. Effects of exposure to violence with a weapon during adolescence on adult hypertension. Ann Epidemiol 24(3):193–198.

Franklin BA, Brook R, Arden Pope C 3rd. 2015. Air pollution and cardiovascular disease. Curr Probl Cardiol 40(5):207–238.

Fuller CH, Feeser KR, Sarnat JA, O'Neill MS. 2017. Air pollution, cardiovascular endpoints and susceptibility by stress and material resources: A systematic review of the evidence. Environ Health 16(1):58.

Gallo LC, Matthews KA. 2003. Understanding the association between socioeconomic status and physical health: Do negative emotions play a role? Psychological Bulletin 129(1):10–51.

Gasparrini A, Armstrong B, Kenward MG. 2010. Distributed lag non? linear models. Stat Med 29:2224–2234.

Gehring U, Heinrich J, Krämer U, Grote V, Hochadel M, Sugiri D, et al. 2006. Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. Epidemiology 17(5):545–551.

Ghelfi E, Rhoden CR, Wellenius GA, Lawrence J, Gonzalez-Flecha B. 2008. Cardiac oxidative stress and electrophysiological changes in rats exposed to concentrated ambient particles are mediated by TRP-dependent pulmonary reflexes. Toxicol Sci 102(2):328–336.

Glaser R, Kiecolt-Glaser JK. 2005. Stress-induced immune dysfunction: Implications for health. Nat Rev Immun 5:243–251.

Godleski JJ. 2006. Responses of the heart to ambient particle inhalation. Clin Occup Environ Med 5(4):849–864.

Godleski JJ, Verrier RL, Koutrakis P, Catalano P, Coull B, Reinisch U, et al. 2000. Mechanisms of morbidity and mortality from exposure to ambient air particles. Res Rep Health Eff Inst 91:5–88.

Hagstrom E, Norlund F, Stebbins A, Armstrong PW, Chiswell K, Granger CB, et al. 2018. Psychosocial stress and major cardiovascular events in patients with stable coronary heart disease. J Intern Med 283(1):83–92.

Hajat A, Diez-Roux AV, Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, et al. 2013. Air pollution and individual and neighborhood socioeconomic status: Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect 121(11–12):1325–1333.

Harrabi I, Rondeau V, Dartigues JF, Tessier JF, Filleul L. 2006. Effects of particulate air pollution on systolic blood pressure: A population-based approach. Environ Res 101(1):89–93.

Hazlehurst MF, Nurius PS, Hajat A. 2018. Individual and neighborhood stressors, air pollution and cardiovascular disease. Int J Environ Res Public Health 15(3):472.

Hicken MT, Adar SD, Diez Roux AV, O'Neill MS, Magzamen S, Auchincloss AH, et al. 2013. Do psychosocial stress and social disadvantage modify the association between air pollution and blood pressure?: The Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 178(10):1550–1562.

Hicken MT, Adar SD, Hajat A, Kershaw KN, Do DP, Barr RG, et al. 2016. Air pollution, cardiovascular outcomes, and social disadvantage: The Multi-Ethnic Study of Atherosclerosis. Epidemiology 27(1):42–50.

Hicken MT, Dvonch JT, Schulz AJ, Mentz G, Max P. 2014. Fine particulate matter air pollution and blood pressure: The modifying role of psychosocial stress. Environ Res 133:195–203.

Hoffmann B, Moebus S, Dragano N, Stang A, Mohlenkamp S, Schmermund A, et al. 2009. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. Environ Health Perspect 117(8):1302–1308.

Humphrey JL, Reid CE, Kinnee EJ, Kubzansky LD, Robinson LF, Clougherty JE. 2019. Putting co-exposures on equal footing: An ecological analysis of same-scale measures of air pollution and social factors on cardiovascular disease in New York City. Int J Environ Res Public Health 16(23):4621; *https://doi.org/10.3390/ijerph16234621.*

Ismail N, Jemain AA. 2007. Handling overdispersion with negative binomial and generalized poisson regression models. Casualty Actuarial Soc Forum:103–158.

Jacquemin B, Lepeule J, Boudier A, Arnould C, Benmerad M, Chappaz C, et al. 2013. Impact of geocoding methods on associations between long-term exposure to urban air pollution and lung function. Environ Health Perspect 121(9):1054–1060.

James SA, Van Hoewyk J, Belli RF, Strogatz DS, Williams DR, Raghunathan TE. 2006. Life-course socioeconomic position and hypertension in African American men: The Pitt County Study. Am J Public Health 96(5):812–817.

Janes H, Sheppard L, Lumley T. 2005a. Case-crossover analyses of air pollution exposure data: Referent selection strategies and their implications for bias. Epidemiology 16(6):717–726.

Janes H, Sheppard L, Lumley T. 2005b. Overlap bias in the case-crossover design, with application to air pollution exposures. Stat Med 24(2):285–300.

Jerrett M, Burnett RT, Brook J, Kanaroglou PS, Giovis C, Finkelstein N, et al. 2004. Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. J Epidemiol Commealth 58:31–40.

Jerrett M, Burnett RT, Pope CA, Ito K, Thurston G, Krewski D, et al. 2009. Long-term ozone exposure and mortality. New Engl J Med 360:1085–1095.

Jones MR, Diez-Roux AV, Hajat A, Kershaw KN, O'Neill MS, Guallar E, et al. 2014. Race/ethnicity, residential segregation, and exposure to ambient air pollution: The Multi-Ethnic Study of Atherosclerosis (MESA). Am J Public Health 104(11):2130–2137.

Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. 2016b. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): A longitudinal cohort study. The Lancet 388(10045):696–704.

Kaufman JD, Spalt EW, Curl CL, Hajat A, Jones MR, Kim SY, et al. 2016a. Advances in understanding air pollution and CVD. Glob Heart 11(3):343–352.

Kelly FJ, Fussell JC. 2017. Role of oxidative stress in cardiovascular disease outcomes following exposure to ambient air pollution. Free Radic Biol Med 110:345–367.

Kershaw KN, Osypuk TL, Do DP, De Chavez PJ, Diez Roux AV. 2015. Neighborhood-level racial/ethnic residential segregation and incident cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis. Circulation 131(2):141–148.

Kinnee EJ, Tripathy S, Schinasi L, Shmool JLC, Sheffield PE, Holguin F, et al. 2020. Geocoding error, spatial uncertainty, and implications for exposure assessment and environmental epidemiology. Int J Environ Res Public Health 17(16):5845.

Kivimäki M. 2018. Psychosocial factors in etiology and prognosis of specific diseases and disorders: Cardiovascular diseases. In: Handbook of Psychosocial Epidemiology(M. Kivimäki, D. G. Batty, I. Kawachi and A. Steptoe, eds). New York:Routledge, 247–262.

Kivimäki M, Virtanen M, Elovainio M,, Kouvonen A, Väänänen A, Vahtera J. 2006. Work stress in the etiology of coronary heart disease — a meta-analysis. Scand J Work EnvironHealth 32(6):431–442.

Kochanek KD, Murphy SL, Xu J, Arias E. 2019. Deaths: Final Data for 2017. National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics 68:1–77. 68:1–77.

Kravitz-Wirtz N, Crowder K, Hajat A, Sass V. 2016. The long-term dynamics of racial/ethnic inequality in neighborhood air pollution exposure, 1990–2009. Du Bois Rev 13(2):237–259.

Krewski D, Burnett RT, Mark S, Goldberg MS, Hoover BK, Siemiatycki J, et al. 2003. Overview of the reanalysis of the Harvard Six Cities Study and American Cancer Society Study of Particulate Air Pollution and Mortality. J Toxicol Environ Health A 66(16–19):1507–1551.

Krieger N, Feldman JM, Waterman PD, Chen JT, Coull BA, Hemenway D. 2017. Local residential segregation matters: Stronger association of census tract compared to conventional city-level measures with fatal and non-fatal assaults (total and firearm related), using the Index of Concentration at the Extremes (ICE) for racial, economic, and racialized economic segregation, Massachusetts (US), 1995–2010. J Urban Health 94(2):244–258.

Kristiansson M, Sorman K, Tekwe C, Calderon-Garciduenas L. 2015. Urban air pollution, poverty, violence and health — Neurological and immunological aspects as mediating factors. Environ Res 140:511–513.

Kubzansky LD, Kawachi I. 2000. Going to the heart of the matter: Do negative emotions cause coronary heart disease? J Psychosom Res 48(4–5):323–327.

Kubzansky LD, Kawachi I, Spiro A 3rd, Weiss ST, Vokonas PS, Sparrow D. 1997. Is worrying bad for your heart? A prospective study of worry and coronary heart disease in the Normative Aging Study. Circulation 95(4):818–824.

Kubzansky LD, Kawachi I, Weiss ST, Sparrow D. 1998. Anxiety and coronary heart disease: A synthesis of epidemiological, psychological, and experimental evidence. Ann Behav Med 20(2):47–58.

Kubzansky LD, Koenen KC, Spiro AR, Vokonas PS, Sparrow D. 2007. Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. Arch Gen Psychiatry 64(1):109–116.

Kubzansky LD, Subramanian SV, Kawachi I, Fay ME, Soobader MJ, Berkman LF. 2005. Neighborhood contextual influences on depressive symptoms in the elderly. Am J Epidemiol 162(3):253–260.

Kunzli N, Jerrett M, Garcia-Esteban R, Basagana X, Beckermann B, Gilliland F, et al. 2010. Ambient air pollution and the progression of atherosclerosis in adults. PLoS One 5(2):e9096.

Lamoureux DP, Diaz EA, Chung Y, Coull BA, Papapostolou V, Lawrence J, et al. 2012. Effects of fresh and aged vehicular particulate emissions on blood pressure in normal adult male rats. Air Quality Atmos Health 6(2):407–418.

Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. 2001. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and white men and women: Atherosclerosis Risk in Communities Study. Am J Epidemiol 154(8):758–764.

Li H, Cai J, Chen R, Zhao Z, Ying Z, Wang L, et al. 2017. Particulate matter exposure and stress hormone levels: A randomized, double-blind, crossover trial of air purification. Circulation 136(7):618–627.

Lin S, Munsie JP, Hwang SA, Fitzgerald E, Cayo MR. 2002. Childhood asthma hospitalization and residential exposure to state route traffic. Environ Res 88(2):73–81.

Lumley T, Levy D. 2000. Bias in the case-crossover design: Implications for studies of air pollution. Environmetrics 11:689–704.

Madrigano J, Baccarelli A, Mittleman MA, Sparrow D, Spiro A 3rd, Vokonas PS, et al. . 2012. Air pollution and DNA methylation: Interaction by psychological factors in the VA Normative Aging Study. Am J Epidemiol 176(3):224–232.

Massey DS, Brodmann S. 2014. Spheres of Influence: The Social Ecology of Racial and Class Inequality. New York, NY:Russell Sage Foundation.

Massey DS, Rothwell J, Domina T. 2009. The changing bases of segregation in the United States. Ann Am Acad Pol Soc Sci 626(1):74–90.

Matte TD, Ross Z, Kheirbek I, Eisl H, Johnson S, Gorczynski JE, et al. 2013. Monitoring intraurban spatial patterns of multiple combustion air pollutants in New York City: Design and implementation. J Expo Sci Environ Epidemiol 23(3):223–231.

Matthews KA, Gallo LC. 2011. Psychological perspectives on pathways linking socioeconomic status and physical health. Annu Rev Psychol 62:501–530.

McEwen BS. 1998a. Protective and damaging effects of stress mediators. N Engl J Med 338(3):171–179.

McEwen BS. 1998b. Stress, adaptation, and disease: Allostasis and allostatic load. Ann N Y Acad Sci 840:33–44.

McEwen BS. 2012. Brain on stress: How the social environment gets under the skin. Proc Natl Acad Sci U S A 109 Suppl 2:17180–17185.

McEwen BS. 2017. Neurobiological and systemic effects of chronic stress. Chronic Stress (Thousand Oaks) 1.

McEwen BS, Seeman T. 1999. Protective and damaging effects of mediators of stress: Elaborating and testing concepts of allostasis and allostatic load. Ann N Y Acad Sci 896:30–47.

McEwen BS, Tucker P. 2011. Critical biological pathways for chronic psychosocial stress and research opportunities to advance the consideration of stress in chemical risk assessment. Am J Public Health 101 Suppl 1:S131–139.

Messer LC, Oakes JM, Mason S. 2010. Effects of socioeconomic and racial residential segregation on preterm birth: A cautionary tale of structural confounding. Am J Epidemiol 171(6):664–673.

Miller GE, Cohen S, Ritchey AK 2002. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. Health Psych 21(6):531–541.

Miller KA, Siscovick D, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. 2007. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356(5):447–458.

Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. 2011. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff (Millwood) 30(5):879–887.

Mulligan CJ. 2016. Early environments, stress, and the epigenetics of human health. Ann Rev Anthro 45(1):233–249.

Nel AE, Diaz-Sanchez D, Li N. 2001. The role of particulate pollutants in pulmonary inflammation and asthma: Evidence for the involvement of organic chemicals and oxidative stress. Curr Opin Pulm Med 7(1):20–26.

New York City Department of Health and Mental Hygiene. 2015. The New York City Community Air Survey. Available*: https://www1.nyc.gov/assets/doh/downloads/pdf/environmental/comm-air-survey-08-13.pdf.*

Oudin A, Astrom DO, Asplund P, Steingrimsson S, Szabo Z, Carlsen HK. 2018. The association between daily concentrations of air pollution and visits to a psychiatric emergency unit: A case-crossover study. Environ Health 17(1):4.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Wright RO, Coull B, et al. 2008. Air pollution and heart rate variability: Effect modification by chronic lead exposure. Epidemiology 19(1):111–120.

Peters A, Doring A, Wichmann HE, Koenig W. 1997. Increased plasma viscosity during an air pollution episode: A link to mortality? Lancet 349(9065):1582–1587.

Pickering T. 1999. Cardiovascular pathways: Socioeconomic status and stress effects on hypertension and cardiovascular function. Ann NY Acad Sci 896:262–277.

Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. Circulation 109(1):71–77.

Rider CV, Boekelheide K, Catlin N, Gordon CJ, Morata T, Selgrade MK, et al. 2014. Cumulative risk: toxicity and interactions of physical and chemical stressors. Toxicol Sci 137(1):3–11.

Rose G, Marmot MG. 1981. Social class and coronary heart disease. Br Heart J 45:13–19.

Ross CE, Mirowsky J. 2001. Neighborhood disadvantage, disorder, and health. J Health Soc Behav 42(3):258–276.

Ross Z, Ito K, Johnson S, Yee M, Pezeshki G, Clougherty J, et al. 2013. Spatial and temporal estimation of air pollutants in New York City: Exposure assignment for use in a birth outcomes study. Environ Health 12:51.

Sanidas E, Papadopoulos DP, Grassos H, Velliou M, Tsioufis K, Barbetseas J, et al. 2017. Air pollution and arterial

hypertension: A new risk factor is in the air. J Am Soc Hypertens 11(11):709–715.

Sass V, Kravitz-Wirtz N, Karceski SM, Hajat A, Crowder K, Takeuchi D. 2017. The effects of air pollution on individual psychological distress. Health Place 48:72–79.

Schulz AJ, Zenk SN, Israel BA, Mentz G, Stokes GC, Galea S. 2008. Do neighborhood economic characteristics, racial composition, and residential stability predict perceptions of stress associated with the physical and social environment? Findings from a multilevel analysis in Detroit. J Urban Health 85(5):642–661.

Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. 2018. Socioeconomic status and cardiovascular outcomes: Challenges and interventions. Circulation 137(20):2166–2178.

Segerstrom SC, Miller GE. 2004. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychol Bull 130(4):601–630.

Sharma S, Malarcher AM, Giles WH, Myers G. 2004. Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. Ethnicity Dis 14(1):43–48.

Sheffield PE, Zhou J, Shmool JL, Clougherty JE. 2015. Ambient ozone exposure and children's acute asthma in New York City: A case-crossover analysis. Environ Health 14:25.

Shmool JL, Bobb JF, Ito K, Elston B, Savitz DA, Ross Z, et al. 2015a. Area-level socioeconomic deprivation, nitrogen dioxide exposure, and term birth weight in New York City. Environ Res 142:624–632.

Shmool JL, Kinnee E, Sheffield PE, Clougherty JE. 2016. Spatio-temporal ozone variation in a case-crossover analysis of childhood asthma hospital visits in New York City. Environ Res 147:108–114.

Shmool JL, Kubzansky L, Newman OD, Spengler J, Shepard P, Clougherty J. 2014. Social stressors and air pollution across New York City communities: A spatial approach for assessing correlations among multiple exposures. Environ Health 13(91).

Shmool JL, Yonas MA, Newman OD, Kubzansky LD, Joseph E, Parks A, et al. 2015b. Identifying perceived neighborhood stressors across diverse communities in New York City. Am J Community Psychol 56(1–2):145–155.

Snyder-Mackler N, Sanz J, Kohn JN, Brinkworth JF, Morrow S, Shaver AO, et al. 2016. Social status alters immune regulation and response to infection in macaques. Science 354(6315):1041–1045.

Spruill TM. 2010. Chronic psychosocial stress and hypertension. Curr Hypertens Rep 12(1):10–16.

Srebot V, Gianicolo EAL, Rainaldi G, Trivella MG, Sicari R. 2009. Ozone and cardiovascular injury. Cardiovas Ultrasound 7(1):30.

Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. 2002. Stress responsivity and socioeconomic status: A mechanism for increased cardiovascular disease risk? Eur Heart J 23(22):1757–1763.

Steptoe A, Kivimäki M. 2012. Stress and cardiovascular disease. Nature Rev Cardiol 9:360–370.

Thurston GD, Burnett RT, Turner MC, Shi Y, Krewski D, Lall R, et al. 2016. Ischemic heart disease mortality and long-term exposure to source-related components of U.S. fine particle air pollution. Environ Health Perspect 124(6):785–794.

Thurston RC, Kubzansky L, Kawachi I, Berkman LF. 2005. Is the association between socioeconomic position and coronary heart disease stronger in women than in men? Am J Epidemiol 162(1):57–65.

Turecki G, Meaney MJ. 2016. Effects of the social environment and stress on glucocorticoid receptor gene methylation: A systematic review. Biol Psychiatry 79(2):87–96.

Vale S. 2005. Psychosocial stress and cardiovascular diseases. Postgrad Med J 81(957):429–435.

Villeneuve PJ, Burnett RT, Shi Y, Krewski D, Goldberg MS, Hertzman C, et al. 2003. A time–series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. J Expo Anal Environ Epidemiol 13(6):427–435.

Villeneuve PJ, Chen L, Stieb D, Rowe BH. 2006. Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol 21(9):689–700.

Virgolini MB, Chen K, Weston DD, Bauter MR, Cory-Slechta DA. 2005. Interactions of chronic lead exposure and intermittent stress: Consequences for brain catecholamine systems and associated behaviors and HPA axis function. Toxicol Sci 87(2):469–482.

Wright EN, Hanlon A, Lozano A, Teitelman AM. 2019. The impact of intimate partner violence, depressive symptoms, alcohol dependence, and perceived stress on 30-year cardiovascular disease risk among young adult women: A multiple mediation analysis. Prev Med 121:47–54.

Zandbergen PA. 2011. Influence of street reference data on geocoding quality. Geocarto Interl 26(1):35–47.

Zeka A, Zanobetti A, Schwartz J. 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. Am J Epidemiol 163(9):849–859.

HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to an independent audit by RTI International staff members* Dr. Linda Brown, Dr. Prakash Doraiswamy, and Dr. David Wilson. These staff members are experienced in quality assurance (QA) oversight for air quality monitoring, modeling, data analysis, epidemiological analysis, and statistical modeling.

The QA oversight program consisted of a remote audit of the final study report and model codes.

Key details are presented below.

Final Remote Audit (February–June 2021)

The final remote audit consisted of two parts: (a) review of final report for the project, and (b) audit of the data processing steps. The audit of the final report focused on ensuring that it is well documented and easy to understand and highlighted key study findings and limitations. This review also provided guidance on specific aspects of the data processing sequence that could be reviewed remotely. The audit of the data included reviewing the scripts for the data reduction, processing and analysis, model development, and visualization. This specific portion of the audit was restricted to the key components of the study and associated findings. Selected scripts (in SAS/R) for final model development for the aims, parts of data reduction, and generation of key plots were sent to RTI. No data were sent to RTI due to data confidentiality restrictions or their proprietary nature. Therefore, data inputs to the codes were not available. Outputs from the scripts and formatted data for input to most of the plotting scripts were provided.

The scripts were reviewed at RTI to verify, to the extent feasible, linkages between the various scripts, confirmation of the models reported, and verification of key plots. Except for scripts generating the plots, other scripts were not executed at RTI due to lack of data inputs. The codes used in the scripts appear to be consistent with the variables, the models, the descriptive statistics, and key plots summarized in the report; the values themselves could not be verified due to unavailability of the input data. No major quality-related issues were identified that would affect the findings. Minor recommendations were made for improved code documentation and editorial clarifications.

An auditors' report was provided to HEI. The QA oversight audit demonstrated that the study was conducted according to the study protocol. The final study report, except as noted in the comments, appears to be representative of the study conducted.

Linda Morris Brown
MPH, DrPH, Epidemiologist, Quality Assurance Auditor

David Wilson
PhD, Statistician, Quality Assurance Auditor

Prakash Doraiswamy
PhD, Air Quality Specialist, Quality Assurance Auditor

June 28, 2021

MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendices 1, 2, 3, and 4 contain supplemental material not included in the printed report. They are available on the HEI website, *www.healtheffects.org/publications.*

Appendix 1: Key Results

Appendix 2: Validation of Noise Sources as Chronic Stress Indicators in NYC

Appendix 3: Development, Validation, and Spatial Analysis of Social Stressor Indicators

Appendix 4: Subanalyses by Sex, Age, and Race/Ethnicity in Case-Crossover Data

* One of the project key personnel, Dr. Humphrey, was a Postdoctoral Research Fellow at Drexel University during the performance of this project. Following completion of the study, she moved to RTI International for her new job. To ensure integrity of the audit process, all communications were with the PI, Dr. Clougherty. The auditors did not have direct contact with Dr. Humphrey except during the virtual project overview meeting in the presence of Dr. Clougherty and HEI representatives. The RTI auditors are also part of research units completely different from that of Dr. Humphrey's and are separated by several layers of management.

ABOUT THE AUTHORS

Jane E. Clougherty, MSc, ScD, is an associate professor at the Dornsife School of Public Health, Department of Environmental and Occupational Health, at Drexel University. She completed her doctorate and postdoctoral training at the Harvard T.H. Chan School of Public Health, worked at the New York City Department of Health and Mental Hygiene from 2008 to 2010, and was on the faculty at the Graduate School of Public Health at the University of Pittsburgh from 2010 to 2016. An interdisciplinary environmental health scientist, she focuses her research on the combined health effects of chronic social stressors and air pollution exposures. She has designed and implemented studies on intra-urban variation in air pollution and source apportionment and has led a number of EPA- and NIH-funded studies on the integration of social and environmental exposures using GIS and epidemiological methods.

Jamie L. Humphrey, MPH, PhD, is an interdisciplinary health researcher with a focus on social and environmental determinants of population health. She completed her doctorate in health and medical geography at the University of Colorado–Boulder, in 2015 and completed a postdoctoral research position in environmental engineering, also at the University of Colorado–Boulder from 2015 to 2017, where she led the implementation of a $1 million EPA-funded project designed to assess associations between climate change, indoor air quality, and respiratory health in low-income urban households. She was a postdoctoral research fellow at the Dornsife School of Public Health, Department of Environmental and Occupational Health, at Drexel University when the study was performed. She is now a research public health analyst in the Center for Health Analytics, Media, and Policy at RTI International in Research Triangle Park, North Carolina.

Ellen J. Kinnee, MA, is a geographic information system analyst in the Urban & Regional Analysis Program at the University Center for Social and Urban Research at the University of Pittsburgh. She is the project manager for a multicity research study, "Validating GIS-Based Methods to Address Spatial Uncertainty in Clinical Trials," which examines variation in the effectiveness of treatments in three AsthmaNet clinical trials by indicators of chronic social and environmental exposures. She was previously a senior GIS specialist supporting the U.S. EPA in Research Triangle Park, North Carolina, where she developed a spatial database to improve regulatory air quality models. She completed her MA in geography at the University of North Carolina at Chapel Hill, focusing on the use of GIS and dispersion modeling to assess community cancer risk from large aboveground gasoline storage tanks in Paw Creek, North Carolina.

Lucy F. Robinson, PhD, is an assistant professor of epidemiology and biostatistics at the Dornsife School of Public Health at Drexel University. She completed a BA in mathematics–statistics from Barnard College and her PhD in statistics from Columbia University. Before joining the Drexel faculty, she was an assistant research professor in the department of Applied Mathematics and Statistics at Johns Hopkins University. Her research has focused on modeling and inference techniques for functional MRI data and on change point detection in network data, with additional interests in spatial analysis and GIS in statistical modeling.

Leslie A. McClure, PhD, MS, is a professor in, and chair of, the Department of Epidemiology and Biostatistics at the Dornsife School of Public Health at Drexel University. She completed a BS in mathematics from the University of Kansas; an MS in preventive medicine and environmental health from the University of Iowa–Iowa City; and a PhD in biostatistics from the University of Michigan–Ann Arbor. She has diverse research interests, ranging from statistical methodology to environmental epidemiology. Methodologically, she is interested in the design and analysis of randomized clinical trials with multiple outcomes and in methodology for re-estimating sample size in ongoing randomized trials. She is the principal investigator for the Coordinating Center for the Diabetes LEAD (Location, Environmental Attributes, and Disparities) Network, a multi-university collaboration sponsored by the U.S. Centers for Disease Control and Prevention (CDC); it has the primary goals of furthering understanding of the role of community-level factors and geographic differences in diabetes incidence and prevalence across the United States and across demographic groups. She also leads the Data Coordinating Center for the Connecting the Dots study at the A.J. Drexel Autism Institute in Philadelphia, Pennsylvania, and is a senior statistician on the REGARDS (REasons for Geographic And Racial Differences in Stroke) study at the University of Alabama at Birmingham, for which she served as principal investigator of a National Aeronautics and Space Administration–funded ancillary study investigating the role of satellite-derived measures of $PM_{2.5}$ in the development of cognitive decline and stroke. She has been recognized by the University of Alabama at Birmingham for her teaching and mentoring skills and is a fellow of the American Heart Association (Epidemiology Council) and of the American Statistical Association.

Laura D. Kubzansky, PhD, MPH, is a professor of social and behavioral sciences and the director of the Society and

Health Lab at the Harvard T.H. Chan School of Public Health. She also serves as codirector of the School's Lee Kum Sheung Center for Health and Happiness and codirector of its JPB Environmental Health Fellows Program. She completed her PhD in social psychology at the University of Michigan and her MPH and a postdoctoral fellowship in social epidemiology at the Harvard T.H. Chan School of Public Health. She has published extensively on the role of psychological and social factors in health, with a particular focus on the effects of stress and emotion on heart disease. She also conducts research on whether stress, emotion, and other psychological factors help to explain the relationship between social status and health. Other research projects and interests include studying the biological mechanisms linking emotions, social relationships, and health; relationships between early childhood environments, resilience, and healthy aging; and how interactions between psychosocial stress and environmental exposures (e.g., lead or air pollution) may influence health. She has advised numerous masters, doctoral, and postdoctoral students as a mentor, academic advisor, and dissertation committee member. She is a fellow of the American Psychological Association and the Academy of Behavioral Medicine Research. She has served as senior advisor to the Robert Wood Johnson–funded Positive Health Research program and as a member of the Healthy People 2020 Health-Related Quality of Life and Well-Being Workgroup and of the American Heart Association's Science of Well-Being Expert Panel. She is principal investigator or co-investigator on a wide variety of grants funded through the U.S. Veterans Administration, Robert Wood Johnson Foundation, EPA, NIH, and others.

Colleen E. Reid, PhD, is an assistant professor of geography at the University of Colorado–Boulder. She is interested in how environmental and social exposures interact to influence health, with a particular focus on exposures caused by global climatic changes and society's responses to those changes. Her research has focused on the health impacts of exposure to air pollution from wildfires, extreme heat events, and proximity to urban vegetation. She was recently selected to be a JPB Environmental Health Fellow through the Harvard T.H. Chan School of Public Health. Earlier, she was a Robert Wood Johnson Foundation Health and Society Scholar at the Harvard T.H. Chan School of Public Health. She completed her PhD in environmental health sciences at the University of California–Berkeley in 2014, where she received doctoral research funding from the EPA's Science to Achieve Results (STAR) program, the CDC, and the Association of Schools of Public Health.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Humphrey JL, Reid CE, Kinnee EJ, Kubzansky LD, Robinson LF, Clougherty JE. 2019. Putting co-exposures on equal footing: An ecological analysis of same-scale measures of air pollution and social factors on cardiovascular disease in New York City. Int J Environ Res Public Health 16(23):4621; *https://doi.org/10.3390/ijerph16234621.*

CRITIQUE

Review Committee

Research Report 206, *Social Susceptibility to Multiple Air Pollutants in Cardiovascular Disease*, J. E. Clougherty et al.

INTRODUCTION AND SCIENTIFIC BACKGROUND

A large number of epidemiological studies (Abrams et al. 2019; Bell et al. 2009; Lippmann 2014; Peng et al. 2009; Sun et al. 2013; Vedal et al. 2013) and toxicological studies (Lippmann et al. 2013; Seilkop et al. 2012; Vincent et al. 2001) have reported associations between short- and long-term exposure to ambient air pollutants and cardiovascular disease (CVD*) events (Brook et al. 2010). People are exposed to complex mixtures of pollutants, and information is still needed about how multiple co-exposures affect CVD events such as heart attack and stroke. Evidence also indicates social and economic disadvantage are association with elevated CVD risk (Clark et al. 2009; Kaplan and Keil 1993; Schultz et al. 2018; Thurston et al. 2005).

Investigators have explored the mechanisms along the pathways from social stressors to CVD, with many finding that chronic stress lies along these pathways (Steptoe 2002; Steptoe and Kivimäki 2013). In the United States, population subgroups with lower socioeconomic position (SEP) that are primarily non-White and that encounter other adverse social stressors experience disproportionately higher levels of air pollution compared with other population subgroups (Hajat et al. 2013, 2015; Morello-Frosch et al. 2001; Pastor et al. 2005). Because of the interplay between air pollution exposures, social stressors, and CVD outcomes, disentangling the role of social stressors as modifiers or confounders of the associations between air pollution and CVD is imperative to identify potentially vulnerable populations and to provide the additional scientific evidence needed to support mitigation measures.

A growing number of epidemiological studies have focused on the role of social stressors in air pollution epidemiology (Fuller et al. 2017). However, many large-scale epidemiological studies have relied on administrative datasets for outcome and covariate information and were therefore limited to the social stressor information available in such datasets, which is often sparse. Questions thus remain about which specific social stressors may result in greater CVD susceptibility to air pollutants.

A systematic review by Fuller and colleagues (2017) examined the role of SEP in the relationships between air pollution and CVD. The investigators found that 18 of the 30 peer-reviewed articles included in the review reported that material resources (e.g., income, poverty, or education) modified the associations between air pollution and CVD and cited weaker evidence of psychosocial stress as a modifier. They recommended that more research was needed, including a thorough assessment of relationships between air pollution and SEP with an evaluation of multiple pollutants in the same study and an evaluation of susceptible populations. The current study aimed to address some of these gaps and to disentangle the SEP construct by identifying which specific variables may act as confounders and modifiers in associations between air pollution and CVD events.

In February 2016, Dr. Jane Clougherty of Drexel University submitted a proposal titled "Susceptibility to Multiple Air Pollutants in Cardiovascular Disease" in response to RFA 15-2 "Health Effects of Air Pollution," which provides a mechanism for investigators to apply for funding for research projects on novel and important aspects of health effects of air pollution that fall outside of other current RFAs. Clougherty and her colleagues proposed to quantify the combined effects of multiple pollutants and stressor exposures (e.g., violence and chronic stress) on CVD using existing datasets from New York City (NYC). The HEI Research Committee recommended the study for funding after the proposal underwent comprehensive peer review, because of the unique datasets, with their detailed spatial resolution, richness of the available social stressor data, and heterogeneity of stressors across the study population. The Committee also liked the proposed stepwise approach across aims that would combine analysis of both short- and long-term health effects using various statistical approaches.

Dr. Jane E. Clougherty's 2-year study, "Susceptibility to Multiple Air Pollutants in Cardiovascular Disease," began in August 2017. Total expenditures were $262,892. The draft Investigators' Report from Clougherty and colleagues was received for review in August 2019. A revised report, received in August 2020, was accepted for publication in October 2020. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Critique.

* A list of abbreviations and other terms appears at the end of this volume.

This Critique provides the HEI Review Committee's evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into a broader scientific perspective.

DESCRIPTION OF THE STUDY

SPECIFIC AIMS

The overall objective of Clougherty and colleagues' study was to understand if social stressors influence susceptibility to the health effects of air pollution. The investigators' stated specific aims were:

- Aim 1: To understand the separate and combined associations of CVD with both social stressors and air pollutants, all measured at the same spatial (census-tract) and temporal (annual average) scales of resolution, and whether the stressors confound or modify the relationships between air pollutants and CVD events.
- Aim 2: To examine spatiotemporal associations between each pollutant (and copollutants) and short-term individual-level risk of CVD events.
- Aim 3: To test effect modification by community-level SEP and/or social stressors on the relationships between short-term air pollution exposures and CVD events.

STUDY DESIGN AND METHODS

Data Sources

The investigators used multiple data sources to examine associations between air pollution, social stressors, and CVD (Critique Table). The study population included all in- and out-patient CVD-related visits to all NYC hospitals from 2005 to 2011 (n = 1,113,185). The investigators defined the health outcome as a "CVD event," which they describe as a new case presenting at an NYC hospital on the admission date listed, specifically those categorized as "emergent" or "urgent," so as to focus on acute cases.

The air pollutants assessed included particulate matter smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). Pollutant data were obtained from the NYC Community Air Survey (NYCCAS), which collects integrated samples of ambient air pollutants at randomly selected sites. The investigators used these data to develop land use regression (LUR) models to produce annual average pollutant concentration surfaces at 100 × 100-m resolution. The investigators also acquired air pollution data at an hourly resolution from the U.S. Environmental Protection Agency (EPA)'s Air Quality System (AQS), which they averaged to days to provide temporally varying pollutant concentrations.

The investigators obtained individual- and community-level data on social stressors from numerous data sources (Critique Table). A unique aspect of the study was the development of several distinct indicators of community-level SEP. Stressors were analyzed at the United Hospital Fund (UHF) spatial resolution (n = 34 in NYC) or census-tract resolution (n = 2,167 in NYC). The community stressor indicators comprised three indices (suites of spatially correlated community stressors) developed from an unrestrained factor analysis of 27 UHF-level stressors that were derived from several different datasets. The investigators categorized the factors derived from the unrestrained factor analysis as representing (1) violence and physical disorder, (2) crowding and poor resource access, and (3) noise and air pollution complaints.

All other social stressors were analyzed at the census-tract level. The investigators chose to assess poverty and violence separately, based on focus group and phone survey data providing some evidence that these two variables were associated with both perceived neighborhood disorder and mental health problems (Shmool et al. 2015). They also developed a socioeconomic deprivation index (SDI) by adapting methods published previously (Messer et al. 2006), which involved conducting a principal component analysis of 25 census-tract-level variables.

At the request of HEI, the investigators added UHF-level noise disturbance variables from the NYC Department of Health and Mental Hygiene (DOHMH) Community Health Survey (CHS) as a potential confounder and/or effect modifier. In a supplementary analysis they assessed whether the UHF-level noise data were correlated with individual-level survey data collected during previous work, to assess whether the ecological-level noise variables (community-level stressors) would capture individual-level variability in perceived stress experience.

Aim 1: Ecological Cross-Sectional Analysis

Design To assess the role of the social stressors as potential confounders of the associations between the air pollutants and CVD events, Clougherty and colleagues performed an ecological cross-sectional analysis. The exposures, outcomes, and stressor data were aggregated to the same temporal (annual average) and spatial scales

Critique Table. Summary of Health, Exposure, and Stressor Variables and Data Sources

Variable	Data Source	Description	Spatial Resolution; Temporal Resolution	Time Period
Health Outcome				
CVD event	New York Department of Health SPARCS	In- and out-patient unscheduled CVD visits (ICD-9 codes: 390–459) and subdiagnoses in all NYC hospitals.	Residence; Daily	2005–2011
Exposure				
Air pollution	U.S. EPA AQS	$PM_{2.5}$, NO_2, SO_2, and O_3 concentrations collected at up to seven monitors	Citywide; Hourly	2005–2011
	NYCCAS	$PM_{2.5}$, NO_2, SO_2, and O_3 concentrations collected for 2-week periods during each meteorological season collected at 155 light pole sites	100 × 100-meter spatial surfaces; 2-week, averaged to annual resolution	Dec. 2008–Nov. 2010
Meteorological data	NOAA	Temperature, relative humidity, and dew point collected at four sites.	100 × 100-meter spatial surfaces; Daily	2005–2011
Social Stressors				
SDI	American Community Survey	One component derived using PCA of 25 variables across seven domains: income, wealth, education, employment/occupation, housing, language, racial/ethnic composition	Census tract; 5-year average	2007–2011
Poverty	American Community Survey	Percentage of households living below 200% of the federal poverty level	Census tract; 5-year average	2007–2011
Income	American Community Survey	Median household income	Census tract; 5-year average	2007–2011
ICE I&R	American Community Survey	The extent to which an area's residents are disproportionately low-income Black or high-income White	Census tract; 5-year average	2007–2011
Suites of spatially correlated community stressors	U.S. Census NYC Housing and Vacancy Survey NYC Community Health Survey NYC Police Department NYC School Districts	Three factors derived from a factor analysis of 27 variables across six domains: SEP, violence and crime, healthcare access, physical disorder, noise and pollution, and school-related stressors	United Health Fund; Annual average	2009 where possible; 2005–2011 for American Community Survey variables
Noise disruption	NYC Department of Health and Mental Hygiene Community Health Survey	Respondents reported whether they were disrupted ≥3 times per week by construction, traffic, sirens, street, or subway	United Health Fund; Average for 2009	2009
Violent crime rates	NYC OpenData and New York City Police Department	Assault rate and total violent crime rate per 10,000	Point level; Average for 2009	2009

ACS = American Community Survey; AQS = Air Quality System (EPA); ICE I&R = Index of Concentration at the Extremes: Income and Race Ethnicity; NOAA = National Oceanic and Atmospheric Administration (U.S.); NYCCAS = New York City Community Air Survey; PCA = principal component analysis; SDI = socioeconomic deprivation index; SPARCS = Statewide Planning and Research Cooperative System (New York State Department of Health).

(census-tract [n = 2,167] or UHF [n = 34]). Census tracts with fewer than 200 residents were excluded.

Exposure Assessment The investigators first geocoded the residential addresses listed on the CVD event record and assigned each residence a census tract based on its location. They then used 2008–2010 NYCCAS data to assess exposures to multiple pollutants over the 2005–2011 study period. They applied 100 × 100–m concentration surfaces that NYCCAS had previously developed using 8 measurements (2-week average measurements in each season) at each of the 155 monitoring sites, collected over two years, in an LUR model combined with spatial smoothing to produce spatially varying pollutant concentrations across the study area. They averaged the 100 × 100–m resolution concentration surfaces to the census-tract level and assigned the census-tract-level concentrations to each residence located in that census tract.

Analytical Methods The investigators used negative binomial models to account for over-dispersion of the data. They first tested the individual association between each NYCCAS air pollutant and each social stressor with CVD events rates per 100,000 population in each populated census tract (n = 1,981). Next, they ran models that included one air pollutant and one social stressor in the same model (called "mutually adjusted" models). Their final model (called a "fully adjusted" model) included multiple pollutants and socioeconomic deprivation index, percentage non–Hispanic Black, and violent crime rate. They also assessed effect modification by social stressors by including interaction terms between each pollutant and the categorical social stressors. They presented P values for interaction for the UHF-level social stressors; no P values for interaction or for trend were presented evaluating effect modification by census-tract level stressors. The investigators conducted several analyses to assess sensitivity of results to spatial autocorrelation and spatial scale.

Aims 2 and 3: Individual-Level Daily Analyses

Design Aims 2 and 3 were performed at the individual level at a daily temporal resolution. These aims included only in-patient CVD events (n = 837,523). To control for non-time-varying covariates (e.g., age, race, and sex), Clougherty and colleagues implemented a case-crossover approach in which individuals with a CVD event served as their own control during a time when they did not have an event. Controls were selected using time-stratified sampling. Case days were defined as the day of the CVD event. The investigators used bidirectional time-stratified methods to select referent (non-case) days, which they defined using the same day of the week, calendar month, and year of the CVD event.

Exposure Assessment The investigators estimated daily- and residence-specific exposures to $PM_{2.5}$, SO_2, NO_2, and O_3. They first assigned annual average NO_2 and $PM_{2.5}$, winter SO_2, and summer O_3 NYCCAS concentration surfaces to each geocoded residence, averaging all the 100 × 100–m grid cell centroids that fell within 300 m of each residence.

They obtained hourly and daily pollutant concentrations from AQS regulatory monitoring stations, using only data from those monitors with data coverage for at least 80% of the year. They then interpolated values at the remaining monitors with missing data. These data were averaged across all monitors to produce a NYC daily average, and time-series estimates were computed for each study year. Time-series were computed for SO_2 and O_3 for the winter and summer, respectively, to correspond to the spatial NYCCAS surfaces.

The final step in the exposure assessment involved computing spatially and temporally varying exposure estimates at each residence for up to 6 days (lag days 0–6) preceding the event and referent dates (defined above). These estimates were calculated using the following formula:

$$\text{Daily and residence-specific exposure estimates} = \text{Daily AQS citywide concentrations} \times \frac{\text{NYCCAS annual concentrations assigned at the residence}}{\text{Mean NYCCAS concentrations at the AQS monitoring sites}}$$

Analytical Methods For Aim 2, Clougherty and colleagues used conditional logistic regression to examine associations between multiple pollutants, over lag days 0–6, and all CVD events and CVD subdiagnoses (e.g., ischemic heart disease, heart failure, stroke, ischemic stroke, and acute myocardial infarction). They assessed the main effects of the air pollutants and then adjusted for multiple pollutants in the same model and accounted for nonlinear associations by using penalized splines of concentrations on the day of the event (lag 0). Pollutants other than the main pollutant of interest were included only when the two pollutants were not highly correlated and did not share the same primary source, to avoid overadjustment. For example, $PM_{2.5}$ and SO_2 were highly correlated, and both are strongly associated with oil-burning in NYC and have

similar spatial and temporal patterns, so the investigators did not include SO_2 in models with $PM_{2.5}$ as the predictor of interest. Also, models for SO_2 (predicted using data collected only in winter) and O_3 (predicted using data collected only in summer) did not include copollutant adjustments, because the other pollutants were collected year-round, and season-specific analyses reduced statistical power for those models. All models were adjusted for minimum temperature, relative humidity, and copollutants on the day of the event (lag 0) using penalized splines; $PM_{2.5}$ and NO_2 models were also adjusted for percent non–Hispanic Black and Hispanic by census tract. They ran models for each lag day independently and tested the sensitivity of their results to the inclusion of lags 0–6 in the same model using a distributed lag nonlinear model.

For Aim 3, the investigators evaluated effect modification for the case-crossover data by including interaction terms between each pollutant and the categorical social stressors. They presented *P* values for tests of interaction for the UHF-level social stressors and *P* values for tests of trend of the air pollution and CVD association across categories of census-tract-level stressors. Aim 3 analyses were performed using lag day 0 estimates. The census-tract-level stressors included SDI, community violent crime and assault rates, percentage of households ≤200% of the federal poverty level, median household income, and the investigators' Index of Concentration at the Extremes: Income and Race–Ethnicity (ICE I&R). The UHF stressors included the three stressor factors and noise. These models were additionally adjusted for census-tract-level percentage non–Hispanic Black and Hispanic. The investigators presented *P* values for interaction for the UHF-level social stressors and a *P* value testing linear trends for census-tract-level stressors.

All Aim 1 and 3 models including census-tract variables were adjusted for multiple comparisons using the false discovery rate (Benjamini-Hochberg procedure). The investigators also conducted sensitivity analyses, including testing the impacts of various methods of categorization of stressor values, varying buffer distances in the exposure assignment, adjusting for sets of copollutants, and varying assumptions of linearity of the association of CVD events with pollutant exposures. They also presented results of single-pollutant models across lag days 0–6.

SUMMARY OF KEY RESULTS

Aim 1: Ecological Models Examining Confounding and Effect Modification

In models evaluating each pollutant separately against census-tract-level CVD events, at the same spatial and temporal scale, annual average NO_2 (incident rate ratio [IRR]: 1.09 [95% confidence interval (CI): 1.07–1.12]), $PM_{2.5}$ (1.14 [95% CI: 1.11–1.17]), and SO_2 (1.07 [95% CI: 1.05–1.09]) were positively associated with CVD, and O_3 (0.94, [95% CI: 0.92–0.96]) was inversely associated with CVD. The IRR corresponds to a one-IQR change for each pollutant. The IQRs were 3.89 ppb, 1.37 μg/m^3, 2.08 ppb, and 1.61 ppb for NO_2, $PM_{2.5}$, SO_2, and O_3, respectively. In models evaluating each social stressor separately against census-tract-level CVD events, all stressors were associated with CVD in the hypothesized directions.

In the investigators' assessment of confounding using mutually and fully adjusted models, the investigators reported that the associations between the pollutants and CVD were generally consistent with the null when socials stressors were added to the model. They also concluded that, within the same model, the associations between social stressors and CVD events were larger than those between the air pollutants and CVD events, in the hypothesized directions. For example, in mutually adjusted models including violent crime and $PM_{2.5}$ (μg/m^3), a one-IQR increase in $PM_{2.5}$ was associated with a 3% (95% CI: 1.01–1.06) increase in CVD events per 100,000 population, while a one-IQR increase in violent crime (IQR = 44.3 per 10,000 population) was associated with a 32% (95% CI: 1.29–1.35) increase in CVD events per 100,000 population.

When they evaluated effect modification via models for associations between air pollutants and CVD within strata of the stressors, the investigators reported higher associations between SO_2 and CVD across quintiles of increasing poverty. They also used *P* values for trend and *P* values for associations between air pollutants and CVD. The investigators also reported that associations between NO_2, $PM_{2.5}$, or SO_2 and CVD were higher across quintiles of increasing felony assault and violent crime rates. On the other hand, larger inverse associations were reported between O_3 and CVD across quintiles of increasing violent crime rate and felony assault rate, which the investigators explained may be because of the inverse spatial and temporal patterns of O_3 compared with the other pollutants in the study. There were no differences in the magnitude of associations between pollutants and CVD by quintiles of SDI, income, or ICE I&R.

The investigators reported higher positive associations for O_3 in above-median measures of UHF-level traffic and construction noise, with significant *P* values for interaction. Positive associations for NO_2 and $PM_{2.5}$ were higher in below-median noise disturbance measures compared with above-median noise disturbance measures. Associations were consistent with the null for UHF Factors 2 and 3 scores, and they reported a significant *P* value for interaction for Factor 1 with NO_2 and $PM_{2.5}$.

Aim 2: Individual-Level Models Examining Copollutant Exposures

When the investigators ran models to assess associations between daily average copollutant exposures and CVD events in case-crossover models, they reported an excess risk of CVD events per 10-unit increase in NO_2 (ppb) (1.51% [95% CI: 1.22–1.8]) or $PM_{2.5}$ ($\mu g/m^3$) (1.09% [95% CI: 0.71–1.47]) exposure and a decreased excess risk with O_3 (ppb) (−0.86% [95% CI: −1.39– −0.33]) exposure on the day of the event (lag day 0). Associations reported between CVD events and NO_2 or $PM_{2.5}$ exposures across all other lag days (1 to 6 days before the event), and for any associations between CVD and wintertime SO_2, were generally consistent with the null.

Aim 3: Individual-Level Models Examining Effect Modification

When they accounted for effect modification via models for associations between air pollutants and CVD within strata of the stressors in case-crossover models, the investigators reported a higher percentage excess risk of CVD for a 10-ppb increase in NO_2 in the highest quintiles compared with lower quintiles of violence, assault, SDI, and poverty. They reported that associations between other pollutants and CVD were consistent with the null within stressor quintiles. They also used *P* values for trend and *P* values for associations between air pollutants and CVD to support their hypotheses and did not report *P* values for interaction of census-level stressors. The investigators reported that there was no evidence of effect modification using *P* values for interaction by the two UHF-level variables: noise and factor scores.

REVIEW COMMITTEE EVALUATION

In its independent review of the study, the HEI Review Committee found that Clougherty and colleagues used several rich and well-validated data sources to address important questions about the role of social stressors as possible confounders or effect modifiers in investigations of the relationships between air pollutants and CVD events. The Committee noted that this is an underexplored topic and that these data offered a unique opportunity to identify stressors of importance in air pollutant and CVD associations as well as the extent to which these stressors modify the associations.

The Committee thought that the investigators used a strong study design to examine individual-level associations between air pollution and CVD, with a dataset that contained more than one million CVD events from 2005 to 2011. The Committee appreciated the use of a case-crossover design to assess associations between CVD events and copollutant exposures on days preceding the CVD events, considering multiple lags. The Committee commended the investigators for their inclusion of noise as a potential stressor as well as their extensive sensitivity analyses to test and assess alternative approaches to the exposure assessment, stressor categorizations, and inclusion of copollutants in the models. The Committee also welcomed the discussion by the investigators of stressor misclassification and the potential implications for the results.

The Committee found that the study included valuable analyses of the roles and magnitude of social stressors in CVD events. Below, the Committee summarizes important methodological and reporting issues that should be considered when interpreting results of this study.

DATA MISALIGNMENT

The Committee thought that a limitation of the study was the temporal mismatch among the CVD data (2005–2011 for individuals), exposure data (e.g., December 2008–November 2010 NYCCAS data at 100-m × 100-m resolution), and stressor data (various time periods at the census-tract and UHF levels) in Aims 2 and 3 (see Critique Table). It was not always clear when temporal mismatches occurred or what the implications of those mismatches were for the results. The Committee thought that this data misalignment may have resulted in error for results in which air pollution and stressor exposures were not aligned with the CVD count data.

EXPOSURE ASSESSMENT

The Committee thought that the investigators implemented appropriate methods to ensure that each residential address was accurately geocoded, thus reducing the potential for exposure measurement error. The use of NYCCAS data provided relatively fine spatial resolution and substantial geographic coverage, and the AQS data provided high temporal resolution air monitoring data for Aims 2 and 3.

A limitation of the exposure assessment approach to generate "spatiotemporal" estimates is that these estimates do not fully vary in time and space, resulting in potential exposure misclassification. Although the investigators cited a previous study demonstrating relative stability of the NYCCAS surfaces across seasons and years, and the approach used was justifiable as a practical approximation, the exposure assessment for Aims 2 and 3 could have been improved with a dataset incorporating day-to-day variations in spatial patterns of pollutant concentrations. Such an

approach would have fully captured variability caused by changes in local source contributions, meteorological variability, and other factors that may have changed spatial patterns of exposure from day to day over the study period.

The investigators endeavored to address this limitation by presenting Pearson correlation coefficients that compared the citywide average daily concentrations with the concentrations estimated for individual NYCCAS grid cells, finding positive correlations (0.97, 0.98, 0.87, and 0.79 for $PM_{2.5}$, O_3, NO_2, and SO_2, respectively). However, this approach estimates the proportion of the variation in their estimated exposures that was temporal versus the proportion that was spatial, rather than assessing the accuracy of their estimates. In the Committee's view, a more appropriate approach to test the accuracy of the exposure assessment methods would have been to compare known pollutant concentrations at the AQS monitoring locations with concentrations for the same sites estimated using the investigators' combinatorial approach and then quantifying the exposure measurement error.

ANALYTIC METHODS

The Committee noted that the use of negative binomial models in Aim 1 and conditional logistic regression in Aims 2 and 3 was appropriate. The Committee also thought that the approach for copollutant adjustment in Aims 2 and 3 due to collinearity was well justified. Innovative statistical techniques have only recently been developed to study complex exposure mixtures (Coull et al. 2015; Molitor et al. 2016; Park et al. 2015) and are available for similar work in the future.

The investigators tested the linearity of the NO_2–CVD association in a sensitivity analysis, finding that associations were "generally linear." However, the Committee noted that the investigators did not indicate whether they tested linearity for each pollutant of interest to support their decision to include penalized splines in models involving copollutant adjustment in Aims 2 and 3.

Because an objective for Aims 1 and 3 of the study was to test effect modification by social stressors, the reporting of statistical tests for interaction across all aims would have strengthened the interpretation of the results. The investigators reported that all models evaluating effect modification included statistical tests of interaction. They did present statistical tests of interaction for the UHF-derived variables in both aims. However, the investigators neither specified the statistical test that they used (e.g., a likelihood ratio test) nor presented the results for statistical tests of interaction for the census-derived variables. Instead, they presented results of tests for trend across quintiles of those variables in Aim 3. Tests for trend do not evaluate effect modification. The investigators did not present results for statistical tests of interaction or trend for census-derived variables in Aim 1.

Additionally, the Committee thought a limitation of Aim 1 was that the investigators did not consider an exhaustive list of potential behavioral and lifestyle factors, such as smoking status and diet, in analytical models. The investigators acknowledged this limitation in the report, describing that they were restricted by the set of data available in the administrative datasets that they compiled.

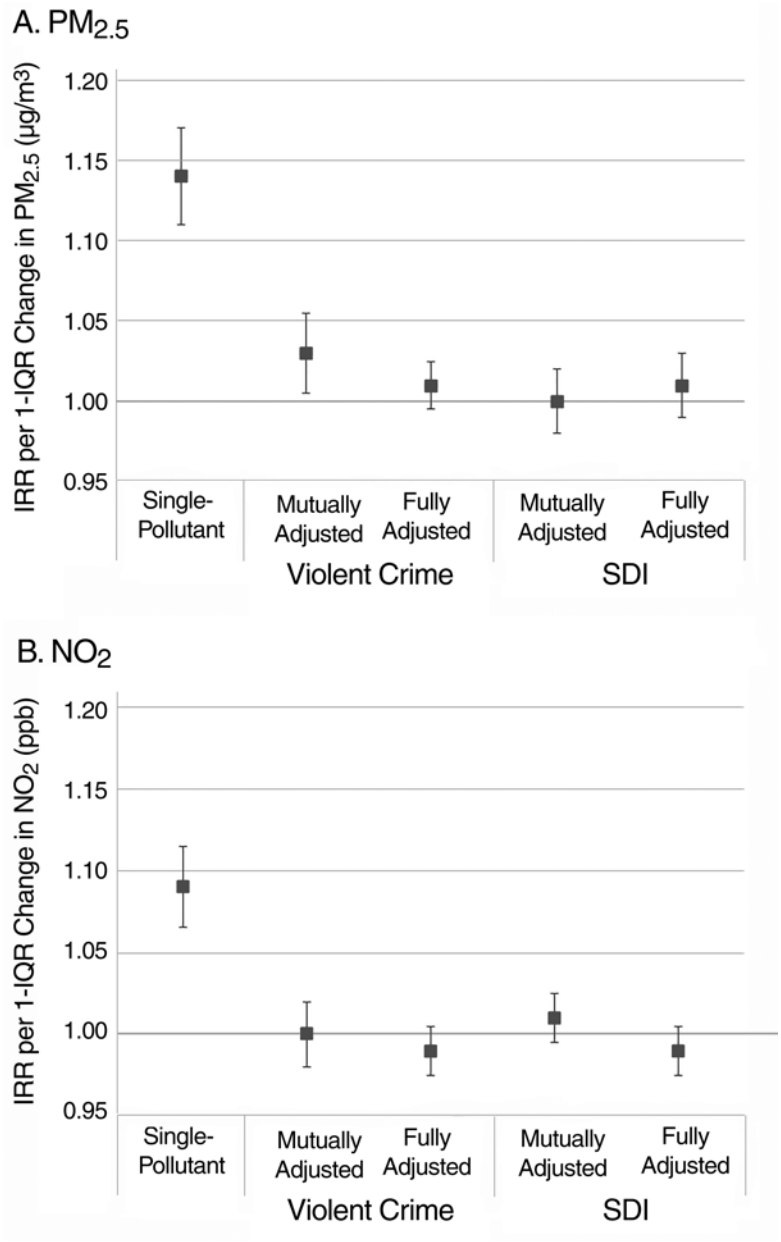
PRESENTATION AND INTERPRETATION

The Committee agreed with the investigators' conclusions in Aim 1 that results were attenuated when social stressors were added to mutually and fully adjusted models. Committee members also agreed with the Aim 2 conclusions that same-day pollution exposure was associated with risk of CVD event, which is broadly consistent with previous literature on short-term exposure to air pollution and CVD hospitalizations.

The Committee thought that the investigators could have improved the interpretation of confounding results by using an approach in which they compared results from their three types of models: (1) single-pollutant models, (2) mutually adjusted models, and (3) fully adjusted models. The Critique Figure, for example, illustrates potential confounding by violent crime and the SDI for $PM_{2.5}$ and NO_2. The investigators reported positive associations between both $PM_{2.5}$ and NO_2 and CVD event rates. However, the results were attenuated when the stressors (i.e., violent crime and the SDI) were added to the models.

By comparing the results of these models, the investigators would have been able to identify and discuss the presence and magnitude of confounding for specific stressors more fully. Although the investigators did present results for single-pollutant models in the Appendix as well as the mutually adjusted and fully adjusted models in the report, they did not display or interpret the results in a way that would allow for an assessment of confounding or of the relative contributions of each stressor to the associations between air pollutants and CVD events.

In addition, the investigators' main conclusion for Aim 1 was that the associations between the social stressors and CVD events were stronger than those between the air pollutants and CVD events. There is an important caveat to this interpretation, which the investigators discussed in the report: on a proportional basis, the variability among the social stressors was greater than the variability among the air pollutants in the study population. Overall, the Committee thought that the investigators missed the opportunity to interpret results beyond the magnitude and statistical significance of the associations and to specify which



Critique Figure. Assessment of confounding in associations between $PM_{2.5}$ (A) and NO_2 (B) and CVD event rates (Aim 1) at the census-tract level (*n* = 1,981) by violent crime and the SDI. Data are shown as the incidence rate ratio (IRR) with 95% confidence intervals per interquartile range (IQR) for $PM_{2.5}$ (IQR = 1.37 µg/m^3) and NO_2 (IQR = 3.89 ppb). Single-pollutant models = unadjusted negative binomial models for each pollutant versus CVD events. Mutually adjusted models = negative binomial models for one pollutant and one stressor in the same model. Fully adjusted models = negative binomial models, adjusting for SDI, percentage non-Hispanic Black, and violent crime rate.

stressors were important modifiers or confounders of the associations. The Committee additionally thought that the report should have included an expanded discussion of the potential importance of residual confounding on Aim 1 results.

For Aim 3, the Committee also disagreed with the investigators' generalization that there was evidence of stronger associations in communities with worse stressor characteristics, which the investigators incorrectly based on *P* values for associations within individual strata of the stressors and tests for trend. The more appropriate

evidence to support conclusions about effect modification would have involved statistical tests of interaction, as discussed above, as well as discussion of differences of the IRRs between strata. The Committee's interpretation of the results in Aim 3 is that magnitude and direction of the associations varied greatly among the stressor categories, which do not support evidence of effect modification. The report would have additionally been strengthened with discussion about the patterns observed for the effect modification results, such as a negative (i.e., protective) association in some of the lower quintiles of the social stressors.

SUMMARY AND CONCLUSIONS

Clougherty and colleagues aimed to answer important questions about the role of social stressors as modifiers or confounders of the associations between exposure to air pollutants and CVD events. They also sought to quantify the effects of multipollutant exposures on CVD events. The investigators used unique stressor and noise data, a large cohort, data on multiple pollutants, and detailed sensitivity analyses to address their study objectives for the specific locale and time period covered by the study. The Committee agreed that these are important questions, and the study used innovative data on social stressors. It concluded that the study would have been strengthened with a clearer presentation of confounding and effect modification results.

The study helped highlight the importance of considering the role of distinct social stressors as risk factors for health outcomes such as CVD events. At the same time the study added to the existing epidemiology literature on associations between air pollutant exposures (in particular $PM_{2.5}$) and CVD events (Brook et al. 2010) while also examining the role of those social stressors on those associations. There is a need for future studies to continue disentangling social stressor effects and build on the initial steps taken in this study. In particular, future studies should ensure a more systematic assessment of confounding and effect modification. They should also identify specific social stressors that act as confounders, the degree of potential confounding, and social stressor modifiers to help understand disproportionate susceptibility to pollution.

ACKNOWLEDGMENTS

The Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Johanna Boogaard, Allison Patton, and Katy Walker for their oversight of the study, to Anna Rosofsky and Lee Ann Adelsheim for their assistance in preparing its Critique, to George Simonson for his editing of this Report and its Critique, and to Kristin Eckles, Hope Green, and Hilary Selby Polk for their roles in preparing this Research Report for publication.

REFERENCES

Abrams JY, Klein M, Henneman LRF, Sarnat SE, Chang HH, Strickland MJ, et al. 2019. Impact of air pollution control policies on cardiorespiratory emergency department visits, Atlanta, GA, 1999–2013. Environ Int 126:627–634; doi:10.1016/j.envint.2019.01.052.

Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. 2009. Hospital admissions and chemical composition of fine particle air pollution. Am J Respir Crit Care Med 179:1115–1120; doi:10.1164/rccm.200808-1240OC.

Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121:2331–2378; doi:10.1161/CIR.0b013e3181dbece1.

Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. 2009. Socioeconomic status and cardiovascular disease: Risks and implications for care. Nat Rev Cardiol 6:712–722; doi:10.1038/nrcardio.2009.163.

Coull BA, Bobb JF, Wellenius GA, Kioumourtzoglou M-A, Mittleman MA, Koutrakis P, et al. 2015. Part 1. Statistical Learning Methods for the Effects of Multiple Air Pollution Constituents. In: Development of Statistical Methods for Multipollutant Research. Research Report 183. Boston, MA:Health Effects Institute.

Fuller CH, Feeser KR, Sarnat JA, O'Neill MS. 2017. Air pollution, cardiovascular endpoints and susceptibility by stress and material resources: A systematic review of the evidence. Environ Health 16:58; doi:10.1186/s12940-017-0270-0.

Hajat A, Diez-Roux AV, Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, et al. 2013. Air pollution and individual and neighborhood socioeconomic status: Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect 121:1325–1333; doi:10.1289/ehp.1206337.

Hajat A, Hsia C, O'Neill MS. 2015. Socioeconomic disparities and air pollution exposure: A global review. Curr Env Health Rep 2:440–450; doi:10.1007/s40572-015-0069-5.

Kaplan GA, Keil JE. 1993. Socioeconomic factors and cardiovascular disease: A review of the literature. Circulation 88:1973–1998; doi:10.1161/01.cir.88.4.1973.

Lippmann M. 2014. Toxicological and epidemiological studies of cardiovascular effects of ambient air fine particulate matter ($PM_{2.5}$) and its chemical components: Coherence and public health implications. Crit Rev Toxicol 44:299–347; doi:10.3109/10408444.2013.861796.

Lippmann M, Chen L-C, Gordon T, Ito K, Thurston GD. 2013. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components. Research Report 177. Boston, MA:Health Effects Institute.

Messer LC, Laraia BA, Kaufman JS, Eyster J, Holzman C, Culhane J, et al. 2006. The development of a standardized neighborhood deprivation index. J Urban Health 83:1041–1062; doi:10.1007/s11524-006-9094-x.

Molitor J, Coker E, Jerrett M, Ritz B, Li A. 2016. Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes. In: Development of Statistical Methods for Multipollutant Research. Research Report 183. Boston, MA:Health Effects Institute.

Morello-Frosch R, Pastor M, Sadd J. 2001. Environmental justice and Southern California's "riskscape": The distribution of air toxics exposures and health risks among diverse communities. Urban Aff Rev 36:551–578: doi.org/10.1177/10780870122184993.

Park ES, Symanski E, Han D, Spiegelman C. 2015. Part 2. Development of Enhanced Statistical Methods for Assessing Health Effects Associated with an Unknown Number of Major Sources of Multiple Air Pollutants. In: Development of Statistical Methods for Multipollutant Research. Research Report 183. Boston, MA:Health Effects Institute.

Pastor M, Morello-Frosch R, Sadd JL. 2005. The air is always cleaner on the other side: Race, space, and ambient air toxics exposures in California. J Urban Aff 27:127–148; *doi.org/10.1111/j.0735-2166.2005.00228.x*.

Peng RD, Bell ML, Geyh AS, McDermott A, Zeger SL, Samet JM, et al. 2009. Emergency admissions for cardiovascular and respiratory diseases and the chemical composition of fine particle air pollution. Environ Health Perspect 117:957–963; doi:10.1289/ehp.0800185.

Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. 2018. Socioeconomic status and cardiovascular outcomes: challenges and interventions. Circulation 137:2166–2178; doi:10.1161/CIRCULATIONAHA.117.029652.

Seilkop SK, Campen MJ, Lund AK, McDonald JD, Mauderly JL. 2012. Identification of chemical components of combustion emissions that affect pro-atherosclerotic vascular responses in mice. Inhal Toxicol 24:270–287; doi:10.3109/08958378.2012.667455.

Shmool JLC, Yonas MA, Newman OD, Kubzansky LD, Joseph E, Parks A, et al. 2015. Identifying perceived neighborhood stressors across diverse communities in New York City. Am J Community Psychol 56:145–155; doi:10.1007/s10464-015-9736-9.

Steptoe A. 2002. The role of psychobiological pathways in socio-economic inequalities in cardiovascular disease risk. Eur Heart J 23:13–25; doi:10.1053/euhj.2001.2611.

Steptoe A, Kivimäki M. 2013. Stress and cardiovascular disease: An update on current knowledge. Annu Rev Public Health 34:337–354; doi:10.1146/annurev-publhealth-031912-114452.

Sun M, Kaufman JD, Kim SY, Larson TV, Gould TR, Polak JF, et al. 2013. Particulate matter components and subclinical atherosclerosis: Common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study. Environ Health 12; doi:10.1186/1476-069x-12-39.

Thurston RC, Kubzansky LD, Kawachi I, Berkman LF. 2005. Is the association between socioeconomic position and coronary heart disease stronger in women than in men? Am J Epidemiol 162:57–65; doi:10.1093/aje/kwi159.

Vedal S, Campen MJ, McDonald JD, Kaufman JD, Larson TV, Sampson PD, et al. 2013. National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects. Research Report 178. Boston, MA:Health Effects Institute.

Vincent R, Kumarathasan P, Goegan P, Bjarnason SG, Guénette J, Bérubé D, et al. 2001. Inhalation Toxicology of Urban Ambient Particulate Matter: Acute Cardiovascular Effects in Rats. Research Report 104. Boston, MA:Health Effects Institute.

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ABBREVIATIONS AND OTHER TERMS

AQS	Air Quality System (U.S. EPA)
CDC	Centers for Disease Control and Prevention (U.S.)
CHS	Community Health Survey
CI	confidence interval
CVD	cardiovascular disease
df	degree(s) of freedom
DOHMH	Department of Health and Mental Hygiene (NYC)
EPA	Environmental Protection Agency (U.S.)
FDR	false discovery rate
GIS	geographic information system
HF	heart failure
ICE I&R	Index of Concentration at the Extremes: Income and Race–Ethnicity
IHD	ischemic heart disease
IQR	interquartile range
IRR	incidence rate ratio
LUR	land use regression
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
NIH	National Institutes of Health (U.S.)
NOAA	National Oceanic and Atmospheric Administration (U.S.)
NO_x	nitrogen oxides
NO_2	nitrogen dioxide
ns	natural spline
NYC	New York City
NYCCAS	New York City Community Air Survey
NYPD	New York Police Department (NYC)
NYS	New York State
O_3	ozone
PCA	principal component analysis
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
RH	relative humidity
SD	standard deviation
SDI	socioeconomic deprivation index
SEP	socioeconomic position
SO_2	sulfur dioxide
SPARCS	Statewide Planning and Research Cooperative System (New York State Department of Health)
Tmin	minimum daily temperature
UHF	United Hospital Fund

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RESEARCH
REPORT

Number 206
July 2021