A growing role for gender analysis in air pollution epidemiology

O papel crescente, na epidemiologia da poluição do ar, da análise relacionada ao sexo da pessoa exposta

Jane E. Clougherty

Abstract: Epidemiologic studies of air pollution effects on respiratory health report significant modification by sex, although results are not uniform. Importantly, it remains unclear whether modifications are attributable to socially derived gendered exposures, to sex-linked physiological differences, or to some interplay thereof. Gender analysis, which aims to disaggregate social from biological differences between males and females, may help to elucidate these possible sources of effect modification. Studies of children suggest stronger effects among boys in early life and among girls in later childhood. The qualitative review describes possible sources of difference in air pollution response between women and men, which may vary by life stage, coexposures, hormonal status, or other factors. The sources of observed effect modifications remain unclear, although gender analytic approaches may help to disentangle gender and sex differences in pollution response. A framework for incorporating gender analysis into environmental epidemiology is offered, along with several potentially useful methods from gender analysis.

Key words: Air pollution, Effect modification, Epidemiology, Gender, Sex

Resumo: Embora sem uniformidade nos resultados, os estudos epidemiológicos dos efeitos da poluição do ar sobre a saúde respiratória relatam variações significativas em função do sexo da pessoa exposta à poluição. Vários estudos sobre adultos relatam efeitos mais severos entre mulheres, particularmente entre as de idade avançada, tais efeitos também estando presentes quando se faz uma avaliação da exposição a um ambiente residencial. Os estudos de crianças sugerem efeitos mais severos na infância de meninos, assim como na pré-adolescência de meninas. A variação na resposta à poluição do ar pode ser uma função quer do estágio vital da pessoa exposta, quer da sua exposição simultânea a fatores diversos, quer do estado hormonal da pessoa em questão ou de outros fatores. As fontes das variações observadas nos efeitos ainda não estão claras, mas as abordagens analíticas relacionadas ao sexo da pessoa exposta poderão ajudar a desemaranhar as diferenças observadas, na resposta à poluição, sujeitas à influência do gênero da pessoa exposta. Apresentamos, aqui, um trabalho estrutural, com o propósito de se passar a incorporar, na epidemiologia ambiental, uma análise em relação ao sexo da pessoa exposta, juntamente com diversos métodos de utilidade potencial a partir da análise relacionada ao sexo da pessoa exposta.

Palavras-chave: Poluição do ar, Variações nos efeitos, Epidemiologia, Gênero, Sexo
There is growing epidemiologic evidence of differing associations between air pollution and respiratory health for females and males. More studies report stronger effects among women and girls than among men and boys, but the literature is far from consistent. Importantly, it is unknown whether observed modification is attributable primarily to biological differences between men and women, to exposure differences (e.g., work-related coexposures), or to some interplay there-of. Gender analysis, which aims to disaggregate social and biological differences between men and women (e.g., hormonal status), may help to elucidate this modification, identify key mechanisms, and design more effective interventions.

The distinction between gender (i.e., self-representation, socially derived activities and roles) and sex (i.e., biological differences by chromosomal complement, including reproductive organs and hormonal composition) speaks to the distinction between exposure and susceptibility. Gender analysis is more common in occupational epidemiology than in environmental health because persistent job stratification by sex has produced marked differences in occupational exposures to chemical agents, ergonomic demands, injury, and psychosocial stressors.

Gender, a social construct, includes cultural norms, roles, and behaviors shaped by relations among women and men and among girls and boys. Gender, inherently social, varies continuously over multiple dimensions over the life course, whereas sex is normally dichotomous. Gender is shaped at the societal level and varies across nation, culture, class, race, ethnicity, nationality, sexuality, and religion. Gender describes patterns of behavior, place, and role, determining where people spend time and their activities, thereby shaping exposure distributions.

Sex, a biological construct, is based on physiologic differences enabling reproduction, defined by physiologic characteristics (especially reproductive organs) or chromosomal complement. Sex-linked traits (e.g., hormonal status, body size) influence biological transport of environment-tally derived chemicals. Lung size and growth, deposition of fine particles (particulate matter d' 2.5 µm in aerodynamic diameter (PM2.5)), gas absorption, gas-blood barrier permeability, airway hyper-responsiveness, vascular response, and inflammation all differ, on average, by sex.

Sex and gender can be difficult to distinguish in epidemiologic data; they are tightly intertwined, with reciprocal effects. Biological characteristics (e.g., body size) become engendered as occupational and family roles, which are gendered expressions of biology. Likewise, gendered work and caregiving roles, smoking, and alcohol consumption influence muscle mass, adiposity, and chemical body burden—collectively, these are socially derived biological expressions of gender.

In this review I present a framework for incorporating gender analysis into air pollution epidemiology, describing pathways through which gender and sex, separately and multiplicatively, may influence pollution response. Current evidence of effect modification in air pollution respiratory epidemiology is summarized, and potentially useful nascent analytic methods from gender analysis are offered.

Gender analysis explores topics far beyond those addressed here, including sexuality and transgender issues. Here I consider only those constructs and tools that may directly inform mean differences between men and women in air pollution epidemiology.

A framework for incorporating gender analysis into environmental epidemiology

Incorporating aspects of gender analysis into the environmental health paradigm (Figure 1) actualizes this distinction between gender and sex. The framework is elucidated by drawing examples.

Figure 1. Possible roles of gender and sex in shaping observed relationships between air pollution and health. Gender affects the presence of the exposure itself (e.g., cosmetic use), whereas biological sex differences determine the consequent dose (e.g., through dermal thickness and permeability). Sex differences in biological transport and target organs determine health outcomes, potentially modified by gendered (behavioral) coexposures and their sequelae.
broadly from environmental epidemiology, elucidating pathways through which gender and sex may, individually and recursively, shape population exposure and susceptibility.

Concentration to exposure

Gender shapes where people spend time and activity patterns—e.g., sports participation, work-related chemical and ergonomic exposures, and use of personal care and cleaning products. Nickel dermatitis and hand eczema are far more prevalent among women than men in Western countries, likely because of chronic exposures from jewelry. Indoor fossil fuel burning for cooking in developing countries drastically increases kitchen PM$_{2.5}$ concentrations; because women generally perform more cooking in these societies, they suffer elevated respiratory symptoms, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), pneumoconiosis, tuberculosis, lung cancer, and mortality. Accordingly, stove-replacement interventions have effectively reduced exposures and improved women’s health in these settings. Gendered home activities shape exposures to cooking exhaust and cleaning products, behaviors and home characteristics that vary by social class, climate, and culture. Residence-based exposure estimates may better capture exposures among homemakers and thus may be more accurate for women than men in most societies.

Exposure to dose

Sex differences in dermal absorption and lung function influence contaminant uptake. Skin metabolizes some xenobiotics, modifying their toxicity; this characteristic differs by sex and is influenced by gendered dermal exposures (e.g., topical creams, cosmetics, jewelry). Respiratory absorption of airborne gases and gas-blood barrier permeability also differ by sex.

Dose to effective dose

Sex determines the availability of target organs and hormonal systemic regulation. Only in women are patterns in ovarian cancer or pregnancy outcomes observable; only in men can testicular cancer patterns be observed. Kinetics and toxicity of chemicals in women’s bodies vary across the life course, during menarche, pregnancy, lactation, and menopause; gastrointestinal cadmium accumulation increases with low iron stores, common during pregnancy and among women of reproductive age. Estradiol and testosterone influence transport of environmentally derived chemicals and accumulation in the brain, kidney, liver, and intestines; mercury retention in kidneys can be three times higher among women than men. During pregnancy (a sex-linked state), activity and exposure patterns change, and hormonal changes affect toxicant transport throughout the body.

Effective dose to health outcome

Sex-linked biological differences influence disease etiology after organ exposure. Women have more arsenic-induced kidney and bladder cancers than do men in regions with arsenic in drinking water, likely because of reduced chemical excretion during pregnancy and lactation. Sex-linked hormonal status alters vascular effects of diesel exhaust. Coexposures from gendered behaviors (e.g., alcohol and tobacco use, cardiovascular exercise) modify the biological fate of environmentally derived chemicals and organ resiliency. Sex and gender effects can interact; sex-linked pregnancy outcomes (observable only among women) are modified by gendered behaviors (e.g., smoking, occupational endocrine disruptors, hairspray exposures). Gender differences in healthcare seeking and illness behaviors influence the progression of environmentally derived illness.

Current evidence of effect modification by sex in air pollution epidemiology

Search methods

A PubMed search, performed in July 2009, retrieved all publications in the database identifiable using the terms “respiratory” and “nitrogen dioxide” (or “NO$_2$”) and any of the following terms: “sex” (n=41 citations), “gender” (n=8), “women and men” (or “men and women”) (n=243), or “girls and boys” (or vice versa) (n=8). Another search retrieved all publications identifiable using “fine particulate matter” (“PM$_{2.5}$”) and “respiratory” and any of the following terms: “sex” (n=11), “gender” (n=5), “women and men” (or vice versa) (n=65), or “girls and boys” (or vice versa) (n=2). Only respiratory outcomes were considered (i.e., diagnosed respiratory illness, symptoms, lung function, respiratory mortality), although the findings and models may apply...
to other outcomes. Papers examining noninhalation pathways were also excluded; thus, effects of prenatal air pollution exposures on infant and child health (which may differentially affect boys) are not considered here.

Of the 383 publications identified, seven review articles were eliminated, along with 30 duplicate citations identified by multiple search criteria, 42 publications not available in English, 50 publications on noninhalation pathways or non-respiratory outcomes, 13 publications on non-human species, and 32 publications not primarily examining air pollution exposures. Abstracts of the remaining 209 publications were reviewed to determine whether effect modification by sex was tested; if the abstract was unclear, the original publication was consulted.

Most publications reported only sex-adjusted effects or examined only one sex. Only 37 unique publications examined air pollution effect modification by sex (summarized in Tables 1 and 2). Given vast differences in analytic methods, outcomes, exposure intensities, and durations – with few studies exploring any combination thereof – meta-analysis was not appropriate. It is beyond the scope of this review to assess the magnitude of effect modification, which varies by study design and outcome measure. Most (not all) of the reviewed publications reported odds ratios or risk ratios, with interactions on the multiplicative scale. Authors also used varying statistical criteria for “significant” interactions (here, p<0.05 unless otherwise stated). Issues in assessment of interactions for epidemiology have been detailed elsewhere50.

The qualitative review documents the widely varying explanations offered to explain observed modifications – as such, only papers in which authors offered such interpretations are included. Accordingly, the results described here, and summarized in Tables 1 and 2, are not exhaustive, but represent effect modification as reported by the authors. Only a few studies took additional analytic steps to examine sources of differences that may account for observed effect modification.

Search results

Because gender differences in behaviors, exposures, or coexposures (e.g., diet, smoking) and biological factors (e.g., hormonal composition) change over the life course, studies are summarized separately for adults and children.

Gender and sex differences in respiratory health effects among adults: studies reporting stronger effects among women

Studies of residential air pollution exposures suggest stronger associations among women. In the Atherosclerosis Risk in Communities (ARIC) study, Kan et al.51 found that living near a major road predicted lower forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) only among women. The authors pointed to women's greater airway reactivity, citing stronger responses to smoking52-54, or better accuracy in residential exposure assessment for homemakers (35% of ARIC women vs. 17% of men).

Franklin et al.55 studied 130,000 respiratory deaths in 27 U.S. communities, using case-crossover methods and meta-analysis, and found that community air pollution better predicted death among women than among men. The authors proposed sex-differing respiratory anatomy and physiology, or PM deposition patterns.

In a comprehensive study of daily air pollution and respiratory hospitalization among adults and children in Windsor, Ontario, using time-series and case-crossover methods, Luginaah et al.56 reported a larger number of significant associations among women, and girls than among men and boys.

Table 1. Studies examining effect modification by sex among adults.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s)</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies reporting stronger effects among women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Franklin et al.55</td>
<td>1.3 million deaths, 27 U.S. cities 1997-2002</td>
<td>Prior day PM $\text{µg/m}^3 &gt; 10$</td>
<td>Percent increase in respiratory mortality</td>
<td>$1.90$ ($0.14$-$3.65$)</td>
<td>$1.57$% ($-0.22$ to $3.35$)</td>
</tr>
<tr>
<td>Ito and Thurston57</td>
<td>Daily deaths in Chicago, IL 1985-1990</td>
<td>Daily PM $\text{µg/m}^3$ at nearest regulatory monitor</td>
<td>RR for respiratory mortality</td>
<td>$RR = 1.10$ ($0.97$-$1.26$)</td>
<td>$RR = 1.17$ ($1.02$-$1.35$)</td>
</tr>
</tbody>
</table>

it continues
### Table 1. continuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s)</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kan et al.(^5^1)</td>
<td>15,792 middle-age U.S. adults, 1987-1989 (ARIC cohort)</td>
<td>Quartiles of residential traffic density</td>
<td>Lung function: FEV1/FVC</td>
<td>β (Q4, age adjusted) = 19.6 (-34.9 to 74.1); p-trend = 0.66</td>
<td>β (Q4, multivariate) = 11.7 (-40.2 to 63.5); p-trend = 0.86</td>
</tr>
<tr>
<td>Kan et al.(^5^8)</td>
<td>Adult population of Shanghai, China (population, 13.1 million)</td>
<td>10-µg/m(^3) increase in daily PM(_{2.5}), SO(_2), NO(_x), O(_3)</td>
<td>Percent increase in respiratory mortality</td>
<td>β (PM(_{2.5})) = 0.17% (0.03 to 0.32); β (SO(_2)) = 0.85% (0.43 to 1.28); β (NO(_x)) = 0.88% (0.49 to 1.28); β (O(_3)) = 0.19% (-0.16 to 0.55)</td>
<td>β (PM(_{2.5})) = 0.33% (0.18-0.48); β (SO(_2)) = 1.06% (0.62-1.51); β (NO(_x)) = 1.10% (0.69-1.51); β (O(_3)) = 0.40% (0.03-0.76)</td>
</tr>
<tr>
<td>Luginaah et al.(^5^6)</td>
<td>1,602 adults (15-64 years) in Windsor, Ontario, Canada 1995-2000</td>
<td>IQR increase in 1-, 2-, 3-day lag NO(_x), SO(_x), CO, COH, O(<em>3), PM(</em>{10}), TRS</td>
<td>Risk of respiratory hospitalization</td>
<td>RR (2-day COH) = 1.04 (0.82-1.32); RR (3-day COH) = 0.95 (0.80-1.13)</td>
<td>RR (2-day COH) = 1.20 (1.00-1.43), by case crossover; RR (3-day COH) = 1.15 (1.02-1.30), by time series</td>
</tr>
<tr>
<td>Sunyer et al.(^5^9)</td>
<td>2,305 adults (≥ 35 years of age) Spain, 1985-1989</td>
<td>20-µg/m(^3) increase in same-day ambient black smoke</td>
<td>Respiratory mortality</td>
<td>OR = 1.14 (0.98-1.33)</td>
<td>OR = 1.52 (0.99-2.31)</td>
</tr>
<tr>
<td>Sunyer et al.(^5^9)</td>
<td>3,232 men and 3,592 women in Europe</td>
<td>Constant traffic density NO(_x) &gt; 50 µg/m(^3)</td>
<td>Prevalence of chronic phlegm</td>
<td>β (traffic) = 6.13% (4.37-8.32); p-trend = 0.47</td>
<td>β (traffic) = 7.69% (5.95-9.75); p-trend = 0.002</td>
</tr>
<tr>
<td>Thaller et al.(^6^1)</td>
<td>142 lifeguards 16-27 years of age (79% male)</td>
<td>10-µg/m(^3) increase daily average PM2.5, maximum O(_3)</td>
<td>FVC FEV1/FVC</td>
<td>β (PM(_{2.5})) = -0.1% (-0.8 to 0.5); β (O(_3)) = -0.006% (-0.2 to 0.05)</td>
<td>β (PM(_{2.5})) = -2.1% (-3.2 to -1.0); β (O(_3)) = -0.3% (-0.4 to -0.6)</td>
</tr>
</tbody>
</table>

**Studies reporting stronger effects among men**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s)</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbey et al.(^6^2)</td>
<td>1,391 nonsmoking U.S. adults</td>
<td>IQR difference of 54.2 days/year &gt; 100 µg/m(^3) PM(_{10})</td>
<td>PPFEV(_i)</td>
<td>β = -7.2 (-11.5 to -2.7) (males w/ parental respiratory illness)</td>
<td>β = 0.9 (-0.8 to 2.5)</td>
</tr>
<tr>
<td>Galizia &amp; Kinney(^6^3)</td>
<td>520 nonsmoking undergraduate students in New Haven, CT</td>
<td>Lived ≥ 4 years in U.S. county with Summer 1-hr O(_3) ≥ 80 ppb</td>
<td>Percent change in FEV1, FEF(<em>{25-75}), FEF(</em>{75}) symptoms</td>
<td>β = -4.7% (-0.7 to -0.8); β = -13.0% (-4.9 to -21.1); β = -10.0% (1.3 to -21.3)</td>
<td>OR = 2.30 (1.15-4.36); OR = 1.79 (0.83-3.89)</td>
</tr>
<tr>
<td>Korrick et al.(^6^4)</td>
<td>530 hikers (18-64 years), Mt. Washington, NH</td>
<td>Ambient O(_3), PM2.5, aerosol acidity</td>
<td>Percent change in FEV1,FVC</td>
<td>β = -0.055 (SE = 0.025); β = 0.051 (SE = 0.016); β = -0.019 (SE = 0.025)</td>
<td>β = -0.039 (SE = 0.039); β = 0.009 (SE = 0.025)</td>
</tr>
<tr>
<td>Wang et al.(^6^5)</td>
<td>1,075 Chinese adults (35-60 years)</td>
<td>Ambient PM(_{15}) and SO(_x) (rural vs urban area)</td>
<td>Mean change FEV1</td>
<td>199 mL (SE = 50 mL)</td>
<td>87 mL (SE = 30 mL)</td>
</tr>
</tbody>
</table>

It continues
Two-day lagged coefficient of haze (COH) exposures predicted increased risks among women. For girls 0-14 years of age, 1- to 2-day lagged NO₂, sulfur dioxide (SO₂), and carbon monoxide (CO) exposures predicted elevated risks. Among males, only 1-day lagged PM₁₀ predicted increased risks among adults. The authors proposed sex-differing biological explanations (e.g., hormonally affected inflammation, smooth muscle and vascular function, lung growth and decline, airway and parenchymal size), citing evidence of sex-differing airway PM₂.₅ deposition⁶⁵,⁷¹ and greater responsivity to tobacco smoke among females⁷²-⁷⁸. They considered gendered explanations; women are, on average, poorer and may experience greater (or different) psychosocial stressors, perform more household tasks (increasing exposures to viral infection, indoor allergens, combustion exhaust, cleaning solvent, and aeroallergens)⁷⁹, and may differ from men in healthcare seeking and illness management behaviors⁸⁰.

One Chicago cohort studied by Ito and Thurston⁵⁷ showed greater all-cause and respiratory mortality with same- and previous-day PM₁₀ among black women than among other sex/race groups. The authors observed that physiologic differences and gender differences in activities, occupation, and class may shape pollution response, noting that race and gender were yet unexplored in environmental epidemiology.

In the Public Health and Air Pollution in Asia (PAPA) study, Kan et al.⁵⁸ reported stronger associations between pollutants [PM₁₀ (PM with aerodynamic diameter < 10 µm) SO₂, NO₂, ozone (O₃)] and daily respiratory mortality among women, elderly, and lower socioeconomic status (SES) persons. The authors offered gendered explanations (e.g., smoking among men may obscure pollution effects; Shanghai women's lower average education may confound gender and SES) and considered biological explanations, including women's smaller airways, greater airway reactivity⁵⁴, and greater deposition of PM₂.₅⁵⁶,⁷¹.

Among 6,824 adults in 10 European countries in the European Community Health Survey 2000-2002 (ECRHS I), Sunyer et al.⁶⁰ found that home traffic intensity and outdoor NO₂ better predicted chronic bronchitis among women than among men. The authors also examined occupational exposures, which better predicted out-

<table>
<thead>
<tr>
<th>Table 1. continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Ackermann-Liebrich et al.⁶⁶</td>
</tr>
<tr>
<td>Chestnut et al.⁶⁴</td>
</tr>
<tr>
<td>Jedrychowski and Krzyzanowski⁶⁸</td>
</tr>
<tr>
<td>Oosterlee et al.⁶⁵</td>
</tr>
<tr>
<td>Zeka et al.⁷⁰</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OR, odds ratio; PPFEV₁, percent predicted FEV₁; RR, relative risk; Q, quartile; SAPALDIA, Study on Air Pollution and Lung Diseases in Adults; TRS, total reduced sulfur; VC%, vital capacity percent. Key results demonstrate observed effect modification, and are not exhaustive of results reported for each study. Values in parentheses are 95% confidence intervals, unless otherwise indicated. *Other outcomes showed no significant effect modification by sex.* Effects did not differ by sex, and therefore are reported here in only one column.
Table 2. Studies examining effect modification by sex among children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s) of interest</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunekreef et al.⁵¹</td>
<td>877 Dutch children (7-12 years of age) in Windsor, Ontario, Canada, 1995-2000</td>
<td>Truck traffic density (for children within 300 m of motorway) IQR increase in 1-, 2-, 3-day lag NO₂, SO₂, CO, COH, O₃, PM₁₀, TRS</td>
<td>Change in FVC, FEV₁</td>
<td>β = -1.1 (-6.7 to 4.9)</td>
<td>β = -6.3 (-11.4 to -0.8)</td>
</tr>
<tr>
<td>Luginaah et al.⁵⁶</td>
<td>883 children (0-14 years of age) in Oslo, Norway</td>
<td>IQR increase in lifetime NO₂, PM₁₀</td>
<td>RR of respiratory hospitalization</td>
<td>RR (lag1 SO₂) = 0.95 (0.87 to 1.04)</td>
<td>RR (lag1 NO₂) = 0.996 (0.93 to 1.06)</td>
</tr>
<tr>
<td>Oftedal et al.⁵²</td>
<td>2,307 9- and 10-year-old children in Oslo, Norway</td>
<td>IQR increase in lifetime NO₂, PM₁₀, PM₂⁵</td>
<td>Change in PEF, FEF₂₅, FEF₅₀</td>
<td>β (NO₂) = -69.1 mL/sec (-135.3 to -3.0)</td>
<td>β (PM₁₀) = -77.9 mL/sec (-141.9 to -14.0)</td>
</tr>
<tr>
<td>Oosterlee et al.⁵⁹</td>
<td>291 Haarlem, Netherlands, children (0-15 years of age)</td>
<td>Living on heavy (vs. light) trafficked streets</td>
<td>Wheeze (ever)</td>
<td>RR = 0.9 (0.2-3.2)</td>
<td>OR = 4.8 (1.3-17.7)</td>
</tr>
<tr>
<td>Pershagen et al.⁵³</td>
<td>197 children (4 months to 4 years) hospitalized with wheeze, 350 controls</td>
<td>Residential outdoor NO₂, presence of gas stove</td>
<td>RR (NO₂ &gt; 0.7) = 0.7 (0.4-1.3); p-trend = 0.10</td>
<td>RR (NO₂ &gt; 0.7) = 0.7 (0.4-1.3); p-trend = 0.10</td>
<td>RR (gas stove) = 2.4 (1.0-5.9)</td>
</tr>
<tr>
<td>Peters et al.⁵⁴</td>
<td>3,293 children in 12 Southern California communities</td>
<td>Lifetime ambient NO₂, PM₁₀, and O₃</td>
<td>Change in FVC, FEV₁, FEV₁, MM EF</td>
<td>β (NO₂) = -29.9 L/min (SE = 29.5)</td>
<td>β (NO₂) = -63.8 (SE = 18.3)</td>
</tr>
<tr>
<td>Rojas-Martinez et al.⁵⁵</td>
<td>3,170 children (8 years of age) in Mexico City, 1996-1999</td>
<td>IQR increase in mean O₃, PM₁₀</td>
<td>Change in FEV₁</td>
<td>β (O₃) = -4 mL (-10 to 2)</td>
<td>β (O₃) = -12 mL (-18 to -6)</td>
</tr>
<tr>
<td>Rosenlund et al.⁵⁶</td>
<td>2,107 children 9-14 years of age in 40 Rome schools</td>
<td>Residual trafficDistance to busy road Modeled NO₂</td>
<td>Percent difference in FEV₁, FEF₂₅</td>
<td>β = -0.4% (p = 0.29 to 0.72)</td>
<td>β = -2.5% (-4.9 to 0.6)</td>
</tr>
<tr>
<td>Stern et al.⁵⁷</td>
<td>1,630 children (7-12 years of age) in rural Canada</td>
<td>High- vs. low-exposure community</td>
<td>Percent difference in FEV₁, FEF₂₅</td>
<td>β = 1.45% (p = 0.05)</td>
<td>β = 2.53% (p &lt; 0.001)</td>
</tr>
<tr>
<td>Van Vliet et al.⁵⁸</td>
<td>1,496 children in 13 schools</td>
<td>Residence within 100 m of freeway</td>
<td>Chronic cough, Wheeze</td>
<td>OR = 1.05 (0.50-2.22)</td>
<td>OR = 2.45 (1.16-5.16)</td>
</tr>
</tbody>
</table>

It continues.
### Table 2. continuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s) of interest</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies reporting stronger effects among boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defino et al.</td>
<td>14 boys and 5 girls with asthma, 9-17 years of age</td>
<td>IQR increase in 4-day personal PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>( \beta = -16% ) (-26 to -6)</td>
<td>( \beta = -1% (-16 to 14)</td>
</tr>
<tr>
<td>Gehring et al.</td>
<td>1,756 German infants</td>
<td>Outdoor residential exposure gradient 1.5 mg/m&lt;sup&gt;3&lt;/sup&gt; in PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Cough without infection</td>
<td>OR (PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.43 (1.14-1.80)</td>
<td>OR (PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.19 (0.84-1.70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dry cough at night</td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.38 (1.11-1.71)</td>
<td>OR (PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.39 (1.08-1.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.52 (1.16-2.00)</td>
<td>OR (PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.07 (0.78-1.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.39 (1.04-1.67)</td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.45 (1.07-1.98)</td>
</tr>
<tr>
<td>Jedrychowski et al.</td>
<td>1,001 children in Krakow, Poland</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt; 0.4 × 10&lt;sup&gt;-5&lt;/sup&gt;/m&lt;sup&gt;3&lt;/sup&gt; in PM&lt;sub&gt;2.5&lt;/sub&gt; NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Slower growth in FVC</td>
<td>OR (FEV&lt;sub&gt;1&lt;/sub&gt;) = 1.90 (1.12-3.25)</td>
<td>OR (FEV&lt;sub&gt;1&lt;/sub&gt;) = 1.90 (1.04-2.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.47 (1.04-2.09)</td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.55 (1.03-2.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (acid) = 1.55 (1.03-2.32)</td>
<td>OR (acid) = 1.55 (1.03-2.32)</td>
</tr>
<tr>
<td>Peters et al.</td>
<td>3,676 children in 12 Southern California communities</td>
<td>IQR difference in community lifetime ambient acid, NO&lt;sub&gt;2&lt;/sub&gt;, PM&lt;sub&gt;2.5&lt;/sub&gt;, O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Prevalence of wheeze</td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.47 (1.04-2.09)</td>
<td>OR (NO&lt;sub&gt;2&lt;/sub&gt;) = 1.47 (1.04-2.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (acid) = 1.55 (1.03-2.32)</td>
<td>OR (acid) = 1.55 (1.03-2.32)</td>
</tr>
<tr>
<td><strong>Studies reporting null or mixed modification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emenius et al.</td>
<td>540 Stockholm children (0-2 years of age)</td>
<td>Indoor and outdoor residential NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>OR for recurrent wheeze (high vs. low quartile)</td>
<td>OR (outdoor NO&lt;sub&gt;2&lt;/sub&gt;) = 1.60 (0.78-3.26)*</td>
<td>OR (outdoor NO&lt;sub&gt;2&lt;/sub&gt;) = 1.60 (0.78-3.26)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (indoor NO&lt;sub&gt;2&lt;/sub&gt;) = 1.51 (0.81-2.82)</td>
<td>OR (indoor NO&lt;sub&gt;2&lt;/sub&gt;) = 1.51 (0.81-2.82)</td>
</tr>
<tr>
<td>Gauderman et al.</td>
<td>1,759 children in 12 Southern California communities</td>
<td>Lifetime community annual average NO&lt;sub&gt;2&lt;/sub&gt;, PM&lt;sub&gt;2.5&lt;/sub&gt;, EC (most vs. least polluted)</td>
<td>Growth in FVC</td>
<td>( \beta ) (NO&lt;sub&gt;2&lt;/sub&gt;) = -95.0 (-189.4 to -0.6)*</td>
<td>( \beta ) (NO&lt;sub&gt;2&lt;/sub&gt;) = -101.4 (-164.5 to -38.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \beta ) (NO&lt;sub&gt;2&lt;/sub&gt;) = -110.1 (-187.6 to -33.4)</td>
<td>( \beta ) (NO&lt;sub&gt;2&lt;/sub&gt;) = -211.0 (-377.6 to -44.4)</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>6,782 Toronto, Canada children, 0-14 years of age</td>
<td>6.5 µg/m&lt;sup&gt;3&lt;/sup&gt; increase in 6-day PM&lt;sub&gt;10-2.5&lt;/sub&gt; exposure</td>
<td>Hospitalizations for respiratory infections</td>
<td>( \beta ) = 1.15% (1.02-1.30)</td>
<td>( \beta ) = 1.18% (1.01-1.36)</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>182 asthmatic children 9-14 years of age in Windsor, Ontario, Canada</td>
<td>IQR change in same-day, lagged SO&lt;sub&gt;2&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;, O&lt;sub&gt;3&lt;/sub&gt;, PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Percent change in FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>( \beta ) (same-day NO&lt;sub&gt;2&lt;/sub&gt;) = -2.4 (-4.3 to -0.4)</td>
<td>( \beta ) (same-day PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.9 (-3.5 to -0.3)</td>
</tr>
<tr>
<td>Roemer et al.</td>
<td>1,621 children in 14 European centers, 1993-1994</td>
<td>24-hr measures of PM&lt;sub&gt;2.5&lt;/sub&gt;, BS, SO&lt;sub&gt;2&lt;/sub&gt;, NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Change in evening PEF per 100 µg/m&lt;sup&gt;3&lt;/sup&gt;</td>
<td>( \beta ) (lag 0 SO&lt;sub&gt;2&lt;/sub&gt;) = 1.9 L/min (p &lt; 0.05)</td>
<td>( \beta ) (lag 0 SO&lt;sub&gt;2&lt;/sub&gt;) = 1.4 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \beta ) (lag 0 BS) = 0.7 L/min (p &lt; 0.10)</td>
<td>( \beta ) (lag 0 BS) = 0.2 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>( \beta ) (lag 2 PM&lt;sub&gt;2.5&lt;/sub&gt;) = -0.5 L/min (NS)</td>
<td>( \beta ) (lag 2 PM&lt;sub&gt;2.5&lt;/sub&gt;) = 1.2 (p &lt; 0.05)</td>
</tr>
</tbody>
</table>

NR: effects did not differ by sex
Table 2. continuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Exposure metric(s)</th>
<th>Outcome(s) of interest</th>
<th>Risk among males</th>
<th>Risk among females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz97</td>
<td>4,300 youths (6-24 years of age), NHANES II, 1976-1980</td>
<td>Annual average SO₂, NO₂, TSP, O₃ at monitors</td>
<td>Change in FVC, FEV₁, PEF</td>
<td>β (NO₂) = -2.94 (p = 0.0004)</td>
<td>NR; effects did not differ by sex</td>
</tr>
<tr>
<td>Smith et al.98</td>
<td>44 asthmatic children (&lt; 14 years of age)</td>
<td>Daily personal NO₂ exposure</td>
<td>Chest tightness</td>
<td>OR = 1.29 (1.16, 1.43)</td>
<td>NR; effects did not differ by sex</td>
</tr>
<tr>
<td>Zhao et al.99</td>
<td>1,993 pupils (11-15 years of age) in urban China</td>
<td>School indoor and outdoor SO₂, NO₂, O₃</td>
<td>Asthma, wheeze</td>
<td>OR (wheeze, indoor SO₂) = 1.18 (1.03-1.35)</td>
<td>NR; effects did not differ by sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR (wheeze, indoor CH₂O) = 1.24 (1.03-1.48)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: abs, absorbance; BS, black smoke; CH₂O, formaldehyde; EC, elemental carbon; IQR, interquartile range; MMEF, median mid-expiratory flow; NR, not reported; NS, not significant; OR, odds ratio; PEFR, peak expiratory flow rate; RR, relative risk; TRS, total reduced sulfur. Key results demonstrate observed effect modification, and are not exhaustive of results reported for each study. Values in parentheses are 95% confidence interval, unless otherwise indicated. *Effects did not differ by sex, and therefore are reported here in only one column.

comes among men, separating some gendered activity pattern effects. The authors suggested sex-linked differences in hormonal status, and gender differences in coexposures, disease perception, health care access and use and differing perceptions of environmental quality and symptoms by gender and education.

Sunyer et al.59 found that older and female Barcelona adults with COPD showed greater all-cause, respiratory, and cardiovascular mortality with same-day black smoke than did younger persons and men. The authors suggested the reasons were a higher prevalence of frail persons among the elderly and women than among men, or biological differences, including inflammatory response (given women's stronger response to smoking77,78), lung size, and airway diameter influencing PM deposition, respiratory patterns, and airway resistance100.

Studies reporting stronger effects among men

In the 20-year prospective California Adventists Health Study, Abbey et al.62 linked PM₁₀ to reduced lung function (FEV₁/FVC) among non-smoking males, and decreased FEV₁ among men with parental respiratory illness. Women and never-smoking males displayed increased peak expiratory flow (PEF) lability. Among males, sulfate exposures predicted reduced FEV₁, and O₃ exposures predicted reduced FEV₁, among men with parental respiratory illness. The authors suggested gender differences in work-related exposures or possible stronger healthy worker effects among women. They confirmed that cohort men spent more time outdoors (16.1 hr/week vs. 9.2 hr/week; p < 0.0005) and suggested that outdoor exposures may trigger responses in males with genetic predisposition to respiratory illness.

Galizia and Kinney63 found that, among Yale freshmen, growing up in areas with high (vs. low) O₃ was associated with symptoms and reduced lung function among males but not among females. The authors suggested the gendered explanation that men may accumulate greater O₃ exposures through outdoor physical activity.

Studies reporting null or mixed modification

Zeka et al.70 found that ambient PM₁₀ was associated with respiratory and all-cause mortality across 20 U.S. cities, using case-crossover analysis. Although modification was nonsignificant, the authors posited that sex, race, and age may indicate SES, increasing susceptibility through lesser health care access, poorer nutrition, greater stress or violence exposures, or increasing actual exposures through residential
proximity to high-ways or occupational coex-
posures. Finally, they suggest sex-linked biologi-
cal differences in PM deposition.

In a 13-year follow-up of Krakow adults, Jedrychowski and Krzyzanowski\textsuperscript{68} found that residence in higher sulfate areas better predicted FEV\textsubscript{1}, decrements among men than among women. Among women, SO\textsubscript{2}, and PM correlated with symptoms; the authors suggested that women's greater average spent time near home produced better accuracy in exposure assessment.

Disentangling gender and sex effects in air pollution-health associations among children may be more complicated, because lung function growth rates (critical periods for pollution effects) differ by sex\textsuperscript{101}. Most air pollution epidemiology studies among children examine chronic exposures, although outcomes considered vary widely, including lung function growth, wheeze, asthma onset and exacerbation, and symptoms.

Studies reporting stronger effects among girls

Using baseline cross-sectional results from the Southern California Children's Health Study (CHS) of children in grades 4, 7, and 10 in 12 communities, Peters et al.\textsuperscript{84} reported that air pol-
lutants (PM\textsubscript{10}, PM\textsubscript{2.5}, acid vapor, NO\textsubscript{2}, O\textsubscript{3}) were more strongly inversely associated with lung function among girls than among boys. The authors suggested gender differences in time outdoors and play activities, and sex differences in growth rates, hormonal factors, and respiratory mechanisms. Using longitudinal CHS analyses, Gauderman et al.\textsuperscript{85} found deficits in FEV\textsubscript{1} growth from 10 to 18 years of age associated with community NO\textsubscript{2}, PM\textsubscript{2.5}, and acid vapor not significantly differ-
ing by sex. McConnell et al.\textsuperscript{100} reported higher asthma risk with out-door sports participation in higher O\textsubscript{3} areas in the CHS cohort, especially among girls, and suggested that higher ventilation during play may increase exposures.

In a U.S. study, Neas et al.\textsuperscript{102} reported stronger associations between home indoor NO\textsubscript{2} and respiratory symptoms among girls than among boys 7-11 years of age. The authors cited reports of stronger effects among girls, including a British study linking gas stove use to symptoms among girls\textsuperscript{104}, a paper reporting FEV\textsubscript{75} (75th percentile) decrements of 1.1% among girls 9-13 years of age but slight increases among boys\textsuperscript{105}, and a British study linking kitchen NO\textsubscript{2} and gas stoves to greater reductions in PEF and forced expiratory flow between 25th and 75th percentile (FEF\textsubscript{25-75}) among girls\textsuperscript{106}.

Among Dutch children 7-12 years of age, Brunekreef et al.\textsuperscript{103} found that truck traffic and black smoke at schools were associated with lung function reductions only among girls, and van Vliet et al.\textsuperscript{88} found that residential distance from freeway, truck traffic density, and school black smoke measures better predicted chronic respiratory symptoms among girls than among boys, after accounting for SES and home exposures. In both studies, the authors contrast their results with evidence of stronger passive smoke effects among boys. However, these studies examine in utero exposures and noninhalation pathways\textsuperscript{107,108}, and suggest that, because boys exhibit it more symptoms overall, air pollution effects may be obscured by other respiratory "noise"\textsuperscript{109}.

Among 673 adults and 106 children in Haarlem, the Netherlands, Oosterlee et al.\textsuperscript{90} reported significant associations between living along busy (vs. quiet) streets and asthma or dyspnea only among girls. They suggested that boys' higher total respiratory symptoms may mask pollution effects, and considered gendered factors (e.g., passive smoking, activity patterns, coexposures) in their analysis.

In Oslo, Norway, Oftedal et al.\textsuperscript{82} found that lifetime residential NO\textsubscript{2}, PM\textsubscript{10}, and PM\textsubscript{2.5} among 9- and 10-year-old children was associated with lower PEF, more strongly among girls, only slightly attenuated by SES adjustment. The authors suggested biological explanations (e.g., girls experience growth spurts earlier, captured within this follow-up, or hormonal status may alter girls' responses) and suggested unmeasured SES-related confounders (e.g., gendered sports-participation).

In a case-control study in Stockholm, Pershagen et al.\textsuperscript{83} reported significant associations between outdoor home NO\textsubscript{2} and gas stove use on wheezing bronchitis only among girls, despite boys' higher wheezing prevalence. Outdoor NO\textsubscript{2}, gas stove use, and smoking conferred multiplicative risks in girls but not in boys, after SES adjustment. The authors reported consistency with prior studies, indicated that results were unlikely due to selection bias or misclassification, and acknowledged a need for activity data to explore gender differences.

Rosenlund et al.\textsuperscript{86} found associations between chronic residential NO\textsubscript{2} exposure and lung function to be stronger among Roman girls than boys.
9-14 years of age; mean FEV\textsubscript{1} and FEF\textsubscript{25-75} decrements were approximately four times greater in girls than boys, corroborating other studies\textsuperscript{82,83,103,108-112}. The authors indicated complexities in comparing childhood cohorts differing by age, pubertal status, pollution mixtures, study designs, and susceptibilities and noted that the consistency of results across Europe reporting stronger air pollution effects among girls, merit further investigation.

Studies reporting stronger effects among boys

In the Traffic-Related Air Pollution on Childhood Asthma (TRAPCA) study, Gehring et al.\textsuperscript{90} reported stronger associations between residential PM\textsubscript{2.5} and symptoms (e.g., cough without infection, cough at night) among boys than among girls 0-2 years of age. The authors suggested that differences in total symptoms, masking pollution effects, were important or that, given sex differences in lung development, infant girls have larger airways relative to body size and lesser airway resistance.

In a prospective cohort study of annual mean total suspended particle (TSP) and SO\textsubscript{2} exposures among preadolescent children in Krakow, Poland, Jedrychowski et al.\textsuperscript{91} reported stronger associations with FVC and FEV\textsubscript{1} among boys than among girls. The authors noted sex-differing lung growth rates, producing different critical periods for pollution effects.

Studies reporting null or mixed effect modification

In a 3-year prospective study of children in Mexico City, Mexico, Rojas-Martinez et al.\textsuperscript{85} associated elevated PM\textsubscript{10}, NO\textsubscript{2}, and O\textsubscript{3} with reduced lung function among boys and girls. Interquartile range increases in NO\textsubscript{2} predicted FEV\textsubscript{1} declines in girls, whereas increases in PM\textsubscript{10} predicted FEV\textsubscript{1} declines among boys. Elevated O\textsubscript{3} predicted FEV\textsubscript{1} decreases three times larger among girls than among boys, unexplained by SES. The authors compared these findings with CHS results on sex-differing lung function growth and suggested higher O\textsubscript{3} exposures among children spending time outdoors\textsuperscript{102,113}.

In Toronto (Ontario, Canada), respiratory hospitalizations were significantly associated with PM\textsubscript{2.5-10} among boys and girls, with PM\textsubscript{10} among boys, and with NO\textsubscript{2} among girls\textsuperscript{84}. The authors proposed sex-linked explanations: boys have smaller airways relative to lung volume and differ in smooth muscle, vascular function, and hormonal status.

Discussion

Among adults, evidence of effect modification by sex remains uncertain; studies of older adults and those using residential exposure estimates suggest stronger effects among women. The range of plausible explanations is very broad, including sex-linked biological factors related to lung volume, deposition, reactivity, and hormonal influences on chemical transport and systemic regulation. Gendered explanations include confounding or modification by smoking behaviors, job-related chemical exposures, differential accuracy in residence-based exposure assignment, exposures to indoor allergens and cleaning agents, and differing exposure and response to psychosocial stressors. Refined distinction between sex and gender may elucidate these associations.

Studies of younger children suggest stronger associations among boys; older childhood cohorts suggest the opposite. Age-related trends may be linked to sex-differing lung function growth rates\textsuperscript{114} and differences in airway function at birth, which suggest lower respiratory volumes and greater airway resistance among boys\textsuperscript{115}. At older ages, gendered activities may also shape pollution response.

Gender, sex, and multiple exposures

Environmental exposures are complex. Traffic-related air pollution includes gaseous species and PM from combustion, tire and brake wear, resuspended roadway dusts, and salts\textsuperscript{116}. Pollution exposures occur in multiplicity, and polluted neighborhoods often also suffer poverty, crime, and lower access to health-related resources\textsuperscript{117}. In workplaces, chemical exposures co-vary with heat, noise, and strain, acting recursively and synergistically on workers’ health\textsuperscript{118}. Gender analysis fits into environmental health under this multiple exposures framework. There is growing interest in pollution effect modification by SES\textsuperscript{119,120} and chronic stress\textsuperscript{117,121-123}. Likewise, SES is a complex mix of social and physical stressors accumulating over the life course\textsuperscript{124}, shaping health and susceptibility. Behavioral and physiologic responses to SES and stressors may vary by gender\textsuperscript{125}; women, on average, may respond more strongly to interpersonal stressors\textsuperscript{126} and experi-
ence different physiologic sequelae\textsuperscript{22,127,128}. Women's behavioral responses may emphasize social support, caregiving, and child tending\textsuperscript{29}, whereas better-known "fight-or-flight" responses emphasize sympathetic-adrenal-medullary enervation and activities linked to traditionally male roles\textsuperscript{29,130}. Stress may be a gendered factor (i.e., exposures differ by gender) and a sex-differing factor as well, if physiologic responses to stress differ (e.g., sex-differing epinephrine responses). If stress modifies pollution response, then understanding gendered stress responses is likely important for accurately characterizing gendered pollution responses.

Research from social geography may help to better elucidate gendered spatial and behavioral exposure patterns. Gendered use of space and exposure patterns in urban communities is evident in the example of fear of violence. One large U.S. survey reported that 26% of women "never" leave home after dark (vs. 9% of men), 51% "always" bring friends for protection (vs. 4% of men), and 71% consider safety when parking (vs. 33% of men)\textsuperscript{131}. Strong gender differences in perceived safety shape activity and exercise patterns; parents' greater restriction of girls' geographic range in U.S. cities shapes exposure paradigms, exercise, experience, and developmental opportunity\textsuperscript{132}. Better understanding the gendered environment can improve exposure assessment, better isolate biological responses, and provide a model for examining other social effect modifiers\textsuperscript{133}.

Analytic approaches for disentangling effects of gender and sex

Because gender and sex are tightly intertwined, their effects can be difficult to distinguish in epidemiologic data. "Gender" and "sex" have commonly been conflated in epidemiologic research\textsuperscript{1}. Most important, careful use of language distinguishing these constructs will enable researchers to better describe and understand sources of difference in exposure-health relationships. Methodology for gender analysis is an evolving field, although the methods described here may help to disentangle some effects of sex and gender and may merit further exploration in environmental epidemiology.

Reporting sex-stratified results is more informative than is adjustment for sex\textsuperscript{2} and can identify associations differing broadly between males and females. However, sex stratification often confounds tightly correlated gender and sex effects, obscuring true sources of difference. Preferably, researchers may stratify data separately by multiple sex- and gender-associated factors (e.g., body size, working outside the home, time spent on household tasks) to elucidate sources of difference. Most epidemiologic data sets are not adequately powered to perform multiple stratifications simultaneously, so these multiple stratifications usually need be performed separately. Stratification variables should reflect time-activity patterns or meaningful biological factors, rather than stereotypical attributes, to identify true factors relevant to the cohort under study.

Population-specific exposure modeling may improve culturally and behaviorally specific exposure assessment, clarifying gendered exposure differences. Residential exposure metrics may be more accurate for women, who spend more time near home on average, especially when caring for children or other family members\textsuperscript{134-137}. Residential activities may require microniche exposure assessment\textsuperscript{138}, because gendered activities (e.g., cooking, cleaning, lawn care) produce different exposure patterns. Exposure measurement may benefit from gendered exposure measurement, comparison of gendered activities across communities\textsuperscript{139}, or foci on temporal exposure characteristics (e.g., diurnal trends in residential exposures and activities, critical life-course periods related to hormonal composition or roles)\textsuperscript{134}. Assignment of gendered exposures broadly to sex-stratified groups, however, should be generally avoided, because this practice obscures sources of variability between men and women, further confounding sex effects in subsequent epidemiologic analyses.

Temporally refined exposure assessment may elucidate gendered activity distributions. Recent approaches include probabilistic modeling of personal exposures\textsuperscript{140}. Techniques from the social sciences may be useful; the experience sampling method\textsuperscript{141} uses cell phones or pagers to prompt individuals throughout the day to record their location, activities, and well-being. The technique improves upon diary entries, which suffer recall bias, and allows more detail in activity reports (e.g., cleaning activity with duration and product name) with contemporaneous physiological or psychological conditions that may modify effects. Aggregated, the data provide population-specific activity distributions and capture mean daily activity and exposure differences between men and women.

Physiologically based pharmacokinetic (PBPK) modeling may help to distinguish sex
differences in dermal absorption, body size, and toxicity from gendered exposures. PBPK models may facilitate analysis of biological processes across multiple life stages (e.g., infancy, childhood, puberty, adulthood) and, among women, by reproductive cycle and hormonal status (e.g., menarche, pregnancy, lactation, menopause). Better understanding of sex and life-stage aspects of bodily chemical transport may help to elucidate differences in effective dose or chemical interactions in the body.

Propensity analysis incorporates predictive modeling for both exposures and responses, enabling researchers to predict subjects' propensity (likelihood) of exposure, given preexposure characteristics and population exposure distributions. Researchers can then examine health responses among individuals with comparable exposure likelihoods, using propensity matching or propensity stratification. For example, sex-stratified propensity models can estimate effects of education, work history, SES, family structure, and home demands on exposure assignment (e.g., job, neighborhood of residence) for men and women. Then researchers can better observe health responses by sex, reasonably isolating effects of mean biological differences from those of gendered exposure assignment. One recent occupational study examined blue-collar status and hypertension among employees of a large U.S. manufacturing company. Family structure influenced exposure (job) assignment for men and women; single mothers were more likely to be blue-collar workers than were other women. Men with partners and children were more likely to be white-collar workers than were other men. Blue-collar status increased risks solely among women predicted to be blue collar, suggesting interaction effects between SES (which predicted job assignment) and on-the-job exposures.

Finally, researchers have proposed variants of multilevel modeling to disaggregate variability between and within the sexes. Researchers may differentiate sex-linked biological effects (e.g., target organs, hormonal composition), which can differ substantially between men and women, from gendered exposures, which generally display more variability among men and women. The technique may be applicable, however, only to illnesses directly involving biological parameters (e.g., sex organs, hormonal composition) which differ strongly by sex. A different method for employing multilevel modeling stems from the societal-level construction of gender, whereas sex is an individual-level biological construct. Examining men's and women's exposure and disease patterns across and within societies that vary in measures of gender equity (e.g., income disparities, female education, reproductive rights) may offer important clues toward understanding root causes of exposure and susceptibility differences.

Conclusions

Studies suggest that health responses to air pollution may differ between women and men and between girls and boys. It remains unclear, however, whether observed modification is a result of sex-linked biological differences (e.g., hormonal complement, body size) or gender differences in activity patterns, coexposures, or exposure measurement accuracy. Most modification likely consists of some combination of these two factors (exposure patterns and biological response); disentangling these effects is challenging yet necessary toward fully understanding the relevant pathways for differential air pollution effects on health.

Because gender varies by state and society, designing effective localized health interventions requires clarity about these distinct sources of difference (gender and sex), with an aim of improving population health. Careful consideration of gender and sex effects and exploration of nascent methods for quantitative gender analysis may help to elucidate sources of difference. More broadly, exploring the role for gender analysis in environmental epidemiology may provide a model for exploring other social factors that can shape population responses to air pollution.

Acknowledgements

Many thanks to N. Krieger, M. Perry, J. Dennerlein, J. Levy, and C. Katz for helpful suggestions in the early development of the manuscript and to N. Jeffrey and M. Simons for reviewing the manuscript. The author declares she has no competing-financial interests.
References


68. Jedrychowski W, Krzyzanowski M. Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols: prospective study in Cracow. Environ Health Perspect 1989; 79:101-107


112. Morello-Frosch R, Shenassa ED. The environmental "risk-scape" and social inequality: implications for explaining maternal and child disparities. Environ Health Perspect 2006; 114:1150-1153.


