Air Pollution, Aging and Lifespan: Air Pollution Inside and Out Accelerates Aging

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Introduction

Air pollution from fossil fuels is best known for irritating eyes and lungs on smoggy days. But it has deeper, long-term associations with excess morbidity and mortality from the acceleration of many aging processes and diseases. While ambient air pollution (AAP) is usually considered as outdoors, household air pollution (HAP) can be even worse. Data from the World Health Organization (WHO) in Table 1 shows that sum of excess mortality from AAP and HAP is only slightly above mortality from cigarette smoke (CS).

Additionally, the combination of both AAP and CS has a super-additive impact for cancer, heart disease, children's obesity, and brain aging (Table 2). These recently recognized synergies suggest shared toxic mechanisms that are poorly understood. The exposure of children to adult CS is largely indoors and should be included in the mortality attributed to HAP.

HAP in developed countries gets inside homes and buildings from urban traffic, industries, brush fires, and other external sources. In developed countries, many buildings are partly protected from outside air pollution by filters in their air conditioning or heating units. Unfortunately, homes in most of the world have no protection or control over invading pollution from outside air particles and gases. Even worse, poor households often produce dense smoke from open fires needed for cooking and heating. Their fuels are generally low quality, including brushwood, dried dung, and low-grade coal. Discussed next, the airborne particles and gases from these fuels are extremely heterogeneous and we lack meaningful assays to evaluate their toxicity.

Table 1 Mortality from airborne toxins.

	Annual excess mortality, millions
Ambient air pollution (AAP)	3.3
Household air pollution (HAP)	4.3
Cigarette smoke:	
Direct	6.0
Second-hand	0.65
Total from airborne toxins of human origin	14.2 million

World Health Organization (2017). *Indoor air pollution*. World Health Organization; Lelieveld, J., Evans, J. S., Fnais, M., Giannadaki, D., and Pozzer, A. (2015). The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature* **525**, 367–371.; GBD 2015 Tobacco Collaborators. (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: A systematic analysis from the global burden of disease study 2015. *Lancet* **389**, 1885–1906.

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Table 2 Synergies of AAP and CS.

	Study	*Synergy (fold-excess above additivity)*
Cancer of lung[a]	ACS Prevention Study II	2.2-Fold excess
Cardiovascular mortality[b]	ACS Prevention Study II	1.1-Fold excess
Body mass index (BMI)[c]	Southern California Children's Health Study	1.3-Fold excess
Aging cognitive decline[d]	Health and Retirement Survey	1.9-Fold excess

[a]12 Million adults (Turner et al., 2014).
[b]429,406 Adults (Turner et al., 2014).
[c]3318 Children, ages 10–18 years (McConnell et al., 2015), also 109,838 mother-child pairs in a meta-analysis of 12 studies (Riedel et al., 2014).
[d]18,575, age $\geq$50 years (Ailshire and Crimmins, 2014).

What is in Air Poll

Air pollution, outside (AAP) and inside (HAP), is measured in the two broad categories of particles and gases.

Particulate Matter

Airborne solids are described as "particulate matter" (PM) of different sizes (**Table 3**). Three size classes are distinguished by their diameter in micrometers (μm): PM10, PM2.5, and PM0.2. By convention, each size class includes all smaller particles. Thus, PM2.5 includes PM0.2. The largest size class (PM10 to PM2.5) is considered less dangerous than the smaller sizes, because these "coarse particles" are mostly trapped in the upper airways and are swallowed before they can reach the lung. The smaller PM2.5 and PM0.1 (fine and ultrafine) particles penetrate deeply into the lung alveoli and are considered the main source of air pollution toxicity (**Table 3**).

The Environmental Protection Agency (EPA) collects data across the United States for PM10, PM2.5, ozone, NO_2, and SO_2. Daily EPA measurements are available across the United States by zipcode at https://airnow.gov/. The EPA goal is to reduce levels below 12 μg of PM2.5 per cubic meter of air (12 $\mu g/m^3$). However, epidemiological studies shown below suggest there may not be any safe lower level. Currently the EPA does not include smallest PM0.1, which are potentially more toxic by their greater number and deeper penetration into the lung. The composition of airborne PM has been characterized in depth for Los Angeles in ongoing studies by Sioutas and colleagues (**Table 4**). Notably, the fine and ultrafine PM have higher concentrations of trace elements and organic carbon, and penetrate more into the lungs than the coarse PM which are mostly swallowed. The chemical reactivity of the smaller PM (DTT assay) is also much higher than for coarse PM.

Gas or Vapor Phase of AAP

Ozone is tightly linked to temperature (Steiner et al., 2010). In Los Angeles, for example, ozone varied threefold in proportion to temperatures within the 20 degrees range, 71–90°F. Inevitably, climate warming will expose us globally to higher ozone levels. Moreover, ozone also contributes to the oxidation of nitrogen and sulfur, yielding NOx and SOx. Besides these airborne gases, AAP includes volatile organic compounds from fossil fuels, chemical industries, and burning brush and garbage.

Source Apportionment

The chemical composition of air pollutants is complex in any urban or rural site. From moment to moment, AAP composition will vary by traffic density and the types of vehicular engine; by wind carrying pollutants from chemical industries, cattle feed lots, and

Table 3 General properties of PM.

Size class, diameter, μm	*Sources*	*Generated by*	*Lung penetration*
Coarse PM, PM10-2.5	Soils, farming, mining, construction, road dust; biomass PM, sea salt	Airborne suspensions; mechanical and natural abrasion; biomass fires; ocean spray	+
Fine PM, PM2.5 (accumulation mode)	Fossil fuel combustion and refining; brake wear; biomass; crustal dust	Fresh emissions; gas-to-particle conversion; biomass and garbage burning	++
Ultrafine PM; PM0.1	Fossil fuel combustion and refining; brake and tire wear	Fresh engine emissions; gas-to-particle conversion; 2ndary photochemical reactions	+++

Classes of particles and their sources.
The diameters of ultrafine PM diameter vary by sampling technology in different studies. Slightly larger PM (0.2 μm) are called "quasi-ultrafine PM."

Table 4 Composition of airborne PM in the Los Angeles Basin.

Size class	*Coarse*	*Fine*	*Ultrafine*
Size (μm)	10–2.5	2.5–0.2	<0.2
Mass ($\mu g/m^3$)	16 ± 8	12 ± 3	2.3 ± 0.7
Number (per m^3), millions[a]	2.5	33,000	530,000
Composition, by % total mass			
Inorganic ions[b]	28 ± 5	32 ± 6	16 ± 5
Crustal plus trace elements[c]	9 ± 1.6	1.6 ± 0.3	5.2 ± 1.2
Elemental carbon	0.25 ± 0.2	1.3 ± 1.2	11 ± 1.6
Organic carbon (OC)	4.9 ± 2.7	15 ± 3.7	52 ± 11
Water soluble OC (%)	0.7	4	7
Water insoluble OC (%)[d]	4.2	11	45
DTT oxidation (pmol/min/μg)[e]	13 ± 3	19 ± 3	39 ± 10

Annual average, mean ± SD.

[a]Size-resolved number concentrations, USC site, 2014–15 (Sowlat et al., 2016).

[b]Inorganic ions: NH_4, NO_3, SO_4, with traces of NA, K, Cl, PO_4.

[c]Crustal elements + trace elements and metals: Al, K, Fe, Ca, Mg, Ti, Si, and trace elements, not in "inorganic ions."

[d]Organic carbon: 25% of total PM mass includes polycyclic aromatic hydrocarbons and aza- and thia-arenes (Rogge et al., 1993).

[e]From six sites in Los Angeles County, 2007: four harbor port sites and one each urban (USC) and ocean shore (Hu et al., 2008). Data provided by Drs. Arian Saffari and Farimah Shirmohammadi from the USC (urban) and Anaheim (suburban) sites, 2013–14 of the Cardiovascular Health and Air Pollution Study (CHAPS) (Shirmohammadi et al., 2015, 2016a,b).

harbor ships; and, by the levels of solar UV that vary by time of day and weather. Smokes from forest fires and cigarettes also contribute particles of different chemistry. D-levoglucosan, a sugar-like derivative from partially combusted cellulose, is a marker for the brush fires that are increasing globally (Saffari et al., 2013). Even cigarette smoke has a chemical signature, n-alkanes (C25–32) from volatile leaf waxes, which represented 1% of Los Angeles PM2.5 in 1982 (Rogge et al., 1994). Air pollution chemistry also shifts widely by season. Even in the mild seasonal changes of Los Angeles, several pollution markers changed cyclically: levoglucosan was 10-fold higher in the winter, in association with seasonal wood smoke from fireplaces and brush fires, while aluminum and iron increased twofold from seasonal winds carrying mineral dust from the earth's crust (Saffari et al., 2013).

These and other chemical signatures can identify sources of most major components of AAP, described as "source apportionment." As shown in **Table 5** for PM2.5 in Los Angeles County and the Southeastern United States, the vehicular contribution is about 20% of PM2.5 in both regions, while meat cooking contributes threefold more PM2.5 in the Southeastern United States than in Los Angeles.

Source apportionments are important for estimating mortality and morbidity from specific sources. The first large-scale analysis of *both* the PM0.20 and PM2.5 for source apportionment was based on the California Teachers Study, a multiethnic cohort of 100,000 older women (57 ± 4 years) studied since 1995. The mass and composition of 50 airborne components in PM2.5 and PM0.20 were assessed for mortality within a 4-km radius of their residence (Ostro et al., 2015). The study included the sources of primary particles and tobacco smoke exposure. For PM2.5, mortality from ischemic heart disease was associated with increments of 10 μg PM2.5/m^3 for PM2.5 mass (hazard ratio, HR = 1.18), nitrate (HR = 1.28), and secondary organic aerosols, SOA (HR = 1.23). For PM0.2, heart disease had similar associations with PM0.2 mass (HR = 1.10): and secondary organic aerosols (HR = 1.25); high-sulfur fuels and smoke from meat cooking had a HR of 1.08. The similar mortality associations for PM2.5 and PM0.2 suggest that ischemic heart disease associations are driven by the PM0.2, which are >95% of the total particle numbers. Provisionally we conclude that no current PM component can yet be considered safe and that specific components of AAP are more important than the density of PM2.5 per se (Forman and Finch, 2018; Hopke, 2016).

We stress the caveat that health associations with specific factors, however strong, do not prove causality (NAS, 2017). Because PM2.5 components are highly intercorrelated, a particular statistical association may still be a surrogate for another pollutant. Moreover, multiple component interactions are more likely than single causes of specific diseases and dysfunctions. For example

Table 5 Source apportionment of PM2.5 in two diverse regions of the United States.

	PM2.5 mass ($\mu g/m^3$)	*Vehicular*	*Biomass*	*Meat cooking*	*Dust*	*Sea salt*	*Secondary nitrogen*	*Secondary sulfur*
Los Angeles[a]	20–30	20%	5%	<1%	5%	3%	27–44%	13–18%
Southeastern United States[b]	8–30	18%	15%	3%	2%		12%	30%

Biomass PM2.5 includes smoke from burning brush and garbage; dust, from roads and soil of the earth's crust. Secondary nitrogen includes NH_4 (cattle) and NOx (vehicular). Secondary sulfur (SO_4) forms by oxidation of sulfur during fuel combustion and petroleum refining.

[a]Hasheminassab et al. (2014)

[b]Zheng et al. (2002).

cocarcinogens, which are not carcinogenic alone, can synergize with another carcinogen. Thus, we may anticipate air pollutants that are co-toxins for brain and other organs. Additionally, psychosocial and socioeconomic factors are largely neglected. For example, cognitive deficits are associated with PM2.5 in stressed urban neighborhoods, but not in upscale homes (Ailshire et al., 2017). Vehicular noise may also increase the health impact of PM2.5 (Basner et al., 2014; Tzivian et al., 2017).

Household Air Pollution (HAP) and Indoor Air

HAP has not been characterized as extensively as outdoor AAP. HAP is particularly affected by cigarette smoke, ingression of particulate matter from AAP, and indoor combustion of solid fuels in food preparation, heating, and lighting. While the practice of using solid fuels for domestic energy needs is infrequent in high-income countries, reliance on polluting solid fuels increases sharply with decreasing economic development at the country level. The use of solid fuels remains a critical yet often overlooked issue. According to the WHO, ~3 billion people at a global level rely on unclean cooking fuels, often used in polluting stoves or open fires to cook food. In turn, this exposure is associated with nearly 4 million premature deaths annually (World Health Organization, 2018). Many homes must use crude stoves with incomplete combustion (Bruce et al., 2000). Characterizing HAP is indeed complex: estimates of indoor PM10 concentrations in homes using unclean cooking fuel vary considerably throughout the day with large spikes during times of food preparation (Bruce et al., 2000) and during cold months when households must rely on polluting fuels for heating and individuals are likely to spend more time indoors and close windows and doors to maintain heat inside the home (Baumgartner et al., 2011; Jin et al., 2006). These estimates vary widely across studies. Smoke from biomass can include many components including types of particulate matter, carbon monoxide, nitrous oxide, sulfur oxide, benzo(a)pyrene, and formaldehyde, among others (Bruce et al., 2000). Moreover, the types of fuels used vary widely across global regions (World Health Organization, 2016). The ensuing differences in chemical composition will evoke different biological responses (Jin et al., 2016). There is also interplay between AAP and HAP, with polluted indoor air that is vented out of the home (Smith and Liu, 1994).

HAP may also include environmental tobacco smoke. While the prevalence of tobacco smoking fell from 2000 to 2010 in many high-income countries, its prevalence is rising in several low- and middle-income countries (Bilano et al., 2015). The negative health effects of second hand tobacco smoke are irrefutable for bystanders throughout the building. For example, smoking households frequently have hazardous levels of PM2.5 and poor air quality (Semple et al., 2012) and higher concentrations of endotoxin than in smoke free homes (Sebastian et al., 2006). Exposure to PM2.5 in smoking homes can exceed the WHO PM2.5 guidance limits by threefold or more (Semple et al., 2015). Reducing exposure to environmental tobacco smoke may not be as simple as spatially separating smokers and nonsmokers within buildings, because levels of PM2.5 are elevated in nonsmoking areas of restaurants, cafes, and bars even when smoking areas are separated spatially into separate rooms compared to establishments that were smoke free (Huss et al., 2010). Other evidence shows the spread of environmental tobacco smoke into nonsmoking units and public areas in multiunit housing buildings (King et al., 2010).

Diseases of Aging

Atherosclerosis: Heart Attack and Stroke

Atherosclerosis is a universal process in human aging that begins early in life (D'Armiento et al., 2001; Finch, 2018). The progression of atherosclerosis varies widely between individuals by diet, exercise, smoking habits, and genetics. In the last 20 years, AAP has recently gained recognition as a major factor in atherosclerotic disease (Rajagopalan et al., 2018). In Los Angeles, the thickening of the carotid artery with aging (CIMT, carotid intima media thickness) increased in proportion to residential levels of PM2.5, for example, residence within 100 m of a freeway accelerated CIMT by twofold (Künzli et al., 2010).

A broader illustration is given by MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution) which recruited participants without clinical cardiovascular disease from four ethnic groups (Hispanic, Black, white, and Chinese), including 6814 individuals from six urban areas (Kaufman et al., 2016). These were monitored by CT for coronary artery calcium (CAC) which is a major clinical risk-indicator for heart disease (Budoff et al., 2013). During a decade of longitudinal study 2000–10, MESA-Air documented that CAC levels increased in close association with residential levels of AAP components (Kaufman et al., 2016). A PM2.5 difference of 5 $\mu g/m^3$ contributed about 15% of CAC increment per year; NOx had similar associations with CAC. The PM2.5 effect on CAC progression was stronger for ages over 65 and for those with hypertension, suggesting synergies with these two major risk factors for ischemic events. MESA also confirmed associations of PM2.5 with CIMT from the Los Angeles studies discussed above. Of major interest, decreases in PM2.5 may have slowed thickening (Adar et al., 2013).

MESA-Air also adjusted individual data for cigarette smoking, which many studies showed to accelerate atherosclerosis. In the Atherosclerosis Risk in Communities (ARIC) Study, active smokers had twofold greater CIMT than never-smokers at middle-age, while the CIMT of former smokers was intermediate between nonsmokers and active smokers, in parallel with their mortality (Howard et al., 1998). We also note the importance of bystander exposure to second-hand smoke (SHS), which increased CIMT in the community-based Bogalusa Heart Study in Mississippi (Chen et al., 2015). Second hand smoke is an important component of indoor air pollution in many countries, as noted above.

Mortality data from heart attack and stroke are pending for MESA-AIR, but may be anticipated from a meta-analysis of 542,991 deaths from cardiovascular disease that shows hazard ratios for PM2.5 of 1.12 per 10 $\mu g/m^3$ (Liu et al., 2018). The People's Republic of China also reports strong associations for stroke with PM2.5 and ozone for hospital admissions (2 million, 172 cities)

(Tian et al., 2018). The implied importance of short-term increases in air pollution to stroke incidence is supported by animal model studies from USC showing that short term exposure to high levels of PM0.2 increased brain ischemic damage (Babadjouni et al., 2018).

Studies have also suggested that HAP may affect cardiovascular outcomes. In rural Guatemalan mountain villages where open wood fires were customary, the introduction of woodstoves with chimneys greatly diminished personal exposure to PM2.5 (264 vs. 102 $\mu g/m^3$), together with lowering blood pressure (systolic, 3.7; diastolic, 3.0 mm Hg) (McCracken et al., 2007). A study of women in rural Honduras similarly found that increased kitchen PM2.5 and black carbon were associated with a greater prevalence of metabolic syndrome (Rajkumar et al., 2019) among women using traditional or cleaner *justa* stoves. In rural China, higher personal exposure to PM2.5 from biomass combustion was associated with higher systolic and diastolic blood pressure among women over age 50 (Baumgartner et al., 2011). Cardiovascular health was also worse in Peruvian women age 35 and older who used biomass fuel, with increased CIMT, more atherosclerotic plaques, and higher systolic blood pressure when compared to those with long-term use of cleaner fuels (Painschab et al., 2013). Moreover, a recent study of women age 15–49 across 10 low- or middle-income countries with prevalent use of solid cooking fuels showed association with slightly higher systolic blood pressure and hypertension (Arku et al., 2018). A simulation study estimated that liquefied petroleum gas interventions to reduce reliance on biomass cooking may reduce systolic blood pressure by 5.5 mmHg for women over age 50 (Steenland et al., 2018).

Lung Cancer

While lung cancer was long ago associated with cigarette smoking in the British Male Doctors' Study (Doll and Hill, 1954; Doll et al., 2004), its associations with PM2.5 from AAP gradually emerged in recent decades (Pope III et al., 2002). Moreover, AAP and CS interactions with super-additive synergies were shown for the Cancer Prevention Study II (Turner et al., 2014). This prospective US cohort of 1,184,588 participants age 30 and over across the United States was tracked since 1984 for cancer incidence by estimated PM2.5 exposure from the residential geocoded address; the data also included tobacco use and second hand exposure, as well as individual risk factors including body mass index, diet, and occupational exposure. The study confirmed prior findings (Pope III et al., 2002) that the relative risk of lung cancer increased for PM2.5 levels by about 8% per 10 $\mu g/m^3$. Worse than additive, the impact of pack-years and PM2.5 had a twofold synergy or super-additivity.

Extending findings on AAP and CS, exposure to HAP is also associated with lung cancer. Data from China shows lung cancer association with HAP, particularly from coal combustion (Du et al., 1996; Kleinerman et al., 2002; Zhao et al., 2006). Other studies of general biomass use and wood smoke among female nonsmokers indicate elevated lung cancer among individuals exposed to biomass fuels in India (Behera and Balamugesh, 2005) and wood smoke in Mexico (Hernández-Garduño et al., 2004).

We must also face the possibility of synergies for all three "global smokes": from fossil fuels, tobacco, and burning biomass in household fuels (**Table 2**). To evaluate these three combustion sources, Burnett et al. (2014) developed an innovative "integrative dose-response model" for ischemic heart disease (IHD), cerebrovascular disease (stroke), lung cancer (LC), and chronic obstructive pulmonary disease (COPD). The model shows two dose-response patterns for relative risk (RR) by PM2.5 exposure, with linear increases that reach plateaus. The risk of ischemic heart disease and stroke increased linearly with PM2.5, even at low levels, reaching increasing maximum risks up to threefold of two- to threefold in upper ranges that represent cigarette smoke. However, lung cancer risks continued to increase in the upper exposure range, approaching 50-fold. The model gave "reasonable predictions over the range of risk" for the higher ambient PM2.5 in highly polluted Asian cities. The lower range of PM2.5 still showed positive risks below 5 $\mu g/m^3$, confirming findings for Canadian cardiovascular mortality (Crouse et al., 2012) and for the recent Medicare analysis (Di et al., 2017).

These calculations assume that PM2.5 from all sources has the same toxicity by weight (Burnett et al., 2014; Pope III et al., 2011). Their calculations assume that each cigarette would deliver the equivalent of the daily intake of ambient PM2.5 at 667 $\mu g/m^3$. While the assumed adult intake of 18 m^3 of air per day is reasonable, the PM2.5 density required per cigarette equivalent raises further questions. We suggest another calculation that includes the differences between the initial nicotine content and the resulting blood levels (Forman and Finch, 2018). Based on the clearance rates (pharmacokinetics) of blood nicotine, only about 10% of the nicotine per cigarette reaches the circulation (Benowitz and Jacob III, 1984). Thus, we suggest that 10% also approximates the delivery of *soluble* cigarette toxin associated with CS PM2.5. This conclusion may still be consistent with findings that lungs retain 60–90% of PM inhaled by smokers (Baker and Dixon, 2006).

These adjustments of delivered PM2.5 would introduce a left-ward shift by about 10-fold for values above 10,000, but would not alter the main conclusion that the IHD risk reaches a plateau, while lung cancer increases linearly with at higher levels of PM2.5 exposure. The analysis also assumed that household biomass PM2.5 had equivalent toxicity, which may be an overestimate. Little is known about the solubility of potential toxins from AAP. For example, the chemical analysis of AAP identifies many components as water insoluble, for example, metals and organic carbon (Saffari et al., 2015). Despite these uncertainties, we cannot ignore interactions of the smokes, which are shown in a further example of obesity below.

Brain and Cognition

Cognitive impairments have received scant attention in studies of HAP. This important gap arises, in part, due to difficulties in measuring exposure to HAP and a lack of available cognitive data in low- and middle-income countries where exposure to HAP from biomass burning remains prevalent. Recent work using data from Mexico (age 50 and over) documents strong associations

between unclean cooking fuel use (wood and coal vs. natural/petroleum gas) and poorer cognitive function in verbal learning, visual scanning, verbal fluency, and orientation tasks; the deficits are equivalent to 3.5–6.5 additional years of cognitive aging (Saenz et al., 2018). A study from rural India (age 30 and over) reported smoke generating cooking fuels (biomass or kerosene vs. liquefied petroleum gas) were associated with doubled risks of cognitive impairment (Krishnamoorthy et al., 2018). Together, these studies suggest that smoky cooking fuels are a potentially modifiable risk factor for cognitive impairment in late-life. However, both of these studies have relied on cross-sectional methodologies and used only cooking fuel as an indicator of HAP. The roles of unclean heating fuel and directly measured indoor air quality for cognitive health, including cognitive decline, remain open research questions. Another study from Guatemala examined carbon monoxide (CO) exposure (an indicator of wood smoke) in mother-child dyads including measures of mother's CO exposure during pregnancy and child's CO exposure at ages: 0–9 months and 6–7 years. The results indicated that in-utero third trimester exposure to CO was most relevant for the child's neuropsychological performance and was associated with poorer performance on four out of 11 neuropsychological tests (Dix-Cooper et al., 2012) suggesting that gestational exposure to HAP impairs neurodevelopment in children.

Alzheimer's disease and accelerated cognitive loss during normal aging are now strongly associated with air pollution. The most comprehensive population-based study of dementia and traffic-related air pollution (TRAP) is from Canada, representing *all* adult residents of the province of Ontario, totaling 6.5 million by Chen et al. (2017). Please note that this Chen is different from Jiu-Chiuan Chen of Chen and Schwartz (2000), which was the first epidemiological study to show neurobehavioral deficits from ambient air pollution. JC Chen is also senior author in Cacciottolo et al. (2017). The TRAP-associated dementia showed a steep gradient by proximity to a major roadway (**Fig. 1**). Both PM2.5 and NO_2 were associated with incident dementia. The population attributable fraction of dementia (PAF) was 7–11%. In contrast to dementia, the incidence of multiple sclerosis or Parkinson's disease was not associated with TRAP. This study is the first to evaluate these three major degenerative conditions for association with TRAP with notable specificity for dementia.

In US women of the WHIMS cohort, dementia was also strongly associated with PM2.5 (Cacciottolo et al., 2017). The senior author Jiu-Chiuan Chen designed and carried out the analysis of WHIMS cognitive data, which was published together with experimental data from the Finch Lab. Their exposure to excess air pollution was based on residential location. According to EPA guidelines for PM2.5 of >12 μg/m^3, about 30% of the WHIMS cohort was exposed to high PM2.5. The main effects increased the risk of all-cause dementia by 92% and of accelerated cognitive declines by 81% (**Figure 2**). For all US women, this risk is equivalent to a PAF of about 20% of Alzheimer cases.

The role of ApoE4, the major genetic risk factor for Alzheimer's disease, has also been explored. **Fig. 2** also shows that ApoE4 carriers in the WHIMS cohort had higher risks of accelerated cognitive aging and of dementia, up to threefold above non-E4 carriers. The non-E4 carriers were mostly ApoE3, which is the majority allele in all human populations. This is the first documentation that ApoE4, the major risk factor for AD, interacts with ambient air pollution in adults as a risk factor for both accelerated cognitive aging and for dementia.

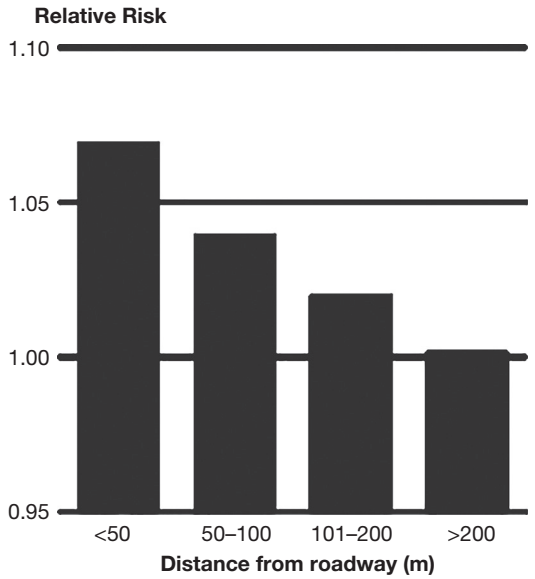

Fig. 1 Dementia risk and residence near roadways with heavy traffic. Risk of dementia by distance of individual residences from roadways with heavy automotive traffic in the province of Ontario, Canada. Two cohorts were analyzed: ages 20–50 years, for multiple sclerosis (4.4 million) and ages 55–85 for dementia and Parkinson's disease; combined total of 6.5 million. Adjusted for smoking, physical activity, BMI, and education; baseline age, 66.8 $\pm$ 8.2 years (range 20–85 at entry in 2010). About 50% resided within 200 m of a busy roadway. Redrawn from Chen, H., Kwong, J. C., Copes, R., Tu, K., Villeneuve, P. J., van Donkelaar, A., et al. (2017). Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: A population-based cohort study. *The Lancet* **389**, 718–726.

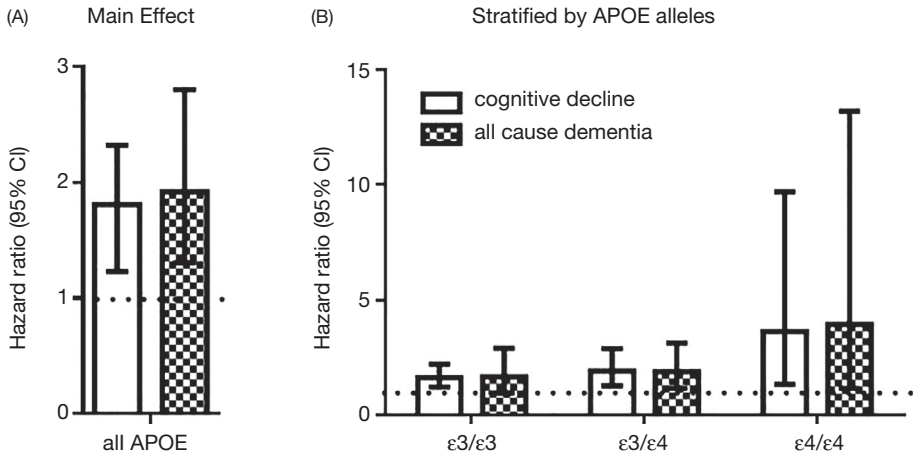

Fig. 2 Risk of dementia and accelerated cognitive decline in WHIMS Cohort. Longitudinal assessment in the Women's Health Initiative Memory Study (WHIMS); 4504 women from 48 states who were initially cognitively normal at age 65–79 years. The PM2.5 was based on data from U.S. EPA Air Quality System (AQS) to calculate a 3-year moving average PM2.5 up through 2010. Regraphed from Cacciottolo, M., Wang, X., Driscoll, I., Woodward, N., Saffari, A., et al. (2017). Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Translational Psychiatry* **7,** e1022.

Obesity—Indoor Air

Children's obesity also showed synergies of AAP with second-hand smoke (SHS) in the Southern California Children's Health Study, ages 10–18. Both SHS and residence close to a roadway with heavy traffic were associated with increased body mass index (BMI) (Fig. 3) (McConnell et al., 2015). By age 18, the combined effect was three BMI units above those with low PM2.5 and with no SHS exposure. The BMI increments were dose dependent with the number of household smokers; maternal smoking during pregnancy also increased BMI at 18 years. As for lung cancer discussed above, the effects of AAP and SHS synergized, yielding 30% higher BMI than expected from simple additivity. The possible mechanisms in these synergies are unknown but could involve obesogenic effects of polyaromatic hydrocarbons (PAH), which inhibit catecholamine-induced lipolysis, and which are present in the smokes of fossil fuels and cigarettes.

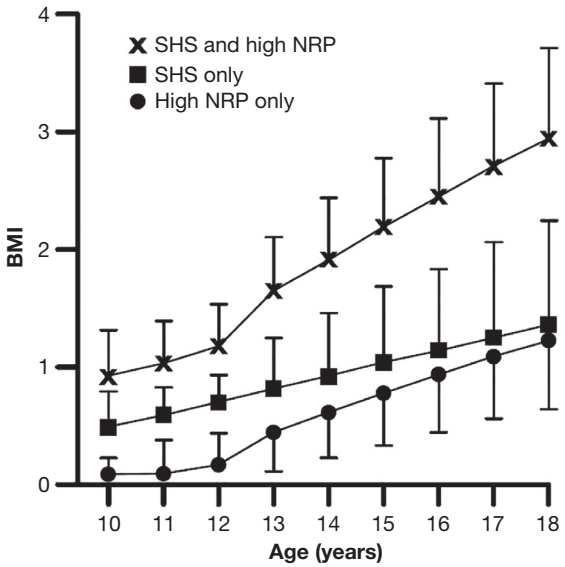

Fig. 3 Adolescent body mass index, cigarette smoke, and air pollution. The body mass index (BMI) of children aged 10–18 years who were exposed to second-hand smoke (SHS) and near roadway air pollution (NRP), from longitudinal annual measurements in the Southern California Children's Health Study. Redrawn from McConnell, R., Shen, E., Gilliland, F. D., Jerrett, M., Wolch, J., Chang, C. C., Lurmann, F., and Berhane, K. (2015). A longitudinal cohort study of body mass index and childhood exposure to secondhand tobacco smoke and air pollution: The Southern California Children's Health Study. *Environmental Health Perspectives* **123**, 360.

Consistent with these findings on obesity, PM2.5 and NOx showed strong correlations with increased insulin resistance in German adolescents (Thiering et al., 2016). Ambient air pollution has become recognized as an endocrine disruptor for insulin resistance (Holmes, 2016). Diabetes prevalence and elevated fasting glucose were associated with PM2.5 in the cross-sectional "33 communities Chinese Study" (Yang et al., 2018). We anticipate that PM2.5 also synergizes with cigarette smoke for insulin resistance and diabetes as it does for obesity. Obesity and diabetes are established risk factors for cardiovascular disease and Alzheimer's disease. In effect, the smokes from fossil fuel and cigarettes accelerate aging processes associated with the major causes of morbidity and mortality at later ages. The mechanisms are largely mysterious.

How It Works—We Don't Know Much

How Does It Get Into the Body

Surprisingly little is known about how inhaled particles of AAP have such profound pathological impacts throughout the body. As inhaled PM enters the respiratory tract, they contact the epithelial cells lining our airways, nose and throat to lung. The "mucocilary escalator" conveys particles, particularly the coarse PM, into the throat where they are swallowed. How much inhaled PM reaches the gut is not well-defined, gut delivery of PM can impact the brain in animal studies (Ejaz et al., 2014; McCallister et al., 2016). The fine and ultrafine PM from CS reach deep lung alveoli with high efficiency, 50–90% (Baker and Dixon, 2006). Deeper into the lung at alveolar surfaces, particles are phagocytosed by macrophages, with greatest efficiency for the ultrafine PM (Geiser and Kreyling, 2010).

Particle translocation from lung to blood is very inefficient: For artificial ultrafine PM, $<25\%$ of that reaching the lung was detected in blood cells. The effects of AAP on the brain could include some particles that enter from the nose by olfactory nerves going directly to the brain (Cheng et al., 2016; Oberdörster et al., 2004). The lung-to-brain route of altered blood proteins and lipids seems more likely to account for the brain-wide responses to air pollution (Forman and Finch, 2018; Mumaw et al., 2016). We are still at the black-box stage of analysis: we know what goes in and its later effects, but we know little of how it works so adversely.

Inflammation, Oxidative Activity, and Stress

Inflammatory responses are widely discussed as mechanisms in all forms of airborne pollutants from the smokes of fossil fuels, cigarettes, and burning biomass. The lungs certainly respond with chronic respiratory distress of coughing, phlegm and asthma. Downstream from the lung, body wide pathological processes of atherosclerosis, adiposity, lung cancer, and neurodegeneration all involve inflammation. Many studies document activated macrophages and local production of inflammatory cytokines, particularly IL-6 and TNFα (Block and Calderón-Garcidueñas, 2009; Finch, 2018). Inflammatory pathways are evident in gene expression studies, particularly involving Nfr2 and TLR4 in multiple organs (Rajagopalan et al., 2018; Woodward et al., 2017; Zhang et al., 2012). However, blood levels of IL-6 and TNFα are not consistently elevated in rodent studies. An extreme example is the "Viking House Study," where young Danes volunteered for exposure to 7 days of high levels of indoor wood smoke that maintained PM2.5 of >700 μg/m^3 and $NO_2 > 125$ μg/m^3 (Jensen et al., 2014). Surprising to all, these huge levels of indoor pollutants did not elevate blood IL-6 or other inflammatory markers. This well done study prompts further thinking on the difference between acute and chronic exposures, and on the complexity of real-world ambient pollutants. We have much to learn about the deep mechanisms of airborne pollutants. A recent review calls for consideration of endocrine responses to air pollution, because inhaled particulate matter and ozone is associated with hypothalamic pituitary adrenal (HPA) axis activation and release of stress hormones which, along with oxidative and inflammatory processes (Thomson, 2019).

The Future

The proportion of our lifetime spent indoors has steadily increased with industrialization. The EPA reports that the average American spends approximately 90% of their time indoors (EPA, 2019). Integrative approaches to air pollution and human health and aging must then consider the importance of environmental exposures from indoor as well as outdoor sources. Achieving this goal has major implications for prevention given scientific evidence for super-additive effects of global smokes.

We note difficulties to measurement of air pollution both in the home and in the ambient environment. Many studies of HAP from biomass fuels have relied on reported cooking fuels, with fewer studies directly measuring particulate matter and pollutants inside the home, or personal exposure. For AAP, the majority of air quality monitors are located in urban areas and do not capture the finest particulate matter PM0.1, leaving many unknowns about air quality in rural areas or the effects of ultrafine particulate matter on human health in large population-based data sets.

Studies have also documented the importance of exposure to air pollution throughout the life-course ranging from in-utero exposures to late-life. However, the majority of studies of the effects of air pollution on health and aging have emphasized exposure during a particular period of the life-course. Future work would be strengthened by considering exposure to the global smokes throughout the life-course, including in-utero and childhood exposures and the potential for interactive effects with late-life exposures.

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