Dear Pam,

I am forwarding these attachments and the email below from Chris Mackensen with additional information for the SEC. He is without proper computer access at this time. Bev

We do have frequent inversions in our Monadnock region, empirically observed, above and beyond what NHDES may declare as "official" inversions.

Considering that current applicants may have not one, but two behemoth 41,000 horsepower (82,000 horsepower total) in the Monadnock region (or abutting Winchester, in Northfield, MA) with emission in tons per year that may exceed minor pollution contribution…. Currently most folks seem to be focused only on the one 41,000 horsepower compressor station proposed for New Ipswich, but Winchester, NH may also be a contingency also in the Monadnock region.

Short term peaks of PM2.5 are important:

24382024: 1 hour peaks in PM2.5 are followed by increase in heart attack rates

PM2.5 even below NAAQS cutoff is deadly:

26038801: Elevations in annual and 24 hour peak PM2.5 concentrations are associated with higher risk of death, this study looked specifically at concentrations **below** NAAQS

Meaning that NAAQS is not effective for health, RSA 125 or humans in general.

Review

Noise Effects on Health in the Context of Air Pollution Exposure

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Abstract: For public health policy and planning it is important to understand the relative contribution of environmental noise on health compared to other environmental stressors. Air pollution is the primary environmental stressor in relation to cardiovascular morbidity and mortality. This paper reports a narrative review of studies in which the associations of both environmental noise and air pollution with health have been examined. Studies of hypertension, myocardial infarction, stroke, mortality and cognitive outcomes were included. Results suggest independent effects of environmental noise from road traffic, aircraft and, with fewer studies, railway noise on cardiovascular outcomes after adjustment for air pollution. Comparative burden of disease studies demonstrate that air pollution is the primary environmental cause of disability adjusted life years lost (DALYs). Environmental noise is ranked second in terms of DALYs in Europe and the DALYs attributed to noise were more than those attributed to lead, ozone and dioxins. In conclusion, in planning and health impact assessment environmental noise should be considered an independent contributor to health risk which has a separate and substantial role in ill-health separate to that of air pollution.

Keywords: environment; noise; transport; air pollution; burden of disease; aircraft; road traffic; cohort studies; DALYs

1. Introduction

A wide range of environmental stressors have an impact on the health of children and adults. Understanding which pollutants have the greatest magnitude of effect on health can have implications

for designing suitable preventive and therapeutic interventions. In the last ten years a number of large scale studies of environmental noise and health have been carried out [1]. In parallel, studies have been published examining the associations of air pollution with health [2]. Because transport sources, such as road traffic, are responsible for both noise exposure and air pollution there has also been an interest in understanding the relative contribution of noise exposure and air pollution to health. Recent studies have strengthened the evidence base for noise and health, beyond effects on noise annoyance and sleep, to providing evidence of convincing health impacts in terms of hypertension, risk of ischaemic heart disease and mortality [3–21]. In terms of public health, and for practical use in health impact assessment, it would be helpful to understand the relative contribution of these different environmental stressors to health outcomes. In this context, this paper examines the evidence for the contribution of environmental noise exposure, largely road, rail and aircraft noise on health, relative to air pollution.

2. Method

A narrative review was carried out without specifying a time limit for the study search. This involved an initial PubMed search on "noise, air pollution and health". "Health" was not further defined in this initial search but the studies found largely relate to cardiovascular disease. Studies of respiratory disease were not found as noise, unlike air pollution, has not been related to this health outcome. This was supplemented by access to recent reviews of noise and health and additional papers revealed by citation tracking. Initially, additional searches were carried out for "environmental noise and pesticides", "environmental noise and heavy metals", "environmental noise and endocrine disrupting chemicals", "environmental noise and climate change". There were very few relevant papers on noise and pesticides, heavy metals, endocrine disrupting chemicals or climate change. In these papers there was insufficient evidence to judge the relative contribution of noise and these environmental stressors on health. Thus the focus of the paper has been confined to studies including environmental noise and air pollution exposure. Environmental noise is defined in this paper as noise from aircraft, road traffic and railways—the main sources of outdoor noise assessed in these studies. Occupational studies and studies of hearing loss have been excluded. Twenty five primary research studies were identified that included assessments of both air pollution and environmental noise and health outcomes. The characteristics and results of studies of noise and air pollution exposure and hypertension, atherosclerosis, ischaemic heart disease, stroke and mortality have been reported in a table (Table 1) to aid comparability. Table 2 reports studies of environmental noise, air pollution and children's cognition and blood pressure. Mental health and cognitive outcomes in adults are also briefly touched on. Quality of the primary studies was assessed in terms of population representativeness, objective measurement of noise and air pollution exposures, sufficient adjustment for confounding factors and objective measurement of health outcomes.

Table 1. Studies of air pollution and noise: effects on health.

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Hypertension and Atherosclerosis						
De Kluizenaar *et al.* 2007 [6]	RTN at most exposed façade, L_{den} using SKM2 model Exposure and transmission path assessed	Regional background data on PM_{10} and modelling of local road traffic to give annual averages	Medication for hypertension in Groningen sample. Measured hypertension BP >140/90 in PREVEND sample	Cross sectional survey of longitudinal cohort study 40,856, 28–75 years Groningen-self report BP medication 8952 screening clinic visit—measured hypertension	Age, sex, SES, fh of CVD, smoking. Additionally for PREVEND: BMI, plasma cholesterol, level of education	For self-reported hypertension OR = 1.31 95% CI 1.25, 1.37 per 10dB(A) increase in L_{den}; In fully adjusted model OR = 1.03 95% CI 0.96, 1.11. In 45–55 year age group fully adjusted OR = 1.19 95% CI 1.02, 1.40 including PM_{10}. For those exposed >55 dB(A) OR = 1.31 95% CI 1.08,1.59 adjusting for PM_{10}. In PREVEND in 45–55 year age group measured hypertension OR = 1.39 95% CI 1.08, 1.77. No differences in men and women
Fuks *et al.* 2011 [7]	RTN Weighted L_{den}	PM_{10}, $PM_{2.5}$	Blood pressure (SBP,DBP). Measured hypertension BP >140/90	Cross sectional survey. 4291, 45–75 years Heinz Nixdorf Recall Study	Smoking, alcohol use, physical activity, diabetes mellitus, social and employment status, daily changes in PM, O3 and temperature	Interquartile increase in $PM_{2.5,}$ increase in SBP 1.4 95% CI 0.5–2.3, DBP 0.9 95% CI 0.4–1.4 adjusting for RTN. RTN>65dB(A) Hypertension OR = 1.28, 95% CI 1.04–1.59

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Hypertension and Atherosclerosis						
Sørensen *et al*, 2011 [8]	RTN SOUNDPLAN using Nordic prediction model from 5 years prior to enrolment to 2000–2002. LAeq at most exposed façade, expressed as L_{den}. Railway noise LA_{eq24} 1993–2000	NOx modelled at each address using AirGIS from 5 years prior to enrolment to 2000–2002	Questionnaire reported hypertension. Measured SBP, DBP	Cross sectional and prospective analyses from cohort study 44,083 out of 160,725, 50–64 years from Diet, cancer and health cohort, Copenhagen, Aarhus	Age, sex, calendar year, area of residence, length of education, SES, BMI, smoking, alcohol intake, leisure time sport, air pollution measured as time weighted average of NOx exposure, mean ambient temperature, humidity, season	RTN: 10% highest exposed had a 0.79 mm Hg (95% CI: −0.04; 1.62) and a 0.85 mm Hg (95% CI: 0.02; 1.67) higher systolic BP compared with the lowest exposure group for 1-year and 5-mean 0.26 (95% CI: −0.11; 0.63) mm Hg higher level of SBP per 10 dB(A) higher level of road traffic noise (1-year mean). No associations between road traffic noise and diastolic BP RTN and BP only associated in men and in over 60s. No prospective association between RTN and self-reported hypertension in sample of 32,635. Exposure to railway noise associated with 8% (95% CI: −2%; 19%, $p = 0.11$) higher risk of hypertension
Dratva *et al.* 2011 [5]	Rail RTN Day Night dB(A) for 10×10 m grids. Rail noise measured within 1000m	Av annual PM_{10} at residence predicted by dispersion modelling NO_2 using a hybrid model	Measured SBP, DBP Measured hypertension BP >140/90	Cross sectional analyses in a cohort study 6450 SAPALDIA 2. 28–72 years 2002/2003 Switzerland	Physician diagnosed illness: hypertension, MI, stroke, diabetes, kidney disease, hearing deficit, antihypertensive drugs, smoking, physical activity, BMI, age, education, employment status, work-related exposures, housing characteristics, age of building, years of residency	Significant effect estimates for a 10 dB(A) increase in railway noise during the night SBP β = 0.84; 95% CI 0.22, 1.46; DBP β = 0.44; 95% CI 0.06, 0.81 and day (SBP β = 0.60; 95% CI: 0.07, 1.13). Adjustment for NO_2 left effect estimates almost unchanged. Stronger associations in participants with chronic disease. Significant associations with traffic noise only in participants with diabetes: β = 3.7 95% CI (–0.09, 7.57) $p = 0.056$

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Hypertension and Atherosclerosis						
Foraster *et al.* 2014 [9]	RTN L_{night} inside at geocoded address adjusted for questionnaire measured insulation	NO_2 with land use regression model	Hypertension BP > 140/90 Use of antihypertensives	Cross sectional analysis of cohort baseline data 2067 36–82 years REGICOR, Girona, Spain	Age, age squared, sex, education level, physical activity, diet, alcohol consumption, diabetes, deprivation, railway noise, daily temperature	Indoor L_{night} was associated both with hypertension (OR = 1.06; 95% CI:0.99, 1.13) and SBP (β = 0.72; 95% CI: 0.29, 1.15) per 5 dB(A); and NO_2 was associated with hypertension (OR = 1.16; 95% CI: 0.99, 1.36), SBP (β = 1.23; 95% CI: 0.21, 2.25), and DBP (β = 0.56; 95% CI: −0.03, 1.14) per 10 μg/m³. L_{night} was associated only with hypertension and NO_2 with BP only
Foraster *et al.* 2014 [10]	RTN Noise model 2005 CadnaA software L_{night}	Annual average NO_2 with land use regression model controlling for short term air pollution with NO_2 from urban background station	Hypertension BP > 140/90 Use of antihypertensives	Cross sectional survey 3700, 35–83 years Girona	Age, age squared, sex, living alone, education level, BMI, alcohol consumption, diabetes, deprivation, road traffic noise, railway noise, night time noise, daily temperature	Correlation of annual mean NO_2 with L_{night} r = 0.74 10 microgm/m³ increase in av annual NO_2 associated with 1.34 mmHg 95% CI 0.14, 2.55 increase after full adjustment in non-medicated sample. Transportation noise main covariate. SBP per 10-dB(A) change in L_{night} in the model for nonmedicated participants were β = −0.94 (95% CI: −2.53, 0.64, p = 0.244) (traffic noise) and β = −0.21 (95% CI: −0.63, 0.21, p = 0.326) (railway noise) Stronger associations of air pollution and BP in those with existing CVD. Interaction between NO_2 and SBP and noise such that individuals exposed to traffic $L_{night} \geq$ 55 dB(A) (β = 1.82; 95% CI: 0.56, 3.07) compared with those exposed to lower noise levels (β = −0.39; 95% CI: −2.17, 1.39), p for interaction = 0.03.

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Hypertension and Atherosclerosis						
Babisch *et al.* 2014 [11]	RTN L_{dn} at most exposed façade, noise maps using CADNA/A software. Also rail noise	Modelled annual average $PM_{2.5}$ using land use regression models	Measured BP, isolated systolic hypertension. Hypertension. BP > 140/90. Antihypertensive medication	Cross sectional 4166, 25–74 years KORA Study Oct 1999–April 2000. RR = 67% 2 samples: City of Augsburg 1893; Greater Augsburg 2273	Age, sex, smoking, alcohol consumption, BMI, physical activity, individual and area level SES	Traffic noise Hypertension OR = 1.11 95% CI 0.94, 1.30 adjusting for $PM_{2.5}$. In 894 longer term residents OR = 1.12 95% CI 0.90, 1.49 adjusting for $PM_{2.5}$. City of Augsburg, *n* = 1601, isolated hypertension OR = 1.43 95% CI 1.10, 1.86 adjusting for $PM_{2.5}$. 1 microgram/m^3 increase in $PM_{2.5}$ OR = 1.11, 95% CI 0.98, 1.27 after adjustment for noise. Traffic noise and air pollution no longer significant after mutual adjustment
Kälsch *et al.* 2014 [12]	RTN façade levels, 24 h mean L_{den}, L_{night}	EURAD-CTM model for $PM_{2.5}$. PM_{10} on a scale of 1 km^2	Thoracic aortic calcification using cardiac electron beam CT scanning	Cross sectional 4238. Mean age 59.6 ± 7.8 years. Heinz Nixdorf Recall Study. Baseline data 2000–2003	Education, income, neighbourhood unemployment, smoking, environmental tobacco smoke, physical activity, alcohol intake, anthropometry, BP, diabetes, current medication	$PM_{2.5}$ associated with increased thoracic aortic calcification of 18.1% 95% CI 6.6, 30.9%. L_{night} associated with increased thoracic aortic calcification of 3.9% 95% CI 0.0, 8.0%. Both analyses mutually adjusted. No effect modification
Cardiovascular Morbidity						
Selander *et al.* 2009 [13]	Residential exposure 1970–1992, 1994. Nordic Prediction model. RTN, ACN and occupational noise	Dispersion methods, historical data on RT emissions	First non-fatal, fatal myocardial infarction (MI)	Population based case control study 1571 with MI, 2095 controls 45–70 years	Sex, age, catchment area, diabetes, physical activity, air pollution, occupational noise exposure	For RTN, MI OR = 1.12 95% CI 0.95, 1.53; Excluding other noise sources and hearing loss OR = 1.38 95% CI 1.11, 1.71. No effect modification by sex or air pollution. Adjustment for air pollution reduced the coefficient by 7%. Air pollution and RTN correlated *r* = 0.6

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Cardiovascular Morbidity						
Sørensen *et al.*, 2012 [14]	RTN SoundPLAN 1990, 1995, 2000, 2005, Nordic Prediction Model L_{den}	NO_x Air GIS model Urban background calculated by area source dispersion model	First incident MI 1600. Included sudden cardiac death	Prospective cohort study 57,053. 50,614 in analytic sample. 50–64 years enrolled in 1993-1997. Mean FU 9.8 years	Age, sex, education, smoking, fruit and vegetable intake, alcohol, physical activity, BMI, calendar year railway, airport noise. In further model measured BP cholesterol and diabetes	RTN L_{den} IRR = 1.12 per 10 dB(A) year exposure at diagnosis 95% CI 1.02, 1.22 adjusting for NO_x. 5 year time weighted mean exposure prior to event IRR = 1.12 95% CI 1.02, 1.23. Still 10% increased risk in further model adjusting for BP, cholesterol and diabetes. NO_x showed similar trends but was not significantly associated with MI
Hart *et al.* 2013 [15]	RTN Distance to major roads <50 m defined as close.	To examine changes in distance to road, each consecutive pair of addresses was categorized: (1) consistently close; (2) consistently far; (3) change from close to far; and (4) change from far to close. Difference in ambient NO_2 between each pair of addresses	Incident non-fatal and fatal MI (2948) All-cause mortality (11,502)	Longitudinal cohort study. Nurses Health Study 84,562 out of 121,700 female nurses 30–55 years in 1976	Age, race, individual SES, physical activity, BMI, alcohol use, diet, smoking, Hypertension, physician diagnosed diabetes, fh of MI	Proximity to roads: MI HR = 1.11 95% CI 1.01, 1.22. All cause mortality HR = 1.05 95% CI 1.00, 1.10. Moving closer to traffic MI HR = 1.50 95% CI 1.11, 2.05. All cause mortality HR = 1.17 95% CI 1.00, 1.37. One ppb increase in NO_2 MI HR = 1.22 95% CI 0.99, 1.50. All cause mortality HR = 1.03 95% CI 0.92, 1.15.

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Cardiovascular Morbidity						
Floud *et al.* 2013 [16]	ACN, RTN Modelled aircraft noise contours Common noise models with 1 dB(A) resolution Road Traffic noise maps 2002 reference year. Expressed as L_{night}, $L_{Aeq16hr}$	Ambient NO_2 in UK, Netherlands and Sweden Assessed around 3 airports NO_2 using APMoSPHERE models $n = 4000$. Mean annual values at place of residence	Self-reported Dr-diagnosed Angina pectoris, MI and stroke 276 events	Cross sectional survey 4712 HYENA Study 45–70 years	Age, sex, BMI, alcohol intake, physical activity, education, smoking, ethnicity	Night time ACN, heart disease and stroke OR = 1.25 95% CI 1.03, 1.51 per 10 dB (A). For those resident ≥ 20 years adjusting for exposure to air pollution. 24 h average RTN, heart disease and stroke OR = 1.19 95% CI 1.00, 1.41 but adjustment for air pollution suggested this may have been due to confounding by air pollution.
De Kluizenaar *et al.* 2013 [17]	RTN calculated using SKM2. Emission and transmission calculated. Expressed as L_{den}	Air pollution at most exposed façade. Dutch National Air Quality Monitoring Network. 1 km × 1 km annual average PM_{10} NO_2	Hospital admissions for IHD, Cerebrovascular disease	Prospective cohort study 18,973 residents of Eindhoven GLOBE Study 15–74 years	Age, gender, marital status, education, smoking, alcohol use, physical activity, BMI, employment status, financial problems, history of CVD	For 10 dB(A) increase in L_{den} RR = 1.12 95% CI 1.04, 1.21 after adjustment non-significant RR = 1.01 95% CI 0.94, 1.09 and additionally PM_{10} RR = 1.00 95% CI 0.91, 1.10 Similar findings for cerebrovascular disease. For PM_{10} RR = 1.06 95% CI 1.01, 1.11 after full adjustment including L_{den} RR = 1.01 95% CI 0.95, 1.08. Similar findings for elemental carbon and NO_2
Correia *et al.* 2013 [18]	ACN contours from US FAA. Integrated noise model version 7A	$PM_{2.5}$ Ozone. For 1165 and 779 zip codes out of 2218 zip codes. EPA Air Quality database.	ICD-9 coded CVD admissions	Ecological small area study. 6,027,363 of US population, >65 years, eligible for Medicare residing near 89 regional airports in 2009	Age, sex, race, zip code level SES, roadway density	For 90th centile of noise exposure a 10 dB(A) increase resulted in 2.9, 95% CI 0.8%, 5.0%, including air pollution increase of 3.5, 95% CI 0.2, 7.0% in relative rate of CVD hospitalization. In zip codes with air pollution data, 6.8% of CVD hospitalizations attributable to fine particulate matter and 4.2% to ozone. Population attributable fraction for noise in the subset of zip codes with air pollution data was 2.2%

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Cardiovascular Morbidity						
Sorensen *et al.* 2014 [19]	RTN Soundplan Nordic Prediction Model L_{Aeq} expressed as L_{den}	Ambient NO_x, NO_2 at residence. AirGIS 1987–2009	Non-fatal and fatal incident Stroke cases validated by physician review 1999 cases	Prospective cohort study. 57,053 enrolled in 1993–1997, 50–64 year Copenhagen/Aarhus. Mean FU 11.2 years	Sex, length of school attendance, area SES, smoking, fruit and vegetable intake, alcohol, coffee, physical activity, BMI, calendar year	Higher mean annual exposure at time of diagnosis of 10 mg/m^3 NO_2 and 10dB(A) RTN was associated with ischemic stroke IRR = 1.11 95% CI 1.03, 1.20% and1.16 95% CI 1.07,1.24 in single exposure models. In two-exposure models RTN IRR = 1.15, 95% CI 1.04, 1.26 and not NO_2 IRR = 1.02 95%CI 0.92, 1.12 was associated with ischemic stroke. Strongest association for combination of high noise and high NO_2 IRR = 1.28 95% CI 1.09, 1.52. Fatal stroke associated with air pollution not traffic noise.
Mortality						
Beelen *et al.* 2009 [2]	RTN EMPARA noise model to 25 × 25 resolution 2000–2001 data	Black smoke, NO_2, $PM_{2.5}$ Sum of regional, urban and local traffic using regression models	Cardiovascular mortality, including Heart failure, cerebrovascular mortality from 1987–1996	Prospective cohort study 120,852 55–69 years from Netherlands Cohort study on cancer	Age, sex, smoking status, neighbourhood SES, local area (COROP score)	Road Traffic noise and black smoke correlated r = 0.24. Black smoke: cerebrovascular RR = 1.39 95% CI 0.99, 1.94; heart failure RR = 1.75 95% CI 1.00, 3.05- not affected by adjustment for RTN. Traffic noise > 65 dB(A) IHD RR = 1.15 95% CI 0.86,1.53; heart failure RR = 1.99 95% CI 1.05, 3.79 reduced by adjustment for black smoke (RR = 1.90 95% CI 0.96–3.78). Similar RRs for NO_2 and PM_{10}. No difference in men and women

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Mortality						
Huss *et al.* 2010 [3]	ACN L_{dn} Yearly av exposure to aircraft noise: Zurich airport dedicated noise exposure model, resolution 100 × 100 m. Model from Federal Office of civil aviation for other 64 airports	Background air pollution dispersion models, resolution 200 × 200 m and proximity to major roads	Deaths from acute MI and circulatory disease, 15,532 deaths from MI	Prospective cohort study 4.6 million, Swiss National Cohort followed end of 2000–2005 30 years plus	Sex, education, marital status, Swiss or other, municipality SES, type of building, distance to major roads, $PM_{10,}$ urbanicity.	For ACN > OR = 60dB(A) HR = 1.3 95% CI 0.96,1.7 adjusting for PM_{10}. For those resident > 15 years HR = 1.5 95% CI 1.0, 2.2. No associations between ACN and all-cause or stroke mortality. Lung cancer associated with PM_{10} and proximity to major roads
Gan *et al.* 2011 [20]	RTN Cadna A model L_{den} dB(A) at postcode. Annual av noise level 63.4 dB(A)	NO_2, NO, Black carbon, $PM_{2.5}$ using land use regression models in 2003	CHD mortality from Provincial Death Registry 3095 deaths	Prospective cohort study 445,368 Vancouver residents 45–85 years, 5 year exposure period January 1994–December 1998, 4 year follow up January 1999–December 2002	Age, sex, neighbourhood SES, COPD, hypertensive heart disease	Equal to interquartile ranges, noise 6, 95% CI 1,11. Black carbon 4, 95% CI 1,8. RTN: Highest noise decile 33 95% CI 4, 43 for CHD mortality compared to lowest decile 10 dB(A) elevation in residential noise associated with 9% increase in cardiac mortality. Effect of noise little altered after adjustment for NO_2 and $PM_{2.5}$ but reduced, still significant after adjustment for black carbon. No exposure response relationship. No interaction between black carbon and noise. Similar effects men and women. No significant effect of aircraft noise (annual average noise level 32dB(A))

Table 1. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Health Outcome	Sample	Adjustments	Direction of Evidence
Mortality						
Hansell *et al.* 2013 [4]	ACN 10 ×10 m grid ANCON model Weighted annual average noise levels calculated for day and night	PM_{10} at spatial resolution 20m by 20m. Dispersion modelling. London emissions toolkit. London air pollution toolkit.	Hospital admission and mortality for stroke, CHD, CVD 2001–2005. Postcode data on hospital admissions	Small area ecological study 12 London Boroughs around Heathrow airport 3.6 million residents Hospital admissions from 12,110 census output areas Mortality in 2378 super output areas.	Ethnicity, deprivation and lung cancer as smoking proxy	Hospital admissions: statistically significant linear trends of increasing risk with higher levels of both LAeq, 16 h and L_{night}) ACN. LAeq, 16 h > 63 dB(A) *v* ≤ 51 dB(A), RR = 1.24 (95% CI 1.08, 1.43 for stroke; RR = 1.21, 95% CI 1.12, 1.31 for CHD; RR = 1.14, 95% CI 1.08, 1.20 for CVD adjusted for age, sex, ethnicity, deprivation, and lung cancer mortality. All robust to adjustment by PM_{10}. Stroke mortality RR = 1.21, 95% CI 0.98,1.49 CHD mortality RR = 1.15, 95% CI 1.02, 1.30 for CVD mortality RR = 1.16, 95% CI 1.04, 1.29 Night time ACN RR (>55 dB(A) *vs.* ≤50 dB(A)) = 1.23, 95% CI 1.02, 1.49, 1.11 95% CI 0.99, 1.24 and 1.14 95% CI 1.03, 1.26
Halonen *et al.* 2015 [21]	Annual RTN levels modelled 2003–2010 at geometric centroids of 190,000 postcode locations TRANEX model Expressed as , L_{night}, $L_{Aeq16hr}$	NOx, $PM_{2.5}$ Average 2003–2010 aggregated to LSOA and COA levels using KCL urban dispersion modelling system	CVD admissions All-cause and CVD mortality	Small area ecological study 8.6 million population of London All adults >25 years. Elderly >75 years	Age, sex, area-level deprivation, ethnicity, smoking, neighbourhood spatial structure	Daytime RTN: hospital admission for stroke RR = 1.05 95% CI 1.02, 1.09 in adults. RR = 1.09 95% CI 1.04, 1.14 in elderly in areas >60 *vs.* <55 dB(A) Night time noise associated with stroke admissions only among elderly. Daytime noise: all-cause mortality RR = 1.04 95% CI 1.00–1.07 in adults in areas >60 *vs.* <55 dB(A). Adjustment for air pollution had minimal or no effect on results

RTN = Road traffic noise; ACN = Aircraft noise; BP = Blood Pressure; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MI = Myocardial infarction; CHD = Coronary heart disease; CVD = Cardiovascular disease; HR = Hazard ratio; OR = Odds ratio; RR = Relative risk; IRR = Incidence rate ratio SES = Socioeconomic status.

Table 2. Environmental noise, air pollution and cognitive outcomes and blood pressure in children.

Reference	Noise Exposure	Air Pollution Exposure	Cognitive/Health Outcome	Sample	Adjustments	Direction of Evidence
Clark *et al*, 2012 [22]	ACN 16 hour outdoor L_{Aeq}. 7 am–11 pm, July–September 2000. Outdoor RTN based on proximity to motorways, A & B roads, traffic flow data and confirmed by measurement at school facade	Annual mean ambient NO_2 Combined emission-dispersion and regression modelling using Kings College London Emissions toolkit	Suffolk Reading Scale Child Memory Scale Search and Memory Task BP	Cross sectional survey using school based sample. 719 children from 22 schools around Heathrow airport. 9–10 years RANCH Study—UK sample	Parental employment status, housing tenure, crowding, maternal education, ethnicity, main language spoken at home. For BP analyses: premature birth, parental high blood pressure, birth weight, cuff size, BMI, ambient temperature	ACN associated with poorer recognition memory ($\beta = -0.045$, -0.073, $-0.017 < 0.01$), conceptual memory recall ($\beta = -0.015$ 95% CI -0.026, -0.003) and reading comprehension ($\beta = -0.012$ 95% CI -0.023, -0.000063 $p = 0.05$) and information recall ($\beta = -0.043$ 95% CI -0.086, -0.000036 0.05 adjusting for ambient NO_2. No effects of NO_2 on cognition. No effects of noise or NO_2 on BP
Van Kempen *et al.* 2012 [23]	Modelled ACN 250×250 grids expressed in LAeq, 7–23 h from NLR for 2001. RTN from modelled composite data 2000–1 Resolution 25×25 grid	Modelled NO_2 using land use regression models	Neurobehavioral Evaluation System (NES): Reaction time, attention (Switching Attention Test), coordination, Digit Symbol Substitution Test, Digit Memory Span Test	Cross sectional survey using school based sample 553 primary school children 9–11 years RANCH Study-Netherlands	Age, sex, crowding, home ownership, mother's education, employment, longstanding illness, parental support, main language spoken at home, school window glazing, road and air traffic noise	NO_2 at school associated with decrease in memory span length measured during DMST ($X^2 = 6.8$, df1, $p < 0.01$)—remained after additional adjustment for transportation noise. RTN, ACN at school associated with the number of errors made during the "arrow" ($X^2 = 7.5$, df1, $p < 0.006$) and "switch" ($X^2 = 4.8$, df1, $p < 0.028$) conditions of the SAT—remained after adjustment for NO_2. Interaction: children living in high RTN have shorter reaction times as concentration of NO_2 increases.

Table 2. *Cont.*

Reference	Noise Exposure	Air Pollution Exposure	Cognitive/Health Outcome	Sample	Adjustments	Direction of Evidence
Bilenko *et al.* 2015 [24]	RTN EMPARA noise mapping model resolution 25 × 25 m. Expressed as L_{den}	Annual mean ambient NO_2 $PM_{2.5}$ PM_{10} at home and school. Land use regression modelling. Short term air pollution based on previous 7 days from background monitoring sites	SBP, DBP	Cross sectional analyses of a cohort study. 1147 12 years old PIAMA Birth cohort	Age, gender, BMI, cuff size, gestational age at birth, birth weight, physical activity, maternal education, maternal smoking in pregnancy, parental smoking, breast feeding, maternal hypertension, respiratory infections, ambient and room temperature	Interquartile range increase in BP: Long term home and school exposure to NO_2, $PM_{2.5}$ associated with raised DBP: for NO_2 adjusted mean difference = 0.83 mm Hg 95% CI 0.06, 1.61 and for $PM_{2.5}$ adjusted mean difference= 0.75%, 95% CI −0.08, 1.58. No effects on SBP or effects of noise

RTN = Road traffic noise; ACN = Aircraft noise; BP = Blood Pressure; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; DMST = Digit Memory Span Test; DSST = Digit Symbol Substitution Test; SES = Socioeconomic status.

Most studies reviewed here employ noise modelling techniques to assess noise exposure. Noise models produce. "A" weighted energy-equivalent sound levels based on noise sources, the models including the acoustic features of environments through which noise is propagated from the source to a receiver. A calculation method is applied taking into account the environmental features to estimate sound levels at the receiver and produce noise contour maps. Typically outdoor exposures at the most exposed building facades are produced and expressed as L_{den} (weighted averages for day, evening and night with 5 dB penalty for evening and a 10 dB(A) penalty for night time exposure).

Two predominant methods are used for air quality modelling. Dispersion modelling attempts to replicate atmospheric conditions (e.g., wind speed, air temperature) in order to provide estimates of air pollution from an emission source. Land use regression models characterize air pollution exposure for individual locations by employing monitored levels of pollutants as dependent variables in multiple regression analyses in which the independent variables include such variables as traffic and topography. The advantage of this method is that it can account for local site specific variables.

3. Results

3.1. Correlation between Environmental Noise and Air Pollution Exposure

For road traffic, noise is largely produced by the engine and by the contact of tyres on the ground, while air pollution is emitted from the exhaust from the engine. For aircraft, noise may arise from the engines but also from the aircraft frame and is most prominent for aircraft landing or taking off as well as the noise of the aircraft on the ground. Air pollution from aircraft arises from the plane's engines. Rail noise arises from the contact of the train wheels with the track, from the locomotive engine, from wind resistance to the train and is often accompanied by vibration. Air pollution arises from train engines, usually diesel fuelled engines, rather than electrically powered trains.

A key consideration in disentangling the associations of noise exposure and air pollution with health is to understand how closely the two exposures are associated. Strong correlations between the two exposures may make it more difficult to separate out the effects of each exposure whereas weak or inconsistent correlations may make geographical separation of the exposures, and thus, the links to health outcomes more feasible. In a Swiss study correlations between road traffic noise and PM_{10} were as low as 0.16 while Pearson's correlations between night time rail noise and PM_{10} were 0.37 [5]. NO_x and L_{den} were moderately correlated in a road traffic noise study (Spearman's $r = 0.62$) [14]. Despite road traffic vehicles being a source of both noise exposure and air pollution many studies have shown that correlations between noise exposure and air pollution in community studies are often not that high; in a study of metropolitan Vancouver modelled road traffic noise levels were not strongly correlated to land use regression modelled air pollutants [20]. The highest correlations were for black carbon and noise exposure (Spearman's $r = 0.44$) while the lowest were for $PM_{2.5}$ (Spearman's $r = 0.14$). Proximity measures to major roads have not been found to be adequate surrogate measures for either sound levels or air pollution [25]. However the strongest correlations were between air pollutants and road traffic noise measured at the roadside and at night rather than during the day [26]. In the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) study two week NO and NO_2 and ultrafine particles were measured in 105 locations near major roads in 9 US communities as

well as 5 min "A" weighted sound pressure levels [25]. Sound levels were most closely associated with NO levels but the correlations were not high ($r = 0.20–0.60$). Downwind correlations from major roads were higher ($r = 0.53–0.74$) whereas upwind correlations were lower. Meteorological conditions are more likely to affect air pollution than noise that tends to be more consistent day by day [27]. On the other hand noise exposure will be more affected by intervening buildings and noise barriers and indoor noise exposure will be modified by access to a quiet side of a building for bedrooms and living rooms. Some transportation sources such as aircraft and electrically powered trains may be more likely to cause noise than be a source of air pollution.

There is a common misconception that certain areas of cities, usually indicated by less advantaged socioeconomic position, may be associated with a range of correlated environmental pollutants and psychosocial stressors. This could indicate that in certain less advantaged urban areas the correlations between noise and air pollution may be higher than in more advantaged areas because there is a clustering of noise and air pollution sources e.g. heavily trafficked roads. While this may be the case in some cities it is by no means an invariable finding. For instance, in an area study of New York City using Geographic Information Systems (GIS) technology to examine the association of social stressors, a derived factor of "noise complaints and property crime" was associated with indicators of air pollution (PM$_{2.5}$ NO$_2$, $r \geq 0.7$) [28]. However, noise included reports of traffic and neighbour noise which were not strongly associated. Interestingly high air pollution levels were not associated with the other two derived factors, "violent crime and physical disorder", and "crowding and poor access to resources". Neither was air pollution associated with area socioeconomic position or area educational attainment suggesting that social and environmental stressors are not always consistently geographically patterned in urban areas. In summary, there is a range of correlations between environmental noise and air pollution indices with the highest correlations close to road traffic sources.

3.2. Noise Exposure, Air Pollution and Cardiovascular Health Outcomes

3.2.1. Studies Performed on the Adult Population

Most studies in the adult population focus on middle-aged and older samples as these age groups are most at risk of cardiovascular disease. The youngest participants in these studies were 15 years old [17].

3.2.2. Hypertension and Atherosclerosis

Measured hypertension was classified in these studies as a systolic blood pressure greater than 140 mm Hg and a diastolic blood pressure greater than 90 mm Hg. Seven studies of measured raised blood pressure in adults or hypertension were reviewed here [5–11]; five studies found associations of road traffic noise with raised blood pressure or hypertension adjusting for air pollution either NO$_2$ or PM$_{2.5}$ (Table 1). But often these associations were confined to subgroups: restricted to 45–55 year olds [6], older men [8], just for systolic blood pressure not diastolic pressure [11]. One study found associations with night time railway noise [8]. Three studies found associations with air pollution [7,9,10], adjusting for noise exposure. One road traffic noise study found that NO$_2$ exposure was associated with SBP in participants exposed to higher traffic noise levels, above the median, ($\beta = 2.28$; 95% CI: 0.58, 3.97) and not in those exposed to lower levels ($\beta = -0.79$; 95% CI: -2.73, 1.15), *p* for interaction = 0.007.

This was also found for $L_{night} \geq 55$ dB(A) ($\beta = 1.82$; 95% CI: 0.56, 3.07) compared with those exposed to lower noise levels ($\beta = -0.39$; 95% CI: -2.17, 1.39), *p* for interaction = 0.03 [10]. Interactions between air pollution and noise exposure may mean that at higher traffic noise levels NO_2 is more representative of near road pollution, rather than background levels, measured in this study, as daily means at an urban background station [10].

One study assessed thoracic aortic artery calcification as a measure of atherosclerosis, a risk factor for coronary heart disease [12]; both L_{night} and $PM_{2.5}$ exposure were associated with increased subclinical atherosclerosis. In summary, both road traffic noise and air pollution have been associated with raised blood pressure although the results are not always consistent across the population.

3.2.3. Cardiovascular Morbidity

Six studies of myocardial infarction were reviewed [13–19], of these four also included stroke or cerebrovascular disease [4,16–18]. There is also one additional study that only considered stroke [19]. Cardiovascular disease was measured by registry or national records (including fatal myocardial infarction) in 4 studies [4,13–15], by hospital admissions in 3 studies [4,17,18], and by self-report in one study [16]. Three studies of road traffic noise found associations with myocardial infarction [13–15], although one study of women measured noise only by distance to major roads and the associations were most prominent in those moving closer to major roads [15]. One study did not find effects of road traffic noise after full confounding factor adjustment [17]. All four studies also showed weak associations between air pollution (NO_x and NO_2, elemental carbon) and myocardial infarction [13–15,17]. The stroke study found effects of both road traffic noise and air pollution on stroke but only air pollution, not noise, was related to incidence of fatal stroke [19]. The strongest associations were found for the combination of noise and air pollution although interactions were not statistically significant, for higher noise levels ($p = 0.67$), for higher air pollution levels (NO_2, $p = 0.34$) [19]. These findings are interesting in the light of acute exposure studies to air pollution ($PM_{2.5}$, Black Carbon) from road traffic where interactions have been shown with noise levels above 65.6 dB(A) showing increased associations with heart rate variability in young healthy adults aged 19 to 32 years [29].

Three studies found effects of aircraft noise on self-reported myocardial infarction [16] and CVD hospital admissions [4,18]; these associations were maintained with adjustment for PM_{10} [4], NO_2 [16] and $PM_{2.5}$ and ozone [18].

3.2.4. All-Cause and Cardiovascular Mortality

Five studies of noise, air pollution and mortality were reviewed [2–4,20,21]. One road traffic noise study found an association with black smoke and cerebrovascular and heart failure mortality not reduced by adjustment for noise exposure while the effect of road traffic noise on heart failure death became non-significant after adjusting for black smoke [2]. One study found associations of road traffic noise with mortality that were diminished but still remained significant after adjusting for $PM_{2.5}$ and NO_x [21]. Two studies found associations of aircraft noise with mortality that were unaffected by adjustment for PM_{10} [3,4].

3.2.5. Summary of Noise, Air Pollution and Cardiovascular Outcomes

In a recent review of nine publications up to 2012 [30], Tétrault found that the point estimates of the association between traffic noise and cardiovascular disease changed less than 10% after adjustment for air pollution with the exception of three studies [2,5,6]. There were similar findings for two air pollution and cardiovascular disease studies adjusted for noise exposure [2,8]. The correlation between noise and air pollution ranged widely between 0.16 and 0.72 in these studies; the conclusion was that the strength of the correlation did not affect the strength of the confounding of noise studies by air pollution or vice versa. Similarly, it was judged that the quality of the study or the exposure assessment did not influence these confounding effects. In this current review, which is able to include studies published since the Tétrault review, there is good evidence of traffic noise effects on cardiovascular outcomes that are only minimally diminished, on the whole, by air pollution. Similar associations have been found in men and women [2,6,20].

All of these studies are of moderately high quality, have good assessment of noise and air pollution exposure and take into account large numbers of confounding factors. Response rates are not always high and the representativeness of some studies may be questionable but it unlikely that this biases the associations between noise and air pollution and the CVD outcomes except in the fewer longitudinal studies. The focus of most of these studies is on noise but they also demonstrate independent effects of air pollution on these cardiovascular outcomes.

3.2.6. Noise Exposure, Air Pollution and Cognitive Effects and Mental Health

There have been few studies that have simultaneously considered the effects of air pollution and noise on cognition and mental health in adults [31]. In a review of 15 studies of adults greater than 18 years, there was a tendency for air pollution exposure to be associated with cognitive decline and noise exposure to be associated with depression and anxiety disorders. Partly this may be that cognitive decline has been studied less in relation to noise exposure but also air pollution and noise may have differing effects on the nervous system. Many of the studies reviewed in this article had methodological problems. For example, in some studies covariates were not adequately adjusted for and the potential overlap between mood and cognitive outcomes was not considered. There is scope for further research on both cognitive and psychiatric disorders examining noise and air pollution simultaneously. In summary, the results are suggestive of effects of air pollution and environmental noise on cognitive function and mental health but more research needs to be done before any conclusions can be drawn.

3.3. Studies Performed on Children and Infants

3.3.1. Noise Exposure, Air Pollution and Reproductive Outcomes

Road traffic noise was associated with term birth weight in 68,238 singleton births adjusting for sex, ethnicity, parity, birth month and year and income and education (mean difference = −19 95% CI −23,−15) [32]. The association with noise remained unchanged after further adjustment for air pollution measured using temporally adjusted land use regression models. Conversely air pollution

estimates decreased after adjustment for noise. In a study of access to greenness, noise and air pollution, noise exposure and air pollution did not influence the association of greenness with birth outcomes although proximity to greenness did reduce the effect of noise by 50% [33]. Greenness within 100m of residence is associated with increased risk of babies having higher term birth weight, and less risk of being small for gestational age and term birth weight. Individual and area socioeconomic status (SES) variables attenuated the association of proximity to greenness and the birth outcomes.

3.3.2. Noise Exposure, Air Pollution and Cognitive Outcomes

Two studies have considered the joint effects of noise and pollution on cognitive outcomes in 9–11 year old children using data from the UK and Dutch samples of the Road traffic and Aircraft Noise exposure and Children's cognition and Health: exposure-effect relationships and combined effects (RANCH) study, respectively [22,23]. Both studies show associations of aircraft noise with cognitive effects including reading comprehension, memory and attention measured with different assessments after taking air pollution into account. One study shows effects of NO_2 on memory span length [23] while the other [22] shows no effects of air pollution on reading comprehension, memory and attention. Generally there are too few studies to definitively judge on whether air pollution or noise, when assessed in the same study, is more prominently associated with childhood cognition. However, this is against a background of a large amount of studies demonstrating associations of noise with cognition and there may be quite different pathways for noise and air pollution effects on the brain [34].

3.3.3. Noise Exposure, Air Pollution and Blood Pressure

Two studies have compared the associations of environmental noise and air pollution with blood pressure in children [22,24]. One study of road traffic, from Bilenko *et al.* found associations of air pollution with diastolic blood pressure but no associations with noise [24] while the other study from Clark *et al.* of aircraft and road traffic finds no associations of either pollutant with blood pressure [22]. The low level of noise in the Bilenko study may account for the lack of noise associations with blood pressure but it had more detailed measures of air pollution since birth including NO_2, PM_{10} and $PM_{2.5}$ [24]. The Clark *et al.* study [22] had only moderate levels of NO_2 and the sample size was relatively small, with blood pressure measurements in only half the original UK sample from the RANCH study which may partly account for the lack of positive associations between the exposures and blood pressure. These two studies are in the context of a larger number of studies examining road traffic noise alone on children's blood pressure which do show moderate consistency in elevation of systolic blood pressure of between 2–5 mm Hg [35]. For example, the study which demonstrated a 4–5 mm Hg difference in systolic blood pressure, had a mean noise level in the high noise area of 66.9 ± 5.3 dB(A) and the mean noise level in the low noise area of 55.7 ± 2.8 dB(A). The implications for adult cardiovascular health of such elevation in blood pressure are unknown but they are indicative of a physiological response to noise in children.

4. Discussion

This paper focuses on noise exposure, air pollution and health. This next section discusses the contribution of noise to the burden of disease relative to other environmental pollutants including air pollution.

4.1. Reviews of Environmental Stressors and Health

4.1.1. Noise and Environmental Burden of Disease

The overall burden of disease from a range of environmental pollutants has been assessed and put into context to assess the comparative contribution of different pollutants. Most of these reviews of the impact of environmental stressors include not only air pollution and noise but also a range of chemical contaminants of the external environment and radioactivity.

4.1.2. National Studies

Initial efforts to assess the burden of disease from environmental pollutants in the Netherlands population used the fourth Dutch National Environmental Outlook to integrate estimates of life expectancy, quality of life and number of people affected, to assess the years of healthy life lost due to environmental pollutants [36]. They estimated that particulate air pollution accounted for 60% of the Disability Adjusted life years lost (DALYs) attributable to environmental factors whereas noise accounted for 24% and indoor air pollution 6%. They estimated that the total mortality from particulate air pollution amounted to 169,000 DALYs while 17,700 DALYs were attributed to noise annoyance, 10,990 to sleep disturbance from noise, 50 DALYs to ischaemic heart disease (IHD) from noise and 10 DALYs to mortality related to noise [36]. This study was carried out before the recent blossoming of cardiovascular research on noise.

Years of cardiorespiratory life lost due to environmental noise (road, rail and air traffic) and air pollution were assessed for Switzerland in 7.8 million people using data from 2010 [37]. Environmental noise was measured as L_{den} above a threshold of no effect of 48 dB(A), air pollution was measured as PM10. In terms of exposure, 84% of 7.8 million residents were exposed to road traffic noise greater than 48 dB(A). Transportation sources contributed 26% of the total load of PM10. In 2010 it was estimated that there were 6000 years of life lost due to noise, largely from cardiovascular disease. At the same time 14,000 years of life lost were estimated for air pollution. The contribution of road traffic noise to years of life lost from cardiovascular disease was assessed as 78%. Morbidity was assessed as hospital days for IHD, stroke and hypertensive disease. 4700 days for cardiovascular disease (CVD) and 4000 days for respiratory disease were assessed as due to air pollution, and 13,800 days for IHD, 4600 for stroke and 4100 days for hypertensive disease were due to noise.

4.1.3. European Studies

In 2011 WHO Europe published the burden of disease from environmental noise [38]. Based on noise exposure assessment, the distribution of exposure and existing exposure response relationships, DALYs lost from environmental noise were calculated for EU member states and other Western European

countries. 61,000 DALYs were attributed to ischaemic heart disease based on hypertension and IHD outcomes, 45,000 DALYs to cognitive impairment in children and young people, aged 7–19 years, 903,000 DALYs to sleep disturbance for people living in towns with more than 50,000 inhabitants, 22,000 DALYs to tinnitus, and 654,000 DALYs for annoyance.

The environmental burden of disease in European countries project assessed burden of disease from nine environmental risk factors in six European countries [39]. Road, rail and air traffic noise were included and linked to health endpoints of severe sleep disturbance and ischaemic heart disease. DALYs were presented as population-weighted, non-discounted and non-age weighted annual averages per million people. Estimates were derived from European Noise Directive (END) reporting from 2007, of agglomerations with >6 million vehicles per year, railways with >60,000 trains per year and airports >50,000 flights per year- which is likely to be an underestimate of the magnitude of effects. Only exposure levels 50 dB(A) L_{night}, 50 dB(A) L_{den} were available so lower noise levels could not be assessed [39]. The relative population-weighted contribution of traffic noise was 8% compared to 68% for particulates; traffic noise accounted 400–1500 DALYs per million people. This was substantial because of high population exposure despite relatively small disability weights for severe sleep disturbance (0.07). The DALYs attributed to noise were more than those attributed to lead (100–900), ozone (30–140) dioxins (200–600) DALYs.

4.1.4. Willingness to Pay Studies

Another way of assessing the burden of environmental stressors, increasingly of interest to governments, is willingness to pay (WTP) for pollutant exposure. In a study of 5243 people exposed to air pollution and 5251 noise exposed people, gender, education, and financial position did not affect willingness to pay [40]. Increased environmental concerns, noise concerns, noise sensitivity and ability to relax in noisy situations did affect willingness to pay but not awareness of current health risks of noise exposure. The mean estimates to avoid road-traffic noise effects for the three vignettes were: €90 pp/y for general health risks, €100 pp/y for a 13% increase in severe annoyance, and €320 pp/y for a combined-risk scenario related to an increase of a noise level from 50 dB(A) to 65 dB(A). Generally people were willing to pay more for better air quality than noise [40]. This reflects the individual variability in tolerance of exposure to noise that cannot easily be taken into account in burden of disease calculations.

4.2. Summary of Findings, Mechanisms and Potential Interventions

In general the studies reviewed suggest independent associations of environmental noise, from road traffic, aircraft and rail, and air pollution with cardiovascular outcomes and mortality and evidence for noise impacts on cognitive outcomes in children and for air pollution too. In terms of burden of disease European studies demonstrate that air pollution leads the environmental factors especially in relation to mortality [39]. Nevertheless, environmental noise comes second in terms of burden of disease and arguably is responsible for more disturbance of quality of life. Environmental noise is also responsible for more life years lost than other significant environmental pollutants such as lead, ozone and dioxins [39].

In terms of designing health interventions in relation to transportation why should planners consider noise in addition to air pollution? First, the distribution of noise and air pollution may be different. The correlations between noise and air pollution vary enormously between studies but are generally

found to be moderate [30]. Although these may be influenced by factors related to pollutant measurement they also reflect the differing dispersion patterns of the two pollutants. Noise is influenced by intervening barriers and buildings, air pollution by meteorological conditions [27]. Thus different people may be affected by the same transport source. Secondly, the evidence on the mechanisms for the two health effects differs between the two pollutants. For instance, black carbon exposure is thought to lead to oxidative stress and inflammation but also to direct effects on the cardiovascular system leading to myocardial ischaemia [2]. Particles may activate the sympathetic nervous system through stimulation of the pulmonary reflex [30]. Noise exposure is thought to activate stress mechanisms with stimulation of secretion of "stress hormones" such as cortisol and catecholamines. Noise may also cause short term vasoconstriction and in the longer term atherosclerosis due to metabolic changes [11]. There may be some overlap in mechanisms as oxidative damage has also been observed after traffic noise exposure in mononuclear blood cells in laboratory conditions [41]. For effects on the brain it is postulated that particles may activate pro-inflammatory cytokines in human macrophages initiating an inflammatory response and oxidative stress and fine particles may be directly absorbed into the nervous system through the olfactory bulb [31]. In contrast noise effects on mood disorders may result from activation of physiological arousal and stress pathways. In summary, the evidence suggests that noise and air pollution may be affecting different aspects of cardiorespiratory health. Moreover, while air pollution may affect the lungs, noise may lead to annoyance and sleep disturbance—thus people are affected in quite disparate ways by noise and air pollution.

Interventions that limit both air pollution and noise would be most beneficial but not all interventions are equally effective for both exposures and some interventions for road traffic may reduce one exposure at the expense of another [42]. Curran et al suggest that two strategies of increasing separation between vehicles and the residential population and reducing the overall volume of vehicles are the most effective strategies for reducing both pollutants but changes in fuel, vehicle speed or driver behavior may have more diverse effects reducing one pollutant while increasing the other because the sources of each pollutant within the vehicle differ [43]. Interventions that tackle the exposures at source are generally more effective than interventions that modify the conditions of the receiver, such as sound insulation. Land use planning, incorporating strategies to reduce overall individual vehicle use may ultimately be most effective in reducing both noise and air pollution [43].

4.3. Limitations of the Studies and the Review

The review was not intended to be comprehensive and it is possible that some important studies have been left out although this is unlikely to change the overall summary findings of the paper. The quality of most recent studies in this field is high with careful measurement and modelling of noise and air pollution, large sample sizes, an increasing focus on "objective" health outcomes and extensive adjustment for confounding factors. There are some methodological weaknesses that limit the conclusions than can be drawn on the relative importance of noise and air pollution.

Exposure misclassification is an important source of error in air pollution [42] and noise modelling. People moving during the study exposure period leading to changes in exposure are often not accounted for, duration of exposure may not be measured accurately [2], and exposure to several sources of noise [13] may not be fully accounted for, especially additional occupational exposure. Many studies

assume people stay in their homes all day which may lead to exposure misclassification. Study selected air pollution indicators are not always specific indicators of road traffic emissions [42] and may differ in toxicity [44]. Temporal misalignment of exposure measurement and health outcomes may lead to an underestimation of the magnitude of effects [45]. A lack of variation in air pollution exposure may explain the lack of effect of air pollution on hypertension [6]. Outdoor residential noise exposures which are usually modelled to represent individual noise exposure are not always associated with personal exposures for noise that may reflect indoor exposure. Some studies, for want of anything better still use to distance to roads as a proxy measure of noise which is a crude indicator [14]. Despite the size of many studies some still lack sufficient power to test for interactions between noise and air pollution [13].

Adjustment for confounding is a pertinent issue in environmental studies where the huge variety of different influences on exposure and health may make effects of noise and air pollution difficult to detect. Confounding may depend on exposure assessment, categorisation of exposure thresholds, study design, the choice of health outcome, and other urban characteristics [42]. The varied results of air pollution and noise on hypertension may result from residual confounding. There may also be negative confounding by noise representing people taking precautions to reduce noise levels such as closing windows. Factors such as bedroom location in relation to noise exposure, closing windows, sound insulation measures, presence of hearing impairment, may also be moderating rather than confounding factors that tend to be included in only the most recent studies. Simultaneous adjustment for traffic intensity in road traffic noise studies may be over-adjustment partly accounting for the effects of traffic noise [2]. There are also limitations in burden of disease studies which rely on exposure-response relationships which have a degree of uncertainty and may not be generalizable across large populations. Additionally, the availability and quality of health data that contribute to burden of disease studies varies, and disease definitions are not constant across component studies. All of these limitations contribute to the variations in the magnitude of estimated effects of environmental stressors. Nevertheless, in broad terms they do not affect the ranking of the importance of stressors.

4.4. Further Research

There is scope for further research. Birth cohorts offer many opportunities for taking into account life course factors but modelling exposures across larger areas can be challenging. Objective noise measurements in accordance with the European Noise Directive (END) using noise propagation modelling are needed with information on non-residential exposure, time activity patterns, insulation of buildings, widow opening behaviour, and position of bedrooms in relation to noise source [44]. More standardisation of indicators of air pollution is needed; black carbon, NO_x and ultrafine particles might be more relevant than currently used indicators [27].

5. Conclusions

There is good evidence from large population studies that environmental noise from road traffic and aircraft is associated with cardiovascular morbidity and mortality independent of the association with air pollution. There may be both independent mechanisms and common mechanisms involving methylation

for these associations of environmental exposures with health. Environmental planning and policy should take both exposures into account when assessing environmental impacts.

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Conflicts of Interest

The authors declare no conflict of interest.

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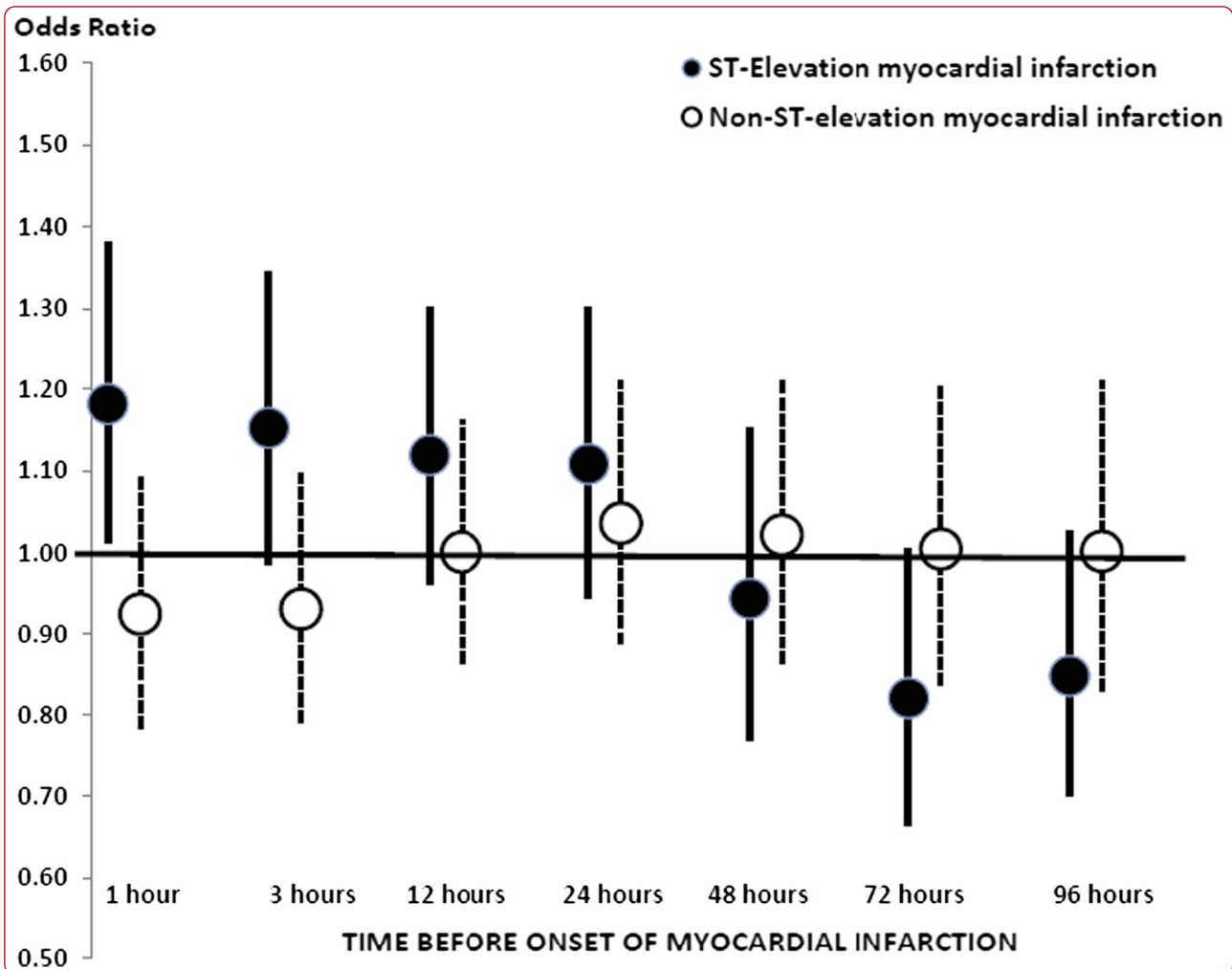
Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: a case-crossover study

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Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: a case-crossover study

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Abstract

Background: We and others have shown that increases in particulate air pollutant (PM) concentrations in the previous hours and days have been associated with increased risks of myocardial infarction, but little is known about the relationships between air pollution and specific subsets of myocardial infarction, such as ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI).

Methods: Using data from acute coronary syndrome patients with STEMI (n = 338) and NSTEMI (n = 339) and case-crossover methods, we estimated the risk of STEMI and NSTEMI associated with increased ambient fine particle (<2.5 um) concentrations, ultrafine particle (10-100 nm) number concentrations, and accumulation mode particle (100-500 nm) number concentrations in the previous few hours and days.

Results: We found a significant 18% increase in the risk of STEMI associated with each 7.1 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the previous hour prior to acute coronary syndrome onset, with smaller, non-significantly increased risks associated with increased fine particle concentrations in the previous 3, 12, and 24 hours. We found no pattern with NSTEMI. Estimates of the risk of STEMI associated with interquartile range increases in ultrafine particle and accumulation mode particle number concentrations in the previous 1 to 96 hours were all greater than 1.0, but not statistically significant. Patients with pre-existing hypertension had a significantly greater risk of STEMI associated with increased fine particle concentration in the previous hour than patients without hypertension.

Conclusions: Increased fine particle concentrations in the hour prior to acute coronary syndrome onset were associated with an increased risk of STEMI, but not NSTEMI. Patients with pre-existing hypertension and other cardiovascular disease appeared particularly susceptible. Further investigation into mechanisms by which PM can preferentially trigger STEMI over NSTEMI within this rapid time scale is needed.

Keywords: Myocardial infarction, Acute coronary syndrome, Epidemiology, Air pollution

Previous studies investigating triggering of myocardial infarction by particulate air pollution (PM) concentrations have, in most cases, reported an increased risk of myocardial infarction associated with increases in PM on the same and previous day [1-9]. Similar acute effects of fine particulate air pollution have been reported for

other cardiovascular outcomes [10,11]. Some studies of myocardial infarction and PM have used symptom onset time, rather than the arrival time at the emergency room, to define myocardial infarction onset, thereby providing a better estimate of the myocardial infarction onset time and less exposure error [1,4,5,7]. Although Peters et al. [4] reported a significantly increased risk of myocardial infarction associated with increased fine particle (particles <2.5 μm in diameter; $PM_{2.5}$) concentrations in the preceding 2 hours,

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a second study by Peters et al. [5] as well as other studies exploring associations at these short lags, did not [1,5,7].

Recently, using hospital admissions data (without symptom onset time data), we reported that myocardial infarction/$PM_{2.5}$ associations may be limited to transmural infarctions [6]. We found a 10% increased risk of transmural infarctions (95% CI = 1%, 20%), but not non-transmural infarctions (−1%; 95% CI = −6%, 5%), associated with each 10.8 $\mu g/m^3$ increase in the $PM_{2.5}$ concentration in the preceding 24 hours. We hypothesized that this may be due to differences in response to air pollution by myocardial infarction type. However, transmural and non-transmural myocardial infarction are estimations of assumed injury to the myocardium, whereas acute coronary syndromes attempt to describe the spectrum of physiologic events occurring in coronary arteries during an acute ischemic event. Therefore, in order to better understand the relationship between the acute pathophysiologic process of myocardial infarction and increased air pollutant concentrations, we sought to study acute coronary syndromes (i.e. ST segment elevation myocardial infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI], and unstable angina) to reflect the spectrum of pathophysiologic events occurring. However, unstable angina was not included in this study since symptom onset times were not available, and the diagnosis is typically based on clinical judgment without objective criteria. STEMI and NSTEMI have clearly distinct objective data leading to their diagnosis, and symptom onset times were available.

STEMI is most often the result of plaque rupture followed by thrombus formation and coronary artery lumen occlusion. In STEMI, the thrombus is a terminal event with few arteries undergoing spontaneous recanalization. NSTEMI typically occurs as a consequence of excessive plaque burden and myocardial oxygen demand/supply mismatch, or plaque rupture and thrombus formation without complete coronary artery occlusion. At times, NSTEMI may include an occlusive thrombus or a transiently occlusive thrombus depending on available collateral vessels and myocardial metabolic demand [12]. Unstable angina is pathophysiologically similar to NSTEMI without the requirement of myocardial cell death during myocardial ischemia.

With plaque rupture, the balance between factors promoting thrombus formation and degradation is altered, which determines whether the vessel is completely or only partially occluded (i.e. STEMI vs. NSTEMI). Thus, a difference in acute coronary syndrome subtype (STEMI vs. NSTEMI) triggering by $PM_{2.5}$ may suggest the mechanisms (e.g. coagulation, inflammation, etc.) most important for explaining how PM triggers myocardial infarction.

Using data (2007–2010) on acute coronary syndrome patients treated at the University of Rochester Medical Center (URMC) Cardiac Catheterization Laboratory, ambient air pollutant concentrations measured in Rochester, New York, and case-crossover methods, we addressed the hypothesis that increased $PM_{2.5}$ (<2.5 μM in aerodynamic diameter) concentrations, and ultrafine particle (10-100 nm), and accumulation mode particle (100-500 nm) number concentrations in the previous 24 hours are associated with an increased risk of STEMI, but not NSTEMI. Using acute coronary syndrome patients' self-reported symptom onset time, we also explored whether air pollutant concentrations at times more proximal to symptom onset of the acute coronary syndrome (e.g. 12 hours, 3 hours, and 1 hour before onset) would be associated with a larger increased risk. To do this, we used a case-crossover study [13,14], which is analogous to a matched case–control study. However, instead of contrasting air pollutant concentrations between people with disease (cases) and without disease (controls), we contrast pollutant concentrations from time periods right before an acute coronary syndrome event (case period) to time periods when that same person did not have an acute coronary syndrome event (control periods).

Methods
Study population and outcome definition
Since 2007, the URMC Cardiac Catheterization Laboratory has stored and maintained a database of all procedures and events treated, including acute coronary syndromes. This database includes information both on the subject (age, race, gender, residential address, previous co-morbidities and procedures, etc.) and the clinical event (i.e. onset date and time, acute coronary syndrome type, etc.).

The acute coronary syndromes in this dataset, seen in the URMC Cardiac Catheterization Laboratory, were defined using the current American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines [15]. For STEMI, on the presenting EKG, this is defined as ST segment elevation greater than 1 mm in 2 or more contiguous precordial leads, or 2 or more adjacent limb leads, or new or presumed new left bundle branch block in the appropriate clinical setting (angina or angina equivalent). For NSTEMI, the diagnosis is made by appearance of detectable cardiac myocyte biomarkers (indicating myocardial necrosis) in the blood of a patient without the requirement of distinctly dynamic changes on the EKG. For STEMI or STEMI equivalents (appearance of a new left bundle branch block), EKG criteria is both necessary and sufficient for the diagnosis in a patient deemed by the treating physician to have symptoms consistent with cardiac chest pain.

Onset time (date and hour) was self-reported by each patient (or kin if patient was unable to communicate) upon arrival to the URMC Cardiac Catheterization Laboratory. Only patients that presented to the URMC Cardiac

Catheterization Laboratory were included in this study. However, unstable anginas were not included since the diagnosis is typically based on clinical judgment without objective criteria, and symptom onset times were not available.

From these acute coronary syndrome data, we retained all STEMI and NSTEMI events occurring from January 1, 2007 to December 31, 2010 (N = 3889), where symptom onset date and time were available, and those where the patient resided within 15 miles of our pollutant monitoring station in Rochester, New York, resulting in n = 338 STEMI and n = 339 NSTEMI available for analysis. This study was approved by the University of Rochester Medical Center Research Subjects Review Board.

Air pollution and meteorology measurements
Pollutant concentration data used in the study were measured at the New York State Department of Environmental Protection site in Rochester, New York, located approximately 1500 m from an interstate highway. Particle number concentrations in the 10–500 nm diameter range were measured using a Scanning Mobility Particle Sizer (SMPS, TSI, Inc., Shoreview, MN), [16] which were used to generate particle number concentrations of ultrafine particles (≤100 nm) and accumulation mode particles (100-500 nm) for each hour during the study period (January 1, 2007 to December 31, 2010). $PM_{2.5}$ was measured continuously using a Tapered Element Oscillating Microbalance (TEOM; ThermoFisher, Franklin, MA). Hourly temperature and relative humidity data were also measured at the site. These hourly pollutant concentration and weather data were used in all statistical analyses described below.

Study design
We used a time-stratified case-crossover design [13,14], which we and others have used in studies of ambient air pollution and myocardial infarction [6-9]. This design is analogous to a matched case–control study. However, instead of contrasting air pollutant concentrations between a person experiencing a acute coronary syndrome (case) and a person who did not (control), it contrasts pollutant concentrations right before the acute coronary syndrome (case-period) to other periods when the subject did not have a acute coronary syndrome, matched to the case-period by calendar month, weekday, and hour of the day (control periods). Since the case and control periods are within the follow-up time of the same person, non-time varying confounders such as health history and smoking status are controlled by design. Factors that vary between case and control time periods (e.g. weather variables) are possible confounders that need to be included in our statistical models.

Statistical analysis – main analysis
Using a conditional logistic regression model stratified on each acute coronary syndrome (one case and three or four control periods), we regressed STEMI case–control status (i.e., case period = 1, control period = 0) against the mean $PM_{2.5}$ concentration in the 24 hours prior to symptom onset (lag hours 0–23). Using Akaike's information criterion to select the optimal lag time and functional form (natural spline with 2, 3, or 4 degrees of freedom versus 1 degree of freedom/linear), we included the mean temperature and mean relative humidity in the previous 3 hours (1 degree of freedom). From this model, we present the risk of STEMI associated with each interquartile range increase in the mean $PM_{2.5}$ concentration in the previous 24 hours and its 95% confidence interval. We also explored the risk of STEMI associated with each interquartile range increase in the mean $PM_{2.5}$ concentration at shorter lag times (lag hours 0–11, 0–2, and 0) and longer lag times (0–47, 0–71, and 0–95), as well as with increased ultrafine particle and accumulation mode particle number concentrations at the same lag times, in the same manner. We then repeated these analyses for NSTEMI.

We also explored whether any increased risk of STEMI or NSTEMI associated with increased $PM_{2.5}$ concentrations, ultrafine particle or accumulation mode particle number concentrations in the previous few hours or days was modified by a subject's health status (i.e. pre-existing co-morbidities [e.g. hypertension, dyslipidemia, diabetes, low left ventricular ejection fraction], prior procedures including coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], myocardial infarction, peripheral artery disease), or subject characteristics (i.e. current vs. non-smoker; age, gender, race). To do this, we used the same conditional logistic regression model described above, adding an interaction term for the pollutant concentration and characteristic (e.g. $PM_{2.5}$*SMOKER) to the model.

Sensitivity analysis
Next, we evaluated whether restricting our study population to only those living within 5 miles of the air pollution monitoring site in Rochester would result in less exposure misclassification and therefore larger risk estimates associated with the same interquartile range increases in ambient $PM_{2.5}$ concentration, ultrafine particle, and accumulation mode particle number concentrations. We ran the same conditional logistic regression models described above and compared the risk estimates from this model to that from the main analysis described above. We used SAS version 9.32 (©SAS Institute, Inc. Cary, NC) to construct all datasets and conduct descriptive analyses, and R (version 2.15.1; R Foundation for Statistical Computing, Vienna, Austria) to perform all conditional logistic regression analyses.

Results

There was little difference between STEMI and NSTEMI patients by gender (66% and 68% male respectively), age (STEMI: mean ± standard deviation = 61 ± 12 years; NSTEMI: mean ± standard deviation = 63 ± 14 years), and ethnicity (STEMI: 85% white, NSTEMI: 85% white; Table 1). Similarly, 41% of STEMI and 39% of NSTEMI patients had left ventricular ejection fractions < 45%. NSTEMI patients were, however, more likely to have had a prior myocardial infarction, coronary artery bypass graft surgery, a cerebrovascular event, more likely to have previously been diagnosed with dyslipidemia, diabetes, heart failure, and chronic lung disease, and more likely to be obese or severely obese than STEMI patients. However, STEMI patients were more likely to have been smokers at the time of their myocardial infarction (65%) compared to NSTEMI patients (31%).

The distributions of ambient fine particle ($PM_{2.5}$) concentrations, and ultrafine and accumulation mode particle number concentrations, as well as temperature and

Table 1 Patient characteristics

Characteristic	STEMI		NSTEMI	
	N = 338	%	N = 339	%
Age				
<50 years	58	17%	58	17%
50-59 years	106	31%	94	28%
60-69 years	92	27%	80	24%
70-79 years	46	14%	54	16%
≥ 80 years	34	10%	53	15%
Missing age	2	1%	0	0%
Male	224	66%	229	68%
Race				
White	207*	87%	240**	86%
Black	27	11%	33	12%
Other	4	2%	7	3%
Clinical presentation (may have more than 1)				
Study subjects with data on ACS presentation	**241**	**71%***	**280**	**83%***
Prior myocardial infarction	54	22%	75	27%
Prior PCI	45	19%	56	20%
Prior CABG	10	4%	33	12%
CVD ("Stroke" in 07–08, "CVD" in 09–10)	12	5%	31	11%
Prior PAD	16	7%	25	9%
Smoking	156	65%	87	31%
Hypertension	160	66%	176	63%
Dyslipidemia	143	59%	199	71%
Diabetes	44	18%	65	23%
Prior HF	6	2%	26	9%
BMI				
Overweight (25 kg/m^2 < = BMI <30 kg/m^2)	99	41%	86	31%
Obesity (BMI ≥30 kg/m^2)	52	22%	80	29%
Severe obesity (BMI ≥35 kg/m^2)	28	12%	42	15%
Mean ± STD	28 ± 5		30 ± 12	
Left ventricular ejection fraction				
≤35%	48	20%	54	19%
≤45%	98	41%	110	39%
Mean ± STD	43 ± 14		45 ± 14	

*STEMI: Total n = 238 with race/ethnicity information. There were n = 100 (30% of n = 338) with missing race/ethnicity.
**NSTEMI: Total n = 280 with race/ethnicity information. There were n = 59 (17% of n = 339) with missing race/ethnicity.

relative humidity in Rochester, NY during the study period (January 2007 to December 2010) are shown in Table 2. Included in Table 2 are the interquartile ranges of each pollutant's hourly concentrations, which we used to scale the 1 hour risk estimates in Tables 3 and 4 and Figure 1. Also presented are the interquartile ranges of the absolute differences between case and control period pollutant concentrations, by which Kunzli and Schindler previously suggested scaling odds ratio estimates in case-crossover studies [17].

Hourly $PM_{2.5}$ concentrations were moderately correlated with accumulation mode particle number concentrations (r = 0.59), but were not correlated with ultrafine particle number concentrations (r = 0.09), temperature (r = 0.08), or relative humidity (r = 0.05). Hourly ultrafine particle number concentrations were weakly correlated with accumulation mode particle number concentrations (r = 0.32), and not correlated with temperature (r = 0.02) or relative humidity (r = –0.17). Similarly, hourly accumulation mode particle number concentrations were not correlated with temperature (r = 0.19) or relative humidity levels (r = –0.03) during the study period.

Next we estimated the risk of STEMI and NSTEMI associated with each interquartile range increase in $PM_{2.5}$, ultrafine, and accumulation mode particle concentrations in the previous 1, 3, 12, 24, 48, 72, and 95 hours (Table 3; Figure 1). We found a significant 18% increase in the risk of STEMI associated with each 7.1 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the previous hour, with smaller, non-significant increases in the risk of STEMI associated with each interquartile range increase in $PM_{2.5}$ concentration in the previous 3 hours (15%), 12 hours (12%), and 24 hours (11%). Estimates of the risk of STEMI associated with interquartile range increase increases in $PM_{2.5}$ concentrations in the previous 48, 72, and 96 hours were all less than 1.0. We found no such pattern with NSTEMI

with all risk estimates close to 1.0 for all $PM_{2.5}$ concentration averaging times before myocardial infarction onset. Estimates of the risk of STEMI associated with interquartile range increases in ultrafine particle and accumulation mode particle number concentrations in the previous 1 to 96 hours were all greater than 1.0, but none were statistically significant.

The risks of STEMI associated with each 7.1 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the previous hour, stratified by patient characteristics, are shown in Table 4. STEMI patients with hypertension had a significantly larger risk of STEMI associated with each 7.1 $\mu g/m^3$ increase in $PM_{2.5}$ concentration in the previous hour than those without hypertension. Although not significantly different, patients with dyslipidemia, left ventricular ejection fractions <35%, prior peripheral arterial disease, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior myocardial infarction, and patients who were non-smokers at the time of the myocardial infarction, not white, ≥ 65 years of age, and female had larger risks of STEMI associated with increased $PM_{2.5}$ concentration in the previous hour than those without these conditions or those who were white, < 65 years of age, or male.

Last, we evaluated whether including only those STEMI patients residing within 5 miles of the pollutant monitoring station would result in less exposure error, less bias, and therefore larger risk of STEMI estimates than in our main analysis (i.e. residence within 15 miles of monitoring site). When including only those STEMI patients living within 5 miles of the pollutant monitoring station, the risk of STEMI associated with IQR increases in $PM_{2.5}$ in the previous hour (OR = 1.17; 95% CI = 0.98, 1.40) and previous 24 hours (OR = 1.12; 95% CI = 0.92, 1.36) were similar to those from the main analysis including myocardial infarction patients within 15 miles of the site (1 hour OR = 1.18, 95% CI = 1.01, 1.38; 24 hour OR = 1.11, 95%

Table 2 Distribution of hourly pollutant concentrations and weather characteristics during the study period (January 1, 2007 to December 31, 2010)

Pollutant/weather parameter	n	Mean	Standard deviation	Minimum	25th	50th	75th	Maximum	IQR	Case–control IQR
$PM_{2.5}$ ($\mu g/m^3$)	1283	8.00	5.70	0.27	3.9	6.7	10.2	43.0	6.3	5.3
Ultrafine particles (#/cm^3)	1231	5466	2,865	480	3503	5029	6874	37,291	3371	3116
Accumulation mode particles (#/cm^3)	1231	996	643	108	501	849	1322	4444	821	713
Temperature (°C)	1460	10	10	−13	2	11	20	30	18	5
Relative humidity (%)	1461	65	12	30	57	66	74	94	17	11

N = 1461 possible days.

Table 3 Risk (and 95% confidence intervals) of STEMI and NSTEMI associated with each interquartile range increase in pollutant concentration

Pollutant	Lag hours	IQR	STEMI				NSTEMI			
			n	Odds ratio	95% confidence interval	p-value	n	Odds ratio	95% confidence interval	p-value
PM$_{2.5}$ (μg/m^3)	0	7.1	338	1.18	1.01-1.38	0.04	339	0.93	0.78-1.09	0.36
	0-2	6.8	335	1.15	0.99-1.35	0.07	338	0.93	0.79-1.10	0.39
	0-11	6.1	333	1.12	0.95-1.31	0.17	338	1.00	0.85-1.17	0.99
	0-23	5.9	329	1.11	0.93-1.32	0.24	335	1.04	0.88-1.22	0.68
	0-47	5.4	332	0.94	0.79-1.13	0.53	330	1.02	0.85-1.22	0.81
	0-71	5.1	318	0.82	0.67-1.00	0.05	327	1.00	0.83-1.21	0.96
	0-95	5.1	314	0.85	0.69-1.05	0.12	328	1.00	0.82-1.23	0.99
UFP (particles/cm^3)	0	4245	270	1.03	0.95-1.12	0.51	283	0.99	0.90-1.10	0.88
	0-2	4159	275	1.00	0.89-1.13	0.99	284	1.02	0.92-1.13	0.69
	0-11	3475	274	1.05	0.90-1.23	0.53	284	1.04	0.91-1.20	0.60
	0-23	3284	274	1.06	0.89-1.26	0.50	276	1.01	0.86-1.18	0.90
	0-47	2989	273	1.01	0.84-1.21	0.92	277	0.96	0.80-1.16	0.70
	0-71	2834	274	1.03	0.84-1.25	0.80	279	0.93	0.75-1.15	0.49
	0-95	2742	278	1.06	0.86-1.30	0.60	278	0.89	0.71-1.12	0.33
AMP (particles/cm^3)	0	860	270	1.07	0.91- 1.27	0.39	283	0.97	0.82-1.15	0.70
	0-2	871	275	1.03	0.86-1.23	0.75	284	0.96	0.80-1.14	0.62
	0-11	840	274	1.11	0.91-1.36	0.32	284	0.97	0.80-1.17	0.73
	0-23	775	274	1.12	0.92- 1.38	0.26	284	0.97	0.81-1.17	0.78
	0-47	673	273	1.10	0.90- 1.35	0.33	277	0.94	0.78-1.12	0.48
	0-71	615	274	1.04	0.85- 1.27	0.69	279	0.92	0.76-1.10	0.34
	0-95	558	278	1.04	0.86- 1.26	0.67	278	0.89	0.74-1.07	0.21

CI = 0.93, 1.32). Similarly, the risk estimates associated with interquartile range increase increases in ultrafine particle number concentrations in the previous 1 hour (OR = 1.01; 95% = 0.92, 1.11) and 24 hours (OR = 1.09; 95% CI = 0.89, 1.33), and with interquartile range increase increases in accumulation mode particle number concentrations in the previous 1 hour (OR = 1.15; 95% = 0.96, 1.38) and 24 hours (OR = 1.17; 95% CI = 0.93, 1.46) were also similar to those from the main analysis.

Discussion

Using data from the URMC Cardiac Catheterization Laboratory with information on the time of symptom onset, acute coronary syndrome subtype (STEMI or NSTEMI), and demographic and clinical variables, we found that increased ambient PM$_{2.5}$ concentrations were associated with immediate (within 1 hour) increases in the risk of STEMI, but not NSTEMI. Effect estimates were largest for those with prior cardiovascular disease/events, specifically those with pre-existing hypertension, and non-smokers, those 65 years and older, Caucasians, and women. This finding of fine particle triggering of STEMI, but not NSTEMI, within 1 hour, suggests potential mechanisms by

which this response could occur, and also that these mechanisms must act on this rapid time scale. Such mechanisms might result in more extensive plaque rupture or the promotion of thrombus formation in the subsequent interplay between prothrombotic and antithrombotic vascular processes.

Previous studies have reported an increased risk of myocardial infarction associated with increased PM$_{2.5}$ and other pollutants in the preceding day or two [3]. Only our previous study [6] investigated PM associations by type of myocardial infarction, finding that increased PM$_{2.5}$ concentration in the 24 hours before emergency room arrival for the myocardial infarction was associated with an increased risk of those infarctions progressing to a transmural infarction but not those progressing only as far as a partial wall infarction [6]. Only a few studies had symptom onset time data and thus were able to examine whether increased pollutant concentrations in the previous few hours, and not just the same day or just within 24 hours, triggered the myocardial infarction [1,4,5,7]. Only our current study and that of Peters et al. [4] report such an immediate response, while other studies do not [1,5,7]. This inconsistency may be due, at least in part, to the distribution of STEMI/

Table 4 Risk (and 95% confidence intervals) of STEMI associated with each 7.1 µg/m^3 increase in PM$_{2.5}$ concentration in the previous hour

Characteristic	Category	n*	Odds ratio	95% confidence interval	p-value	Interaction term p-value
Gender	Male	224	1.11	0.91-1.35	0.30	0.27
	Female	114	1.31	1.03-1.65	0.03	
Age	< 65 years	220	1.09	0.90-1.32	0.36	0.14
	≥ 65 years	118	1.37	1.07-1.75	0.01	
Race	White	207	1.15	0.94-1.41	0.18	0.83
	Other	32	1.21	0.78-1.89	0.40	
Smoker	Yes	104	1.07	0.81-1.41	0.65	0.75
	No	106	1.22	0.92-1.60	0.17	
Prior myocardial infarction	Yes	54	1.52	1.04-2.22	0.03	0.11
	No	185	1.08	0.87-1.33	0.49	
Prior CABG	Yes	10	1.27	0.60-2.66	0.53	0.80
	No	229	1.15	0.95-1.40	0.15	
Prior PCI	Yes	45	1.37	0.91-2.05	0.13	0.36
	No	195	1.11	0.90-1.37	0.33	
Prior PAD	Yes	16	1.31	0.66-2.61	0.45	0.76
	No	222	1.17	0.96-1.43	0.12	
Hypertension	Yes	160	1.39	1.10-1.76	<0.01	0.02
	No	76	0.90	0.66-1.23	0.51	
Left ventricle ejection fraction	< 35%	48	1.35	0.94-1.93	0.10	0.37
	≥ 35%	133	1.11	0.85-1.43	0.44	
Diabetes	Yes	44	1.15	0.75-1.76	0.53	0.98
	No	152	1.16	0.91-1.46	0.23	
Dyslipidemia	Yes	143	1.24	0.97-1.58	0.09	0.60
	No	94	1.12	0.85-1.49	0.42	

*Of the total possible N = 338 STEMI patients, some had missing data on subject characteristics and thus were not included in the specific stratified analysis.

NSTEMI within the sample of acute coronary syndrome included in each study. Our findings of greater risk of STEMI associated with increased PM$_{2.5}$ concentrations among those subjects with pre-existing cardiovascular disease and/or prior acute cardiovascular events are consistent with findings from previous studies, [6,8,9] and affirm a hypothesis of increased susceptibility for those with pre-existing coronary artery disease.

There are multiple mechanisms for acute coronary syndrome and specifically STEMI and NSTEMI, including coagulation, inflammation, vascular dysfunction, and autonomic dysfunction. However, when a thrombus forms, circulating platelets are tethered via intermediate filaments to one another and to the injured vascular wall. Mechanistically, STEMI differ from NSTEMI in that STEMIs progress acutely to complete arterial occlusion following plaque rupture, whereas plaque-rupture mediated NSTEMIs do not. It is important to note that plaque rupture itself is necessary, but in isolation is insufficient to promote full arterial occlusion, and a cascade of coordinated cellular events must occur prior to thrombus formation.

Furthermore, endogenous thrombolysis is an important protective process which can abrogate complete arterial occlusion (i.e. STEMI). Due to fundamental mechanistic differences between STEMI and NSTEMI, morbidity and mortality are higher with STEMI [18,19]. Thus, one may propose that the intracellular signal transduction mechanisms committing a patient to a STEMI distinguish it from NSTEMI by a different balance between thrombosis and thrombolysis. PM may be more likely to cause a STEMI than a NSTEMI if PM enhances the rate or extent of thrombus formation following plaque rupture and/or if PM exposure impairs thrombolysis, increasing the chance for complete vessel occlusion.

Plaque rupture and subsequent acute thrombosis of previously narrowed or unstable plaque-lined arteries is recognized as the proximal event in the evolution of myocardial infarction [20]. Previously, we reported large changes in circulating markers of platelet and endothelial cell activation (p-selectin, CD40L, von Willebrand factor [vWF]), in healthy young medical residents, associated with increased PM$_{2.5}$ and other pollutants during
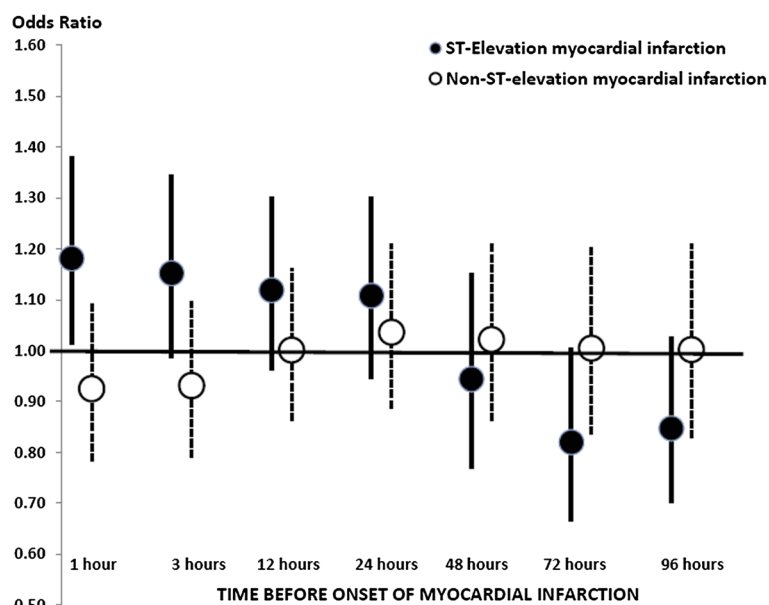
Figure 1 Risk (and 95% confidence interval) of STEMI and NSTEMI associated with each interquartile range increase in PM$_{2.5}$ concentration, by lag hours.

the 2008 Beijing Summer Olympics [21,22]. We have also found increased platelet activation following controlled ultrafine particle exposure in diabetics [23]. We and others have found increased fibrinogen and C-reactive protein levels (inflammatory markers) associated with increased ambient PM$_{2.5}$ concentrations, and accumulation mode and ultrafine particle number concentrations in the preceding few days, [22] especially in subjects with underlying cardiovascular risk factors [24,25]. However, some controlled human exposure studies have not reproduced these data [26,27]. Furthermore, changes in vWF, p-selectin, CD40L, and platelet aggregation have also been repeatedly associated with acute increases in PM concentration in both humans and animals, [25,27-30] suggesting these interacting coagulation/inflammation pathways may be acutely affected by PM air pollution exposure. Consistent with this, controlled exposure studies have reported impaired vascular function and increased thrombogenesis following diesel exhaust exposure [31-35]. Only a few studies have contrasted the circulating concentration of inflammatory and thrombotic biomarker levels in STEMI and NSTEMI from blood samples drawn upon arrival in the emergency room, and reported increases in thrombotic/inflammatory markers (e.g. WBC, C-reactive protein, ferritin, serum amyloid A) [36,37]. Other studies found no difference in these and other platelet markers (e.g. mean platelet volume, platelet count) [38,39]. However, of the biochemical and physiological mechanisms associated with ambient PM exposure, only thrombus formation and vasoconstriction occur on such a rapid time scale. Vascular constriction is an instantaneous response to offending

stimuli mediated by endothelial and non-endothelial factors, whereas thrombus formation is a continuum of events that is initiated by platelet activation, aggregation, and adhesion to an injured vessel wall. This time continuum makes thrombus formation more variable, and may explain fundamental differences between STEMI and NSTEMI with respect to PM exposure.

Although our study had several strengths including well characterized acute coronary syndrome events in the Cardiac Catheterization Laboratory, there are several important limitations that should be considered when making inference. First, we had limited sample size due to our use of existing data, the requirement of symptom onset time data, and a residence within 15 miles of the monitoring site. This limited sample size resulted in reduced statistical power and limited precision in our risk estimates. Second, we used ambient PM$_{2.5}$ concentrations, and ultrafine particle and accumulation mode particle number concentrations, measured at one central site monitoring location, to represent each myocardial infarction patient's exposure to PM of outdoor origin, regardless of how close subjects lived, worked, or spent time to the monitoring site. This exposure error, however, is not likely different for time periods immediately preceding the myocardial infarction and other time periods in the weeks before or after the STEMI/NSTEMI, likely resulting in biases toward the null and underestimates of the risk. Further, when we included only those STEMI patients living within 5 miles of the monitoring site, our estimates of the risk of STEMI associated with increased PM$_{2.5}$ concentration, ultrafine particle number concentration and accumulation mode particle

number concentration in the previous hour were similar. Since UFP and AMP number concentrations are more spatially variable across space than $PM_{2.5}$ concentrations, in part due to differences in sources (AMP formed by atmospheric chemistry oxidizing precursor gases like SO_2 and NO_2; UFP locally emitted and having a shorter atmospheric lifetime), it is not surprising they are not well correlated with $PM_{2.5}$ concentrations [40]. Thus it is also not surprising we did not find increased risks of STEMI associated with increased UFP and AMP number concentrations.

Third, symptom onset time was determined by patient self-report upon arrival to the Cardiac Catheterization Laboratory. This is a reasonable surrogate marker for ischemia onset, but cannot be extrapolated to infarction onset with confidence. The temporal relationship between plaque rupture, ischemia and infarction may differ between individuals as much as it differs between STEMI and NSTEMI. If STEMI and NSTEMI have the same true OR associated with increased $PM_{2.5}$ concentration (e.g. 1.50), but there is a greater degree of error in estimating NSTEMI onset time than STEMI onset time, the risk of NSTEMI associated with increased $PM_{2.5}$ concentration could be underestimated to a greater degree (i.e. OR = 1.00) than the risk of STEMI associated with increased $PM_{2.5}$ concentration (i.e. OR = 1.18). Further work is therefore needed to confirm that our findings were not due to this exposure error.

It is also possible that our finding is due to residual confounding by an unmeasured confounder. However, for such a factor to exist, it would have to vary temporally between weeks within each subject, be correlated with ambient air pollution levels, and also be a risk factor for myocardial infarction independent of air pollution. Outside of temperature and relative humidity, numerous studies examining the acute risk of cardiovascular events including myocardial infarction associated with air pollution exposure have not identified such a factor.

As shown in Table 1, STEMI patients were slightly younger, less likely to be obese, more likely to be smokers, and were less likely to have several cardiovascular comorbidities or procedures than NSTEMI patients. Although not significantly different for most factors, STEMI patients with many of these factors had an even larger relative risk of STEMI associated with increased $PM_{2.5}$ in the previous hour than STEMI patient without them. If these factors put one at increased risk for an ACS, then we would have expected to see an increased risk of NSTEMI associated with increased $PM_{2.5}$ concentrations, rather than STEMI. Thus, although it is possible that our findings of $PM_{2.5}$ triggering of STEMI but non NSTEMI might simply reflect differences in the population presenting rather than a different biological mechanism, our effect modification findings do not support this.

We only studied patients receiving care in the Cardiac Catheterization Laboratory of a tertiary care hospital.

Thus our subjects may not be representative of the broader population of acute coronary syndrome patients that do not have access to cardiac catheterization, or who are medically managed. However, if our findings can be confirmed in a prospective study addressing many of the weaknesses described above, the findings can be generalized to all US adults who would be treated at a hospital's cardiac catheterization laboratory, since plaque rupture with thrombus formation generally is the most prevalent cause of STEMI and NSTEMI [41].

Conclusions
Using data from acute coronary syndrome patients with STEMI and NSTEMI, ambient measurements of particulate air pollution concentrations, and case-crossover methods, we found that increased $PM_{2.5}$ concentrations in the hour prior to acute coronary syndrome onset were associated with an increased risk of STEMI, but not NSTEMI. Further investigation into mechanisms by which $PM_{2.5}$ can preferentially trigger STEMI over NSTEMI within this rapid time scale is needed. These investigations may provide information needed to develop interventions to prevent air pollution mediated acute coronary syndromes.

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ENVIRONMENTAL HEALTH

RESEARCH Open Access

Saturation sampling for spatial variation in multiple air pollutants across an inversion-prone metropolitan area of complex terrain

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Abstract

Background: Characterizing intra-urban variation in air quality is important for epidemiological investigation of health outcomes and disparities. To date, however, few studies have been designed to capture spatial variation during select hours of the day, or to examine the roles of meteorology and complex terrain in shaping intra-urban exposure gradients.

Methods: We designed a spatial saturation monitoring study to target local air pollution sources, and to understand the role of topography and temperature inversions on fine-scale pollution variation by systematically allocating sampling locations across gradients in key local emissions sources (vehicle traffic, industrial facilities) and topography (elevation) in the Pittsburgh area. Street-level integrated samples of fine particulate matter ($PM_{2.5}$), black carbon (BC), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) were collected during morning rush and probable inversion hours (6-11 AM), during summer and winter. We hypothesized that pollution concentrations would be: 1) higher under inversion conditions, 2) exacerbated in lower-elevation areas, and 3) vary by season.

Results: During July - August 2011 and January - March 2012, we observed wide spatial and seasonal variability in pollution concentrations, exceeding the range measured at regulatory monitors. We identified elevated concentrations of multiple pollutants at lower-elevation sites, and a positive association between inversion frequency and NO_2 concentration. We examined temporal adjustment methods for deriving seasonal concentration estimates, and found that the appropriate reference temporal trend differs between pollutants.

Conclusions: Our time-stratified spatial saturation approach found some evidence for modification of inversion-concentration relationships by topography, and provided useful insights for refining and interpreting GIS-based pollution source indicators for Land Use Regression modeling.

Keywords: Air pollution monitoring, Black carbon (BC), Fine particulate matter ($PM_{2.5}$), Airborne particles with a diameter of 2.5 micrometers or less, Geographic information systems (GIS), Nitrogen dioxide (NO_2), Spatial variability, Temperature inversion

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Background

Advances in intra-urban air monitoring, such as spatial saturation sampling and land use regression (LUR) modeling [1-8], have substantially improved epidemiological estimation of air pollution impacts on health in urban areas [9,10]. However, few studies have been designed to capture spatial variation during select hours of the day, and important challenges remain for incorporating time-varying meteorological factors and local topography into the assessment of fine-scale spatial variation in air quality [11,12]. The Pittsburgh metropolitan area represents an opportunity to extend air monitoring methods to address spatial and temporal drivers of air quality variability – specifically spatial confounding among multiple pollution sources (e.g., legacy industry, vehicle traffic), and potential modifiers of source-concentration relationships (e.g., elevation, temperature inversions) – toward better characterizing risk factors for multiple health outcomes, and growing regional health disparities [13,14].

Spatial saturation monitoring and land use regression (LUR) modeling are standard exposure assessment methodologies for characterizing intra-urban variability in air pollution concentrations [1,4-6,11] and pollution source apportionment [15]. For spatial saturation studies, Geographic Information System (GIS)-based indicators of local air pollution sources are used to systematically allocate monitoring locations to saturate hypothesized pollution concentration gradients across complex domains. This spatially-informed study design enables estimation of fine-scale variation in air quality, and can generate chronic air pollution exposure assessments for environmental epidemiology.

Integrating primarily spatial (e.g., distribution of roadways and industrial facilities) and temporal (e.g., temperature, weather) factors that contribute to local air pollution, and understanding their potential interactions, is an important methodological challenge for LUR-based analysis. One common approach to disentangling spatial and temporal factors is designating 'reference,' or 'background,' monitors to, first, determine the proportion of local pollution explained by temporally-varying factors (e.g., meteorology, long-range transport) [7,16], and, second, to adjust samples collected at different locations and points in time to indicate seasonally-representative concentrations. As such, siting reference monitors is important for robust study design; it is well established that locating monitors away from local source influence will produce more accurate measurements of temporally-mediated pollution patterns [17], but there is little guidance in the literature to help investigators target meteorological interactions with local topography, especially for chemically reactive or photochemically active pollutants (e.g., NO_2). As more urban studies are monitoring multiple pollutants, for which the relative spatio-temporal components are different [18], the citing of reference monitors in a way that is interpretable for multiple pollutants and across topographic regimes is an important challenge.

Despite over two decades of air quality improvements following the decline of the steel industry in western Pennsylvania, the Pittsburgh metropolitan area exceeds national health-based air quality standards for criteria pollutants [19]. While high air pollution levels are partially attributable to regional transport of emissions from coal-fired power plants of the Ohio valley, local pollution sources are substantial drivers [20-22]. Local emissions inventories are dominated by a small number of remaining large industrial facilities strategically located along river valleys [19], including the nation's largest coke works, which sits approximately 24 kilometers south of downtown. A diverse transportation network of rail, barge, diesel trucks, and passenger vehicles contribute mobile emissions. Though a relatively small city (approximately 300,000 residents), urban sprawl and roadway vehicle congestion is a substantial problem, as a large number of tunnels and bridges lead to traffic bottlenecks, and some highway segments rank among the twenty most congested outside of Los Angeles and New York City [23]. Finally, population susceptibility factors (e.g., poor access to healthcare, concentrated poverty) are spatially patterned with topography and pollution sources, clustered in industrial river valleys, creating the potential for joint and synergistic health effects. In the City of Pittsburgh, for example, median household income is approximately $10,000 less among census block groups in the 20th percentile of elevation, as compared to highest-elevation (80th percentile) census block groups [24].

In the Pittsburgh metropolitan area, complex topography at the confluence of three rivers combines with meteorology to drive frequent atmospheric temperature inversions [25], which can prevent vertical dispersion of airborne pollutants, trapping emissions near the earth's surface. Inversion layers form when the warm-to-cool vertical temperature gradient of the atmosphere is inverted, and are generally accompanied by low surface wind speeds. Causes of inversions are dependent upon local topography and meteorology interactions, including when rapid overnight cooling of the earth's surface causes cooling of air near the surface, compared to higher altitude air (i.e., radiative inversion), or when high pressure systems descend into relatively cooler low elevation areas (i.e., subsidence), both of which may occur in the Pittsburgh region. In areas of complex terrain, inversion effects on local air pollution may be exacerbated in low-lying areas and valleys, where the earth's surface is shadowed and slower to warm with the sunrise [26,27]. Inversions have been linked with acute pollution events of photochemical smog and particulate matter,

such as occurred in nearby Donora, PA in 1948 [28], and have been linked with cardiovascular [29] and respiratory health [30,31]. In the pilot mobile monitoring study which informed the design of this campaign, we identified regional inversion conditions on 50% of summer-time sampling days, and, accordingly, $PM_{2.5}$ concentrations were greater during morning sampling hours (8-10 AM) than afternoon (12-2 PM) [32].

Here, we present a spatial saturation approach designed to capture the impact of inversion effects across complex terrain – towards evaluating the efficacy of topographic information for capturing potential modification of local source-concentration relationships by meteorology. We describe study design and implementation of a two-season (winter and summer) multi-pollutant monitoring campaign across the Pittsburgh metropolitan area, using programmable integrated monitors to sample solely during morning hours when atmospheric inversions are most frequent. We report GIS-based methods for systematically allocating monitors across locally-specific pollution source and topography profiles, and address challenges of distinguishing spatial and temporal components of local pollution variation in different pollutants by comparing two temporal adjustment approaches. This is the first study, to our knowledge, to explicitly capture spatial variation in pollution during selected hours of the day – here, targeting topography-meteorology interactions by collecting spatially-distributed samples only during inversion-prone hours of the day, and including topography in monitoring site allocation. Air quality data derived from this study will ultimately be applied towards: (a) LUR modeling of intra-urban variability in multiple pollutants and seasons, and (b) epidemiologic investigation of health outcomes.

Methods

We used GIS-based indicators of local pollution sources and topography to systematically allocate 36 air monitoring sites across the metropolitan area during two seasons – June-August 2011 (summer) and January-March 2012 (winter). The same sites were repeated in each season, within which monitors were distributed between six 5-day weekday sessions in each season. We collected integrated samples of criteria pollutants, and derived seasonal averages using two reference monitors – one urban and one regional background. We tested the hypothesis that lower-elevation areas may experience higher pollution concentrations under inversion conditions [20,32], and that these effects may vary by season.

Sampling instrumentation and laboratory analyses

We collected integrated samples of nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), fine particulate matter ($PM_{2.5}$) black carbon (BC), and constituents using portable ambient air sampling units originally designed for the New York City Community Air Survey [7]. Particle sampling instruments include a Dual Stage $PM_{2.5}$ Harvard Impactor (Air Diagnostics and Engineering Inc.) with particulate matter collected onto 37 mm Teflon filters (PTFE membrane, 2 μm pores, Pall Life Sciences), a HOBO data logger for relative humidity, temperature, and barometric pressure readings (Onset Computer Corporation). Battery-operated vacuum pumps (SKC, Inc.) moved ambient air through particle filters at a constant rate of 4 liters per minute, and pre - and post-flow rates were recorded for data quality assurance. Passive gaseous samplers (Ogawa & Co. USA) were placed into weather tight shelters on the exterior of sampling units. Sampling instruments were housed in weather tight boxes, and mounted 3-4 meters above ground on utility poles, near the breathing zone.

$PM_{2.5}$ and BC were measured solely during weekday morning rush hours and potential inversion hours, using a chrontroller (ChronTrol Corporation) to program the sampling units to simultaneously sample all locations (including reference sites) each weekday (Monday-Friday) from 6:00 AM to 11:00 AM. Deployment and retrieval schedules were aimed at minimizing differences in exposed time for passive badges between monitors and across sessions.

Teflon filters were pre- and post-weighed at the University of Pittsburgh, Department of Environmental & Occupational Health, in a temperature and relative humidity-controlled glove box (PlasLabs Model 890 THC) using an ultra-microbalance (Mettler Toledo Model XP2U) for total $PM_{2.5}$ mass, and reflectometry for BC absorbance was performed using the EEL43M Smokestain Reflectometer (Diffusion Systems). Ogawa passive badges were analyzed at the University of Pittsburgh, Department of Geology & Planetary Sciences using water-based extraction and spectrophotometry (Thermo Scientific Evolution 60S UV-Visible Spectrophotometer) for NO_2 ppb concentration. SO_2 and O_3 sample analyses are ongoing, and we do not report their results here.

Quality assurance and controls

To account for possible contamination, we used one laboratory blank and multiple field blanks each session for gases and particles, and co-located paired distributed monitors at four randomly-selected sites during one sampling session each season. $PM_{2.5}$ pump flow rates were calibrated to 4.0 liters per minute (LPM) (temperature-adjusted based on weather forecasts) prior to deployment, and compared to post-collection rates. We verified program completion for each sampler run using the sampling unit program log.

Summer sampling was performed from July 25 to September 9, 2011 (the week of August 29 skipped for

logistical reasons), and winter sampling from January 16 to February 24, 2012. Across seasons, all $PM_{2.5}$ samples met acceptable pre- and post-collection flow rate (within 5% of 4.0 LPM). Instrumentation failure occurred at only one site, which was re-sampled during a later session. Co-located measures of $PM_{2.5}$ and NO_2 were highly correlated (rho = 0.93 and 0.97, respectively) across four monitoring locations. Field blanks for $PM_{2.5}$ and NO_2 ranged from 0.07-1.50 $\mu g/m^3$ and 0.01-0.05 ppb, respectively, and were similar across seasons. Pollutant concentrations were field blank-corrected. Data completeness was 100% for $PM_{2.5}$, NO_2, and BC, with no statistical outliers (outside of mean +/- 3 standard deviations).

Study domain selection and characterization

We aimed to capture large industrial point sources, major roadways, and river valleys across an urban-to-suburban gradient of Allegheny County, within a feasible coverage area, extending at least 10 km Northeast of industrial point sources, with respect to the prevailing wind direction (West/Southwest). In a GIS, we fit a polygon to meet coverage and distance criteria, and selected intersecting contiguous census tracts, to enable subsequent merging of population indicators. Our domain stretched northwest of downtown Pittsburgh along the Ohio River, and southeast along the Monongahela River,

covering approximately 500 km^2, including 258 contiguous census tracts within Allegheny County, PA (Figure 1), and captured wide variability in population density: from 272 to 55,343 residents per km^2 [24]. Large industrial point sources within our domain include two coke smelting works (Neville Island and Clairton) and a steel mill (Braddock).

For purposes of sampling site selection, we explored spatial variability across a range of local source indicators, and potential modifiers of source-concentration relationships. Based on recent source apportionment of $PM_{2.5}$ measurements collected at Allegheny County Health Department (ACHD) regulatory monitors, which attributed the majority of measured fine particles to local industrial and mobile sources [19], we developed GIS-based indicators of local industrial emissions and on-road vehicle traffic. Because traffic-related pollution varies within 50-200 m from roadways [33,34], and because of steep elevation gradients in the Pittsburgh area, we used relatively small regular 100 m^2 lattice grid cells to characterize the study domain according to three key local pollution indicators: (a) traffic density, (b) emission-weighted proximity to industrial point sources, and (c) topography. GIS-based analysis and mapping were implemented in ArcInfo, v10 (ESRI, Redlands, CA).

We evaluated multiple indicators of traffic emissions (e.g., proximity to roadways, heavy track traffic), and
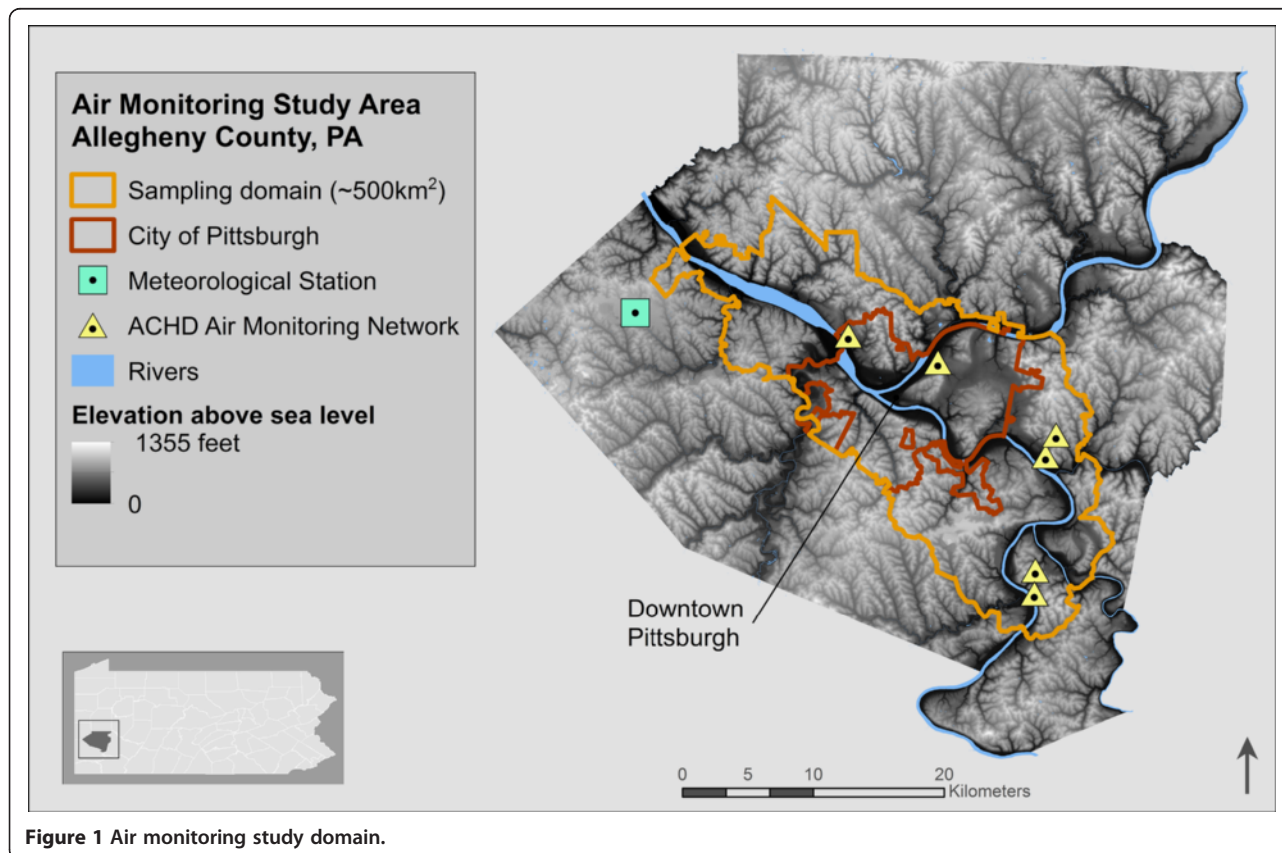

Figure 1 Air monitoring study domain.

decided on the most inclusive indictor – total on-road traffic density – to prevent biasing our study design toward one class of vehicle emissions. First, we created road-segment counts by summing total vehicles on major road segments plus an estimated 500-vehicle count on minor road segments (based on major road count distribution), using Pennsylvania Department of Transportation Annualized Average Daily Traffic (AADT) counts (2011) [35]. Using ArcInfo's Spatial Analyst toolbox, we derived a continuous kernel traffic density surface by applying a Gaussian decay function to traffic counts on all road segments within our domain. From this traffic density surface, we calculated mean traffic density within each 100 m^2 grid cell.

We created a multi-pollutant indicator of industrial emissions to prevent biasing our sampling design toward one pollutant or industry type. Using emissions data from the U.S. Environmental Protection Agency's National Emissions Inventory [36], we first summed emissions mass in tons of multiple pollutants PM$_{2.5}$ (filterable and condensable), nitrogen oxides (NO$_X$), sulfur dioxide (SO$_2$), and volatile organic compounds (VOCs) – from reporting facilities in Allegheny County, PA. We then used inverse-distance interpolation to calculate an emission-weighted proximity to industry indicator for each 100 m^2 grid cell centroid, drawing emissions information from facilities within an 80 km radial buffer threshold. Inverse-distance interpolation weights emissions values at locations in between facilities as a function of distance,

such that relatively near facilities will have a greater influence than far facilities on local air quality.

As there is no standard metric to demarcate 'valley' versus 'non-valley' areas, we opted to use continuous elevation above sea level to maximize spatial resolution and comparability with previous LUR studies [8,37-39]. We calculated mean elevation within each 100 m^2 grid cell from the U.S. Geological Survey National Elevation Dataset 30 m^2-resolution raster data set [40]. Across sampling locations, elevation is correlated with distance-to-river-centerlines at rho = 0.67, supporting our interpretation of elevation as an indicator of river valleys, where cool air pools may exacerbate inversion formation. Furthermore, in our pilot mobile monitoring study, we found a strong relationship between elevation, atmospheric inversions, and PM$_{2.5}$ and PM$_{10}$ concentrations in one relatively low-lying Pittsburgh community (Braddock, PA) [32].

Distributed site selection & allocation

Across our study domain, the distribution of source indicators used for sampling site selection – traffic density, emission-weighted proximity to industrial facilities, and elevation – varied substantially (Figure 2); source indicators were not collinear (rho = -0.08 to -0.21, across all 100 m^2 grid cells). We dichotomized each source indicator at the 70th percentile, and cross-stratified each 100 m^2 grid cell across eight classifications, representing combinations of 'high' and 'low' source profiles (e.g., 'low' traffic
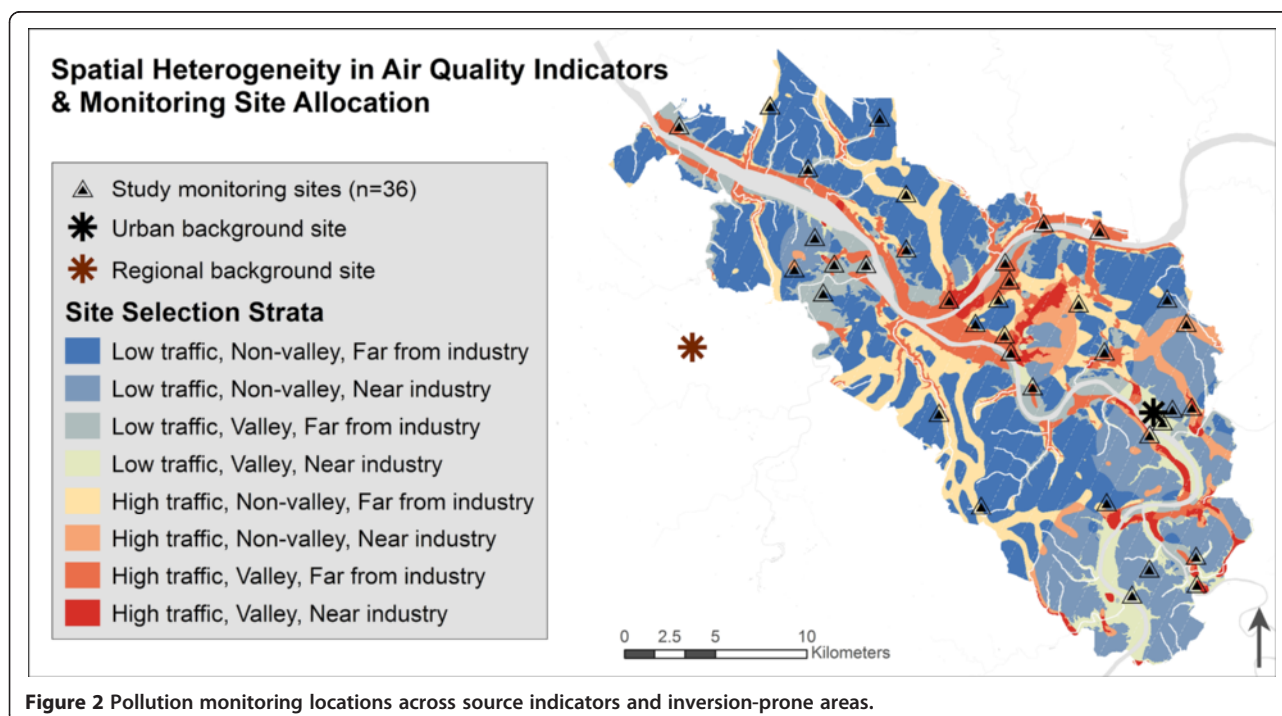

Figure 2 Pollution monitoring locations across source indicators and inversion-prone areas.

density, 'near' industrial sources, low elevation 'valley'). This dichotomization point was chosen based on left-skewed distribution of source indicators, to systematically over-sample hypothesized high-pollution areas.

We used stratified random sampling without replacement to select 30 spatially-distributed monitoring grid cells across eight source indicator cross-strata, using Geospatial Modeling Environment software, v 0.7.2.0 (Spatial Ecology, LLC). Six additional grid cells were selected to fill spatial gaps in the periphery of our large domain. Specifically, three 30 km^2 areas in which no cells had been allocated were selected in GIS, and two cells randomly selected from each. Rivers and riverbank areas (<20 m from a river's edge) were not eligible for sampling site selection, for logistical reasons. Sample size was determined by available resources, domain size, logistical limitations, and precedent of 40 monitoring sites for urban LUR modeling [41,42]. Figure 2 shows spatial allocation of distributed and reference monitoring sites, which were repeated in summer and winter.

Suitable locations to mount sampling units (e.g., utility or telephone poles) were identified near the centroid of selected 100 m^2 grid cells by field teams, using consistent protocols. Mounting pole eligibility criteria included: no obstructions within 3 m of the monitors, street accessible, three or more meters from buildings, identifiable pole ownership (to obtain permissions), away from bus stops, and without overhanging tree branches. Latitude and longitude coordinates of selected mounting poles were pinpointed using GPS (Colorado® 400 t, Garmin), and verified in Google Earth™. A detailed site survey was conducted for each sampling location, to document relevant information potentially unavailable in GIS datasets (e.g., construction). Permissions to mount monitors on utility poles were obtained from Duquesne Light Co., Verizon, Inc., Allegheny County Parks Department, and the City of Pittsburgh Department of Public Works.

As sampling at the 36 sites was evenly allocated across six Monday-through-Friday sampling sessions (six sites sampled per session), we sought to balance source indicator strata and spatial distribution across sessions to avoid confounding spatial and temporal patterns in pollution concentrations. For each session, we used traffic density, the most spatially dispersed indicator, to draw a stratified-random sample (without replacement) of six sites (e.g., randomly allocate 3 'high' and 'low' traffic density sites per session). Because pollution source and topography indicators may be spatially clustered in Pittsburgh (i.e., industrial facilities located in low-elevation river valleys and/or near highways), we required spatial representation of four regions of our domain (i.e., east and west banks of the Monongahela River, northeast and southeast of downtown) within each session. Temporal allocation of sites across sessions

was the same during winter and summer sampling seasons.

Reference monitors and temporal adjustment

We designated two reference sites, which were sampled during all sessions to provide information on overall temporal trends in air quality. First, an upwind reference site (Regional background site – Figure 2) located in a relatively rural area west of our domain, in Settlers Cabin County Park, Oakdale, PA, would provide information on regional background air quality. Second, a relatively urban reference site (Urban background site – Figure 2) within our domain, in Braddock, PA, was selected for comparison. The urban reference site is located in a low-elevation area, to capture topography-related inversion effects in seasonal air quality trends. We compared ACHD regulatory monitoring data to the weekly temporal patterns in NO_2 and $PM_{2.5}$ measured at study reference monitors, and found variable correlation between both reference monitors with ACHD monitors (Spearman rho from -0.71 to 0.90 (mean = 0.23)). Figure 3 plots weekly $PM_{2.5}$ and NO_2, trends across ACHD regulatory monitors and study reference monitors (regional and urban background); regional and urban reference trends are variably correlated in both seasons (Spearman rho 0.04 to 0.91). As expected, regional background concentrations were consistently lower than urban reference site measurements, and lower than ACHD regulatory monitors. This difference is larger for NO_2 in both seasons, compared to $PM_{2.5}$.

To facilitate comparison between site-specific concentrations, collected during one of six sampling sessions, we apply a temporal adjustment to adjust distributed site samples for between-session variability primarily driven by time-varying meteorology or long-range transport, and to derive seasonally representative mean values. Specifically, to estimate the expected, seasonally representative concentration at a given site – as if it had been sampled during an "average" week – the observed concentration is multiplied by the ratio of the seasonal average reference concentration, and then divided by the session-specific reference concentration. As such, it is the relationship of the session relative to the seasonal average at the reference site(s) that determines the temporal adjustment, which can therefore adjust distributed concentration to both lesser and greater values. These adjusted seasonal mean values allow for examination of spatial source-concentration relationships, with reduced influence of time-varying factors (i.e., meteorology, long-range transport). Because the appropriate reference trend for temporal adjustment may vary by season and/or pollutant, we evaluate two methods: one using the only the regional background reference trend (Equation 1), and a second using the mean trend of the urban and regional
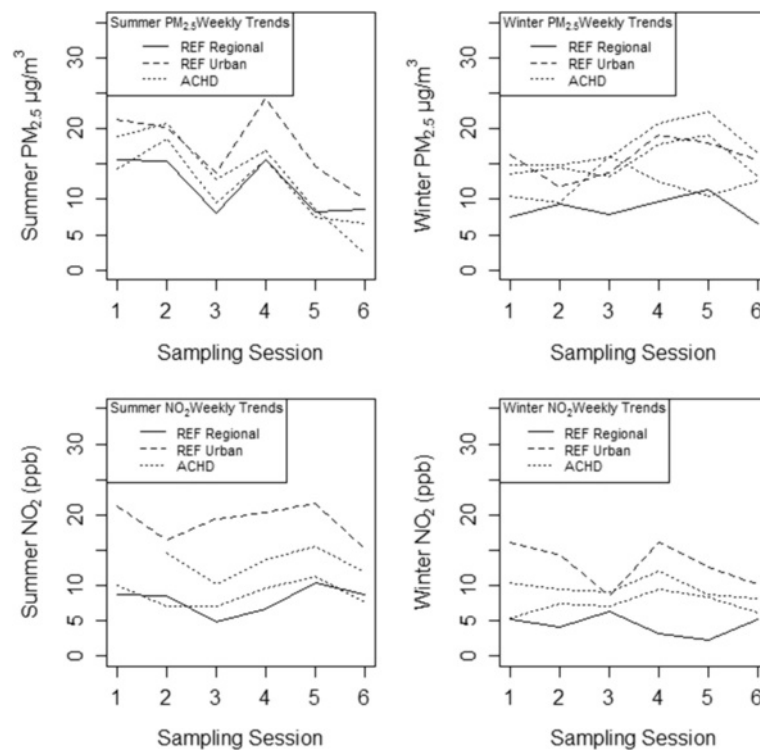
Figure 3 Weekly PM$_{2.5}$ and NO$_2$ trends between study reference sites and ACHD regulatory monitors, by season.

background sites (Equation 2). Both of these approaches have been successfully applied in other studies of intra-urban air quality variability [7,16].

Within each season, sampled pollutant concentrations were temporally adjusted as:

$$[\text{adjConc}]_{ij} = \frac{[\text{Conc}]_{ij}}{[\text{Ref}_{\text{Regional}}]_j} * [\text{Ref}_{\text{Regional}}]_{\text{Season}}$$

(1)

$$[\text{adjConc}]_{ij} = \frac{[\text{Conc}]_{ij}}{[\text{Ref}_{\mu(\text{Regional}+\text{Urban})}]_j} * [\text{Ref}_{\mu(\text{Regional}+\text{Urban})}]_{\text{Season}}$$

(2)

where $[\text{adjConc}]_{ij}$ is the temporally-adjusted pollutant concentration at monitoring site i during sampling session j, $[\text{Conc}]_{ij}$ is the pollutant concentration at monitoring site i during sampling session j, $[\text{Ref}_{\text{Regional}}]_j$ is the regional background reference site concentration during sampling session j, $[\text{Ref}_{\mu(\text{Regional}+\text{Urban})}]_j$ is the mean concentration of the regional background and urban reference sites during sampling session j, $[\text{Ref}_{\text{Regional}}]_{\text{Season}}$ is the seasonal average regional background reference site pollutant concentration, and $[\text{Ref}_{\mu(\text{Regional}+\text{Urban})}]_{\text{Season}}$ is the mean seasonal average pollutant concentration of the regional background and urban reference sites.

Temperature inversions and meteorology

We identified probable morning inversion hours as 6:00-11:00 AM by examining: (a) meteorological sounding data, (b) hourly ACHD regulatory monitor data, and (c) pilot mobile monitoring study data [32]. We used meteorological sounding data (i.e., Skew-T diagrams) recorded daily at 7:00 AM from the Pittsburgh International Airport, approximately 25 km Northwest of downtown Pittsburgh (Figure 1), to identify lapses in the vertical temperature gradient characteristic of inversion events. To confirm the number of inversion hours overlapping with sampling intervals (6:00-11:00 AM), inversion hours per event were evaluated using Bufkit 10.11, a forecast profile visualization and analysis software developed by the National Oceanic and Atmospheric Association (NOAA) and National Weather Service [32]. Inversions were defined as two or more hours of inverted temperature gradient during sampling hours. Inversion frequency was operationalized as number of inversion mornings per sampling session (1-4), and as a binary indicator (fewer than 3, vs. 3 or more days per session), based on overall frequency distribution. Importantly, these characterizations are regional scale, and do not reflect the complex interactions between topography, surface thermal variability in urbanized areas (i.e., urban heat island effect), and pollution.

Wind speed and direction influence local pollution concentrations through horizontal advection, however, the metrics that can elucidate spatial gradients in these processes are not well specified [43]. Wind speed and direction data measured at NOAA's weather station at the Pittsburgh International Airport (and obtained from NOAA's online National Climatic Data Center) were clipped to each sampling session, and used to generate wind rose diagrams (using Lakes Environmental WRPLOT View freeware) to examine within and between session variability. We then determined dominant wind direction and average wind speed (from any direction) for each sampling session. We compared wind speed and direction on inversion versus non-inversion mornings, in each season, to better understand the relationship between inversion conditions and local pollutant concentrations.

Statistical analysis

We calculated descriptive statistics for $PM_{2.5}$, BC and NO_2, during each season, to identify potential outliers, and to compare temporally adjusted values by method (i.e., Regional-only vs. Urban + Regional). We examined pollutant concentration distributions across pollution indicator strata used for site selection and allocation: traffic density, emission-weighted proximity to industry, and elevation above sea level using Spearman correlation analysis, to account for non-normal distribution of pollution concentrations. We examined between-season differences using paired t-tests on log-transformed (base 10) concentrations, to account for non-normality of distributions, and compared results across temporal adjustment methods. We examined the relationship between log-transformed pollutant concentrations and inversion frequency, by elevation and temporal adjustment method. Further analyses of meteorological factors examined associations between temporally adjusted pollutant concentrations and within-session average wind speed (continuous and binary (median-stratified) measures), and dominant wind direction (e.g., West, Northwest). Statistical analyses were performed in SAS, v 9.2 (Cary, NC) and R statistical software v 2.12.1.
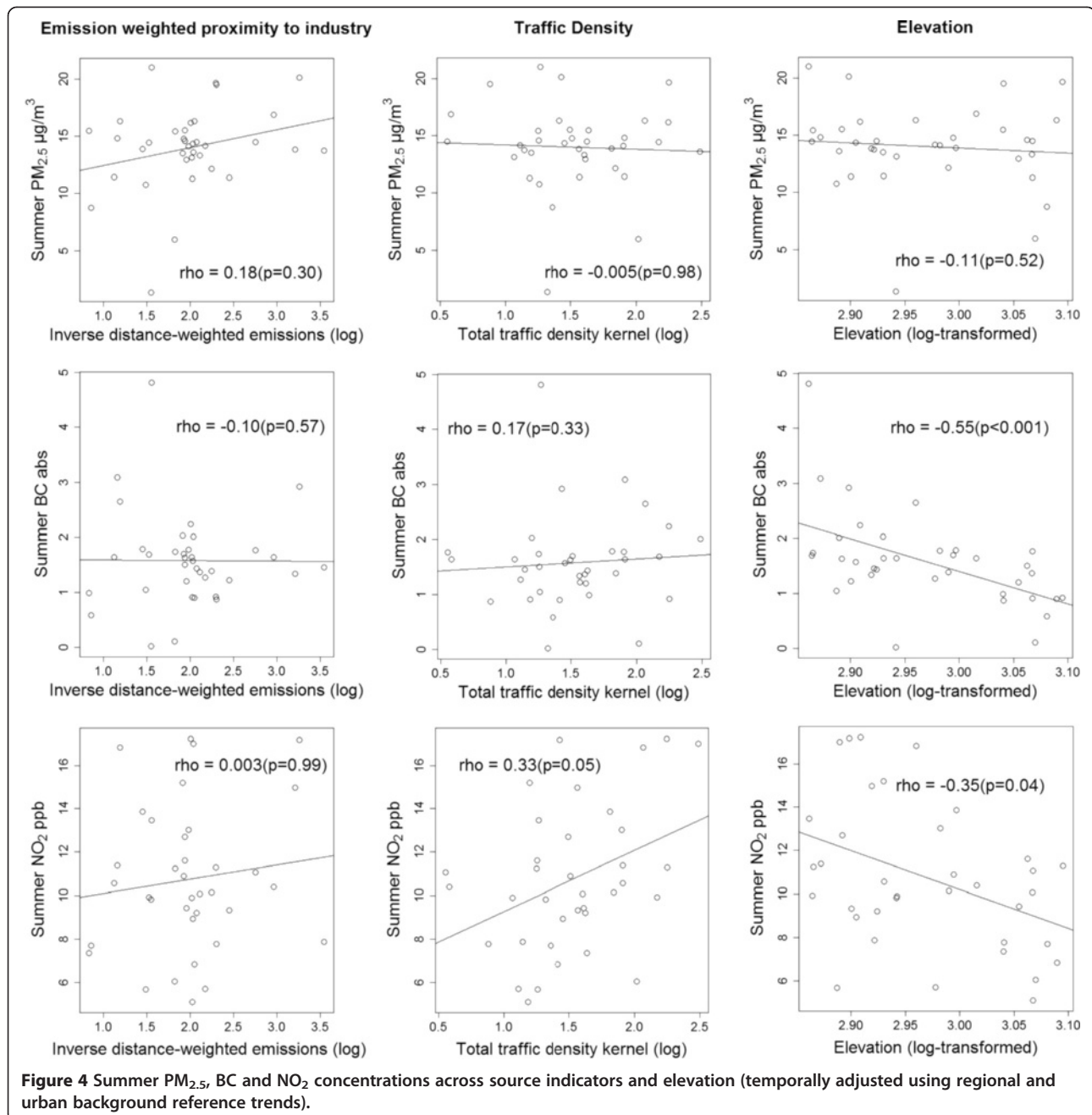
Results

$PM_{2.5}$, BC, and NO_2 concentrations varied across monitoring locations, capturing a wider range of concentrations than at ACHD regulatory monitoring locations during corresponding sampling weeks. Table 1 reports summary statistics of pollutant concentrations measured across distributed sites, by season, and compares temporal adjustment methods (Equations 1 and 2). Under both temporal adjustment methods, NO_2 concentrations were higher during winter ($p < 0.001$), and $PM_{2.5}$ concentrations were higher during summer sampling ($p < 0.10$). Within-season, distributed pollution measurements varied by temporal adjustment method, (e.g., summer NO_2 under regional-only vs. urban and regional background adjustment), with Spearman rho values ranging from 0.59 to 0.95. Specifically, adjustment using the mean of urban and regional background trends (Equation 2) produced attenuated seasonal average concentrations across sites, particularly for NO_2, in both seasons (Table 1). Weakest between-method correlations were observed for summer NO_2 and winter $PM_{2.5}$ (rho 0.59 and 0.60, respectively), and strongest correlation for BC in both seasons (summer rho 0.81, winter 0.95).

Figures 4 and 5 show scatterplots comparing relationships between sampled pollutant concentrations and pollution indicators, by season, under temporal adjustment Equation 2. In both seasons, measured concentrations were inversely correlated with elevation (i.e., river valley); stronger correlations occurred during winter sampling (Spearman rho -0.42 to -0.72), and $PM_{2.5}$ showed the weakest correlation with elevation, overall (summer rho -0.11, winter -0.42). Traffic density was positively correlated with NO_2 concentrations, in both seasons (summer rho 0.33, winter 0.36). Emission-weighted proximity to industry, a highly left-skewed indicator, was not significantly correlated (i.e., $p < 0.05$) with measured pollution concentrations in either season. Under regional background temporal adjustment (Equation 1), correlation patterns are qualitatively similar, with notable exceptions: a) the inverse relationship between elevation and pollutant concentrations is attenuated by at least 10%

Table 1 Summary statistics of $PM_{2.5}$ (µg/m^3), BC (abs), and NO_2 (ppb) concentrations, by season, comparing temporal adjustment methods
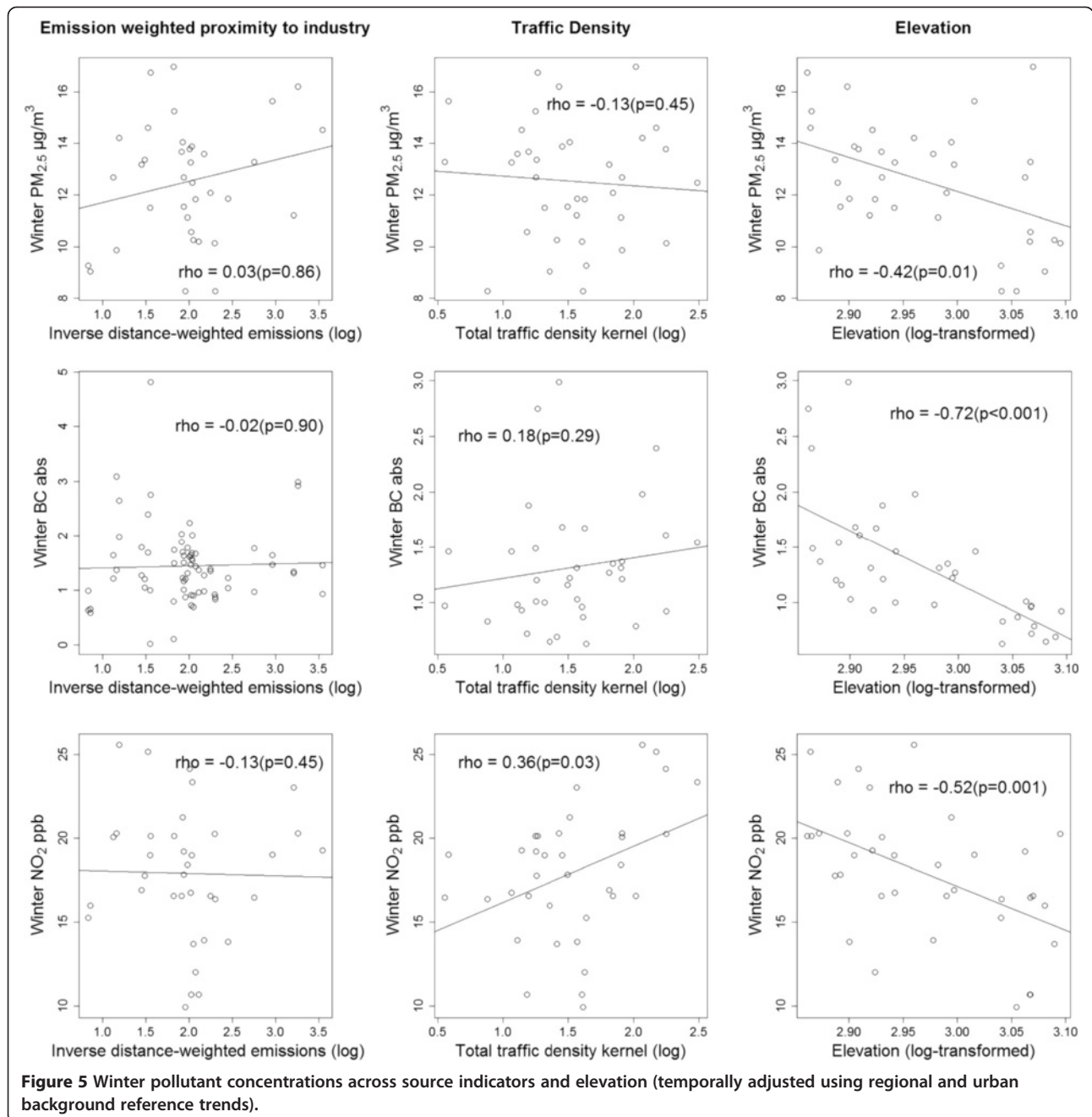
	Urban and Background Adjustment (n = 36)				Background-only Temporal Adjustment (n = 36)			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Summer PM$_{2.5}$ (µg/m^3)	14.00	3.68	1.28	21.06	14.24	3.97	1.33	22.71
Summer BC (abs)	1.58	0.85	0.02	4.82	1.61	0.91	0.02	4.64
Summer NO$_2$ (ppb)	10.75	3.36	5.12	17.25	12.30	6.50	4.46	27.72
Winter PM$_{2.5}$ (µg/m^3)	12.53	2.28	8.28	16.98	12.64	2.52	8.02	20.10
Winter BC (abs)	1.31	0.55	0.63	2.99	1.31	0.53	0.70	2.72
Winter NO$_2$ (ppb)	17.93	3.90	9.93	25.60	18.69	6.21	10.90	34.10

Figure 4 Summer $PM_{2.5}$, BC and NO_2 concentrations across source indicators and elevation (temporally adjusted using regional and urban background reference trends).

across pollutants and seasons; b) traffic density is not significantly correlated ($p > 0.05$) with NO_2 in either season (summer rho 0.01, winter 0.19); and c) summer $PM_{2.5}$ is more strongly correlated with emission-weighted proximity to industry (rho 0.32, $p = 0.05$) (Additional file 1: Figures S1 and Additional file 2: Figure S2).

Temperature inversion conditions were slightly more common during winter (2 to 4 mornings per 5-day sampling session) than summer sampling (1 to 3 mornings per session). Wind rose diagrams comparing inversion vs. non-inversion mornings show differing patterns in wind speed and direction (Figure 6). Across summer inversion mornings, wind directions were variable, with roughly 50% of all winds coming from either West, Northwest or South-Southeast directions, compared to predominantly Westerly winds on non-inversion mornings. Winds on winter inversion mornings were predominantly from the West and West-Southwest directions, while non-inversion morning winds were predominantly from the Southwest. Overall, wind speeds were generally higher during winter sampling sessions (winter mean = 3.20 m/sec, vs. summer mean = 1.79 m/sec), and sessions

Figure 5 Winter pollutant concentrations across source indicators and elevation (temporally adjusted using regional and urban background reference trends).

with lower average wind speeds (stratified at median) had higher concentrations of summer NO_2 and winter BC (p < 0.05). Dominant wind directions were associated with winter $PM_{2.5}$ (winds form South/Southwest) and winter NO_2 (West/Northwest) concentrations, but not summer.

Figure 7 compares the relationship between inversion frequency and pollutant concentrations, by temporal adjustment method, illustrating the importance of adjustment method for assessing the role of short-term meteorological

events in spatial saturation studies. NO_2 concentrations increased with number of inversion mornings per 5-day sampling session under the temporal adjustment method drawing information from both regional and local temporal trends (Equation 2), but not under regional-only adjustment (Equation 1). These relationships did not vary by season. This positive relationship between inversion frequency and NO_2 was present among low- and high-elevation sites, however, with higher concentrations across low-elevation sights (Figure 8).
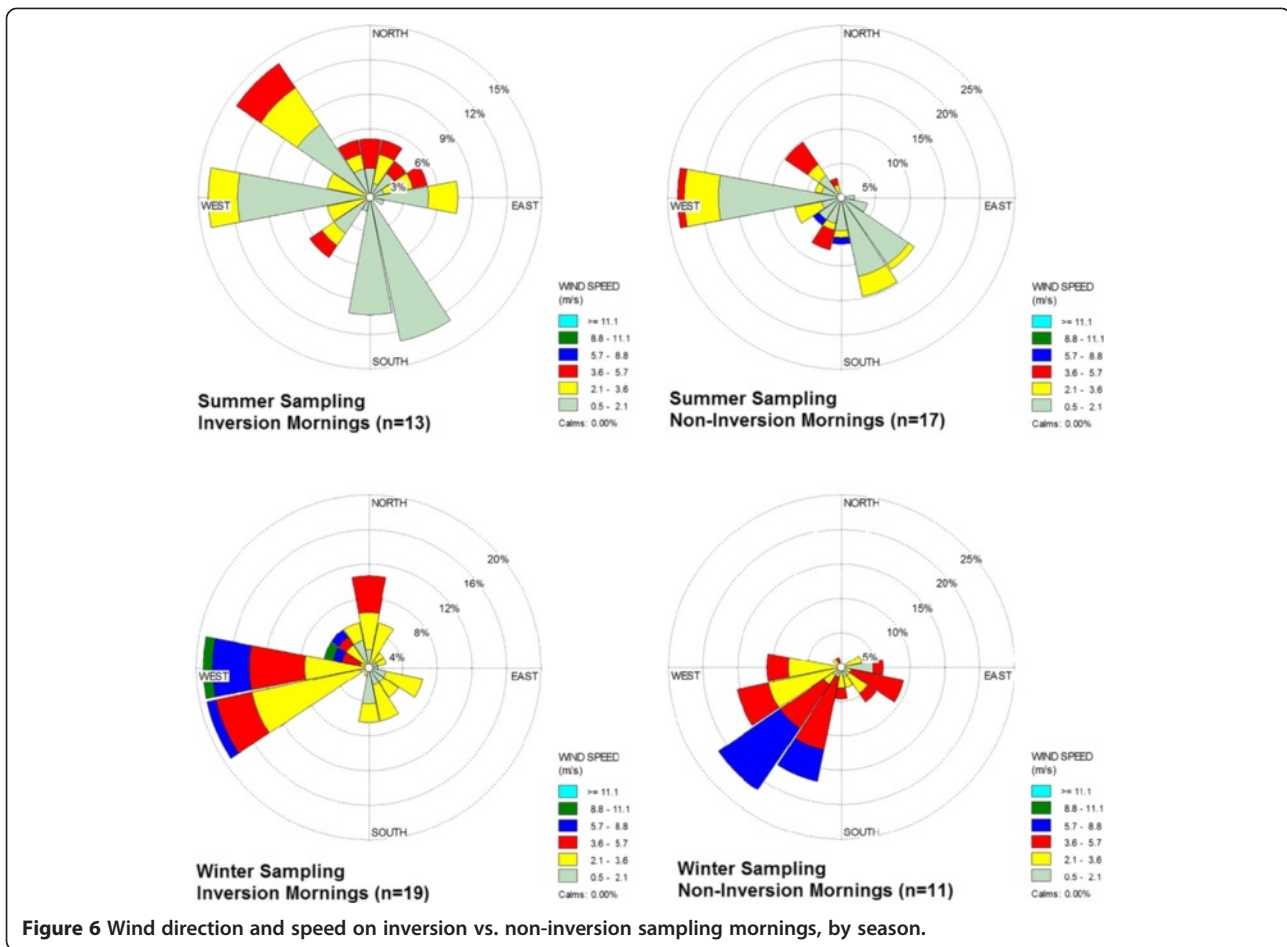
Figure 6 Wind direction and speed on inversion vs. non-inversion sampling mornings, by season.

Discussion

We present an approach for capturing intra-urban spatial contrasts in pollution concentrations, across complex terrain, during select hours of the day – here, to examine meteorological regimes. Our spatial saturation design captured source heterogeneity across our study domain, minimized spatial and temporal confounding within and across sampling sessions, and included topographic indicators to provide additional information on intra-urban variability in air quality. We offer an approach towards better understanding the impacts of short-term temperature inversions on spatial variation in air quality, by leveraging a programmable spatial monitoring system, diurnal variation in meteorology, and spatial gradients in topographic modifiers (i.e., elevation), and compare the efficacy of multiple temporal adjustment methods for this temporally-stratified spatial dataset.

This is the first study, to our knowledge, to use a spatial saturation approach to disentangle local pollution sources across the Pittsburgh region, with specific attention to complex terrain and atmospheric inversions. We observed seasonal differences in pollutant concentrations, and spatially-distributed sampling captured greater variability in pollutant concentrations than did County regulatory monitors. $PM_{2.5}$ concentrations were higher during summer sampling, consistent with a previous central-site particle monitoring study in Pittsburgh [22], and NO_2 concentrations were higher during winter sampling.

We examined two temporal adjustment methods for deriving seasonal mean concentration estimates at distributed locations, and found that the choice of reference site(s) influenced observed relationships between measured concentrations and emissions indicator strata (i.e., elevation, traffic density, industrial emissions) for NO_2, but not for $PM_{2.5}$ or BC. This discrepancy is likely because our upwind (regional) site, in a sparely-populated area, effectively captured background variation in non-reactive pollutants with upwind sources (such as $PM_{2.5}$ or BC), but not highly photochemically reactive pollutants (such as NO_2). Averaging the two reference monitors effectively captured some aspects of both the regional (i.e., long-range transport, meteorology) and local (i.e., topography, urban source activity variation) time-varying factors that influence intra-urban air quality. As such, we found that the appropriate background reference trend
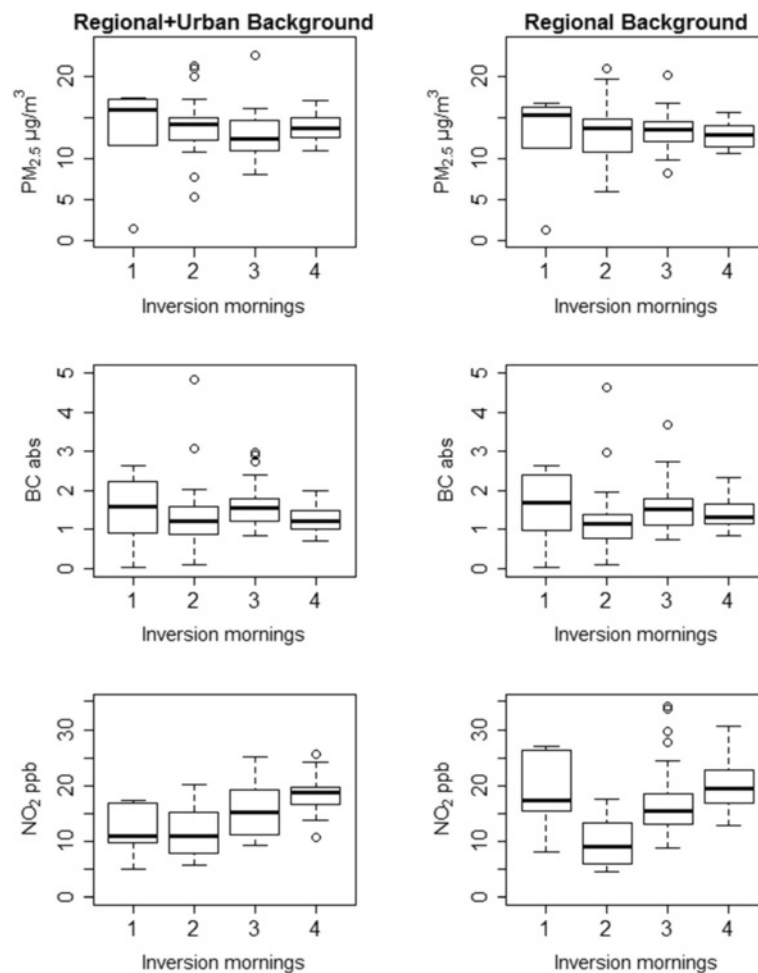
Figure 7 Pollutant concentrations by inversion frequency, by temporal adjustment method.

differs between pollutants, and determined that temporal adjustment using regional and urban background trends was more robust for a multi-pollutant study with a focus on potential meteorological effects on local concentrations.

While the pollution source indicators used to allocate sampling sites were consistent with the LUR literature, we did not find strong overall relationships between measured pollutants and traffic density or emissions-weighted proximity to industry. This is not entirely surprising, as the GIS-based indicators used for site selection and allocation were intentionally inclusive of multiple components of source activity. For example, we developed a multi-pollutant indicator of industrial emissions to prevent biasing study design toward one type of facility or chemical, and this underlying study design is well-suited for future LUR models that will use refined metrics (e.g., SO_2 emissions in tons, stack height). Likewise, our traffic density indicator includes total vehicle counts on major and minor roads, but local traffic-related pollution may be driven by specific aspects of

traffic patterns (e.g., average vehicle speed, idling) and fleet composition (e.g., diesel trucks, bus traffic).

An alternate explanation for weak overall source-concentration relationships are modifying effects of topography and meteorology. Across our distributed monitoring sites, elevation was inversely associated with BC and NO_2 concentrations, in both seasons. Among low-elevation sites, where we hypothesized that inversion effects would be exacerbated, NO_2 concentrations were higher during sampling sessions with 3 or more inversion mornings across low-elevation monitoring sites, but no statistically significant differences were found for $PM_{2.5}$ or BC. This finding suggests that inversions have different effects across pollutants. This difference may by a function of local sources versus long-range pollution transport; if $PM_{2.5}$ predominantly originates from long-range sources, it may demonstrate lesser local trapping in industrial valleys during inversion events, while the opposite may be true for BC and NO_2, if they primarily arise from local sources. Lower regional wind speeds on inversion
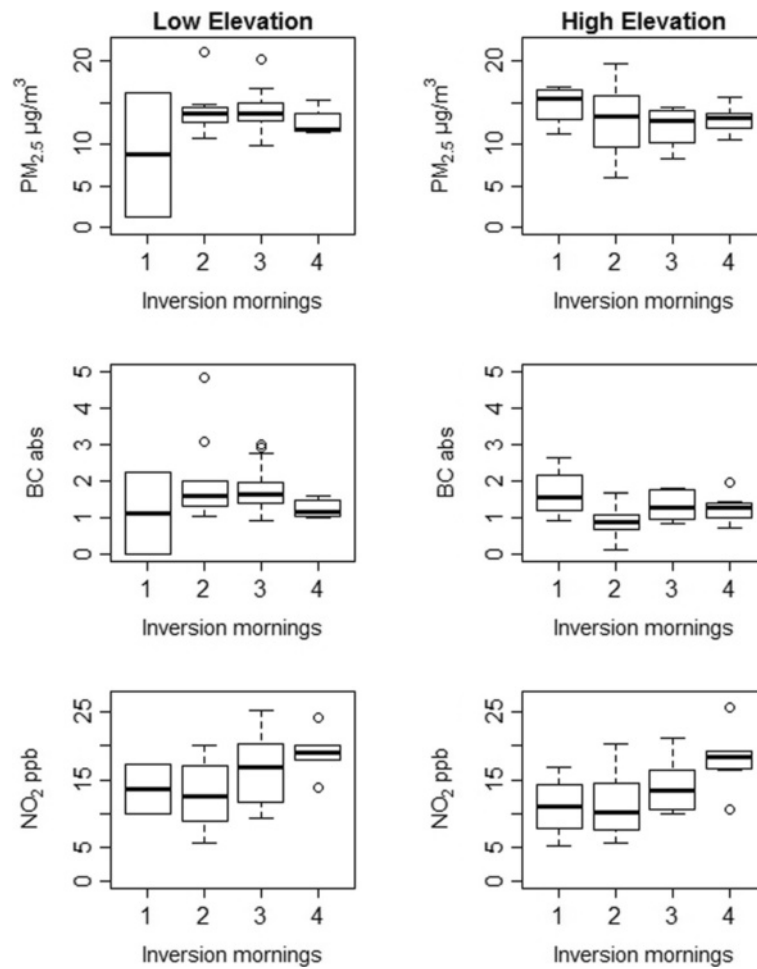
Figure 8 Pollutant concentrations by inversion frequency, among low- and high-elevation monitoring sites (n = 36 in each group).

mornings also help explain different effects across pollutants, particularly during summer sampling; higher NO_2 and BC during sampling sessions with multiple inversions may be attributable to less advection and dispersion of locally-generated pollutants, compared to long-range $PM_{2.5}$. Other potential explanations for different observed inversion effects across pollutants, which are not mutually exclusive, include vertical emission location (i.e., industrial stacks versus on-road traffic), and atmospheric chemistry (i.e., reactivity and transformation rates) [44].

These findings are in keeping with other urban-scale (as opposed to simulation or regional-scale) monitoring studies of inversion effects on pollutants. Wallace et al. (2010) identified similar differential inversion effects by elevation in a mobile monitoring study in Hamilton, Ontario, but saw effects for both $PM_{2.5}$ and NO_2 [45]. These inconsistent $PM_{2.5}$ findings may be due to different topography-meteorology interactions in Hamilton (steep escarpment dividing the city into contiguous elevation zones), versus Pittsburgh (complex river valleys),

or to different study designs; Wallace et al. took multiple observations at six Hamilton locations over three years under variable inversion conditions, while our study collected samples across 36 sites spatially distributed across a finer gradient of source-elevation profiles. In a separate fixed-site (n = 3) study of inversion effects on pollutants in Hamilton, Ontario, Wallace and Kanaroglou (2009) identified differential inversion effects on $PM_{2.5}$ and NO_2 by timing of inversion and season, and explained this difference by a range of meteorological factors, including prevailing wind directions [46].

We found some evidence that the impact of inversion conditions on the source-concentration relationship may vary by topography, pointing to complex challenges for integrating meteorological factors into saturation studies. Spatially, regional-scale meteorological data (e.g., atmospheric sounding, airport-measured wind direction) may not accurately capture intra-urban spatial variation of inversion dynamics. For example, the thermal profile of urban areas differs from relatively suburban areas, and katabatic cold air drainage from more densely built,

warmer areas (i.e., urban heat island) can result in greater heating of clouds and inversion layer thickness, as compared to suburban areas [47,48]. Similarly, cool air pooling in river valleys may delay surface warming, and extend inversion conditions longer than reflected by sounding data. Temporally, integrated samples, though well-suited for deriving spatially-refined seasonal concentration estimated, are not ideal for interpreting effects of short-term meteorological events. Our approach examining inversion frequency within integrated sampling sessions was sensitive enough to detect some differences between inversion and non-inversion days, but not to examine how specific inversion characteristics (e.g., mixing height, vertical lapse rate) are implicated in inversion-related pollution effects. However, just as spatial saturation studies control for time-varying day-of-week and within-day variations in pollution source activity (e.g., rush hour) by design, this work, and others' [45], supports conditioning site allocation on topographic modifiers of inversion effects (i.e., elevation) as a useful approach.

Strengths

A unique strength of our study is the use of programmable monitors to synchronize active $PM_{2.5}$ sampling across many locations, with a focus on inversion-prone morning rush hours. The primary strength and novelty of this work is the contribution to methods and metrics for understanding the role of topographic and meteorological factors on intra-urban air quality variability using a spatial saturation approach. Strengths of our study design include: monitoring across multiple seasons, measuring multiple pollutants, and spatially saturating a complex domain to systematically disentangle important local exposure factors. Key strengths of our instrumentation and data quality include: sampling near breathing zone height and excellent data quality and completeness. Our site allocation methodology minimized confounding of spatial and temporal factors, and provided useful information for refining and interpreting GIS-based pollution source indicators for LUR modeling.

Limitations

Regional meteorological measures (e.g., wind speed and direction) limit our ability to assess differential effects on source-concentration relationships; integrated wind measurement instrumentation with each monitor, for example, would be ideal, but infeasible within allowed resources. Temporally, the potential effect of morning inversions on particle concentrations may have been diluted, if highest inversion-related pollution concentrations are found pre-sunrise, as our monitoring began at 6:00 AM, coinciding with morning rush hour. Additionally, low between-session variability in inversion frequency – all sessions in summer and winter had at least

one inversion morning – limited examination of pollution effects; this observation also reinforced the importance of understanding this potentially important driver of regional air quality variability. Power calculations for spatial saturation designs vary by location, and 36 sampling locations may have been insufficient to saturate our domain, despite systematic allocation. Though previous LUR studies have cited 40 cites as a minimum for urban monitoring [41,42], and others have successfully used as few as 20 sites [49], one study in New York City demonstrated the utility of as many as 150 sites in a dense, spatially heterogeneous urban area [5,7]. To increase saturation for multi-year LUR modeling, we repeated this study design during a second year (summer and winter). Finally, due to monitoring solely during winter and summer months, we are unable to draw any conclusions about potential interaction of meteorology, topography and pollution during spring and fall seasons.

Conclusion

In conclusion, we measured wide variability in multiple pollutants across the Pittsburgh metropolitan area, and found some evidence for modification of the inversion-concentration relationship by topography. This work contributes to methods for accurately capturing time-varying factors in spatial saturation studies by design, through targeting specific hours during which meteorological processes are hypothesized to have greatest impacts on local pollution concentrations, utilizing multiple reference monitors to understand spatial heterogeneity in temporal trends, and incorporating topographic gradients, which may interact with meteorological process, in sample allocation.

Additional files

Additional file 1: Figure S1. Summer $PM_{2.5}$, BC and NO_2 concentrations across source indicators and elevation (temporally adjusted using regional reference trend (Equation 1)).

Additional file 2: Figure S2. Winter $PM_{2.5}$, BC and NO_2 concentrations across source indicators and elevation (temporally adjusted using regional reference trend (Equation 1)).

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Review

Reproductive Outcomes Associated with Noise Exposure — A Systematic Review of the Literature

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Abstract: *Introduction*: High noise exposure during critical periods in gestation is a potential stressor that may result in increased risk of implantation failure, dysregulation of placentation or decrease of uterine blood flow. This paper systematically reviews published evidence on associations between reproductive outcomes and occupational and environmental noise exposure. *Methods*: The Web of Science, PubMed and Embase electronic databases were searched for papers published between 1970 to June 2014 and via colleagues. We included 14 epidemiological studies related to occupational noise exposure and nine epidemiological studies related to environmental noise exposure. There was some evidence for associations between occupational noise exposure and low birthweight, preterm birth and small for gestational age, either independently or together with other occupational risk factors. Five of six epidemiologic studies, including the two largest studies, found significant associations between lower birthweight and higher noise exposure. There were few studies on other outcomes and study design issues may have led to bias in assessments in some studies. *Conclusions*: There is evidence for associations between noise exposure and adverse reproductive outcomes from animal studies. Few studies in have been conducted in humans but there is some suggestive evidence of adverse associations with environmental noise from both occupational and epidemiological studies, especially for low birthweight.

1. Introduction

Noise from the environment, occupational or residential setting is recognized as a stressor agent with sufficient evidence for impacts on hearing impairment, hypertension and ischemic heart disease, annoyance, sleep disturbance, decreased school performance cardiovascular effects and sleep disturbance. For other effects such as changes in the immune system and birth defects, the evidence is limited [1–3]. There is no doubt that noise along with a variety of other occupational and environmental conditions acts as general stressor on the mother inducing a variety of physiological and psychological changes that may affect pregnancy [4,5].

Sufficient published evidence supports the notion that stress triggers the release of neurohormones by the hypothalamus-pituitary-adrenal (HPA) axis, and subsequently the activation of the HPA axis stimulates up-regulation of key stress hormones such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids (GCs) [6]. Neurohormonal responses to stress also include an activation of the sympathetic nervous system with successive increased secretion of catecholamines, a phenomenon that has received much less attention than the stress-triggered activation of the HPA axis [7]. Research findings suggest that neurotrophin nerve growth factor (NGF) has a role of a critical arbitrator of stress responses. Circulating levels of NGF undergo considerable modification during a stress challenge and promote 'cross-talk' between neuronal and immune cells, ultimately skewing the immune response towards inflammation [8]. The neuropeptide substance P (SP) is another major mediator of the systemic stress response and SP can be considered a pivotal stress-related neuropeptide, triggering distortion of the immune response towards inflammation [6].

Investigators in experimental studies have exposed animals to different noise types and intensity, with the aim to simulate environmental conditions for noise exposure in humans. In the course of studying the mechanism for development of reproductive outcomes, plasma levels of stress hormones like corticosterone [9], norepinephrine (NE), epinephrine (EPI), uterine NE [10], adrenocorticitropic hormone (ACTH) plasma levels [11] have been investigated. Nawrot *et al.* didn't find significant noise-related changes in plasma corticosterone levels, but did find decreased mean foetal weight and increased embryo and foetal mortality in studies in mice [9]. Cook *et al.* found significant elevation of plasma EPI and NE levels in noise-exposed mice, significantly decreased foetal weights and decreased maternal weight gain [10]. Bailey *et al.* found elevation of ACTH plasma level in noise-exposed guineapigs [11]. Kimmel *et al.* [12] observed significantly increased resorption rates and decreased number of live fetuses per litter in each of exposed groups of animal, but no teratogenic effects were noticed among the exposed mice. Murata *et al.* [13] found significant differences in malformed fetuses between the control and group exposed to noise on day seven of pregnancy. Rasmusen *et al.* [14] found significant correlation between number of stillborn pups and noise exposure, even at 70 dBA for 1 h. Sato *et al.* [15] found significant decrease of birth rates in female rats exposed to noise during

copulation and pregnancy, and number of offspring by group decreased in exposed female rats through copulation and pregnancy.

Meyer *et al.* reviewed six epidemiological studies on reproductive outcomes and concluded that effects of noise were equivocal. The authors commented on the ecological nature of the studies, misclassification bias in exposure assessment and inadequacies in addressing the impact of confounding factors [4]. Hepper and Shahidullah reviewed eight epidemiological studies in a report published in 1994, including five of the six studies reviewed by Meyer *et al.* [4]. They comment that several of the studies reported some evidence of an association, but overall there was no conclusive evidence for an association between reproductive outcomes like low birthweight, prematurity, congenital malformations and noise exposure [5]. Hohmann *et al.* performed a systematic review on noise exposure and birth outcomes published in 2013 [16], which included 12 studies, nine studies with information on occupational noise and three with information on environmental noise, two of which had been included in the previous reviews [4,5]. Hohmann *et al.* [16] concluded that chronic occupational exposure of pregnant women did not seem to be associated with birthweight, preterm birth and fetal growth, while studies of environmental noise were inconclusive.

Low birthweight (LBW) is defined as an infant weight of less than 2500 g irrespective of gestational age. LBW infants are either those who experience normal growth, but are born too early (preterm) or those who are born pre-term or full term, but have inadequate fetal growth (intrauterine growth retardation) [17]. The World Health Organization defines preterm birth as a gestational age at birth of less than 37 completed gestational weeks [18]. Low birthweight and preterm births are recognized as a major public health problem by both, clinicians and researchers because they are the leading cause of infant mortality and also contribute to substantial neurological, cognitive, pulmonary and ophthalmologic morbidity [19]. Caring for preterm infants also incurs large health care expenditures. Mild- and moderate-preterm birth infants are at high relative risk for death during infancy and are responsible for an important fraction of infant deaths [20]. Reduction to one third of the proportion of infants with LBW is one of the seven major goals of the current decade of the "A world fit for children", program of the United Nations [19].

The aim of this paper is to undertake a systematic review of published evidence investigating reproductive outcomes like low birthweight (LBW), preterm births (PB), spontaneous abortions, congenital malformations in humans related to occupational and environmental noise exposure and to give directions and recommendations for further research on reproductive outcomes.

2. Material and Methods

2.1. Search Strategy

A systematic search was conducted on noise and reproductive outcomes. Web of Science, PubMed and Embase electronic databases were searched for papers published between 1970 to June 2014. Studies were also screened in the reference list of relevant reviews/articles. In addition, hand searching was used for acoustical conference proceedings (Internoise 2000–2002, 2004–2005, 2007–2008, 2010). No language restriction was applied. The following search terms were used:

noise AND health AND perinatal OR prenatal OR labour OR birth OR malformation OR gestation OR preterm OR foetus OR pregnancy.

2.2. Study Selection

Five inclusion criteria were defined. The paper was included if: (a) it described noise exposure (objective/subjective assessment), (b) the source of noise was either environmental (road traffic, railway or aircraft noise) or occupational, (c) the study investigated the following reproductive outcomes: birthweight/gestation length/preterm birth/prematurity/reproductive health/congenital malformation/foetal growth retardation/small-for-gestational-age infant/spontaneous abortion, (d) the above health outcomes occurred during pregnancy or delivery up to 4 weeks after birth and (e) the paper examined a direct relationship between the above health outcomes and noise exposure. Studies investigating health outcomes other than those listed in the inclusion criteria such as pre-eclampsia, hearing development, male reproductive function, or health outcomes that occurred after the 4th week of birth were not included in this review. Case studies or case reports, studies containing no original research and studies investigating different noise source such as neonatal intensive care unit (NICU) noise were excluded as were studies looking at distance from road only without other assessment of noise exposures.

The database search yielded 2356 references (last access on 7 July 2014, 598 records in Web of Science, 1489 records in PubMed and 269 records in Embase). Abstracts of potentially eligible studies were read and judged against inclusion criteria by one reviewer (HL). Sixty potential papers were then retrieved and read in full by two reviewers (GR, HL). We could not find the full paper for five articles and three references were books or Ph.D. theses; they were not available and we decided to exclude them from the list (GR, HL). No conference proceedings matched the inclusion criteria. After carefully reading full papers, we found that 12 of them were reviews, 11 papers had different outcomes that defined in inclusion criteria, two papers had results already published in other articles, two papers had very low quality assessment score, and two papers were without noise exposure assessment. Discussion about exclusion of these papers was performed with the third review author (AH). Finally we agreed on 23 papers to be included in this review.

2.3. Data Extraction and Quality Assessment

We developed data extraction sheets which contained the following characteristics: author, year of publication, country, study design, sample size, exposure assessment (indicators and range of exposure), outcome, confounding factors, effect size and quality score. Two reviewers (GR and HL) independently worked on data extraction and quality assessment of the studies and agreement was reached via consensus. For the purpose of this review we developed our own method for quality assessment (QA) of the epidemiological studies, using some criteria from the Newcastle–Ottawa quality assessment scale for case control and cohort studies [21]. Final criteria for QA of the studies were:

- Publication type (0 = not peer reviewed, 1 = peer reviewed article),
- Study design (1 = ecological, 2 = case control or cohort study, 3 = RCT, 0 = other),
- Noise exposure assessment (1 = subjective assessment by the mother, 2 = expert assessment e.g., conducted by an industrial hygienist, 3 = objective assessment with noise measurements),

- Assessment of reproductive outcomes (1 = subjective assessment by report of mother, 2 = objective e.g., from medical records),
- Confounding factors (0 = no confounding factors considered, 1 = confounding factors considered but some key confounders omitted, 3 = careful consideration of confounders),
- Statistics (0 = flaws in or inappropriate statistical testing or interpretation of statistical tests that may have affected results, 1 = appropriate statistical testing and interpretation of tests),
- Bias (0 = other study design or conduct issues that may have led to bias, 1 = no other serious study flaws).

For this scale, the maximum total score can be 14. Where the total score of the study ≥10, this was assessed as a study with strong evidence, a study with score from 6–9 was assessed as moderate evidence, and score ≤ 5 was assessed as insufficient evidence. Differences in the review process were solved with the opinion from the third reviewer (AH).

3. Results and Discussion

We selected 14 epidemiological studies related to occupational noise exposure and 9 epidemiological studies related to environmental noise exposure for this review.

3.1. Evidence from Occupational Studies

Table 1 summarizes the characteristics of epidemiological studies performed to investigate independent effects of noise exposure on reproductive outcomes in occupational environment. We identified 14 studies for this review eligible for this review, two of them were surveys [22,23], ten case control studies [24–33] and two prospective studies [34,35].

The following ten studies were assessed as studies with strong evidence (quality scores ≥10); findings were not consistent across these studies. Nurminen and Kurppa (1989) performed a case-control study to examine threatened abortion and they found significant risk in noise exposed women together with shift work (RR = 2.1 95% CI 1.0–4.6). Noise exposure was blindly assessed from a description of the mother's workday by two industrial hygienists. Women with an estimated level of noise of Leq 8 h > 80 dB were considered exposed [25]. Zhan *et al.* in their study performed in China, used objective noise exposure assessment and divided exposed groups into subgroups according to noise exposure levels. The subgroup exposed to noise level from 95–99 dBA showed significant risk for LBW (OR = 3.9 95% CI 2.3–6.7) and for spontaneous abortion (OR = 2.2 95% CI 1.3–3.8) compared with those <75 dBA. The subgroup exposed to noise level from 100–104 dBA showed significant risk for LBW (OR = 3.7 95% CI 3.2–6.2) and spontaneous abortion (OR = 3.0 95% CI 1.8–4.9) [27]. Another study where noise exposure assessment was subjectively evaluated, did not show a significant risk for preterm birth, threatened abortion and congenital malformations [28]. Luke *et al.* performed a large case control study in nurses in the USA and found significant risk for preterm births (OR = 2, *p* = 0.005, no confidence intervals reported) [29], but another study with strong evidence performed in Europe did not find significant risk for preterm birth where other occupational conditions were carefully considered [32]. Hruba *et al.* [30] conducted a case control study investigating intrauterine growth retardation in newborns in the Czech Republic and found significant risk in noise exposed women, according to the women's subjective assessment of noise exposure.

Table 1. Summary of epidemiological studies of occupational noise exposure and reproductive outcomes (ordered by year of publication).

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounding Factors	Effect Size for Noise*	Quality Score
Mcdonald *et al*., 1986 [22]	Canada	Survey	56,012 women	Subjective	Spontaneous abortion, (before 28th week of pregnancy)	Maternal age, education, smoking, parity, obstetric history, occupationla factors	O/E = 1.17; *p* < 0.05 in office work O/E = 1.48; *p* < 0.05 in sales O/E = 1.40; *p* < 0.01 in service	9
McDonald *et al*., 1988 [23]	Canada	Survey	22,761 live newborns	Subjective	LBW Gestation length (<37 weeks)	Maternal age, education, ethnic group, gravidity, smoking, alcohol intake	O/E = 1.49 (*p* < 0.01)for health sector O/E = 1.20 (*p* < 0.05) for manufacturing sector *p* = 0.02 Nonsignificant O/E	9
Hartikainen-Sorri *et al*., 1988 [24]	Finland	Case-control study	284 cases and 299 controls	Subjective	Preterm birth LBW	Socioeconomic factors, type of the work, occupational coexposures, smoking	RR = 0.7 (95% CI 0.1–3.4) RR = 2.4 (95% CI 0.2–20.2)	9
Nurminen *et al*., 1989 [25]	Finland	Case-control study	1475 subjects	Subjective, Three groups exposed to Leq 80 dBA, 85 dBA and 90 dBA	Threatened abortion SGA	Maternal age and weight, parity, smoking, alcohol intake	RR = 2.1 (95% CI 1.0–4.6) with shift work RR = 1.4 (95% CI 0.8–2.6)	12
Kurppa *et al*., 1989 [26]	Finland	Case-control study	402 cases and 440 controls	Subjective, three groups exposed to Leq 80 dBA, 85dBA and 90dBA	Structural malformations	Socioeconomic factors, obstetric history, type of the work, occupational coexposures	OR=0.9 (95% CI 0.7–1.0) According to mother's evaluation OR=1.7 (95% CI 0.7-4.1) According to industrial hygienist evaluation	12

Table 1. *Cont.*

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounding Factors	Effect Size for Noise*	Quality Score
Zhan *et al.*, 1991 [27]	China	Case-control study	978 cases and 402 controls	Objective, Three groups exposed to Leq = 85–94 dBA, 95–99 dBA, 100–104 dBA	Spontaneous abortion LBW	Maternal age, occupational factors	95–99 dBA OR = 2.2 (95% CI 1.3–3.8) 100–104 dBA OR = 3 (95% CI 1.8–4.9) 95–99 dBA OR = 3.9 (95% CI 2.3–6.7) 100–104 dBA OR = 3.7 (95% CI 3.2–6.2)	13
Zhang *et al.*, 1992 [28]	China	Case-control study	1875 cases and 1875 controls	Subjective	Small for gestational age Preterm birth Threatened abortion Congenital malformations	Gender, mother's age, plurality, parity, coexposures to radiation, chemicals, pesticides	OR = 0.8 (95% CI 0.5–1.5) OR = 1.1 (95% CI 0.7–1.9) OR = 1.1 (95% CI 0.5–2.1) OR = 1.3 (95% CI 0.8–2.2)	11
Hartikainen *et al.*, 1994 [34]	Finland	Prospective study	111 exposed women and 181 unexposed women	Objective, cut off point for exposure Leq 8 h > 90 dBA	Low birthweight (LBW)	Socioeconomic factors, age, parity, marital status, smoking alcohol, type of the work	Decline in absolute birthweight, (mean 3304 g (SD 585) for the exposed *vs.* mean 3622 g SD 548) for the unexposed.	9
Luke *et al.*, 1995 [29]	USA	Case-control study	210 cases and 1260 controls	Subjective	Preterm births (<37 weeks)	Maternal age, race, education, marital status, smoking, occupational fatigue score	OR = 2 $p = 0.005$	10
Hrubá *et al.*, 1999 [30]	Czech Republic	Case-control study	3897	Subjective	Intauterine growth retardation (IUGR)	Maternal age, education, smoking, shiftwork, standing, lifting, exposure to chemicals	OR = 1.9 CI not available $p = 0.03$	11

Table 1. *Cont.*

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounding Factors	Effect Size for Noise*	Quality Score
Chen *et al.*, 2000 [31]	China	Case-control study		Subjective	LBW	Maternal age, education, occupation, smoking, alcohol intake, occupational coexposures	Estimated change in birthweight 14 *p* = 0.69	10
Saurel-Cubizolles *et al.*, 2004 [32]	European study	Case-control study	5145 preterm and 7911 term births,	Subjective	Preterm birth (<37 weeks)	Maternal age, education, marital status, obstetric history, occupation, working conditions, occupational coexposures	OR = 0.99 95% CI =0.9–1.1	10
Magann *et al.*, 2005 [35]	USA	Prospective study	814 low risk healthy women	Objective, LAeq 8 h, cut off point for exposure was 85 dBA	Preterm birth Preterm labor IUGR Perinatal death	Maternal age, weight, education, family factors, occupational coexposures	OR = 0.8 (95% CI 0.1–2.9) OR = 2.5 (95% CI 0.6–7.5) OR = 0.2 (95% CI 0.02–0.5) OR = 0.9 (95% CI 0.2–2.7)	13
Croteau *et al.*, 2006 [33]	Canada	Case-control study	276 cases 640 controls	Subjective	Small for gestational age (SGA)	Maternal age, weight, education, family factors, obstetric history, smoking, alcohol intake, occupational coexposures	OR = 1.2 (95% CI 1.0–1.5)	11

Notes: OR (Odds Ratio), CI (Confidence Intervals), O/E (Observed/Expected); * results are reported to two decimal points except where original paper uses one decimal point.

A large follow up study in petrochemical industry investigated effects on birthweight due to noise exposure and other chemical and physical occupational factors in women but didn't find independent influence of noise on birthweight in multivariate models [31].

The effects of occupational factors on pregnancy were analyzed in a large prospective study with low-risk healthy working women [33]. The independent effect of noise exposure on reproductive outcomes didn't reach statistical significance, but a multivariate analysis of non-exposed compared with exposed women found an effect of standing on preterm labor (OR 1.80, 95% CI 1.05–3.16) and preterm birth (OR 1.69, 95% CI 1.03–2.80) and showed a trend towards an effect of noise exposure on preterm labor (OR 1.76, 95% CI 0.78–3.39) after controlling for other exposures.

Croteau *et al.* [33] performed a case–control study to evaluate whether some occupational conditions during pregnancy increase the risk of delivering a small-for gestational-age (SGA) infant and whether taking measures to eliminate these conditions decreased that risk. The risk of having an SGA infant increased with an irregular or shiftwork schedule alone and with a cumulative index of the occupational condition like noise exposure. When the noise exposure was not eliminated, the risk increased OR = 1.2 (1.0–1.5), but prevention of noise exposure before 24th week of pregnancy brought the risks close to those of unexposed women (OR = 0.9, 95% CI 0.6–1.4).

Kurppa *et al.* [26] tested the hypothesis that occupational noise exposure during pregnancy was teratogenic. They obtained data from Finnish Register of Congenital Malformations supplemented by special interviews on the mothers' work conditions. This included 1475 Finnish mothers who had given birth to a malformed child (orofacial cleft or structural defect of the central nervous system, skeleton, or heart and great vessels) and 1475 reference mothers. Occupational hygiene assessment according to expert opinion of industrial hygienist indicated that 102 case mothers and 103 referents had been exposed in the first trimester to a noise level of Leq (8 h) > 80 dB, the overall OR being 1.0 (95 % CI 0.7–1.3).

Four studies were assessed as providing moderate evidence. Within a large survey of pregnancies in Montreal, McDonald *et al.* [23] studied the frequency of LBW (<2500 g) and GL (<37 weeks) of 22,761 single live births in relation to maternal employment, taking into account of 11 non-occupational confounding factors. Noise exposure was associated with LBW, only in the women who worked in health and manufacturing sectors. Gestation length was not associated with noise exposure. The authors also investigated spontaneous abortion [22] and found significant risks only in women who worked in sales (OR = 1.48) and service (OR = 1.40) and office work (OR = 1.17), but the association with noise was not statistically significant when ranking by job demands rather than occupational groupings (while physical effort was consistently statistically significant). Subjective assessment was used to determine noise exposure, while other occupational conditions and individual factors were controlled. Hartikainen-Sorri *et al.* [24] performed a case-control study of 299 women with LBW babies (<25th centile) and 284 women with preterm birth and matched controls. The study did not find a significant association with occupational noise, but they had a very small sample (26 subjects) of highly noise-exposed women, Leq(A) 8 h (≥81 dB). Hartikainen *et al.* [34] performed a prospective cohort study with objective noise exposure assessment where the cut-off point for noise exposure was LAeq > 78 dBA. They found birthweight was on average 200–300 g lower in the group exposed to >90 dBA (Leq, 8 h) with mean 3304 (SD 585) g for the exposed *vs.* mean 3622 (SD 548) g for the unexposed.

The main limitation of epidemiological studies regarding occupational noise exposure was subjective noise exposure assessment, *i.e.*, according to the mother's opinion of whether she considered that she was exposed to occupational noise during pregnancy. Subjective evaluation of noise exposure is important because it is likely to be in close relation to the stress response of each person, but we also need accurate noise exposure assessment, which can be readily obtained in occupational settings. The other option for subjective assessment is according to the judgment of industrial hygienist, e.g., did he/she consider that specific occupational settings had a higher level of noise exposure (such as above 85 dBA). There is big possibility for exposure bias in performing such studies. Only three of the 14 occupational studies—two prospective studies [34,35] and one case control study [27] used objective exposure assessment methods, with noise measurements. In the two prospective studies using objectively assessed noise exposure, which also assessed influence of other occupational factors, the independent effect of noise didn't reach statistical significance [34,35]. In the case-control study, the two subgroups exposed to (objectively assessed) noise above 95 dBA (*i.e.*, very high noise levels) showed significant risk for LBW and spontaneous abortion [27].

3.2. Evidence from Epidemiological Studies

Table 2 summarizes characteristics about the nine epidemiological studies included in the review investigating environmental noise exposure and reproductive outcomes. Four of these were case-control studies [36–39], two were surveys [40,41], one was a cross-sectional study [42], one was a prospective study [43] and one was population based cohort study [44]. Objective noise exposure assessment was used in eight of these studies. Most of the studies examined aircraft noise exposure and its influence on LBW and some of them investigated dose-response relationships between noise exposure and low birthweight. According to the quality assessment score, six studies were assessed as providing strong evidence and three studies provided a moderate evidence score. Those scored as providing strong evidence are discussed first.

Schell in 1981 [42] examined the association between maternal exposure to aircraft noise and birthweight or gestation length in a relatively small study involving 115 infants but where noise exposure assessment was performed with measurements of SEL during airplane take-off, ranging from 75–100 dBA. The birthweight and other data were collected through personal interviews with the mothers. They found a significant negative partial correlation between noise exposure and gestation length in female infants, controlling for maternal age, smoking, parity, socioeconomic status, and parental height and weight ($r = -0.49$, $p < 0.001$). Noise exposure also showed a slightly negative correlation with male birthweight and gestation length and with female birthweight; however, these correlations were not statistically significant.

Table 2. Summary of epidemiological studies on environmental noise exposure and reproductive outcomes (ordered by year of publication).

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounfing Factors	Effect Size	Quality Score
Ando and Hattori, 1973 [36]	Japan	Case-control study	713	Objective assessment, aircraft noise, ECPNL (dB)	LBW (<2500 g)	Gender, maternal age, occupation, parity	Higher rate of LBW in noisy area above 75 dBA	8
Ando and Hattori, 1977 [37]	Japan	Case-control study	343 cases and 112 controls	Objective assessment, aircraft noise, 75–95 dBA noise exposure	Human placental lactogen (HPL) levels in maternal serum Birthweight	No confounders	Significant lower HPL level in noise exposed women after 32nd week of pregnancy Significant correlation between birthweight and lower HPL level (≤4 mg/mL)	9
Edmonds *et al.*, 1979 [40]	USA	Survey	1745 birth defects	Objective assessment, aircraft noise, high noise level exposure above 65dBA Ldn	17 categories of birth defects	Socioeconomic status, race	Non significant differences in rates of birth defects in exposed and nonexposed groups	10
Knipschild *et al.*, 1981 [38]	Netherlands	Case-control study	1840	Objective assessment, aircraft noise, 3 subgroups Ldn < 65 dBA, Ldn 65–70 dBA, Ldn > 70 dBA	LBW	Gender, parental income	18% LBW in low noise exposed group, 24% LBW in high noise exposed group, 29% in noise exposed above 70 dBA Dose response relationship between aircraft noise and LBW	8

Table 2. *Cont.*

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounfing Factors	Effect Size	Quality Score
Schell, 1981 [42]	USA	Cross-sectional study	115	Objective assessment, aircraft noise, SEL = 75–100 dBA	Birthweight Gestation length	Maternal age, obstetric history, parental weight and height, education, smoking, family income	r = −0.04 p = 0.76 males r = −0.22 p = 0.014 females r = −0.18 p = 0.16 males r = −0.38 p = 0.008 females	11
Wu *et al.*, 1996 [43]	Taiwan	Prospective study	200	Objective and subjective assessment, Leq24 hours	LBW	Maternal age, weight gain, gender and gestational age, socioeconomic status	Non-significant correlation between noise exposure and LBW	13
Matsui *et al.*, 2003 [41]	Japan	Survey	160,460 births	Objective assessment, aircraft noise, WECPNL (dB) Control group <75 dBA Exposed subgroups 75–80 dBA, 81–85 dBA, >85 dBA	LBW (<2500 g) Preterm birth (<37 weeks)	Gender, maternal age, socieocnomic status, live birth order	OR = 1.3 (95% CI = 1.1–1.4), p = 0.0001 in the highest level of exposure OR = 1.25 (95% CI = 1.1–1.4), p = 0.0018 in the highest level of exposure	10

Table 2. *Cont.*

Author, Year	Country	Study Design	Sample Size	Exposure Assessment	Outcome	Confounfing Factors	Effect Size	Quality Score
Wang *et al.*, 2011 [39]	China	Case-control study	60 cases and 120 controls	Subjective assessment, residential noise exposure	Recurrent spontaneous abortion	Individual and family factors, other environmental factors	OR = 5.39 95% CI 1.03–28.20 Noise exposure over 6 hours increased the risk for spontaneous abortion	11
Gehring *et al.*, 2014 [44]	Canada	Retrospective study of birth records population based cohort study	68,238 births	Objective, noise modeling	Preterm birth LBW Small for gestational age	Gender, ethnicity, parity, family income, education, smoking, air pollution	OR = 1.03 (95% CI 0.99–1.07) OR = 1,11 (95% CI 1.02–1.19) OR = 1.10 (95% CI 1.06–1.13)	13

Notes: OR (Odds Ratio), CI (Confidence Intervals), ECPNL (Equivalent Continuous Perceived Noise Level), SEL (Sound Exposure Level), r (correlation coefficient), WECPNL (Weighted Equivalent Continuous Perceived Noise Level).

Wu *et al.* [43] performed most detailed exposure assessment, using three different methods: personal noise dosimeter performing noise measurements for 24 h; traffic noise exposure assessment using noise maps for residential areas of the participants; and self evaluation of the habits for listening to loud music and using personal listening devices during pregnancy. The mean value and standard deviation of individual exposure Leq 24 h was 67.9 dBA, (52.4 dBA–86.8 dBA). A well-characterized cohort of 200 pregnant women was followed during pregnancy and data for birthweight were obtained from medical records. The authors didn't find any statistically significant associations between personal noise exposure measured and low birthweight ($p = 0.24$), between traffic noise exposure indicating by the distance between the home and main streets and low birthweight ($p = 0.17$), between using personal listening musical devices during pregnancy and infant birthweight ($p = 0.34$).

Matsui *et al.* [41] conducted a large study of 160,460 birth records from 1974 to 1993 and found a very highly statistically significant dose-response relationship between LBW and aircraft noise exposure. The adjusted OR for LBW was 1.3 and for preterm birth OR = 1.2 in highest noise exposure group. The authors adjusted for confounding factors like gender of the infant, maternal age, birth order, occupation of householder, but they didn't adjust for smoking habit of mothers, which may have resulted in some residual confounding.

Only one study used subjective noise exposure assessment, using the mother's opinion about whether she felt she was living in noisy environment. Wang *et al.* [39] investigated recurrent spontaneous abortions in a case-control study, performed in China and they found noise exposures of more than 6 hours in a residential area was associated with recurrent spontaneous abortion (OR = 5.3 95% CI 1.0–28.2). This outcome was adjusted for education, infections of the reproductive tract and husband's alcohol drinking, but the study had serious limitations with great possibility of exposure measurement bias as this was assessed subjectively and thus may relate to general stress levels or other environmental factors rather than noise level itself.

Gering *et al.* [44] linked nearly 70,000 administrative birth records in Vancouver, Canada to modeled residential road traffic and all transportation noise exposure. After controlling for various factors including income and education, a statistically significant negative association was seen between road traffic exposure and term birthweight with mean difference = −19 g (95% CI = −23 to −15) per 6 dBA. Results were robust to adjustment for air pollution exposure. Similar sized negative associations were also seen with combined road, aircraft and railway noise, but the latter two sources were only a minor contribution to community noise. The study also found significant risk for small for gestational age OR= 1.10 (1.06–1.13), but not on preterm or very preterm birth. In joint noise-air pollution models, there were independent effects of noise and air pollution exposure on small for gestational age.

Edmonds *et al.* [40] investigated the incidence of birth defects in two groups of infants whose mothers lived around Atlanta airport, exposed to Ldn above 65 dB and below 65 dB, but did not find a significant association.

The three studies whose quality was assessed as moderate investigated aircraft noise. In a case-control study, Ando and Hattori [36] found increased incidence of low birthweight in mothers who were exposed to aircraft noise. Noise exposure assessment was performed using the indicator ECPNL (dB), divided into five subgroups of exposure in range of 74–90 dBA. The relative low birthweight rate was 3% lower for the three year period in the noisy area (above 75 dBA)

compared to the neighboring quiet cities, not exposed to jet aircraft flights. Following jet planes starting to fly regularly, relative low birthweight rate increased and it was over 5% for both males and females. Ando and Hattori also [37] investigated the levels of human placental lactogen HPL in the serum of mothers both subjected to and not subjected to aircraft noise. HPL is also known as human chorionic somatomamotrophin with biological properties known as growth stimulation and lactogenic activity and impacts on HPL may be a potential mechanism for growth inhibition. The HPL levels in the quiet reference area and in the noise area were similar before the 29th week of pregnancy. However, the HPL levels of noise exposed subjects tended to be lower than those in the reference area after the 30th week of pregnancy and the difference became significant after the 36th week of pregnancy. The percentage of mothers with HPL levels that could be potentially dangerous for the fetus tended to be higher in the noise exposed group. The lower HPL levels were associated with lower birthweight for infants from mothers exposed to noise.

Knipschild *et al.* in a study published in 1981 [38] compared the birthweight of 498 infants whose mother lived in a noisy area near the Amsterdam airport with that of 404 infants from less noisy areas. Mothers exposed to Ldn < 65 dBA had 18% infants with LBW, mothers exposed to Ldn 65–70 dBA had 23% infants with LBW and mothers exposed to Ldn > 65 dBA had 29% infants with LBW. These findings were then adjusted for parent's income, mother's age, birth order, twinship and sex of the infant (but not for mother's smoking). After adjustment for family income, the association was present only among female infants.

Only the abstract could be located for a study by Jones and Tauscher [45] so it could not be fully assessed and is not included in Table 2. The authors investigated congenital anomalies near Los Angeles airport and found greater incidence of all birth defects among black infants in areas where the noise exposure was >90 dBA compared to those who were not exposed to aircraft noise. However, when the incidence of anencepahaly and spina bifida was examined alone in white infants an increased incidence was noted among infants whose mothers lived near the airport.

3.3. Potential Confounding Factors

Occupational studies included in this review found that several occupational and non-occupational factors influenced reproductive outcomes. Occupational factors involved were standing, lifting and exposure to chemicals—usually persons who were exposed to noise were exposed to other occupational factors. Important non-occupational factors were mother's age, mothers weight and height, mother's weight gain during pregnancy, smoking, education, race and socioeconomic status. Gravidity and parity, and chronic diseases of the mother were also important factors for examination of spontaneous abortion or preterm labour.

The impact of confounding factors with strong evidence that they influence on birthweight was inadequately addressed in most of the environmental noise studies. Included among these factors are maternal age, parity, gravidity history, smoking and socioeconomic status. Some of this information (e.g., age, parity) probably would have been readily available on the vital records and other sources of data used in these studies, yet it was not utilised.

3.4. Summarising the Evidence from Occupational and Epidemiological Studies

LBW was investigated in five occupational studies [23,24,27,28,31] but only two used objective exposure assessment and these found significant risk for noise level above 95 dBA [27] and decline of mean birthweight from mothers exposed to noise above 90 dBA [34]. The other studies used subjective evaluation of noise exposure assessment and adjustment for other occupational factors, and they didn't find significant associations. One study found significant risks of noise only for mothers who work in health and manufacturing sector [23]. LBW or birthweight was also investigated in six epidemiological studies [36,38,39,41–44]. The two largest studies found associations with LBW. One study from Japan [41] found significant risk for LBW for mothers exposed to aircraft noise above 85dBA and another large population base cohort study from Canada [44] that found adverse effects of road traffic noise exposure and for all transportation noise associated with term birthweight and term very low birthweight. The noise effect on term birthweight was largely unchanged after adjustment for air pollution [44]. Two smaller studies with lower quality scores also saw higher risk of LBW with higher noise exposure [36,38]. A further two studies investigated correlations not risks, finding associations with birthweight in female but not male babies [42] or no association with LBW [43]. There is therefore evidence supportive of associations between LBW and noise exposure including from the better designed and larger occupational and epidemiologic studies, although associations were not consistently found across all studies located and the total number of studies to date is small.

Findings and conclusions for LBW differ with conclusions of Hohmann's review [16] because we have included one large population based cohort study [44] published after the Hohmann review, one large study from Japan [41] and one case control study from China [27] which were not included in that previous systematic review. These three studies gave supportive evidence for association between higher level of noise exposure and LBW.

Small for gestational age was investigated in three occupational studies [25,28,33] and noise didn't reach statistical significance alone, but only in combination with other occupational factors like shift work. A large epidemiological study published in 2014 that used noise modeling software found that road traffic noise exposure was associated with SGA [44].

Gestation length was investigated in one occupational study [23] and one epidemiological study [41], but neither found significant risk for noise exposure.

Preterm birth was investigated in five occupational studies [24,28,29,32,35] and only one study found an increased risk. This outcome was investigated in two epidemiological studies, one of which found significant associations for aircraft noise exposure above 85 dBA [41], while a second did not find an association with transportation noise (with lower exposure levels) [44].

Spontaneous abortion was investigated in three studies: one occupational study with subjective evaluation of noise exposure, which found significant risk in women that work in sales, service and office work [22], in another study was found significant risk in exposed women on the noise level above 95 dBA [27]. One study for environmental noise exposure over 6 hours daily (subjective evaluation) had found risk for recurrent spontaneous abortion [39].

Threatened abortion was associated with shift work and noise exposure in one occupational study [25], but another occupational study didn't show significant risk [28].

Congenital anomalies were investigated in two studies [10,26], one occupational and one epidemiological, but neither study found significant associations.

Taken together, the small number of available studies were generally supportive of an association between noise exposure and adverse effects on birthweight, but publication bias cannot be ruled out and some studies of the studies had limitations in design. There was a very small number of studies on other reproductive outcomes and no clear suggestion of adverse associations other than for SGA.

3.4. The Biological Mechanism Underlying Influence of Noise Exposure on Reproductive Outcomes

New multi-disciplinary research on brain–body interactions triggered by stress in early pregnancy has shown that maternal biological responses, including localized inflammation in uterine tissue and sustained depression of progesterone production, challenge the endocrine-immune steady state during pregnancy, leading to serious consequences for the fetal environment. Recent basic science findings and new theoretical development around a 'pregnancy stress syndrome' associated with over-activation of the HPA axis warrant a new look at the epidemiological evidence around the age-old question of whether or not stress can actually cause human reproductive failure [6,7].

Noise exposure has been linked to increased levels of plasma catecholamines (norepinephrine and epinephrine) and this may be one of the mechanisms involved in observed effects noted above. In rats, norepinephrine infusion acutely reduces ovarian and uterine blood flow [13] and in guinea pigs, infusion of norepinephrine decreases placental blood flow by 24% to 46%, depending on the dose administered. Therefore, increased norepinephrine could cause decreases in blood flow that could adversely influence implantation and fetal health [14]. A mechanism by which the postimplantation stage might be affected by endogenously elevated maternal plasma CA levels is by reduction in blood flow through uterus. The noise exposed *vs.* control group plasma NE differences were less on the first day of exposure in both exposed groups and increased with exposure duration, indicating a cumulative effects [13]. CA synthesis is maintained at elevated levels during chronic restraint stress in rats [10,11,13].

Corticotropin-releasing hormone (CRH), the principal regulator of the HPA axis, has been identified in most female reproductive tissues including the uterus, the placenta, and the ovary [45]. Placental CRH has been proposed to directly modulate the endocrine function of placental trophoblasts, including the production of estrogen, ACTH, and prostaglandin, and is involved in the timing of parturition [45,46]. Remarkably the trajectory of CRH increase during pregnancy has been described to differ by ethnicity and also upon statistical adjusting for sociodemographic and biomedical factors [47]. Besides the regulatory function of CRH during pregnancy and parturition, a wealth of data indicates that high levels of glucocorticoids wield harmful effects on the uterus and fetus, and inhibit pituitary luteinizing hormone, and ovarian estrogen, and progesterone secretion. The notion of stress-triggered inhibition of progesterone secretion—or a more rapid metabolism—is supported by experimental evidence from animal studies. Here, exposure to stress in the form of restraint or sound induces abortion in pregnant mice via a significant reduction in progesterone levels, along with a reduce expression of progesterone receptor at the feto-maternal interface [48–50].

To summarize what is known currently about the human biological response to stress, the sympathetic nervous system is activated and NGF and SP are released and trigger an intense local inflammatory response, whereas a systemic inflammatory response generally may be suppressed.

Accordingly it may be proposed that the immune response plays a sentinel role within the complex bodily response to stress, characterized on the one hand by the bias towards pro-inflammation/Th1 in response to SP, NGF and catecholamines, and on the other by the bias towards immunosuppression/Th2 in response to glucocorticoids.

4. Conclusions

Reproductive outcomes in humans result from complex interactions of individual physiological and psychological characteristics with demographic, ethnic factors, environmental and socioeconomic factors. Evidence considering the plausibility of an independent association between noise exposure and reproductive outcomes like LBW, preterm birth, spontaneous abortion, gestation length is sparse. However, the evidence available found to support these interactions.

The biological evidence points to contribution of noise exposure to reproductive failure in critical windows of gestational time via implantation failure, dysregulation of placentation, decrease of uterine blood flow. Recent evidence describes a hierarchy of biological mediators involved in a stress trigger to reproductive failure and a relatively new conceptual approach describes the stress susceptibility in mother and fetus via a pregnancy stress syndrome.

Epidemiological studies related to environmental or occupational noise exposure have shown that very high noise exposure on higher levels could be associated with low birthweight, but not with other investigated reproductive outcomes.

A major limitation of the studies investigated was the exposure assessment. As with other authors who have reviewed literature for noise related health outcomes, we would recommend inclusion of objective as well as subjective noise exposure assessments, assessment of time-activity patterns of subjects and use of noise propagation modeling. The numbers of studies identified was small and the methods were heterogeneous so it is difficult to draw firm conclusions. Further research on the relation between noise exposure and reproductive outcomes is needed, given the ubiquitous exposure to different sources of noise and rising noise level in urban centers. LBW defined as birthweight < 2500 g and preterm birth defined as gestational age at birth less than 37 completed gestational weeks should be key outcomes in further prospective studies with emphasis on accurate and objective noise exposure assessment.

5. Recommendations

More research on associations between environmental noise exposures and reproductive outcomes is needed, using:

- objective and well-designed environmental noise exposure assessment
- well-designed epidemiological studies
- adjustment for confounding factors, such as life-style factors (smoking, alcohol use, drug use), characteristics of parents (parental weight and height, mother's age, race, ethnicity, socioeconomic status *etc*. and gravidity and parity history for spontaneous abortion and congenital malformations
- adjustment for air pollution when considering outdoor transportation noise

- harmonized outcome definitions including use of birthweight < 2500 g for LBW preferably with information on gestational age and birth less than 37 completed gestational weeks for preterm birth, in order to obtain comparable results

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Author Contributions

Helga Laszlo was responsible for the inventory that served as a basis for the evaluations presented in this paper. All authors participated in discussions and the decision for inclusion of papers in this review. Gordana Ristovska wrote the manuscript; Helga Laszlo and Anna Hansell critically reviewed the manuscript and approved the final version of the manuscript for submission.

Conflicts of Interest

The authors declare no conflict of interest.

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Low-Concentration PM$_{2.5}$ and Mortality: Estimating Acute and Chronic Effects in a Population-Based Study

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BACKGROUND: Both short- and long-term exposures to fine particulate matter (≤ 2.5 µm; PM$_{2.5}$) are associated with mortality. However, whether the associations exist at levels below the new U.S. Environmental Protection Agency (EPA) standards (12 µg/m^3 of annual average PM$_{2.5}$, 35 µg/m^3 daily) is unclear. In addition, it is not clear whether results from previous time series studies (fit in larger cities) and cohort studies (fit in convenience samples) are generalizable.

OBJECTIVES: We estimated the effects of low-concentration PM$_{2.5}$ on mortality.

METHODS: High resolution (1 km × 1 km) daily PM$_{2.5}$ predictions, derived from satellite aerosol optical depth retrievals, were used. Poisson regressions were applied to a Medicare population (≥ 65 years of age) in New England to simultaneously estimate the acute and chronic effects of exposure to PM$_{2.5}$, with mutual adjustment for short- and long-term exposure, as well as for area-based confounders. Models were also restricted to annual concentrations < 10 µg/m^3 or daily concentrations < 30 µg/m^3.

RESULTS: PM$_{2.5}$ was associated with increased mortality. In the study cohort, 2.14% (95% CI: 1.38, 2.89%) and 7.52% (95% CI: 1.95, 13.40%) increases were estimated for each 10-µg/m^3 increase in short- (2 day) and long-term (1 year) exposure, respectively. The associations held for analyses restricted to low-concentration PM$_{2.5}$ exposure, and the corresponding estimates were 2.14% (95% CI: 1.34, 2.95%) and 9.28% (95% CI: 0.76, 18.52%). Penalized spline models of long-term exposure indicated a larger effect for mortality in association with exposures ≥ 6 µg/m^3 versus those < 6 µg/m^3. In contrast, the association between short-term exposure and mortality appeared to be linear across the entire exposure distribution.

CONCLUSIONS: Using a mutually adjusted model, we estimated significant acute and chronic effects of PM$_{2.5}$ exposure below the current U.S. EPA standards. These findings suggest that improving air quality with even lower PM$_{2.5}$ than currently allowed by U.S. EPA standards may benefit public health.

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Introduction

Many studies have found associations between fine particulate matter [PM with aerodynamic diameter ≤ 2.5 µm (PM$_{2.5}$)] and increased mortality (Dockery et al. 1993; Franklin et al. 2007; Pope et al. 2002; Schwartz 1994; Zanobetti and Schwartz 2009). Biological evidence has been established for plausible mechanisms between PM$_{2.5}$ and mortality, such as increased risk of ventricular arrhythmia and thrombotic processes, increased system inflammation and oxidative stress, increased blood pressure, decreased plaque stability, and reduced lung function, among others (Brook et al. 2009; Gauderman et al. 2004; Gurgueira et al. 2002; Suwa et al. 2002; Yue et al. 2007). Based on evidence from epidemiological and toxicological studies (Chen and Nadziejko 2005; Furuyama et al. 2006; Ohtoshi et al. 1998), National Ambient Air Quality Standards (NAAQS) were implemented for fine particulate matter. For example, the U.S. Environmental Protection Agency (EPA) revised the fine particle NAAQS in 1997, 2006, and 2012 in order to protect public

health (U.S. EPA 1997, 2006, 2013). Further changes in the standards require additional studies to elucidate whether health effects occur at levels below the current annual and daily U.S. EPA NAAQS of 12 and 35 µg/m^3, respectively. The Clean Air Act Amendments of 1990 require the U.S. EPA to review national air quality standards every 5 years to determine whether they should be retained or revised; thus, whether health effects can be observed below the current standards is of great interest and importance.

Previous studies have generally focused on either long-term (Hart et al. 2011; Jerrett et al. 2005; Puett et al. 2009; Schwartz 2000) or short-term (Dominici et al. 2006; Katsouyanni et al. 1997; Samoli et al. 2008; Schwartz and Dockery 1992) exposures across the entire range of PM$_{2.5}$ concentrations. In the case of time series analyses of short-term exposures, the need to ensure the relevance of the monitoring data as well as the need to have a study population of a size for sufficent power has limited analyses to large cities; hence, exurbs, small cities, and

rural areas are not generally represented in the literature, which may compromise the generalizability of the results. In addition, there is spatial variability in PM$_{2.5}$ concentrations within cities that time series studies generally do not take into account, which can introduce exposure measurement error (Laden et al. 2006; Lepeule et al. 2012).

Chronic effects studies began using comparisons across cities of mortality experiences of cohorts living in various communities and the monitored air pollutant concentrations in those communities (Dockery et al. 1993; Pope et al. 1995). Again, these studies suffered from exposure error due to failure to capture within-city spatial variability in exposure. Because the geographic exposure gradient is the exposure contrast in these studies, the failure to capture within-city contrasts leads to classical measurement error with expected downward bias. Studies with, for example, land use regression estimates of exposure have generally reported larger effect sizes (Miller et al. 2007; Puett et al. 2009). Previous cohort studies have not controlled for the acute effects of particles when estimating chronic effects, raising the question of whether there are independent chronic effects that represent more than the cumulative effects of acute responses.

In general, existing study cohorts are not representative of the overall population. For example, the American Cancer Society (ACS) cohort has a higher level of education than the U.S. population as a whole (Stellman

and Garfinkel 1986). Hence, few population-based cohort studies have been conducted until recently (Kloog et al. 2013).

Several time series studies examined the concentration–response relationship between PM$_{2.5}$ and mortality below concentrations of 100 μg/m^3; these studies generally reported a linear concentration–response relationship (Samoli et al. 2008; Schwartz and Zanobetti 2000). However, there have been few studies focusing on exposures below the current daily U.S. EPA standard of 35 μg/m^3.

Many studies have examined the shape of the concentration–response curve for long-term exposure versus short-term exposure, but in general, they have not covered population-based cohorts, or have only included very low exposures (Schwartz et al. 2008; Crouse et al. 2012).

We recently presented a new hybrid method of assessing temporally and spatially resolved PM$_{2.5}$ exposure for epidemiological studies by combining 1 km × 1 km resolution satellite-retrieved aerosol optical depth (AOD) measurements with traditional land use terms, meteorological variables, and their interactions (Kloog et al. 2014a). This approach allows for predicting daily PM$_{2.5}$ concentrations at a 1 km × 1 km spatial resolution throughout the New England area of the northeastern United States. We also validated our model's performance in rural areas: 10-fold cross-validation (CV) of our model in rural areas (using the IMPROVE stations)

resulted in a CV R^2 of 0.92. Further details have been published (Kloog et al. 2014a).

The present study aimed to simultaneously estimate acute and chronic health effects of PM$_{2.5}$ in a population-based Medicare cohort (≥ 65 years of age) encompassing the New England region. We used high-spatial-resolution exposure estimates based on satellite measurements that are available across the region and not just in limited locations. To make this study relevant to future assessments of current U.S. EPA standards, we repeated the analysis after restricting the data to long-term exposures (365-day moving average) < 10 μg/m^3 and repeated the time series analysis of short-term exposures after restricting the data to 2-day average exposures < 30 μg/m^3.

Methods

Study domain. The spatial domain of our study included the New England area, comprising the states of Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont (Figure 1A).

Exposure data. A 3-stage statistical modeling approach for predicting daily PM$_{2.5}$ was previously reported incorporating AOD and land use data for the New England region (Kloog et al. 2011). Previous studies have shown that using actual physical measurements in our prediction models improved predictive accuracy over that of comparable land use or spatial smoothing models

(Kloog et al. 2011). With AOD retrieved by the multi-angle implementation of atmospheric correction (MAIAC) algorithm, a similar approach was applied for estimating daily PM$_{2.5}$ exposures in New England at a spatial resolution of 1 km × 1 km (Kloog et al. 2014a). In this study, the same PM$_{2.5}$ exposure predictions were employed.

Briefly, we calibrated the AOD–PM$_{2.5}$ relationship on each day of the study period (2003–2008) using data from grid cells with both ground PM$_{2.5}$ monitors and AOD measurements (stage 1), and we used inverse probability weighting to address selection bias due to nonrandom missingness patterns in the AOD measurements. We then used the AOD–PM$_{2.5}$ relationship to predict PM$_{2.5}$ concentrations for grid cells that lacked monitors but had available AOD measurement data (stage 2). Finally, we used a generalized additive mixed model (GAMM) with spatial smoothing and a random intercept for each 1 km × 1 km grid cell to impute data for grid cells/days for which AOD measurements were not available (stage 3). The performance of the estimated PM$_{2.5}$ was validated by 10-fold cross-validation. High out-of-sample R^2 (R^2 = 0.89, year-to-year variation 0.88–0.90 for the years 2003–2008) was found for days with available AOD data. Excellent performance held even in cells/days with no available AOD (R^2 = 0.89, year-to-year variation 0.87–0.91 for the years 2003–2008). The 1-km model had better spatial (0.87)
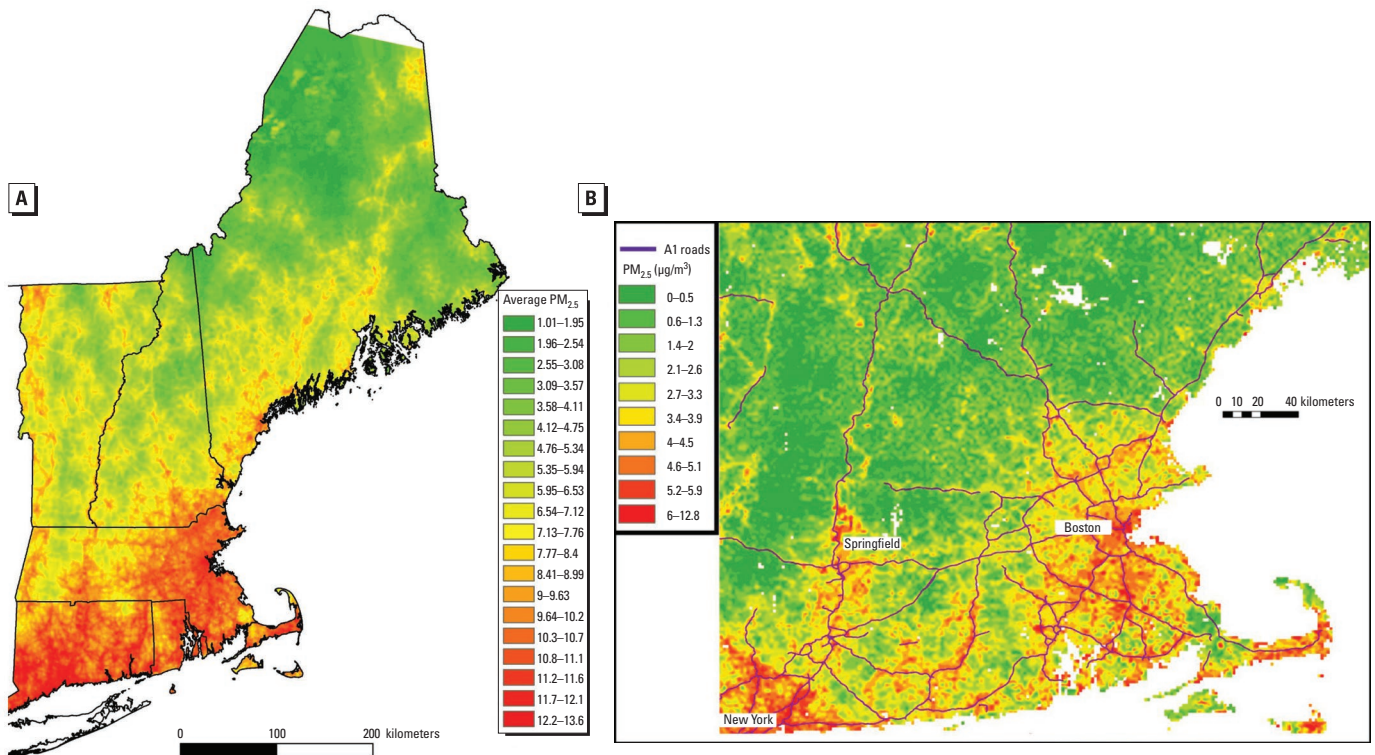

Figure 1. (*A*) Mean PM$_{2.5}$ concentrations in 2004 at a high resolution (1 km × 1 km) across New England predicted by the AOD models. (*B*) Predicted PM$_{2.5}$ concentrations at a 1 km × 1 km grid for 15 November 2003.

and temporal (0.87) out-of-sample R^2 than the previous 10-km model (0.78 and 0.84, respectively). Details of the $PM_{2.5}$ prediction models are in Kloog et al. (2014a).

Figure 1A shows an example of mean $PM_{2.5}$ concentrations in 2004 at a 1 km × 1 km spatial resolution across New England. By averaging the estimated daily exposures at each location, we generated long-term exposures.

Figure 1B (a subset of the study area) shows that spatial variability existed even for daily data and was not identical to the long-term pattern shown in Figure 1A. That is, there was space–time variation in the $PM_{2.5}$ exposure captured in this analysis, but not in previous time-series analyses.

Because the deaths were coded at the ZIP code level, both long- and short-term predictions were matched to ZIP codes by using ArcGIS (ESRI, Redlands, CA) and SAS (SAS Institute Inc., Cary, NC) to link the ZIP code centroid to the nearest $PM_{2.5}$ grid.

Traditionally, studies of acute air pollution effects have controlled for temperature using values taken from the nearest airport. This approach is not feasible for the entire region because many residences are distant from airports. In addition, there is spatiotemporal variation in temperature. We have applied a similar 3-stage statistical modeling approach to estimate daily ambient temperature at 1 km × 1 km resolution in New England using satellite-derived surface temperature (Kloog et al. 2014b). To our knowledge, such fine control for temperature has not previously been used in air pollution epidemiology.

Mortality data. Individual mortality records were obtained from the U.S. Medicare program for all residents ≥ 65 years of age for all available years during 2003–2008 (CMS 2013b). The Medicare cohort was used because of the availability of ZIP code of residence data, whereas National Center for Health Statistics mortality data are only available at the county level. Additionally, previous studies found that elderly people are highly susceptible to the effects of particulate matter (Pope 2000). The Medicare beneficiary denominator file from the Centers for Medicare and Medicaid services (CMS 2013a) lists all beneficiaries enrolled in the Medicare fee-for-service (FFS) program and contains information on beneficiaries' eligibility and enrollment in Medicare and the date of death. The Medicare Provider Analysis and Review (MEDPAR) file includes information on age, sex, race, ZIP code of residence, and one record for each hospital admission (CMS 2013c).

Daily mortality was first aggregated by ZIP code and then matched with the corresponding $PM_{2.5}$ exposure. We summarized the mortality data by ZIP code and day because that was the finest resolution we could obtain for addresses. Because the mortality data sets

did not include changes of residence, we assumed that the subjects lived at their current address over the entire study period.

Covariates. We used daily 1-km temperature data estimated from surface temperature measured by satellites (Kloog et al. 2014b). All socioeconomic variables were obtained through the U.S. Census Bureau 2000 Census Summary File 3, which includes social, economic, and housing characteristics (U.S. Census Bureau 2000). ZIP code tabulation area–level socioeconomic variables, including race, education, and median household income, were used. The county-level percentage of people who currently smoke every day, obtained from the CDC Behavioral Risk Factor Surveillance survey for the entire country, was also adjusted (CDC 2013). Dummy variables were used to control for day of the week.

Statistical models. Conventionally, the acute effects of air pollution are estimated by Poisson log-linear models, and the chronic effects of air pollution are estimated by Cox proportional hazard models (Kloog et al. 2013; Laden et al. 2006). Laird and Olivier (1981) noted the equivalence of the likelihood of a proportional hazard model with piecewise constant hazard for each year of follow-up and a Poisson regression with a dummy variable for each year of follow-up. We have taken advantage of this equivalence to generalize from dummy variables for each year to a spline of time to represent the baseline hazard and to aggregate subjects into counts per person time at risk, and we obtained a mixed Poisson regression model (Kloog et al. 2012). This approach allows the rate of death as a function of both long- and short-term exposures to be modeled simultaneously. By doing so, we achieved the equivalence of a separate time series analysis for each ZIP code, greatly reducing the exposure error in that part of the model, while simultaneously conducting a survival analysis on the participants, and we were also able to estimate the independent effects of both exposures.

Most time series studies have reported stronger associations with acute exposures when exposures were defined as the mean $PM_{2.5}$ on the day of death and the previous day (lag01) than when they were defined as the mean $PM_{2.5}$ on the current day only, or for exposures with longer lags (Schwartz et al. 1996; Schwartz 2004). We used the lag01 average for our main analysis but performed a sensitivity analysis on that choice. Long-term exposure was calculated as the 365-day moving average ending on the date of death so that our results were comparable with those of previous studies (Lepeule et al. 2012; Schwartz et al. 2008). Short-term exposure was defined as the difference between the 2-day average and the long-term average, ensuring that acute and chronic effects were

independent. We subtracted the long-term average from the short-term average to avoid collinearity issues and to ensure that differences between ZIP codes in $PM_{2.5}$ at a given time did not contribute to the short-term effect estimate. Thus, the short-term effect could not be confounded by variables that differed across ZIP codes.

Specifically, we fit a Poisson survival analysis with a logarithmic link function and a log (population) offset term and modeled the expected daily death counts (μ_{it}) in the ith ZIP code on the tth day as follows:

$$\log(\mu_{it}) = \lambda_i + \beta_1 PM_{it} + \beta_2 \Delta PM_{it} \\ + \lambda(t) + \text{temporal covariates} \\ + \text{spatial covariates} + \text{offset,} \quad [1]$$

where λ_i is a random intercept for each ZIP code, PM_{it} is the 365-day moving average ending on day t in ZIP code i, ΔPM_{it} is the deviation of the 2-day average from its long-term average (PM_{it}) in ZIP code i, $\lambda(t)$ is a smooth function of time, temporal covariates are temperature and day of the week, and spatial covariates are socioeconomic factors defined at the ZIP code level (percent of people without high school education, percent of white people, median household income) and smoking data at the county level. Additionally, a quasi-Poisson model was used to control for possible overdispersion (Ver Hoef and Boveng 2007).

We estimated $\lambda(t)$ with a natural cubic spline with 5 degrees of freedom (df) per year to control for time and season trends. The specific temporal and spatial covariates that we used were a natural cubic spline for temperature with 3 df in total; a categorical variable for day of the week; linear variables for percent of people without high school education, percent of white people, median household income, and percent of people who currently smoke every day.

The number of deaths per ZIP code area over the study period (2003–2008) averaged 319 with a standard deviation of 430. Because the outcome was counts, we could not adjust for age and sex as in a Cox model. Instead, we adjusted for variables that varied by ZIP code. The analyses were repeated without mutual adjustment for short- and long-term $PM_{2.5}$.

We modeled the association between all-cause mortality and $PM_{2.5}$ at low doses in which the person-time at risk in each year of follow-up in each ZIP code was used as the offset. We also conducted effect modification by population size by choosing the median (4,628) of the ZIP code–level total population as the cutoff between urban and rural areas.

Estimating the effects of low-level $PM_{2.5}$. For full cohort analyses with 10,938,852 person-years of follow-up, all observed deaths were used. To estimate effects at low

levels of exposure, we performed restricted analyses: we conducted one analysis restricted to annual exposures < 10 μg/m^3, below the current annual PM$_{2.5}$ NAAQS of 12 μg/m^3, and another restricted to observations with short-term exposure < 30 μg/m^3, below the current daily PM$_{2.5}$ NAAQS of 35 μg/m^3. After these exclusions, the chronic analyses were restricted to 268,050 deaths out of 551,024 deaths in total, and the acute analyses were restricted to 422,637 deaths.

Assessing the dose–response relationship. For both the acute and chronic analyses, we fit penalized regression splines in the restricted analyses to estimate the shape of the dose–response curve below current U.S. EPA standards. The degrees of freedom of the penalized splines for PM$_{2.5}$ were estimated by generalized cross-validation (GCV).

Results

Table 1 presents a summary of the predicted exposures for both short- and long-term PM$_{2.5}$ exposure across all grid cells in the study area.

Table 2 presents the estimated percent change in all-cause mortality with 95% CIs for a 10-μg/m^3 increase in both short- and long-term PM$_{2.5}$ in the restricted and full cohort. In the restricted population, we found an estimated 9.28% increase in mortality (95% CI: 0.76, 18.52%) for every 10-μg/m^3 increase in long-term PM$_{2.5}$ exposure. A 2.14% increase in mortality (95% CI: 1.34, 2.95%) was observed for every 10-μg/m^3 increase in short-term PM$_{2.5}$ exposure. For long-term exposure, the effect estimates were smaller when higher pollution days were included (7.52%; 95% CI: 1.95, 13.40%), suggesting larger effects between low-concentration long-term PM$_{2.5}$ and mortality.

Without mutual adjustment, lower estimates were found for both acute and chronic

effects than for those with mutual adjustment. In full-cohort analyses, a 2.08% (95% CI: 1.32, 2.84%) and a 6.46% (95% CI: 0.93, 12.30%) increase in mortality was found for each 10-μg/m^3 increase in short- and long-term PM$_{2.5}$, respectively. In restricted analyses, the corresponding effect estimates were 2.07% (95% CI: 1.27, 2.89%) and 7.16% (95% CI: −1.23, 16.27%), respectively.

Our results were robust to the choice of lag period for acute exposure. We analyzed different averaging periods (Figure 2): for example, lag0 (day of death exposure) and lag04 (a moving average of day of death exposure and previous 4-day exposure). For the acute effects, we found a significant but smaller association for lag0 PM$_{2.5}$ (1.71%; 95% CI: 1.09, 2.34%) and lag04 PM$_{2.5}$ (1.76%; 95% CI: 0.72, 2.81%) than for lag01 analysis. The lag period used for short-term exposure did not affect estimates of chronic effects. For example, estimated increases in mortality with a 10-μg/m^3 increase in long-term PM$_{2.5}$ were 7.35% (95% CI: 1.79, 13.21%) and 7.25% (95% CI: 1.69, 13.12%) when short-term PM$_{2.5}$ was classified using lag0 or lag04, respectively.

We also examined effect modification by population size. In the full cohort, a significant interaction was found for chronic effects ($p < 0.01$), with a larger effect of 12.56% (95% CI: 5.71, 19.85%) in urban areas compared with 3.21% (95% CI: −2.92, 9.72%) in rural areas. Such a significant interaction, however, was not observed in the restricted analysis ($p = 0.16$). Estimates were 14.27% (95% CI: 3.19, 26.53%) and 5.48% (95% CI: −4.21, 16.16%) in urban and rural areas, respectively. For short-term exposure, population size did not modify the acute effects in either the full cohort or the restricted analysis ($p = 0.74$ and 0.46, respectively).

In our penalized spline model for long-term exposure below the cutoff of 10 μg/m^3 (Figure 3A), we found a nonlinear relationship between long-term PM$_{2.5}$ and mortality. The association was linear with evidence of a smaller effect < 6 μg/m^3. However, a large confidence interval was observed; hence, we could not be confident whether the slope of the dose–response curve changed for long-term exposures < 6 μg/m^3. When examining the shape of the dose–response curve for chronic effects, both a linear term for short-term exposure (the difference) and a penalized spline for long-term average exposure were included in the model, resulting in a penalized spline with a df of 1.71. In contrast, we only included the 2-day average in the penalized spline model of acute effects in order to provide an interpretable dose–response relationship (Figure 3B). The results of this analysis indicated a linear association across the exposure distribution, but we could not be certain about the shape of the slope for acute effects < 3 μg/m^3.

Discussion

When we applied the predicted daily PM$_{2.5}$ with 1-km spatial resolution from our novel hybrid models, we observed that both short- and long-term PM$_{2.5}$ exposure were significantly associated with all-cause mortality among residents of New England ≥ 65 years of age, even when restricted to ZIP codes and times with annual exposures < 10 μg/m^3 or with daily exposure < 30 μg/m^3. Hence, the association of particle exposure with mortality exists for concentrations below the current standards established by the United States, the World Health Organization (WHO) (10 μg/m^3 of annual average PM$_{2.5}$, 25 μg/m^3 daily), and the European Union (EU) (25 μg/m^3 of annual average PM$_{2.5}$) (EU 2013; WHO 2013). Notably, this analysis includes all areas in New England and all Medicare enrollees ≥ 65 years of age in this region, and it provides chronic effect estimates that are independent of acute effects. Based

Table 1. Descriptive statistics for PM$_{2.5}$ exposure and temperature in New England, 2003–2008.

Covariate	Mean	SD	Minimum	Median	Maximum	Range	Q1	Q3	IQR
Lag01 PM$_{2.5}$ (μg/m^3)	8.21	5.10	0.00	7.10	53.98	53.98	4.60	10.65	6.05
1-year PM$_{2.5}$ (μg/m^3)	8.12	2.28	0.08	8.15	20.22	20.14	6.22	10.00	3.78
Temperature (°C)	9.24	6.50	−36.79	9.81	41.51	78.30	4.90	14.39	9.49

Table 2. Percent increase in mortality (95% CI) for a 10-μg/m^3 increase for both short-term and long-term PM$_{2.5}$.

PM$_{2.5}$ exposure	Model	Percent increase	*p*-Value
With mutual adjustment			
Short-term PM$_{2.5}$	Low daily exposure[a]	2.14 ± 0.81	< 0.001
	Full cohort	2.14 ± 0.75	< 0.001
Long-term PM$_{2.5}$	Low chronic exposure[b]	9.28 ± 8.88	0.032
	Full cohort	7.52 ± 5.73	0.007
Without mutual adjustment			
Short-term PM$_{2.5}$	Low daily exposure[a]	2.07 ± 0.80	< 0.001
	Full cohort	2.08 ± 0.76	< 0.001
Long-term PM$_{2.5}$	Low chronic exposure[b]	7.16 ± 8.75	0.109
	Full cohort	6.46 ± 5.69	0.026

The full cohort analysis had 551,024 deaths.
[a]The analysis was restricted only to person time with daily PM$_{2.5}$ < 30 μg/m^3 (422,637 deaths). [b]The analysis was restricted only to person time with chronic PM$_{2.5}$ < 10 μg/m^3 (268,050 deaths).
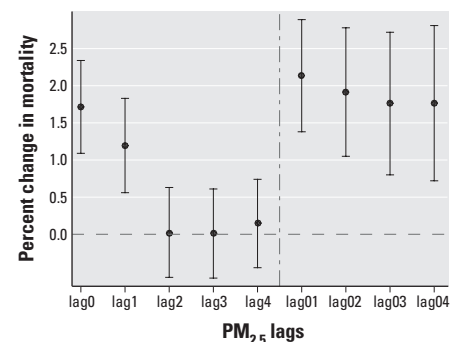

Figure 2. Percent change in mortality per 10-μg/m^3 increase in short-term PM$_{2.5}$ with different lags with mutual adjustment. Error bars indicate the 95% CIs.

on a penalized spline model, the positive dose–response relationship between chronic exposure and mortality appears to be linear for $PM_{2.5}$ concentrations ≥ 6 μg/m³, with a positive (though smaller and less precise) dose–response slope continuing below this level. This lack of power is likely due to the small exposed population in areas with annual $PM_{2.5}$ < 6 μg/m³, which were quite rural.

For acute effects, we found a 2.14% (95% CI: 1.38, 2.89%) increase in all-cause mortality per 10-μg/m³ increment in $PM_{2.5}$ for the full cohort of our study, which is higher than the effect size of most studies using city averages obtained from monitors. For instance, in a U.S. national study by Zanobetti and Schwartz (2009), the effect size was 0.98% (95% CI: 0.75, 1.22%). Similar results were also obtained in a systematic review, where researchers determined that the overall summary estimate was 1.04% (95% CI: 0.52, 1.56%) per 10-μg/m³ increment in $PM_{2.5}$ (Atkinson et al. 2014). The exposure data used in most previous studies had low spatial resolution (citywide average, not ZIP code), which introduced exposure measurement error and likely resulted in a downward bias in estimates; our results (for the acute effect) are consistent with such a phenomenon. Our restricted study estimated a 2.14% (95% CI: 1.34, 2.95%) increase in all-cause mortality per 10-μg/m³ increment in $PM_{2.5}$, which was close to the effect size of the full cohort study, possibly because the sample size of the restricted study for acute effects was close to that of the full cohort. Furthermore, the U.S. EPA daily standard (35 μg/m³) was almost never exceeded in this study. In addition, lower effect estimates for short-term exposure were observed with mutual adjustment for both full cohort and restricted analyses. This finding has important implications for the interpretation of previous studies without such mutual adjustment.

For chronic effects, the effect estimate in our full cohort study was consistent with findings of previous studies with comparable sample sizes (Hoek et al. 2013; Laden et al. 2006; Lepeule et al. 2012). For example, an ACS study comprising 500,000 adults from 51 U.S. cities reported a 6% (95% CI: 2, 11%) increase in all-cause mortality for each 10-μg/m³ increment in $PM_{2.5}$ (Pope et al. 2002). A study of 13.2 million elderly Medicare recipients across the eastern United States found a 6.8% (95% CI: 4.9, 8.7%) increase in all-cause mortality for each 10-μg/m³ increment in $PM_{2.5}$ (Zeger et al. 2008). When we restricted our analysis to annual concentrations < 10 μg/m³, a larger slope of 9.28% (95% CI: 0.76, 18.52%) increase per 10 μg/m³ was observed. Our findings suggest a larger effect at low concentrations among those ≥ 65 years of age, which may also reflect particle composition. The sources and composition of the particles may differ between low-pollution days and high-pollution days, which are likely more affected by secondary aerosols. Compared with the effect estimate for the full cohort, the effect estimate from the restricted analysis was closer to estimates published in the literature that reported larger effect estimates, such as those reported by the ESCAPE (European Study of Cohorts for Air Pollution Effects) study, the Harvard Six Cities study, and the Women's Health Initiative study (Beelen et al. 2014; Puett et al. 2008). Smaller effect estimates were also observed for chronic effects without mutual adjustment.

To the best of our knowledge, this study is the first of its kind to restrict exposure and to explore the dose–response relationship between $PM_{2.5}$ below the current U.S. EPA standards (12 μg/m³ of annual average $PM_{2.5}$, 35 μg/m³ daily) and mortality. Moreover, the use of the Medicare cohort means that we studied the entire population of Medicare enrollees ≥ 65 years of age and not a convenience sample. In addition, temperature was controlled on a 1 km × 1 km fine geographic scale. The acute and chronic effects observed in analyses restricted to low $PM_{2.5}$ exposure were similar to or even higher than those of the full cohort analyses. These results indicate that the adverse health effects of $PM_{2.5}$ are at least retained, if not strengthened, at low levels of exposure. However, the findings from the penalized spline model did not support a strong association at the lowest range of $PM_{2.5}$ concentrations. This finding provides epidemiological evidence for the reevaluation of U.S. EPA guidelines and standards, although more evidence is needed to confirm the association < 6 μg/m³.

The Poisson survival analysis applied in this study provided a novel method of simultaneously assessing acute and chronic effects. As shown in our analysis, the chronic effect estimate was much larger than the acute effect estimate after controlling for the acute estimate, indicating that there were chronic effects of $PM_{2.5}$, which cannot be solely explained by the short-term exposure.

Another key component of this study is that the application of high spatial (1 km × 1 km) and temporal (daily) resolution of $PM_{2.5}$ concentrations reduced exposure error to a certain extent. The out-of-sample R^2 was higher than that for the predictions with 10 km × 10 km spatial resolution.

A potential limitation is the limited availability of individual-level confounders, such as smoking status, which could bias the health effect estimates. We were able to control for ZIP code–level education, median income, race, and county-level smoking data. However, Brochu et al. (2011) reported that census tract–level socioeconomic indicators were uncorrelated with $PM_{2.5}$ on the subregional and local scale, providing some assurance that confounding by socioeconomic status may not be much of an issue. The results reported by Brochu et al. (2011) suggest that those variables may not confound the association, but the inability to control for them remains an issue. Another limitation is that we did not examine other pollutants such as ozone (O_3) or nitrogen dioxide (NO_2) owing to a lack of data at the same spatial level as that of $PM_{2.5}$.

Conclusions

In conclusion, the acute and chronic effects of low-concentration $PM_{2.5}$ were examined for a Medicare population using a comprehensive exposure data set obtained from a satellite-based prediction model. Our findings show that both short- and long-term exposure to $PM_{2.5}$ were associated with all-cause mortality, even for exposure levels not exceeding the newly revised U.S. EPA standards, suggesting that adverse health effects occur at low levels of fine particles. The policy implication of these findings is that improving the air quality at even lower levels of $PM_{2.5}$ than presently allowed by U.S. EPA standards can yield health benefits.
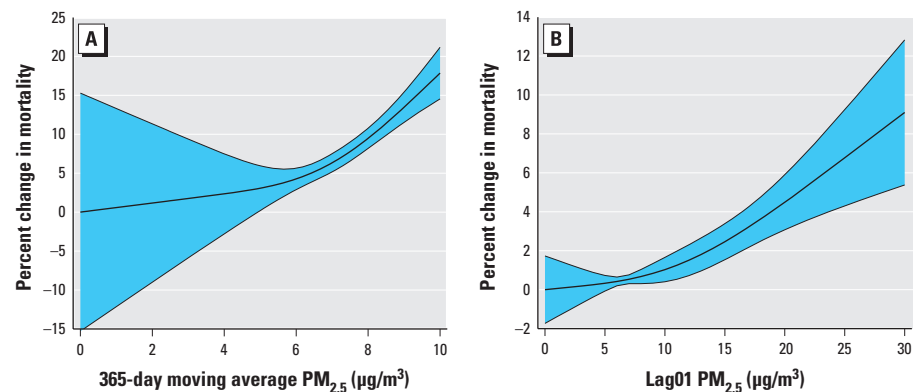

Figure 3. The dose–response relationship between long-term $PM_{2.5}$ and mortality at low doses with mutual adjustment (*A*) and the dose–response relationship between short-term $PM_{2.5}$ and mortality at low doses without mutual adjustment (*B*). Shaded areas indicate the 95% CIs.

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