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Respiratory health effects of air pollution: Update on biomass smoke and traffic pollution

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Activity Objectives

1. To understand the nature of biomass and traffic-related emissions and their effect on human disease.
2. To define the relationship of air pollution to features of chronic obstructive pulmonary disease.
3. To identify the effects of traffic-related air pollution (TRAP) and biomass fuels (BMFs) on asthma.
4. To analyze the effect of air pollution on mechanisms of inflammation and risks for respiratory tract infection.

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Mounting evidence suggests that air pollution contributes to the large global burden of respiratory and allergic diseases, including asthma, chronic obstructive pulmonary disease, pneumonia, and possibly tuberculosis. Although associations between air pollution and respiratory disease are complex, recent epidemiologic studies have led to an increased recognition of the emerging importance of traffic-related air pollution in both developed and less-developed countries, as well as the continued importance of emissions from domestic fires burning biomass fuels, primarily in the less-developed world. Emissions from these sources lead to personal exposures to complex mixtures of air pollutants that change rapidly in space and time because of varying emission rates, distances from source, ventilation rates, and other factors. Although the high degree of variability in personal exposure to pollutants from these sources remains a challenge, newer methods for measuring and modeling these exposures are beginning to unravel complex associations with asthma and other respiratory tract diseases. These studies indicate that air pollution from these sources is a major preventable cause of increased incidence and exacerbation of respiratory disease. Physicians can help to reduce the risk of adverse respiratory effects of exposure to biomass and traffic air pollutants by promoting awareness and supporting individual and community-level interventions. (J Allergy Clin Immunol 2012;129:3-11.)

Key words: *Biomass, traffic, chronic obstructive pulmonary disease, asthma, air pollutants, particulate matter*

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Worldwide increases in rates of asthma and chronic obstructive pulmonary disease (COPD) over the past several decades have motivated intensive investigation into the role of environmental factors, including air pollution, in their causation. Recent research also suggests that air pollution contributes to the substantial worldwide burden of disease from acute lower respiratory tract infections and possibly tuberculosis. Although the health effects of air pollution have been an international public health concern

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Abbreviations used
BMF: Biomass fuel
COPD: Chronic obstructive pulmonary disease
DC: Developed country
FENO: Fraction of exhaled nitric oxide
ISAAC: International Study of Asthma and Allergies in Childhood
LDC: Less developed country
LUR: Land-use regression
NO: Nitric oxide
NO_2: Nitrogen dioxide
OR: Odds ratio
PM: Particulate matter
$PM_{2.5}$: Particulate matter with a diameter of 2.5 μm or less
PM_{10}: Particulate matter with a diameter of 10 μm or less
PN: Particle number
TRAP: Traffic-related air pollution
UFP: Ultrafine particulate matter
WHO: World Health Organization

since at least the 1950s, recent research has heightened the focus on 2 broad sources of air pollution: biomass fuels (BMFs) and motor vehicles. Understanding of the health effects of BMFs and traffic-related air pollution (TRAP) has lagged behind that of ambient air pollution, at least in part because of challenges in estimating highly variable individual exposure from these widespread but very localized air pollution sources.

Of course, air pollution is only one of many environmental (nongenetic) factors for which a causative role in the exacerbation or incidence of complex respiratory diseases has been suggested. Indeed, based on ecologic analyses from the International Study of Asthma and Allergies in Childhood (ISAAC),[1] generally less-polluted developed countries (DCs) have much higher rates of asthma than many countries with higher levels of air pollution. However, studies with individual-level analyses that control for potential confounding have demonstrated associations between air pollutants, including TRAP, and asthma exacerbation, as well as possible links to increased asthma incidence. Additional evidence suggests that exposure to TRAP is correlated with the increasing rates of allergic respiratory disease.[2] Although tobacco smoke is clearly the dominant cause of COPD worldwide, BMF smoke is now recognized as a major cause of COPD, especially among women in less-developed countries (LDCs). Current evidence also indicates that BMF smoke plays a causative role in mortality from lower respiratory tract infections among children living in homes where BMFs are used.

The effects of indoor air exposures and individual ambient pollutants on asthma have recently been discussed in this forum.[3] Here we emphasize the growing body of recent research pertaining to the relationship between respiratory health effects and exposure to TRAP and BMF air pollution. For recent reviews of the respiratory health effects of traffic exposures, see Kelly and Fussell[4] and Salam et al,[5] and for BMFs, see Torres-Duque et al,[6] Balmes,[7] and Fullerton et al.[8]

EXPOSURES TO BMFs AND TRAFFIC POLLUTANTS

Exposures to BMF smoke and TRAP are widespread. Domestic fires burning biomass (wood, charcoal, dung, crop residues, and other raw plant materials) for cooking, heating, or both remain the most pervasive and important source of exposure to air pollution for much of humanity. About 2.4 billion persons live in households in which BMFs are the primary fuel for cooking, heating, or both,[9,10] with more than 90% of subjects in rural areas of LDCs using BMFs.[9] Exposures are often exacerbated by use of open fires or traditional stove designs that lack flues or hoods to exhaust emissions away from the living area.[7]

Although stationary industrial "smokestacks" continue to be a major source of outdoor air pollution from the burning of fossil fuels throughout the world, TRAP from motor vehicles is a growing concern in both DCs and LDCs.[11] Regulation of ambient (widespread, regional) "criteria" pollutants in the United States and other DCs has resulted in relatively effective stationary and mobile source controls. However, an increased number of vehicles and vehicle miles driven has lessened the effect of vehicle emissions controls. At the same time, heavy industry has moved to LDCs, resulting in a higher relative contribution from mobile sources in DCs, whereas in LDCs both total stationary- and mobile-source emissions have been increasing. Most of the worldwide growth in fleets of gasoline and diesel vehicles is occurring in LDCs.[11] As discussed below, in addition to making large contributions to background ambient air pollution, mobile sources might dominate exposures near roadways in urban areas, where a growing proportion of the world's population lives.

Although one is rooted in longstanding cultural practices and the other arises from modern economic development, emissions from domestic fires and from motor vehicles have similarities in composition, toxicity, and exposure characteristics. Complex aerosol emissions from use of BMFs share many components with TRAP and other outdoor pollution, including particulate matter (PM), carbon monoxide, nitrogen oxides, and scores of toxic organic compounds, such as formaldehyde, acrolein, and polynuclear aromatic hydrocarbons.[12] However, the physical and chemical characteristics of both BMF smoke and TRAP can vary substantially depending on the type of fuel burned and combustion conditions.[13]

On the basis of robust epidemiologic associations between ambient PM and respiratory and cardiovascular health effects, much attention has focused on the PM component of BMFs and motor vehicle emissions.[14] PM of respirable size is classified by size fractions based on aerodynamic diameter. Ultrafine particulate matter (UFP), with diameters of 0.1 μm or less, is a major component of emissions near fires and tailpipes but in seconds to minutes accumulates into somewhat larger fine PM (particulate matter with a diameter of ≤2.5 μm [$PM_{2.5}$]), within short distances from the point of release. Particulate matter with a diameter of 10 μm or less (PM_{10}) consists of $PM_{2.5}$ and larger particles of mainly crustal or biological origin, including many aeroallergens. On the basis of epidemiologic and laboratory studies, $PM_{2.5}$ appears to be more potent for respiratory and cardiovascular disease effects compared with PM_{10}.[15] According to the "ultrafine hypothesis," UFP might be still more toxic because of increased surface area and other characteristics.[16] Although they contribute little to the mass concentration of PM because of their small size, ultrafine particles emitted by combustion dominate the particle number (PN) concentrations near these sources.

In contrast to large-scale industrial sources of air pollution, the sources of BMF and traffic emissions tend to be in close proximity to individual "receptors." BMF emissions occur primarily indoors, where women and children are most highly exposed during cooking and other domestic activities (Fig 1). Exposures are exacerbated by reduced ventilation in homes in which BMFs are used[7] or under conditions in which vehicle emissions might be concentrated,

FIG 1. Cooking with wood BMFs in Nigeria.

such as urban street canyons or tunnels.[17] Concentrations of TRAP have steep gradients near roadways, with heightened exposure to persons living, attending school, or working near major roads in urban areas and return of TRAP to background levels within several hundred meters away from roadways.[18,19] For both BMF emissions and TRAP, time-activity patterns are a critical determinant of exposure. Household members who cook have high peak exposures, as when standing over the fire, as well as high time-averaged exposures to BMF pollutants.[20] Persons living and working in urban areas might have a substantial part of their daily air pollutant exposure during usually relatively brief commuting times on roadways where TRAP is concentrated.[21,22] Substantial differences in TRAP concentrations and in inhaled doses as a consequence of travel mode (biking vs car vs bus) have been demonstrated, with bicyclists generally having the highest doses and electric bus riders having the lowest doses.[23] Moreover, with distance and time away from sources, both BMF and vehicle emissions undergo complex "aging" processes that include oxidation, other chemical reactions, and physical processes that alter exposure and toxic properties in ways that are not fully understood.[24]

The levels of BMF air pollutants measured in homes are typically far higher than those of ambient air pollutants, but they have received less attention from the international research community. Concentrations of PM and other air pollutants in indoor air during BMF burning can be orders of magnitude higher than levels that occur in ambient air in developed cities.[20] Levels of PM_{10} in homes using BMFs often exceed several thousand micrograms per cubic meter[20] compared with the US Environmental Protection Agency's 24-hour ambient air quality standard of 150 $\mu g/m^3$ PM_{10} and the guideline of 50 $\mu g/m^3$ PM_{10} from the World Health Organization (WHO).[25] Few data are available on $PM_{2.5}$ and UFP indoors from BMF burning. The near-roadway microenvironment is mainly affected by freshly emitted UFPs and gas-phase compounds, such as carbon monoxide, nitrogen oxides, and volatile organic compounds, although resuspended road dust, mainly in the "coarse" mode of the PM_{10} fraction, might be an important exposure.[11]

The uneven distributions of exposure to BMF smoke and TRAP leads to uneven distribution of health risks and environmental justice considerations at local, regional, national, and global scales.[26] There are age, sex, and socioeconomic differences in who is most exposed and most vulnerable to the health effects of BMF emissions and TRAP.[8] Exposure to BMF smoke is greatest among women and young children who can be carried on the mother's back during cooking activities or spend more time indoors with the mother.[26] BMFs that are least expensive and more affordable for impoverished households also burn less efficiently, increasing pollutant emissions.[8] TRAP exposures are concentrated in areas of greater traffic density, which, at least in the United States, tend to be inner-city communities of lower socioeconomic status with a higher burden of environmental contamination/effects.

Epidemiology of health effects of BMFs and TRAP

Individual exposure assessment has been a major challenge for epidemiologic studies of both BMFs and TRAP, which is in contrast to studies of ambient air pollution in which assigning personal exposure based on central air-monitoring data has had demonstrated utility. Few epidemiologic studies of respiratory effects of BMF smoke have measured exposure, relying instead on self-report of fuel use despite evidence for wide variation in exposure depending on combustion and ventilation conditions and time-activity patterns. More recent studies, including controlled trials of stove interventions, have begun to measure exposure. As described above, the spatial and temporal distributions of urban air

pollutants are characterized by significant variability, with steep gradients in intensity near sources.[27,28] Thus the use of land-use regression (LUR) and other techniques for modeling microenvironmental exposures for various particle and gas pollutants has become widespread and is featured in a number of the newer studies of TRAP described below. LUR uses the monitored levels of the pollutant of interest as the dependent variable and variables such as meteorology, traffic, topography, building shapes and sizes, and other geographic variables as the independent variables in a multivariate regression model.[29] Levels of pollution can then be predicted for any other geographic locations, such as residences or schools, by using the parameter estimates derived from the regression model. A limitation is that LUR often captures only one time period and might miss prior or neonatal exposures; however, some studies have overcome this.[30,31] Further details are available in recent reviews.[32,33]

The most firmly established health effects of BMF emissions are acute lower respiratory tract infections in children and COPD in adults. Although studies of ambient pollution's effects have repeatedly demonstrated increased cardiovascular and respiratory morbidity and mortality for a variety of outcomes,[14] those that have studied TRAP specifically have largely focused on asthma and related phenomena, with some investigations of allergy.

The WHO has estimated that BMF smoke exposure is responsible for about 1.5 million premature deaths per year[34] and a global burden of disease of approximately 2.5% of all healthy life years lost. Most of this burden of disease is due to respiratory tract infections, mainly among children less than 5 years of age, and COPD among adult women.[35] Several case-control and cross-sectional studies have evaluated associations between use of BMFs and the prevalence of asthma, with equivocal results among children and women.[36-43] Other studies have found strong associations between BMF smoke and COPD among nonsmoking women.[9,20,44] Important new studies, as discussed below, have strengthened the link between TRAP and asthma incidence in children,[30,45-47] asthma incidence in adults,[48] and asthma severity in adults.[49]

BMFs and COPD

Given that cigarette smoke is a type of BMF smoke, a causal association between exposure to BMF smoke and COPD would not be surprising. Three recent meta-analyses have evaluated associations between BMF smoke and COPD.[50-52] In a systematic review and meta-analysis of 23 studies, Kurmi et al[50] found that exposure to all types of BMF smoke was consistently associated with COPD, with risk more than doubled and greater risk suggested for wood smoke compared with other fuels. Hu et al[52] analyzed 15 studies and found that BMF smoke was associated with increased risk of COPD among both women and men and in both Asian and non-Asian populations. In a meta-analysis of 6 studies that evaluated COPD among women using BMFs compared with alternative fuels, Po et al[51] also found a statistically significant pooled estimate of greater than 2-fold increased risk. In another 6 studies that assessed chronic bronchitis, the pooled risk estimate was also greater than 2-fold. However, most studies have lacked direct exposure measurements, none have described a dose-response relationship, and estimated effect sizes have varied widely. This variation might be due to heterogeneity in fuel types and conditions of use, as well as in study design and differences in control of confounders, such as exposure to mainstream or second-hand cigarette smoke, occupational exposures, socioeconomic factors, and changes in fuel use over time.[50] In a study of 841 nonsmoking women in Mexico that was notable for objective exposure and outcome measurements, Regalado et al[53] found that peak PM_{10} values of greater than 2600 $\mu g/m^3$ among those using BMFs was related to small but significant reductions in FEV_1 (81 mL), forced vital capacity (122 mL), and FEV_1 percent predicted (4.7%) compared with values seen in women who cooked with gas. In an accompanying editorial, Jaakkola and Jaakkola[54] noted that these effects were comparable with the estimates from environmental tobacco smoke exposure in adults. Cigarette smoking rates are relatively low in most LDCs, especially among women.[55] Among women living in rural Turkey, the fraction of COPD attributed to exposure to BMF smoke was 23% after adjusting for possible confounders.[56]

TRAP and COPD

A number of studies have established that children living in more polluted areas have reduced lung growth compared with those living in cleaner areas and that moving from a more polluted to a cleaner area demonstrates improved growth.[57] Similar findings for lung function have been reported in adults, as well as a limited database of studies documenting an association between ambient air pollutants and objectively defined COPD.[57]

Most recently, a 35-year prospective study of more than 57,000 Danes used individual modeled assignments of traffic pollution and extensive control of confounders, with the end point of first hospital admission for COPD.[58] This outcome was associated with chronic nitrogen dioxide (NO_2) exposure (hazard ratio, 1.08; 95% CI, 1.02-1.14), with a stronger association in asthmatic patients. This is the first longitudinal study of COPD with hard outcomes in association with modeled TRAP exposures and seems to confirm the previous findings of cross-sectional studies that TRAP is likely to be a cause of COPD.

TRAP and asthma overview

Studies have long shown that asthma can be exacerbated, often measured as visits to emergency departments, on days with higher levels of ozone and other pollutants.[59] More complex cohort study designs have been required to understand whether traffic-related pollutants play a role in the genesis or causation of asthma. To date, all such investigations in a nonoccupational setting have related to chronic rather than acute air pollution exposures. More sophisticated designs have been used in recent years, and this part of the review will focus on those reported since 2009.

TRAP and childhood asthma. Initial studies of air pollution and asthma examined associations in children, looking first at exacerbations and, more recently, through cohort studies at incidence. Initial reports of incidence in children were variable in their results. Investigators interpreted these inconsistencies to result from misclassification of pollution exposure to the individual cases, likely because of reliance on central or regional air-monitoring stations that do not reflect urban microgeographies. Subsequent studies using LUR or dispersion modeling produced significant associations in both children and adults, with refinement of exposure through the use of LUR techniques yielding larger and significant associations with chronic pollution exposure.

Two recent studies, one a birth cohort, add substantially to our confidence that TRAP exposure of young children contributes to the development of asthma.[30,45] Both used sophisticated exposure assessment in the form of LUR or a related technique to study the association between childhood asthma and TRAP exposure at

home, school, or both. Increased risk of childhood asthma incidence demonstrated significant increases of 26% up to 51%, with good control of relevant confounders. Interestingly, the birth cohort study did not find corresponding associations of potentially explanatory mechanistic variables, such as atopic eczema, allergic sensitization, and bronchial hyperresponsiveness, leaving open questions about pathophysiology and roles of irritancy versus allergy. For the Southern California Children's Study,[45] nonfreeway pollutants demonstrated a stronger effect than those from freeways, possibly reflecting an effect of frequent acceleration and deceleration on TRAP characteristics.

In a smaller study, Carlsten et al[31] recruited infants at high familial risk for asthma and examined birth-year home exposures to nitric oxide (NO), NO_2, black carbon, and $PM_{2.5}$ by using LUR with follow-up at 7 years of age. Birth-year $PM_{2.5}$ (interquartile range, 4.1 $\mu g/m^3$) was associated with a significantly increased risk of asthma with an odds ratio (OR) of 3.1 (95% CI, 1.3-7.4). NO and NO_2 demonstrated similar associations, but black carbon did not. This dramatic finding with relatively small exposure magnitude is intriguing but needs replication.

A study of self-reported allergic disease (using the ISAAC questionnaire) and home traffic density based on distance to major roadways found approximately 1.5- to 3-fold prevalence ratios for heavy traffic density for wheeze, asthma, rhinitis, and rhinoconjunctivitis, with no associations for children who slept in air-conditioned homes[46] and obvious important implications for prevention in atopic subjects and others at heightened risk.

Using a cross-sectional design and an enhanced ISAAC protocol for outcomes,[47] 6683 children in the French Six Cities Study were studied, with exposures based on a 3-year dispersion model for each school address to assign individual school exposures. Asthma (either in the past year or lifetime) was significantly associated with benzene, sulfur dioxide, PM_{10}, NOx, and CO levels; all but sulfur dioxide levels were associated with eczema, and allergic rhinitis was associated with PM_{10} levels. Sensitization to pollens was associated with benzene and PM_{10} levels. The findings for benzene and CO are somewhat surprising, and given their presence as constituents of motor vehicle fuel, exhaust, or both, uncontrolled confounding might be present.

TRAP and adult asthma. The recent database on asthma and traffic is less robust in adults. The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults is a population-based cohort of adult lung disease–free nonsmokers initiated in 1991 with 11-year follow-up in 2002.[48] Using a dispersion model that included hourly meteorological and emissions data on industrial, construction, heating, agricultural and forestry, and traffic emissions, the latter separated by type of vehicle (truck vs car), each participant was assigned an exposure to PM_{10}. Outcomes were adjusted for age, sex, baseline atopy, body mass index, bronchial reactivity, and maternal allergies. They found a hazard ratio for doctor-diagnosed asthma of 1.30 (95% CI, 1.05-1.61) new cases for a given (1 $\mu g/m^3$ as PM_{10}) change in traffic pollution over the 10 years, and this was more frequent in those with baseline atopy or bronchial hyperreactivity.

Trupin et al[49] looked at the simultaneous effect on FEV_1 percent predicted and an asthma severity score of diverse social and physical environmental exposures on adult asthma in 176 subjects. Their final model had an R^2 value of 0.30 for FEV_1 percent predicted and 0.16 for the severity of asthma score. Distance to the nearest road was a significant predictor of FEV_1 but not the severity of asthma score. The importance here is that even when other variables strongly associated with usual clinical management of asthma are accounted for, a role for roadway traffic still persists.

On the basis of the high-quality studies discussed herein, there is an increasingly robust literature that supports a causal relationship between various aspects of TRAP and new-onset asthma or worsened asthma in children and adults. These risks need to be both incorporated into public policy and explored for their role in medical decision making at the individual level.

BMFs and asthma

In contrast to the abundance of studies showing exacerbation of asthma from increased exposure to ambient air pollution and TRAP, asthma prevalence has been the main outcome considered in studies of BMF smoke. Using Burden of Obstructive Lung Disease data on self-reported prevalence of asthma among 508 subjects in southeastern Kentucky, increased odds of reporting current asthma was associated with cooking indoors with wood or coal for more than 6 months of one's life (OR, 2.3; 95% CI, 1.1-5.0) but not with a history of domestic heating with wood or coal (OR, 0.8; 95% CI, 0.4-1.8).[60] However, a handful of earlier studies had not found compelling evidence of an increased risk of asthma among women or children in households using BMFs.[36,40] Among 6 studies that examined risk of asthma among women using BMFs in rural India, Iran, and Turkey, 2 found a statistically significant increased risk,[61] and 2 showed increased risks that were not statistically significant.[38,41] Using national health survey data, Mishra[61] found that elderly Indian men and women who lived in households using BMFs had a higher prevalence of self-reported asthma compared with those who used cleaner fuels (OR, 1.59; 95% CI, 1.30-1.94). Also in India, Padhi[62] found increased physician-diagnosed asthma and a decrease in lung function among rural BMF burners. In a recent meta-analysis, Po et al[51] found that pooled risk estimates did not provide evidence of overall increased risk of asthma in children or women using BMFs. Limitations of the available studies include likely exposure misclassification, outcome misclassification, low power, and/or incomplete control for confounding.

Respiratory tract infection

The WHO has concluded that exposure to indoor air pollution doubles the risk of pneumonia and other acute lower respiratory tract infections and might account for half of the roughly 800,000 annual worldwide deaths in children less than 5 years of age attributed to pneumonia.[25,63] Dherani et al[64] conducted a meta-analysis of 24 studies and found that exposure to BMFs increased the risk of pneumonia by almost 2-fold.[64] In a meta-analysis that included 8 studies, Po et al[51] found a greater than 3-fold increased risk of acute respiratory tract infection in children. Deaths among children contribute disproportionately to years of life lost in global burden-of-disease calculations. Increased rates of chronic bronchitis and viral infection have been associated with both gaseous and particulate ambient pollutants, although not specifically with TRAP.[4,65]

Tuberculosis

Greater use of BMFs appears to be correlated with higher rates of tuberculosis infection in global geographic regions, but few studies have evaluated associations at the individual level. In a cross-sectional study of a large national sample of Indian households, Mishra[61] found increased risk of self-reported tuberculosis infection with BMF use (OR, 2.58; 95% CI, 1.98-3.37),

but neither active nor passive smoking was measured. In a later well-designed case-control study in India, Shetty et al[66] found that the risk of bacteriologically or radiographically confirmed tuberculosis was not increased after adjustment for smoking, education, income, and other possible confounders. Although a recent systematic review concluded that there was not sufficient epidemiologic evidence to support an association between BMFs and tuberculosis infection[67] and no epidemiologic associations between TRAP and tuberculosis have been reported, ambient particles and diesel exhaust particles have been shown to impair macrophage function in animal models, suggesting that such associations are biologically plausible.[68,69]

MECHANISTIC INSIGHT

As discussed above, oxidative stress is a commonly cited mechanism for the relationship between air pollutants, many of them with oxidant constituents, and asthma worsening or onset. Both particles and gases can produce oxidative stress and can act in concert. Polymorphisms of the genes encoding glutathione-S-transferase M1, glutathione-S-transferase P1, and TNF-α are all reported to have associations/interactions with asthma and air pollution, but data are not consistent enough to allow firm causal conclusions.[70,71] Further support for oxidative stress as an explanatory mechanism as to how TRAP exerts its effects on intracellular regulation of inflammation and the oxidative stress response comes from an experimental study of air pollution aerosols, including fresh diesel exhaust, demonstrating approximately a 10% decrease in the WBC proteasome activity after 2 hours of aerosol exposure.[72]

Diesel exhaust inhalation is frequently used as a model for acute inhalation of TRAP. Acute exposure to diesel exhaust in a real-world street canyon setting has been shown to significantly reduce pulmonary function in asthmatic patients (up to a 6% decrease in FEV_1), along with an increase in sputum inflammation as measured by using myeloperoxidase.[73] However, experimental exposures to diesel exhaust, despite showing increased airway reactivity in asthmatic patients, have not elicited evidence of airway inflammation in asthmatic patients, which is in surprising contrast to elicitation of inflammatory changes in healthy subjects.[74-76] Diesel exhaust particles have been shown to have adjuvant effects on IgE synthesis in atopic subjects, so that allergen-specific IgE production upregulates by as much as 50-fold, skewing toward a T_H2 profile.[77] Diesel exhaust has been shown to acutely produce human bronchial epithelial inflammation characterized by inflammatory cell recruitment and increased expression of vascular endothelial adhesion molecules, cytokines, mitogen-activated protein kinases, and transcription factors. It has been proposed that epithelial damage from diesel exhaust might lead to decreased mucociliary clearance and consequent increased access of allergens to immune cells in the mucosa.[75,76] Another recent study examined diesel exhaust produced under realistic conditions to simulate actual driving conditions and emissions.[78] Evaluating inflammatory markers 6 hours after a 1-hour exposure, the authors found increased expression of P-selectin ($P = .036$) and vascular cell adhesion molecule 1 ($P = .030$) in bronchial mucosal biopsy specimens, as well as the novel finding of increased eosinophil counts in bronchial alveolar lavage fluid ($P = .017$), which has not previously been seen under idling engine conditions. The implications for diesel potentiation of allergic respiratory disease are substantial, especially in light of previous experimental work.[79]

A number of panel or experimental studies have measured biomarkers of oxidative stress and inflammation after exposure to TRAP to improve understanding of the biological pathways underlying respiratory and cardiovascular effects. Examining respiratory effects associated with studies in commuters, there were modest effects of 2-hour commuting exposures on peak flow, exhaled NO levels, and airway resistance.[80] PN doses were associated with decreased maximum midexpiratory flow and FEV_1 6 hours after exposure. PNs and soot were associated with decreased maximum midexpiratory flow and FEV_1 immediately after exposure, and increased fraction of exhaled nitric oxide (FENO) after car and bus but not bicycle trips. PNs were also associated with an increase in airway resistance immediately but not 6 hours after exposure. There were no associations of exposures or doses with symptoms. They interpreted these findings in healthy subjects to show modest effects of a 2-hour in-traffic exposure on peak flow, exhaled NO levels, and airway resistance. Examining inflammation and coagulation as a consequence of TRAP exposure, an accompanying study in the same subjects found no consistent associations in blood cell counts, activated partial thromboplastin time, and C-reactive protein, IL-6, IL-8, IL-10, TNF-α, fibrinogen, Factor VII, von Willebrand factor, and CC16 levels 6 hours after the commute.[81] Thus these data do not indicate that short-term changes predict the serious long-term consequences seen with chronic exposure.

POLLUTION INTERVENTION STUDIES

Beijing Olympics intervention studies

Natural (or politically organized) changes in the environment are viewed by researchers as great opportunities to study the effects on human health of greater than usual degrees of independent variable (pollution) change. This has been applied to the effects of sudden or dramatic changes in air pollution.[82,83] When these changes are anticipated, detailed clinical studies can be designed.[84] One such example was the Beijing Olympics of 2008 (Fig 2). One study that came out of this event examined visits for outpatient treatment of asthma at a Beijing Hospital.[85] During the Olympics, the Chinese government endeavored to reduce air pollution by substantial amounts.[86] Although somewhat sparse in clinical detail, they reported a reduction from 12.5 visits per day to 7.3 visits per day, a 41.6% reduction during the Olympic Games.

Also based on the Beijing Olympics, Lin et al[87] measured serial FENO levels as a function of ambient black carbon, a marker of diesel exhaust, in 36 fourth-grade Beijing children before, during, and after the 2008 Beijing Olympics. FENO levels were significantly lower during the Olympic period, and increased 16.6% (14.1% to 19.2%) per interquartile range increase in black carbon levels, particularly in the first hours after exposure, suggesting rapid changes in inflammation. Asthmatic patients were not significantly different from healthy children.

Intervention studies for BMFs

Romieu et al[88] randomized an improved stove (Patsari stove) among 668 households in central Mexico in which open wood-burning fires were used for cooking. The stoves had been shown in previous studies to reduce indoor air pollution levels by 70%.[89] At the 1-year follow-up, among the 50% of households still using the stove, there was a significant reduction in respiratory symptoms and a significantly lower decrease in FEV_1.[88] Using a randomized controlled trial, Smith et al[90] found that an improved

FIG 2. Two photographs in Beijing taken from the same vantage point and time of day: early June of 2008 **(A)** and mid-July during the height of the Olympic reductions in heavy industry, power generation, construction, truck traffic, and a 50% reduction in automobile traffic **(B)**.

cooking stove halved average exposure to carbon monoxide but did not significantly reduce physician-diagnosed pneumonia among infants in Guatemala. However, there was a significant reduction in severe pneumonia, and a 50% reduction in exposure was significantly associated with a lower rate of diagnosis of pneumonia. Other randomized controlled trials of improved stoves are underway, but results are yet to be published.[91]

CLINICAL GUIDANCE

Reducing the effects of BMF smoke and TRAP on respiratory health will require both public policy and the actions of individual patients. Consensus standards recognize the importance of air pollutants in the prevention and management of asthma and COPD and have recommended that clinicians counsel patients to become aware of and avoid exposures to air pollution (see the Global Initiative for Chronic Obstructive Lung Disease and National Heart, Lung, and Blood Institute Expert Panel 3 reports). Interventions at the individual level might include recommendations by clinicians that patients avoid exercising or cycling near busy roadways to reduce exposure to TRAP and to improve ventilation in homes in which BMFs are used. Public policy can encourage or mandate engineering solutions that drastically reduce emissions from cooking stoves and vehicles, but adoption of new technologies can be slowed by lack of awareness of health risks, traditional cultural practices, and economic costs.[8] In some respects public health and regulatory approaches to traffic emissions can be considered the low-hanging fruit for opportunities

toward health improvement on a societal scale. Experiments such as the Beijing Olympics have demonstrated how such changes might have health implications.

Photo credit goes to Jicheng Gong, MS, UMDNJ Graduate School of Biomedical Sciences.

What do we know?

1. **It is more difficult to estimate individual exposures to BMFs and TRAP than to ambient air pollution.**
2. **BMFs, including wood, charcoal, dung, and crop residues, are important sources of air pollution in DCs.**
3. **BMF is the major cause of COPD in women from DCs.**
4. **BMFs are an important cause of lower respiratory tract infections but not clearly asthma in LDCs.**
5. **Children who move to less-polluted areas from more polluted ones have been shown to have reversed impaired lung growth.**
6. **TRAP has been shown to increase the risk of COPD in well-controlled studies.**
7. **TRAP is associated with the development of asthma in adults.**
8. **Short-term air pollution interventions have been shown to decrease respiratory morbidity.**
9. **Use of air conditioning has been shown to decrease the effects of TRAP on asthma.**

What is still unknown?

1. **How much asthma risk is actually attributable to TRAP**
2. **A widely approved and acceptable method to reduce pollution from burning BMFs**
3. **Effects of TRAP on respiratory outcomes beyond asthma**
4. **How TRAP causes asthma: allergic, irritant, and/or other**
5. **Whether neonatal exposures to TRAP actually represent a critical window to cause childhood asthma**
6. **Whether BMFs cause asthma**
7. **Whether BMFs or TRAP increase the risk for tuberculosis**

REFERENCES

1. Beasley R. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998;351:1225-32.
2. D'Amato G, Cecchi L, D'Amato M, Liccardi G. Urban air pollution and climate change as environmental risk factors of respiratory allergy: an update. J Invest Allergol Clin Immunol 2010;20:95-102.
3. Peden D, Reed CE. Environmental and occupational allergies. J Allergy Clin Immunol 2010;125(suppl 2):S150-60.
4. Kelly FJ, Fussell JC. Air pollution and airway disease. Clin Exp Allergy 2011;41:1059-71.
5. Salam MT, Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. Curr Opin Pulm Med 2008;14:3-8.
6. Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G. Forum of International Respiratory Studies Task Force on Health Effects of Biomass E. Biomass fuels and respiratory diseases: a review of the evidence. Proc Am Thorac Soc 2008;5:577-90.
7. Balmes JR. When smoke gets in your lungs. Proc Am Thorac Soc 2010;7:98-101.
8. Fullerton DG, Bruce N, Gordon SB. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. Trans R Soc Trop Med Hyg 2008;102:843-51.
9. Smith KR, Mehta S, Maeusezahl-Feuz M. Indoor air-pollution from solid fuel use. In: Ezzatti M, Lopez AD, Rodgers A, Murray CJL, editors. Comparative quantification of health risks: global and regional burden of diseases attributable to selected major risk factors. Geneva (Switzerland): World Health Organization; 2004. p. 1435-93.
10. Reddy A, editor. Energy after Rio. Prospects and challenges. New York: United Nations Development Programme; 1996.
11. Health Effects Institute. Traffic-related air pollution: a critical review of the literature on emissions, exposure and health effects; 2010 Special Report #17. Boston: Health Effects Institute.
12. Zhang JJ, Smith KR. Household air pollution from coal and biomass fuels in China: measurements, health impacts, and interventions. Environ Health Perspect 2007;115:848-55.
13. Naeher LP, Brauer M, Lipsett M, Zelikoff JT, Simpson CD, Koenig JQ, et al. Woodsmoke health effects: a review. Inhal Toxicol 2007;19:67-106.
14. Brook RD. Cardiovascular effects of air pollution. Clin Sci 2008;115:175-87.
15. Brook RD, Rajagopalan S, Pope I, Arden C, Brook JR, Bhatnagar A, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 2010;121:2331-78.
16. Utell MJ, Frampton MW. Acute Health effects of ambient air pollution: the ultrafine hypothesis. J Aerosol Med 2000;13:355-9.
17. Zhou Y, Levy JI. The impact of urban street canyons on population exposure to traffic-related primary pollutants. Atmos Environ 2008;42:3087-98.
18. Zhu Y, Hinds WC, Shen S, Sioutas C. Seasonal trends of concentration and size distribution of ultrafine particles near major highways in Los Angeles. Aerosol Sci Technol 2004;38:5-13.
19. Gilbert NL, Woodhouse S, Stieb DM, Brook JR. Ambient nitrogen dioxide and distance from a major highway. Sci Total Environ 2003;312:43-6.
20. Ezzati M, Kammen DM. The health impacts of exposure to indoor air pollution from solid fuels in developing countries: knowledge, gaps, and data needs. Environ Health Perspect 2002;110:1057-68.
21. Fruin SA, Winer AM, Rodes CE. Black carbon concentrations in California vehicles and estimation of in-vehicle diesel exhaust particulate matter exposures. Atmos Environ 2004;38:4123-33.
22. Zhu Y, Fung DC, Kennedy N, Hinds WC, Eiguren-Fernandez A. Measurements of ultrafine particles and other vehicular pollutants inside a mobile exposure system on Los Angeles freeways. J Air Waste Manag Assoc 2008;58:424-34.
23. Zuurbier M, Hoek G, van den Hazel P, Brunekreef B. Minute ventilation of cyclists, car and bus passengers: an experimental study. Environ Health 2009;8:48.
24. US Environmental Protection Agency. Air quality criteria for particulate matter. Available at: http://www.epa.gov/EPA-AIR/2004/October/Day-29/a24232.htm. Accessed September 5, 2011.
25. World Health Organization. Air quality and health. In: Centre WM, editor. WHO Fact Sheet No. 313. Geneva (Switzerland): World Health Organization; 2011.
26. Smith KR. Fuel combustion, air-pollution exposure, and health—the situation in developing countries. Annu Rev Energy Environ 1993;18:529-66.
27. Briggs DJ, de Hoogh C, Gulliver J, Wills J, Elliott P, Kingham S, et al. A regression-based method for mapping traffic-related air pollution: application and testing in four contrasting urban environments. Sci Total Environ 2000;253:151-67.
28. Brauer M, Hoek G, van Vliet P, Meliefste K, Fischer P, Gehring U, et al. Estimating long-term average particulate air pollution concentrations: application of traffic indicators and geographic information systems. Epidemiology 2003;14:228-39.
29. Gilliland F, Avol E, Kinney P, Jerrett M, Dvonch T, Lurmann F, et al. Air pollution exposure assessment for epidemiologic studies of pregnant women and children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention research. Environ Health Perspect 2005;113:1447.
30. Gehring U, Wilga AH, Brauer M, Fischer P, deJongste JC, Kerkhof M, et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 2010;181:596-603.
31. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. Traffic-related air pollution and incident asthma in a high-risk birth cohort. Occup Environ Med 2011;68:291-5.
32. Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, et al. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 2005;16:727-36.
33. Ryan PH, Lemasters GK, Biswas P, Levin L, Hu S, Lindsey M, et al. A comparison of proximity and land use regression traffic exposure models and wheezing in infants. Environ Health Perspect 2007;115:278-84.
34. Pruss-Ustun A, Bonjour S, Corvalan C. The impact of the environment on health by country: a meta-synthesis. Environ Health 2008;7:7.
35. Rehfuess E, Corvalan C, Neira M. Indoor air pollution: 4000 deaths a day must no longer be ignored. Bull World Health Organ 2006;84:508.
36. Fagbule D, Ekanem EE. Some environmental risk factors for childhood asthma: a case-control study. Ann Trop Paediatr 1994;14:15-9.
37. Behera D, Sood P, Singh S. Passive smoking, domestic fuels and lung function in north Indian children. Indian J Chest Dis Allied Sci 1998;40:89-98.
38. Behera D, Chakrabarti T, Khanduja KL. Effect of exposure to domestic cooking fuels on bronchial asthma. Indian J Chest Dis Allied Sci 2001;43:27-31.
39. Noorhassim I, Rampal KG, Hashim JH. The relationship between prevalence of asthma and environmental factors in rural households. Med J Malaysia 1995;50:263-7.
40. Melsom T, Brinch L, Hessen JO, Schei MA, Kolstrup N, Jacobsen BK, et al. Asthma and indoor environment in Nepal. Thorax 2001;56:477-81.

41. Golshan M, Faghihi M, Marandi MM. Indoor women jobs and pulmonary risks in rural areas of Isfahan, Iran, 2000. Respir Med 2002;96:382-8.
42. Qureshi KA. Domestic smoke pollution and prevalence of chronic bronchitis/asthma in a rural area of Kashmir. Indian J Chest Dis Allied Sci 1994;36:61-72.
43. Uzun K, Ozbay B, Ceylan E, Gencer M, Zehir I. Prevalence of chronic bronchitis-asthma symptoms in biomass fuel exposed females. Environ Health Prev Med 2003;8:13-7.
44. Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Eur Respir J 2006;27:542-6.
45. McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, et al. Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect 2010;118:1021-6.
46. Zuraimi MS, Tham K-W, Chew F-T, Ooi P-L, Koh D. Home air-conditioning, traffic exposure, and asthma and allergic symptoms among preschool children. Pediatr Allergy Immunol 2011;22:e112-8.
47. Penard-Morand C, Raherison C, Charpin D, Kopferschmitt C, Lavaud F, Caillaud D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. Eur Respir J 2010;36:33-40.
48. Kunzli N, Bridevaux P-O, Liu L-JS, Garcia-Esteban R, Schindler C, Gerbase MW, et al. Traffic-related air pollution correlates with adult-onset asthma among never-smokers. Thorax 2009;64:664-70.
49. Trupin L, Balmes JR, Chen H, Eisner MD, Hammond SK, Katz PP, et al. An integrated model of environmental factors in adult asthma lung function and disease severity: a cross-sectional study. Environ Health 2010;9:24.
50. Kurmi OP, Semple S, Simkhada P, Smith WC, Ayres JG, Kurmi OP, et al. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Thorax 2010;65:221-8.
51. Po JYT, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax 2011;66:232-9.
52. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest 2010;138:20-31.
53. Regalado J, Perez-Padilla R, Sansores R, Paramo Ramirez JI, Brauer M, Pare P, et al. The effect of biomass burning on respiratory symptoms and lung function in rural Mexican women. Am J Respir Crit Care Med 2006;174:901-5.
54. Jaakkola MS, Jaakkola JJK. Biomass fuels and health: the gap between global relevance and research activity. Am J Respir Crit Care Med 2006;174:851-2.
55. Mackay J, Eriksen MP. World Health Organization. The tobacco atlas [1 atlas (128 p)]. Geneva (Switzerland): World Health Organization; 2002.
56. Ekici A, Ekici M, Kurtipek E, Akin A, Arslan M, Kara T, et al. Obstructive airway diseases in women exposed to biomass smoke. Environ Res 2005;99:93-8.
57. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An Official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.
58. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am J Respir Crit Care Med 2011;183:455-61.
59. Weisel CP, Cody RP, Lioy PJ. Relationship between summertime ambient ozone levels and emergency department visits for asthma in central New Jersey. Environ Health Perspect 1995;103(suppl 2):97-102.
60. Barry AC, Mannino DM, Hopenhayn C, Bush H, Barry AC, Mannino DM, et al. Exposure to indoor biomass fuel pollutants and asthma prevalence in Southeastern Kentucky: results from the Burden of Lung Disease (BOLD) study. J Asthma 2010;47:735-41.
61. Mishra V. Effect of indoor air pollution from biomass combustion on prevalence of asthma in the elderly. Environ Health Perspect 2003;111:71-8.
62. Padhi BK, Padhy PK. Domestic fuels, indoor air pollution, and children's health. Ann NY Acad Sci 2008;1140:209-17.
63. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 2009;374:893-902.
64. Dherani M, Pope D, Mascarenhas M, Smith KR, Weber M, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: a systematic review and meta-analysis. Bull World Health Organ 2008;86:390-8.
65. Cienciwicki J, Jaspers I. Air pollution and respiratory viral infection. Inhal Toxicol 2007;19:1135-46.
66. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis 2006;10:80-6.
67. Slama K, Chiang CY, Hinderaker SG, Bruce N, Vedal S, Enarson DA. Indoor solid fuel combustion and tuberculosis: is there an association? Int J Tuberc Lung Dis 2010;14:6-14.
68. Zhou H, Kobzik L. Effect of concentrated ambient particles on macrophage phagocytosis and killing of *Streptococcus pneumoniae*. Am J Respir Cell Mol Biol 2007;36:460-5.
69. Yang HM, Antonini JM, Barger MW, Butterworth L, Roberts BR, Ma JK, et al. Diesel exhaust particles suppress macrophage function and slow the pulmonary clearance of *Listeria monocytogenes* in rats. Environ Health Perspect 2001;109:515-21.
70. London SJ. Gene-air pollution interactions in asthma. Proc Am Thorac Soc 2007;4:217-20.
71. Romieu I, Moreno-Macias H, London SJ. Gene by environment interaction and ambient air pollution. Proc Am Thorac Soc 2010;7:116-22.
72. Kipen HM, Gandhi S, Rich DQ, Ohman-Strickland P, Laumbach R, Fan Z-H, et al. Acute decreases in proteasome pathway activity after inhalation of fresh diesel exhaust or secondary organic aerosol. Environ Health Perspect 2011;119:658-63.
73. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, et al. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med 2007;357:2348-58.
74. Stenfors N, Nordenhall C, Salvi SS, Mudway I, Soderberg M, Blomberg A, et al. Different airway inflammatory responses in asthmatic and healthy humans exposed to diesel. Eur Respir J 2004;23:82-6.
75. Nordenhall C, Pourazar J, Ledin MC, Levin JO, Sandstrom T, Adelroth E. Diesel exhaust enhances airway responsiveness in asthmatic subjects. Eur Respir J 2001;17:909-15.
76. Behndig AF, Larsson N, Brown JL, Stenfors N, Helleday R, Duggan ST, et al. Proinflammatory doses of diesel exhaust in healthy subjects fail to elicit equivalent or augmented airway inflammation in subjects with asthma. Thorax 2011;66:12-9.
77. Diaz-Sanchez D. The role of diesel exhaust particles and their associated polyaromatic hydrocarbons in the induction of allergic airway disease. Allergy 1997;52(suppl):52-6.
78. Sehlstedt M, Behndig AF, Boman C, Blomberg A, Sandström T, Pourazar J. Airway inflammatory response to diesel exhaust generated at urban cycle running conditions. Inhal Toxicol 2010;22:1144-50.
79. Diaz-Sanchez D, Dotson AR, Takenaka H, Saxon A. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. J Clin Invest 1994;94:1417-25.
80. Zuurbier M, Hoek G, Oldenwening M, Meliefste K, van den Hazel P, Brunekreef B. Respiratory effects of commuters' exposure to air pollution in traffic. Epidemiology 2011;22:219-27.
81. Zuurbier M, Hoek G, Oldenwening M, Meliefste K, Krop E, van den Hazel P, et al. In traffic air pollution exposure and CC16, blood coagulation, and inflammation markers in healthy adults. Environ Health Perspect 2011;119:1384-9.
82. Clancy L, Goodman P. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. Lancet 2002;360:1210-4.
83. Peel JL, Klein M, Flanders WD, Mulholland JA, Tolbert PE. HEI Health Review Committee. Impact of improved air quality during the 1996 Summer Olympic Games in Atlanta on multiple cardiovascular and respiratory outcomes. Res Rep Health Eff Inst 2010;(148):3-23; discussion 25-33.
84. Kipen H, Rich D, Huang W, Zhu T, Wang G, Hu M, et al. Measurement of inflammation and oxidative stress following drastic changes in air pollution during the Beijing Olympics: a panel study approach. Ann N Y Acad Sci 2010;1203:160-7.
85. Li Y, Wang W, Kan H, Xu X, Chen B. Air quality and outpatient visits for asthma in adults during the 2008 Summer Olympic Games in Beijing. Sci Total Environ 2010;408:1226-7.
86. Cai H, Xie S. Traffic-related air pollution modeling during the 2008 Beijing Olympic Games: the effects of an odd-even day traffic restriction scheme. Sci Total Environ 2011;409:1935-48.
87. Lin W, Zhu T, Huang W, Hu M, Brunekreff B, Zhang Y, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. Environ Health Perspect 2011;119:1507-12.
88. Romieu I, Riojas-Rodriguez H, Marron-Mares AT, Schilmann A, Perez-Padilla R, Masera O. Improved biomass stove intervention in rural Mexico: impact on the respiratory health of women. Am J Respir Crit Care Med 2009;180:649-56.
89. Armendariz-Arnez C, Edwards RD, Johnson M, Zuk M, Rojas L, Jimenez RD, et al. Reduction in personal exposures to particulate matter and carbon monoxide as a result of the installation of a Patsari improved cook stove in Michoacan Mexico. Indoor Air 2008;18:93-105.
90. Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, et al. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. Lancet 2011;378:1717-26.
91. Bruce N, Weber M, Arana B, Diaz A, Jenny A, Thompson L, et al. Pneumonia case-finding in the RESPIRE Guatemala indoor air pollution trial: standardizing methods for resource-poor settings. Bull World Health Organ 2007;85:535-44.