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Indoor Air Pollution and Cardiovascular Disease: New Evidence from Iran

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Serious attention was first focused on indoor air pollution as a public health problem in the 1960s, when some of the first measurements of indoor pollutant concentrations were made, including nitrogen dioxide, carbon monoxide, and particles [1]. Studies combining the tracking of activity patterns with monitoring of indoor and outdoor concentrations for key air pollutants soon led to an appreciation of the dominant contributions of indoor exposures to total personal exposures (i.e., the total exposure experienced by an individual across the multiple environments where time is spent) [2]. A wave of epidemiological studies was also launched, directed at secondhand tobacco smoke (SHS), nitrogen dioxide from natural gas-fueled stoves and heaters, and other pollutants with indoor sources. The focus of these studies was on the pollution sources present in higher-income countries, particularly in North America and Europe, and their adverse effects on health, particularly the respiratory health of children and adults. Collectively, the resulting evidence has given us an understanding of the critical role of indoor environments in driving exposures to inhaled pollutants and provided sufficient evidence to causally link SHS exposure to increased disease risk, including coronary heart disease and stroke, and other adverse effects in infants, children, and adults [3].

By the 1980s, the problem of indoor exposure to smoke from the burning of biomass fuels for cooking and heating received its first recognition. Kirk Smith reported pioneering observations from India, measuring remarkably high personal exposures to particulate matter for women as they cooked over an open fire [4]. The repeated documentation of such high exposures to biomass fuel smoke, generally using particulate matter as the indicator of combustion pollution, motivated epidemiological studies of the consequences. The resulting body of evidence is substantial and supports inference of causal association of smoke from biomass fuels with acute lower respiratory illness in childhood and chronic lung disease in

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adulthood [5, 6]. Firm causal conclusions have yet to be reached for the associations of exposure to biomass smoke with either lung cancer [7] or cardiovascular disease [8], although there is mounting evidence related to both.

In this issue of *Circulation*, Mitter and colleagues [9] provide new evidence on household fuel use, a surrogate for indoor air pollution, and cardiovascular mortality based on the Golestan Cohort Study in Iran. The study population includes more than 50,000 adults, primarily from rural locations, who were enrolled in 2004–2008 and followed through 2012 for this report. Baseline data collected by an administered questionnaire covered cardiovascular risk factors and also included a lifetime history of the types of fuels used in the home for cooking and heating. Follow-up for mortality was quite complete and cause-of-death was assigned based on review of medical information by a physician panel. The investigators attempted to obtain a lifetime history of fuel use at home for cooking and heating separately. A temporal profile of use was obtained for four fuel types: natural gas, kerosene/diesel, wood, and *pehen* (cow dung). With the resulting data, cumulative exposures could be calculated for each fuel type so that the analyses attempted to disentangle associations of the four fuel types with risk for cardiovascular mortality and other outcomes. Exposure time for *pehen* was limited, reported by only 12% of respondents. Most had exposure to emissions from combustion of kerosene/diesel, gas, and wood. As measurements of pollutant levels, e.g., particulate matter, were not made, the questionnaire-based exposure measures cannot be directly linked to exposures to particulate matter or other pollutants.

The findings point to increased risk associated with burning of kerosene/diesel and lower risk for gas, compared to the other fuels. The estimated increase in risk for cardiovascular mortality for 10-years of use of kerosene/diesel was about 10%, while risk for cardiovascular death was reduced by 6% per 10-years of gas use, a cleaner fuel. As would be expected from gender differences in time-activity patterns, the effect for total cardiovascular mortality was greater in women. Additional factors that could contribute to this effect modification by gender could include the significantly lower rate of smoking among women in this cohort (2% in women versus 33% in men), resulting in a lower baseline cardiovascular disease risk due to smoking in women and, as a result, higher hazard ratios associated with use of kerosene/disease and greater benefit from gas as a fuel[10]. This lower baseline smoking-related risk of cardiovascular disease in women has resulted in higher hazard ratios for other exposures studied in this population as well [11]. Not surprisingly, fuel use patterns varied by residence location (urban versus rural) and educational level. To the extent possible with available data, the investigators attempted to control for potential confounding by correlates of fuel use pattern. While the study was not necessarily designed to have a comprehensive look at mediation and effect modification, attempts were also made to examine these issues.

What does this new report from the Golestan Cohort Study add to our understanding of indoor air pollution and cardiovascular disease? Iran is a higher-income country than the countries of Africa and Central and South America that have been the site of most research on biomass fuel smoke, including observational studies for associations of smoke exposure with adverse health effects, and intervention trials involving cook stove replacement. In 2014, the Gross Domestic Product (GDP) per capita for Iran was around $5,500 (USD) compared with Ethiopia at $574 and Kenya at $1,358 [12]. Intervention programs involving replacement of traditional stoves and of biomass fuels have had a similar geographic placement, focused on the lowest income countries. Furthermore, with the modernization of Iran over recent decades, cooking stoves and ventilation systems have significantly improved and natural gas is now abundant in this gas-rich country. Therefore, the results reported from Golestan Cohort Study are indicative of long-term historical use of older types of cooking stoves inside poorly-ventilated houses or yurts (portable tents used by Turkmens and other ethnicities in Central Asia) and under "Korsi"s (tables covered with linen with wood burning underneath). In fact, the fuels used by participants in the Golestan cohort--kerosene, diesel, and gas—are well above the very low quality and inefficient fuels used by billions of households worldwide.

The literature to date has almost exclusively addressed solid fuels, which were used by less than 5% of households in Iran in 2013, according to the World Health Organization [13]. A recent systematic review that extended through June, 2015 identified 26 articles on household solid fuels and risk for cardiovascular disease [8]. In a number of the studies, use of gas was the reference category for assessing the hazard of biomass fuels. In fact, there is a growing consensus in the scientific community that only use of very clean fuels (Tier 4: such as natural gas, ethanol or bio- gas), and not just improved biomass-fueled cookstoves will lead to significant health benefits). Thus, the findings of this new paper, should not be interpreted within the extensive literature on exposure to biomass smoke from combustion of solid fuels. Rather, the findings demonstrate lower risk for gas compared with kerosene and diesel as a fuel for cooking and heating, adding to the limited data previously available on the risks of kerosene [14]. The benefits from the use of natural gas that were reported in the Golestan Cohort Study are also likely to be underestimated as it is very likely that there was mixed use of non-clean (kerosene/diesel, wood or *Pehen*) fuels for cooking and heating.

As participants in the Golestan Cohort Study were largely exposed to emissions from burning of kerosene/diesel, gas, and wood, what component of the resulting indoor air pollution could underlie the observed associations? The fresh carbon particles generated by combustion would predominantly be in the ultrafine size range, i.e., less than 0.1 microns in aerodynamic diameter; such particles are dynamic and agglomerate to form larger particles. The emitted particles are in a size range that reaches the small airways and alveoli when inhaled and that can translocate across the alveolar capillary epithelium and reach the circulation. The particles would likely contain metals present in the fuels. Both kerosene and diesel may contain sulfur and their combustion would produce sulfur oxides as well. Indoor contamination by sulfur oxides from unvented kerosene-fueled space heaters was identified decades ago in the United States [15].

Ambient air pollution, now studied extensively using epidemiological and experimental approaches, has already been causally linked to cardiovascular disease [16]. We interpret the findings of the Golestan Cohort Study as suggesting that yet another type of air pollution could be contributing to the burden of cardiovascular disease globally—the indoor pollution from burning kerosene and diesel.

The wordwide mortality burden attributable to household air pollution is enormous, estimated as 4.3 million deaths, and 7.7% of the global mortality in 2012 [17]. Of these, 60% were attributed to ischemic heart disease and stroke, based on calculations using indoor particulate matter concentration as the relevant exposure metric. The contribution of ambient air pollution is almost as large. Activities are underway around the world that address this burden. Seven Global Environmental and Occupational Health (GEOHealth) Hubs (funded by the Fogarty International Center of the National Institutes of Health and several partners) have recently been established to address environmental and occupational health issues in low- and middle-income country settings in partnership with US based institutions as training partners [18]. These hubs are based in Africa, Asia, Latin America and the Caribbean and will provide much needed primary data on indoor and outdoor pollution levels and associated health effects. The Global Alliance for Clean Cookstoves (GACC), hosted by the UN Foundation, is fostering research and implementation initiatives, including work directed at non-communicable diseases, [19] and collaborating with the new GEOHealth Hubs. The National Institutes of Health is planning a large intervention trial (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-012.html). These initiatives will strengthen the foundation of scientific evidence needed to reduce the global burden of cardiovascular disease caused by indoor and outdoor air pollution.

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