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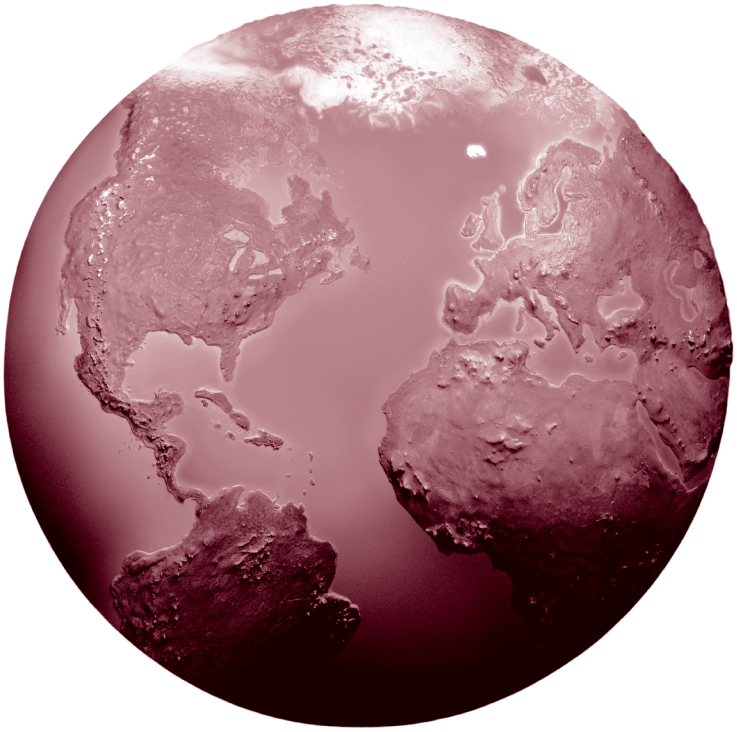

COMMENTARY BY THE HEI REVIEW COMMITTEE SUMMARIZING AND EVALUATING THE INVESTIGATORS' REPORT

Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts

Downward and Vermuelen

Health Effects Institute

Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts

George S. Downward and Roel Vermeulen

with a Commentary by HEI's Review Committee

Research Report 213
Health Effects Institute
Boston, Massachusetts

Trusted Science · Cleaner Air · Better Health

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- Identifies the highest-priority areas for health effects research
- Competitively funds and oversees research projects
- Provides intensive independent review of HEI-supported studies and related research
- Integrates HEI's research results with those of other institutions into broader evaluations
- Communicates the results of HEI's research and analyses to public and private decision makers.

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All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

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Research Report 213, *Ambient Air Pollution and All-Cause and Cause-Specific Mortality in an Analysis of Asian Cohorts*, G. S. Downward and R. Vermeulen

INTRODUCTION

Air pollution is a major global public health risk factor. There is now broad expert consensus that exposure to air pollution causes an array of adverse health effects based on evidence from a large body of scientific literature that has grown exponentially since the mid-1990s (IARC 2016; Thurston et al. 2017; U.S. EPA 2016, 2019; WHO 2021).

Based on that evidence, the Global Burden of Disease (GBD*) project estimated that in 2019 air pollution ranked as the leading environmental risk factor for global mortality, surpassed only by high blood pressure, tobacco use, and poor diet (HEI 2020). The air pollution burden varies widely around the globe, and is highest in countries in Asia and Africa, partly due to the typically high exposure levels in those regions.

Much of what is currently known about the adverse effects of ambient air pollution comes from studies conducted in high-income regions, especially North America and Europe, with relatively low air pollution levels. Studies of long-term exposure and morbidity and mortality in low- and middle-income countries have emerged more recently. Hence, an integrated exposure–response (IER) function was developed to estimate mortality relative risks across the global exposure range and has been used by the GBD collaboration and the World Health Organization (WHO) to estimate the burden of disease attributable to particulate matter ≤2.5 µm in aerodynamic diameter ($PM_{2.5}$). The IER function combines relative risk estimates from various $PM_{2.5}$ sources, including active and passive smoking, to fill in the knowledge gap of air pollution studies in high exposure settings (Burnett et al. 2014). In the most recent GBD estimates (GBD 2019 Risk Factors Collaborators 2020), active smoking studies were excluded from the IER function to characterize risks at high exposure, because the few new studies of high air pollution conditions in Asia provided enough information so that evidence from active smoking data is no longer necessary to use. The number of studies of long-term air pollution and health in Asia, however, remains limited to date, and there is a clear research gap with respect to the true size of the ambient air pollution and mortality associations in that region.

Dr. Vermeulen's study was funded through a special invitation based on several scientific and strategic considerations. At Utrecht University, the Netherlands, Dr. Vermeulen proposed to evaluate the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in a pooled analysis of 23 Asian cohorts from the Asia Cohort Consortium (Aim 1). Moreover, he proposed to explore the heterogeneity in mortality risks among cohorts in the context of cultural, social, economic, or infrastructural differences between countries (Aim 2). Although the application came outside of a specific Request for Applications, it was reviewed using the same two-stage process: external reviewers evaluated the technical quality of the proposed work, followed by a discussion of strengths and limitations by the Research Committee. The HEI Research Committee recommended Dr. Vermeulen's application for funding because of the strong design features, the large number of participating cohorts, and the availability of individual-level covariate information. In addition, they appreciated that the cohorts were already harmonized, making it a cost-efficient and low-risk proposal. Dr. Vermeulen recruited Dr. George S. Downward as the analytical project lead.

During the course of the work, there were several unforeseen setbacks regarding cohort participation for various reasons, and only six of the original 23 cohorts that had expressed interest in participating were eventually included in the analyses. Therefore, the current report is focused solely on Aim 1. Aim 2 was not further pursued due to the small number of cohorts included in the final analyses.

This Commentary provides the HEI Review Committee's evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the Investigators' Report into a broader scientific perspective.

Dr. Roel Vermeulen's (principal investigator) 2-year study, "Long-Term Outdoor Air Pollution and Cause-Specific Mortality in a Pooled Analysis of 23 Asian Cohorts," began in July 2018. Total expenditures were $236,000. The draft Investigators' Report from Downward (first author) and Vermeulen was received for review in September 2021. A revised report, received in August 2022, was accepted for publication in September 2022. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Commentary.

* A list of abbreviations and other terms appears at the end of this volume.

SCIENTIFIC BACKGROUND

The study by Downward and Vermeulen assessed the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in an analysis of six Asian cohorts, with more than 340,000 participants (see Commentary Table 1 and Commentary Figure 1). The investigators estimated exposure to $PM_{2.5}$ and nitrogen dioxide (NO_2) at the residence of the participants for the year of recruitment using global satellite-based models. They applied single-pollutant Cox proportional hazard models to assess the association between air pollution exposure and all-cause and cause-specific mortality adjusted for important confounders, as described in more detail below.

STUDY POPULATION

The current study leverages the *Asia Cohort Consortium,* a multicenter collaborative effort since 2008 that consists of more than one million people to date from several dozen cohorts from 10 Asian countries. The Consortium seeks to understand the relation between genetics, environmental exposures, and the etiology of disease. To be eligible, cohorts must have information on mortality outcomes and important confounding variables, such as smoking and body mass index. Data on those variables were harmonized before entering the Consortium to ensure comparability.

The final analyses included six cohorts from the Asia Cohort Consortium and represented more than 340,000 adult participants in six countries (Commentary Figure 1, which includes the study name abbreviations). The study included three high-income countries (Japan, Taiwan, and Republic of Korea), one lower-middle country (Iran), and two low-income countries (Bangladesh, and India); designations are based on 2006 World Bank classifications. The cohorts were general population studies and varied widely in size, study period, recruitment method, geographical scope, exposure assignment, and outcome assessment (Commentary Table 1). The Indian MCS and the Japanese JPHC studies were the largest cohorts by far. Participants were recruited from 1991 to 2008 and followed-up between 5 and 23 years. Some cohorts were conducted in a single city or district (e.g., the Indian MCS and Bangladeshi HEALS), and others included much larger areas in a country (e.g., the Japanese JPHC). Mean exposures varied from 8 to 58 $\mu g/m^3$ for $PM_{2.5}$ and 7 to 23 ppb for NO_2. Correlations between $PM_{2.5}$ and NO_2 exposures varied from <0.01 to 0.57 (Commentary Table 1).

EXPOSURE ASSESSMENT

The investigators estimated exposure at the residence of the participants for $PM_{2.5}$ and NO_2 by using existing global satellite-based models and building on the exposure methods that were also used in the GBD project (Larkin et al. 2017; van Donkelaar et al. 2015, 2016). The global models provided high resolution (1 km^2 for $PM_{2.5}$, 100 m^2 for NO_2) annual average concentrations for 1998 (or 1997 in case of NO_2) to 2008. The method is a sophisticated integration of primarily satellite data, with a chemical transport model, land-use information, and ground-monitoring data included as well. The models were validated against ground-based monitor data, with an overall R^2 of 0.81 and 0.54 for $PM_{2.5}$ and NO_2, respectively. The estimates were assigned to study participants based on geocoded residential location data, but for the year of recruitment only. The 1998 exposure estimate was assigned for the participants that were recruited from 1991 to 1997 (i.e., before the global model estimates became available). Note that in four cohorts, exact address data were available for the year of recruitment; for the remaining cohorts (Indian MCS and Iranian Golestan) aggregated address data were used (e.g., postal codes).

OUTCOME ASSESSMENT

The study included both all-cause mortality and cause-specific mortality outcomes: nonaccidental, all cancer, lung cancer, cardiovascular disease, and noncancer lung disease mortality. The outcome assessment was performed by each individual cohort, typically through active follow-up or linkage to death registries. The same International Classification of Diseases (ICD) 9 or 10 coding was used for the different outcome categories across the cohorts except for the Japanese JPHC cohort. The JPHC cohort used slightly different ICD codes, particularly for cardiovascular disease. The JPHC cohort also did not have information on nonaccidental deaths.

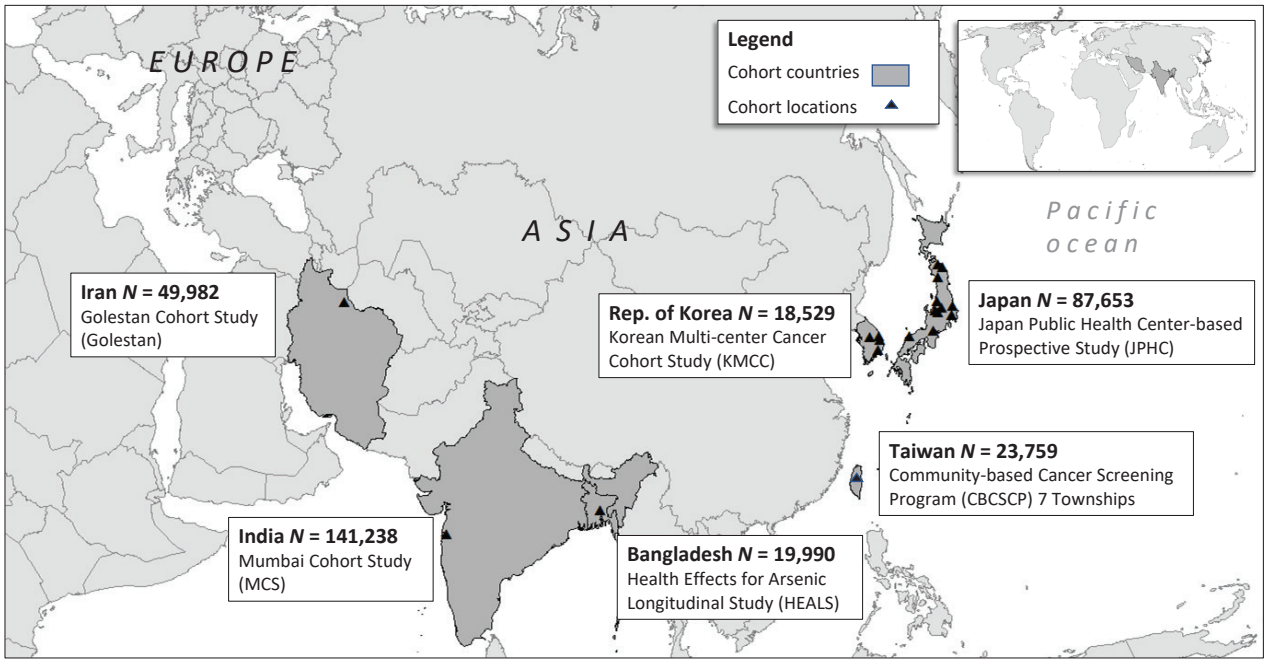
ANALYSES

The investigators applied single-pollutant Cox proportional hazard models to assess the association between air pollution exposure and all-cause and cause-specific mortality. Models were adjusted for age (time axis), sex, recruitment year, smoking status, pack-years, body mass index, and a measure of socioeconomic status (education or employment). In addition, models adjusted for alcohol intake or diet for all cohorts except the Indian MCS and Bangladeshi HEALS cohorts. Models from one cohort (Iranian Golestan) were also adjusted for domestic fuel use — an indicator of household air pollution. That indicator was missing for the other cohorts.

The investigators calculated hazard ratios for each cohort separately and then combined using random effects meta-analysis. Associations were reported per 5- and 10-ppb increment in $PM_{2.5}$ and NO_2, respectively. For each cohort, the investigators tested assumptions for the Cox proportional hazard models, ran two-pollutant models, and characterized the exposure–response function using splines and exposures by quartiles. Furthermore, they assessed the robustness of the associations by conducting several sensitivity and subgroup analyses. Notably, they conducted a sensitivity analysis in which associations were adjusted for urbanicity. Moreover, they reran analyses for the subcohorts of participants alive in 1998 when global model estimates became available. Note that no meta-analyses were conducted on any of the sensitivity analysis results.

Commentary Table 1. Key Characteristics of the Six Asian Cohorts at Recruitment (ordered by sample size)

Study Name	Location	Recruitment Years	Average Years of Follow-up	Sample Size	Mean Age	Mean Exposure $PM_{2.5}$ ($\mu g/m^3$)	Mean Exposure NO_2 (ppb)	Correlation $PM_{2.5}$ and NO_2	Exposure Assignment	Outcome Assessment
MCS	Mumbai, India	1991–1997	5	141,238	51	34	23	<0.01	Postal code	Active follow-up at regular intervals
JPHC	11 regions in Japan	1990–1995	20	87,653	52	11	9	0.50	Residential address	Death registries
Golestan	Gonbad city and surrounding rural area in Iran	2004–2008	11	49,982	52	32	9	0.54	Community level	Active follow-up at 1-year intervals
CBCSCP	7 townships in Taiwan	1991–1992	23	23,759	47	8	9	0.14	Residential address	Health examinations, medical records, and cancer and death registries
HEALS	Araihazar in Bangladesh	2000–2008	10	19,990	37	58	7	0.46	Residential address	Active follow-up at 1-year intervals
KMCC	4 areas in the Republic of Korea	1993–2005	13	18,529	55	23	11	0.57	Residential address	Health insurance, cancer, and death registries
TOTAL	6 countries	1991–2008	5–23	341,151	37–55	8–58	7–23	<0.01–0.57		



Commentary Figure 1. Geographical location of the six Asian cohorts.

SUMMARY OF RESULTS ACROSS COHORTS

- The meta-analytical summary effect estimates documented no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality, except for a positive association with cardiovascular mortality (Commentary Figure 2). The combined estimate for cardiovascular mortality was 1.05 per 5-μg/m^3 increment and was borderline significant (95% confidence interval 0.99–1.12).
- For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes. The combined estimate for all-cancer and lung cancer mortality were 1.18 and 1.13 per 10-ppb increment, respectively; both estimates were statistically significant. Combined estimates were heavily driven by positive associations from a single cohort (see below).

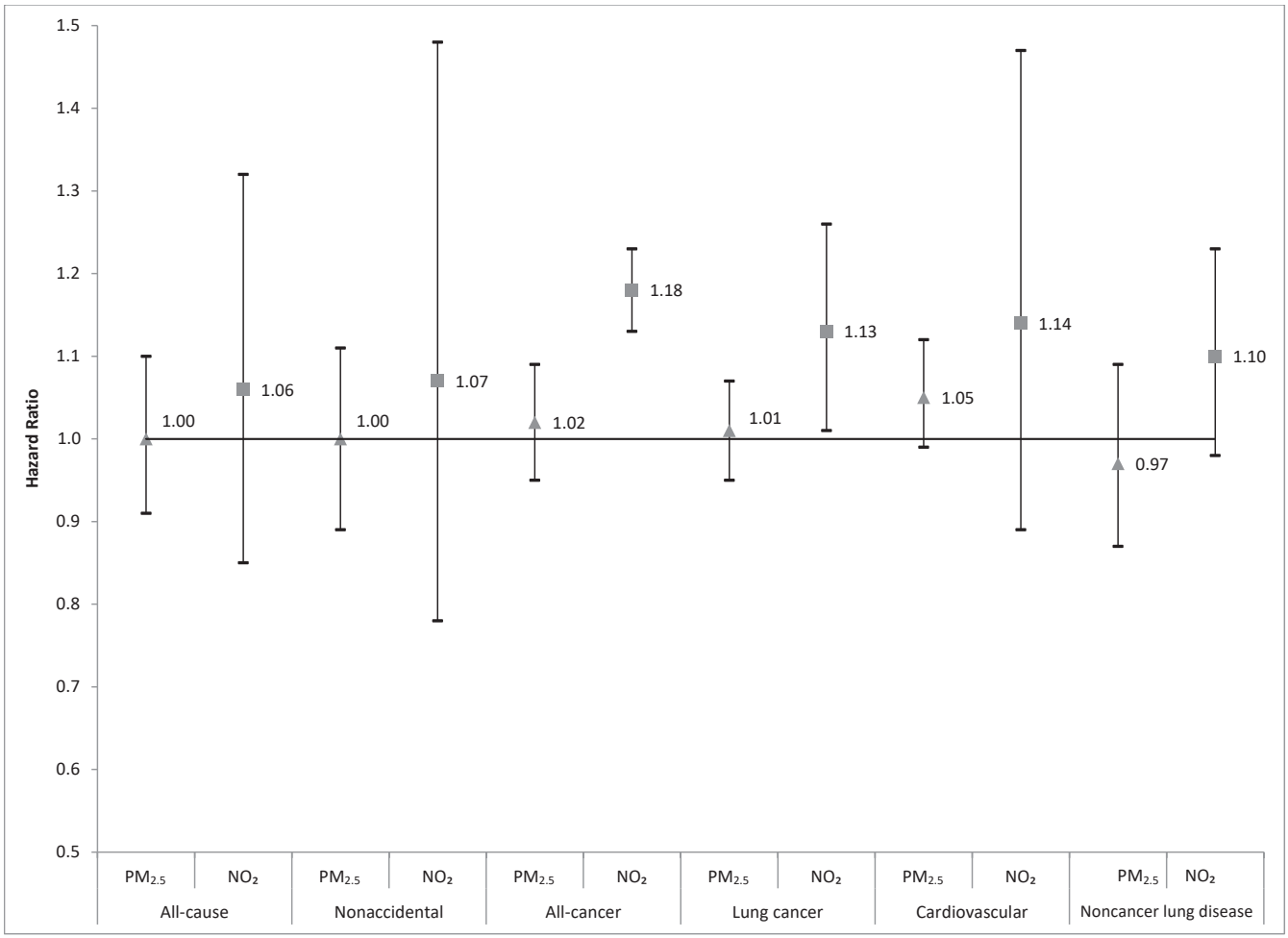
SUMMARY OF RESULTS WITHIN COHORTS

- The two largest cohorts — the Indian MCS and the Japanese JPHC — and the smaller Taiwanese CBCSCP cohort reported positive associations between ambient $PM_{2.5}$ and cardiovascular mortality (Commentary Table 2). Those associations were statistically significant and fairly robust to further adjustment for urbanicity. The other three cohorts did not find an association with cardiovascular mortality.
- For ambient NO_2, the combined estimates for cancer outcomes were heavily influenced by the positive association in the Japanese JPHC cohort. This cohort carried greater than 90% of the weight in meta-analyses. Most other cohorts documented no association with cancer outcomes.
- Large heterogeneity of the findings was reported across the cohorts, with null, negative, or positive findings, with sometimes no apparent pattern (Commentary Table 2). The Iranian Golestan and Korean KMCC cohorts consistently reported null findings. Findings from the Bangladeshi HEALS cohort were uninformative, due partly to the large confidence intervals and minimal exposure contrast. Hence, this cohort carried the lowest weight in the meta-analyses (often below 1%).

HEI REVIEW COMMITTEE'S EVALUATION

In its independent review of the study, the HEI Review Committee thought the research was well motivated and addressed a clear research gap. There are few long-term air pollution and health studies in Asia, and additional studies are urgently needed. This report adds to the overall knowledge base on health outcomes associated with air pollution in Asia. Although the number of cohorts participating was lower than anticipated when the study was funded, the inclusion of six harmonized cohorts ensured a large sample size.

In summary, the study documented large heterogeneity of the findings across the individual cohorts, with no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality in meta-analyses of all cohorts combined, except for a borderline significant positive association with cardiovascular mortality. Several individual cohorts (i.e., Indian MCS, Japanese JPHC, and Taiwanese



Commentary Figure 2. Meta-analysis for the association between exposure to $PM_{2.5}$ (per 5 µg/m³) and NO_2 (per 10 ppb) and mortality in the six Asian cohorts combined. Associations were from single-pollutant models and adjusted for important potential confounders, such as smoking, body mass index, and socioeconomic status.

CBCSCP), however, did display positive significant associations between ambient $PM_{2.5}$ and cardiovascular mortality. For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes, although estimates were heavily driven by positive associations from the Japanese JPHC cohort.

The Committee noted several strengths of the research. First, it recognized the benefits of leveraging the Asia Cohort Consortium to study health effects of ambient air pollution. The study included data from six cohorts, representing more than 340,000 adult participants, which is a large sample size. The data were already harmonized and included both all-cause mortality and cause-specific mortality outcomes. There were also data available for several individual-level lifestyle factors, such as smoking status and intensity, body mass index, and diet, and the analyses were adjusted accordingly. As such, the study provides a useful model for future applications of harmonized cohort data to study the effects of air pollution on human health.

Second, the Committee appreciated the uniform assessment of long-term $PM_{2.5}$ and NO_2 using state-of-the-art exposure estimation methods. Exposures to $PM_{2.5}$ and NO_2 were estimated at a reasonably high spatial resolution — residential address level for most of the cohorts — and took advantage of global satellite-based models. The existing monitoring networks have limited spatial coverage with typically few stations in suburban and rural locations, particularly in low- and middle-income countries. According to the 2022 WHO Air Quality database, 40% of countries have no ground-level PM monitors. Ground-based monitor data are even sparser for NO_2, with 62% of countries with no monitors (WHO 2022). In addition, most existing monitoring networks have insufficient density to capture small-scale (within-city) variation of air pollution, which can be substantial for certain pollutants, such as NO_2.

Recent developments in satellite-based remote sensing and other exposure methods and models offer new ways to

Commentary Table 2. Summary of Null, Negative, or Positive Findings in the Six Asian Cohorts

	$PM_{2.5}$						NO_2					
	MCS	JPHC	Goles-tan	CBCSCP	HEALS	KMCC	MCS	JPHC	Goles-tan	CBCSCP	HEALS	KMCC
	India	Japan	Iran	Taiwan	Bangla-desh	Korea	India	Japan	Iran	Taiwan	Bangla-desh	Korea
All-cause	+	+	0	0	0	– (0)	+	+	0	–	+	0
Nonaccidental	+	NR	0	0 (+)	0	– (0)	+	NR	0	–	+	0
All-cancer	0	+	0	0 (+)	0	0	+	+	0	0	0	0
Lung cancer	0	0	0	0	0	0	0	+	0	0	0	0
Cardiovascular	+	+	0	+	0	0	+	+	0	0	+	0
Noncancer lung disease	0	–	0	0	0	0	0	0 (+)	0	– (0)	0	0

0 = null findings; – = negative association; + = positive association; NR = not reported. In parentheses, the summary of findings after additional adjustment for urbanicity when those findings differed from the main analysis. Note that in the Indian MCS cohort it was assumed that this cohort was fully urban, and no further adjustment was conducted.

provide air pollution estimates that cover large areas in a country, whole countries, or even multiple countries, with a sufficiently high degree of spatial resolution. The global satellite-based models applied in this study allowed exposure to be estimated for a large urban and rural population in six Asian countries. The Committee also thought the analyses were generally straightforward and clearly presented in the report. For example, the Committee appreciated the various sensitivity and subgroup analyses, including the additional adjustment for urbanicity in a sensitivity analysis.

Although the Review Committee broadly agreed with the investigators' conclusions, it identified limitations detailed below that should be considered when interpreting the results.

INADEQUATE ADJUSTMENT LIKELY FOR CHARACTERISTICS THAT CORRELATE WITH AIR POLLUTION AND MORTALITY

The Committee was concerned that residual confounding was likely in the main analyses due to inadequate adjustment for characteristics that correlate with air pollution and mortality, most notably socioeconomic status and urbanicity. These characteristics are likely related to both exposure and health, and difficult to fully capture based on the available indicators. Findings sometimes differed for models that adjusted for urbanicity as compared to those that did not (see Commentary Table 2). The Committee thought the authors should have adjusted for urbanicity in their main models instead of adjusting for urbanicity in a sensitivity analysis, even if there was some modest collinearity between air pollution estimates and urbanicity in some cohorts, as documented by the investigators. The Committee does appreciate the tables in the main text that compare the results with and without the urbanicity variable, additions made in response to earlier Committee comments.

The need for adjustment for urbanicity was also shown in the recent Prospective Urban and Rural Epidemiology (PURE) study (Hystad et al. 2020). The primary analyses adjusted for an indicator variable (urban or rural location). Models that further adjusted for "unmeasured differences between urban and rural areas within centers, as well as differences across centres" resulted in notable different results, especially for mortality. For example, the negative association between $PM_{2.5}$ and all-cause mortality flipped to a positive association.

In the PURE study a notable negative association was also observed between markers of healthcare (hospital admissions or medication use) and deaths; this result suggests that poorer access to healthcare could be responsible, at least partly, for the higher mortality rates in low- and middle-income countries. Socioeconomic status and access to healthcare are closely related in many settings (Dagenais et al. 2020).

Since socioeconomic status influences where people live and is related to both exposure and health, this is often considered to be one of the most important confounders in air pollution epidemiology (Clark et al. 2014; Hajat et al. 2015; O'Neill et al. 2003). Additionally, there is evidence of differing correlations between socioeconomic status and air pollution exposure by location, highlighting the importance of adjusting for socioeconomic status based on the specific setting (Cesaroni et al. 2010; Hajat et al. 2013; Wang et al. 2022).

The current study adjusted for socioeconomic status in a fairly basic way with the use of an individual socioeconomic status indicator (i.e., education or employment) as a fixed covariate effect in the health model of the individual cohorts. The Committee thought that more effort to capture individual or area-level socioeconomic status in the study would have been beneficial.

HETEROGENEITY IN EFFECT ESTIMATES

The Committee noted that although the same exposure assessment and statistical methods were used, large heterogeneity of the findings was reported across the cohorts, with null, negative, or positive findings, with sometimes no apparent pattern. Some heterogeneity of the findings is expected, given the wide diversity of the six Asian cohorts. Heterogeneity is likely due, for example, to differences in populations, with different exposure levels, pollution sources and mixtures, time periods, age structure and follow-up times, socioeconomic status, urban–rural status, health status, access to healthcare, and outcome misclassification. Some specific differences across the cohorts were particularly striking, such as the low exposure contrast (Indian MCS and Bangladeshi HEALS), the low correlation between $PM_{2.5}$ and NO_2 (Indian MCS and Taiwan CBCSCP), the large percentage of illiterate population (Iranian Golestan), the short follow-up time (Indian MCS), the young study population (Bangladeshi HEALS), the rural location (Bangladeshi HEALS), particularly urban location (Indian MCS), and the low percentage of number of deaths, in particular for cancer (Indian MCS). Those and other differences could have contributed to the large heterogeneity of the findings observed in the current study.

In the systematic reviews underpinning the 2021 WHO Air Quality Guidelines for long-term exposure to $PM_{2.5}$ and NO_2, a high degree of heterogeneity of the findings was also observed; this result was expected given that studies were included from across the globe (Chen and Hoek 2020; Huangfu and Atkinson 2020). Most of the heterogeneity in those studies, however, was due to heterogeneity in the magnitude of the positive association, not in the direction of the association (negative or positive). In particular, the negative associations in the current study are puzzling and run counter to the evidence base that documents clear evidence that long-term exposure to ambient air pollution is associated with increased mortality.

In the current study, a thorough evaluation of heterogeneity in mortality risks between cohorts in the context of cultural, social, economic, or infrastructural differences between countries was originally planned but was not pursued due to the small number of cohorts included in the final analyses. Although that decision is understandable given the data available to the investigators, the Committee would have been interested in better understanding potential sources of heterogeneity in the findings and noted that many questions have been unresolved.

Although the analyses were straightforward and clearly presented in the report, the study could have benefitted from a more detailed discussion and interpretation of all results, including the various sensitivity and subgroup analyses. For example, the added exposure–response function analysis was not tied together with the predetermined categorical analysis. Also, the Cox proportional hazards assumptions were violated for $PM_{2.5}$ (Indian MCS) and NO_2 (Japanese JPHC) for some mortality outcomes; the implications of which were not thoroughly addressed by the investigators. Also, an evaluation of potential selection bias due to the loss of several key cohorts from their original plans would have been useful. These and other issues limit what can be inferred from this study.

SUBSTANTIAL TEMPORAL AND SPATIAL MISALIGNMENT OF THE EXPOSURE DATA

The Committee had concerns about the exposure assessment approach because of the substantial temporal and spatial misalignment of the data. The study relies on an historical exposure assessment at recruitment that can be temporally misaligned with the health data by 5 to 23 years, depending on the cohort. Several issues of concern with the exposure assessment were noted by the Committee. First, the back extrapolations used for the participants before 1998 when the global model estimates became available to match the exact period of interest could introduce additional exposure error. The two largest cohorts (Indian MCS and Japanese JPHC) might be particularly affected by this misalignment, because those were also among the oldest cohorts. A sensitivity analysis in the subcohorts of participants alive in 1998 when global model estimates became available were generally consistent with the findings from the full cohorts, which was reassuring. Second, information on residential addresses after recruitment (i.e., moving history) was not available. Hence, residential mobility was not incorporated in the exposure assessment. Residential mobility can be substantial, especially in some low-and middle-income regions that are undergoing rapid urbanization in recent decades with population migration from rural to urban regions. Third, for a few cohorts (Indian MCS and Iranian Golestan) aggregated residential address data were used since individual address data were unavailable. That might be a particular issue for a pollutant such as NO_2, which is characterized by greater spatial variability than $PM_{2.5}$ and is influenced heavily by local emission sources. $PM_{2.5}$, in contrast, has long-range and secondary components and thus varies primarily at a regional level (Cyrys et al. 2012; Eeftens et al. 2012). More broadly, although the study applied state-of-the art exposure estimation methods with validated models, model performance differed regionally, with poorer $PM_{2.5}$ performance in Asia compared to the global evaluation, as described by van Donkelaar and colleagues (2015, 2016). For NO_2, the model performance in Asia approximately matched the global evaluation estimate (Larkin et al. 2017). Nonetheless, in a later GBD application, NO_2 adjustments were made to correct the Larkin estimates for a "high bias in rural areas" (Anenberg et al. 2022). It should be noted that in model evaluations, estimates are compared to ground-based monitor data, but such evaluations are hampered by the paucity of ground-based monitors, with most of them located in urban areas of North America and Europe, as discussed in an earlier section. Although the Committee understands that Drs. Downward and Vermeulen made best use of the global exposure models available, the substantial temporal and spatial misalignment of the exposure data might have influenced the analysis of mortality outcomes in unpredictable ways.

HOUSEHOLD AIR POLLUTION WAS NOT EXAMINED

Like most other ambient air pollution and health studies, household air pollution was not examined in the current study. The Committee thought household air pollution might be a potential confounder or effect modifier. The investigators also alluded to that issue in the discussion of the findings. Household air pollution results from the burning of various fuels (coal, charcoal, wood, agricultural residue, animal dung, and kerosene, among others) for heating or for cooking using open fires or cookstoves with limited ventilation. Burning those fuels produces an array of pollutants that could harm human health, including $PM_{2.5}$, black carbon, and carbon monoxide. This practice is carried out by about half of the world's population, primarily from low- and middle-income countries. According to the most recent estimates from the GBD project, household air pollution contributes to about one third of the overall deaths linked to air pollution in 2019 (HEI 2020).

Only one cohort (Iranian Golestan) adjusted for domestic fuel use — an indicator of household air pollution. That indicator was missing for the other cohorts, unfortunately. The investigators reported consistent null findings between ambient air pollution and mortality for the Golestan cohort but found positive associations between some polluting fuel use (i.e., wood, kerosene, or "other" organic fuel) and mortality, that remained after adjusting for ambient $PM_{2.5}$. Similarly, in the PURE study, associations with solid fuel use for cooking and all-cause and cardiovascular mortality and morbidity were much more pronounced than the ambient $PM_{2.5}$ associations (Hystad et al. 2019, 2020).

Investigating the complex interplay between household and ambient air pollution with health is difficult because household air pollution is typically not measured for large populations over long periods of time. Hence, most studies rely on use of fuel types as an indicator of household air pollution. The Committee welcomes the investigators' future work on this topic using the Asian Cohort Consortium as described by Hosgood and colleagues (2019).

BROADER CONTEXT OF AIR POLLUTION AND HEALTH IN ASIA

The current study adds to a small evidence base in Asia, where the levels of air pollution are often high, and the types and sources of air pollution markedly differ from those in high-income settings. Although cross-sectional or short-term health studies are increasingly available in Asia, there are few studies focused on long-term exposure to ambient air pollution (Baumgartner et al. 2020). The evidence base documenting clear evidence that long-term exposure to ambient air pollution is associated with increased mortality from all causes, cardiovascular disease, respiratory disease, and lung cancer continues to be dominated by studies from North America and Europe. The recent systematic reviews underpinning the 2021 WHO Air Quality Guidelines for $PM_{2.5}$ and NO_2 identified only a few long-term studies in Asia, and no single study from Africa, Central America, or South America (Chen and Hoek 2020; Huangfu and Atkinson 2020). For example, only three studies from Asia entered the $PM_{2.5}$ meta-analysis for all-cause and cardiovascular mortality (Tsjeng et al. 2015; Yang et al. 2018; Yin et al. 2017). Some studies of long-term exposure and morbidity and mortality in Asia emerged more recently (Commentary Table 3). Most of the studies from Asia documented a positive association between long-term exposure to $PM_{2.5}$ and mortality outcomes, but there remains uncertainty about the true size of the $PM_{2.5}$ mortality relative risks. A recent study particularly relevant for the current study is the PURE study, which also used similar satellite-based global models (Hystad et al. 2020). The PURE study investigated the association between long-term exposure to $PM_{2.5}$ and all-cause and cardiovascular mortality and morbidity in a large, pooled cohort of adults from 21 countries, with most of the study population residing in low- and middle-income countries. The PURE study reported that long-term exposure to $PM_{2.5}$ was associated with increased risk for cardiovascular mortality and morbidity and adjusted for many important confounders, such as smoking, physical activity, socioeconomic status, urban or rural location and fuel use for cooking. No consistent association was observed for all-cause mortality and noncardiovascular mortality, and models were sensitive to adjustment for urbanicity, similar to the current study.

Given the paucity of studies in high air pollution settings, an IER function was developed for the GBD study to estimate mortality relative risks across the global exposure range for burden assessments. The function integrated four types of $PM_{2.5}$ exposures (outdoor $PM_{2.5}$, household air pollution, active smoking, and second-hand smoking) associated with cause-specific mortality (Burnett et al. 2014). In the most recent GBD estimates (GBD 2019 Risk Factors Collaborators 2020), active smoking studies were excluded from the IER function to characterize risks at high exposure, because the few new studies of high air pollution conditions in Asia provided enough information so that evidence from active smoking data is no longer necessary to use. This led to substantial increases in the relative risk curve for ischemic heart disease and stroke at the high end of the curve compared to the integrated curve that included active smoking studies. Notable increases in the relative risk curve were also reported in a $PM_{2.5}$ exposure–response function (global exposure mortality model [GEMM]), which was solely based on ambient $PM_{2.5}$ studies (Burnett et al. 2018). The use of GEMM resulted in burden estimates that were two to three times higher than those from the IER function. For the GEMM they included data from 41 cohorts in 16 different countries, including three studies from Asia (Tseng et al. 2015; Wong et al. 2015; Yin et al. 2017).

The differences in burden estimates reflect current uncertainty about key assumptions underlying the IER and GEMM models and therefore about the true size of the $PM_{2.5}$ mortality relative risks, particularly at the low- and high-end of the global exposure range (Burnett and Cohen 2020). The study by Downward and Vermeulen highlights the urgent need for future studies that could prove to be useful in reducing this

Commentary Table 3. Summary of Selected Studies on Long-Term Exposure to $PM_{2.5}$ and Mortality in Asia (in order of publication year)

Reference	Study Name	Location	Study Period	Sample Size	Mean $PM_{2.5}$	Mortality Outcome	Hazard Ratio per 5 μg/m³[a]
Tseng et al. 2015	Civil servants' cohort	Greater Taipei, Taiwan	1989–2008	43,227	~29	All-cause	0.96 (0.85–1.08)
						Cardiovascular	0.89 (0.65–1.22)
Yin et al. 2017	Chinese men	45 districts in China	1990–2005	189,793	43.7	All-cause	1.04 (1.04–1.05)
						Cardiovascular	1.04 (1.04–1.05)
						Lung cancer	1.06 (1.04–1.08)
Yang et al. 2018	Hong Kong elderly	Hong Kong	1998–2011	66,820	42.2	All-cause	1.03 (1.01–1.05)
						Cardiovascular	1.05 (1.02–1.09)
						Respiratory	1.01 (0.97–1.06)
Li et al. 2018	CLHLS	China	2008–2014	13,344	50.7	All-cause	1.04 (1.03–1.05)
Yorifuji et al. 2019	Okayama City	Okayama City, Japan	2006–2016	75,569	14.0	All-cause	1.29 (1.18–1.41)
						Cardiovascular	1.06 (0.90–1.26)
						Lung cancer	1.63 (1.13–2.34)
Hystad et al. 2020	PURE	17 low- and middle-income countries	2003–2018	140,020	47.5 (all 21 countries)	All-cause	0.99 (0.98–1.00)
						Cardiovascular	1.02 (1.00–1.03)
						Noncardiovascular mortality	0.98 (0.96–0.99)
						Cardiovascular event (fatal + nonfatal)	1.03 (1.01–1.04)
Kim et al. 2020	NHIS-NSC	Republic of Korea	2002–2013	436,933	18.8	All-cause	1.02 (1.01–1.02)
						Cardiovascular	1.03 (1.02–1.03)
Brown et al. 2022	MDS	India	2004–2013	6.8 million	24.3	All-cause	1.01 (1.01–1.02)
						Ischemic heart disease	1.00 (0.99–1.02)
						Stroke	1.04 (1.02–1.07)
						Respiratory	1.01 (0.98–1.03)

CLHLS = Chinese Longitudinal Healthy Longevity Survey; MDS = Million Death Study; NHIS-NSC = National Health Insurance Service-National Sample Cohort; PURE = Prospective Urban and Rural Epidemiology (PURE).

[a]Findings are converted to 5-μg/m³ increase in $PM_{2.5}$ to allow comparison with the current study.

uncertainty. At some point in the near future with sufficient studies, it might be possible to develop separate risk curves for outdoor air pollution, second-hand smoking, and household air pollution in the GBD study. Having those separate risk curves would remove an important source of uncertainty related to equitoxicity of particles (assuming no differences in health impact by PM source, size, and chemical composition) as well as uncertainties related to some other aspects of exposure to those distinct sources of PM.

SUMMARY AND CONCLUSION

Drs. Downward and Vermeulen have assessed the association between long-term exposure to ambient air pollution and all-cause and cause-specific mortality in an analysis of six Asian cohorts. The research was well motivated and addressed a clear research gap. The large sample size and leverage of harmonized data from the Asia Cohort Consortium were considered to be strengths of the study. Furthermore, data were available for several individual-level lifestyle factors, such as smoking status and intensity, body mass index, and diet, and the analyses were adjusted accordingly. Application of existing global satellite-based models allowed for a uniform estimation of exposure at a reasonably high spatial resolution for a large urban and rural population in six Asian countries. Such a study would otherwise not have been possible given the paucity of ground-based monitors, particularly in low- and middle-income countries.

The study documented no association between long-term exposure to ambient $PM_{2.5}$ and all-cause mortality and cause-specific mortality in meta-analyses, except for a borderline significant positive association with cardiovascular mortality. Several individual cohorts (i.e., Indian MCS, Japanese JPHC, and Taiwanese CBCSCP), however, did display positive significant associations between ambient $PM_{2.5}$ and cardiovascular mortality. For ambient NO_2, the combined estimates showed positive associations for all mortality outcomes, in particular the cancer outcomes, although estimates were heavily driven by positive associations from the Japanese JPHC cohort. The cohorts were very diverse and large heterogeneity of the findings was reported across the individual cohorts, with null, negative, or positive findings, with sometimes no apparent pattern. Although the Review Committee broadly agreed with the investigators' conclusions, it identified limitations that should be considered when interpreting the results.

Importantly, the Committee was concerned that residual confounding was likely in the main analyses due to inadequate adjustment for characteristics that correlate with air pollution and mortality, most notably socioeconomic status and urbanicity. Findings sometimes differed for models that adjusted for urbanicity as compared to those that did not. The Committee would have been interested in better understanding potential sources of heterogeneity in the findings. There were also concerns about the exposure assessment approach because of the substantial temporal and spatial misalignment of the data, which might have influenced the analysis of mortality outcomes in unpredictable ways.

Overall, there remains uncertainty about the true size of the ambient air pollution and mortality associations in Asia, where the levels of air pollution are often high, and the types and sources of air pollution, including household air pollution, markedly differ from those in high-income settings. The study by Downward and Vermeulen highlights the urgent need for future studies that could prove to be useful in reducing this uncertainty. At the same time, these populations are experiencing very high levels of air pollution, meriting attention and action to reduce ambient air pollution regardless of the uncertainties.

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ABBREVIATIONS AND OTHER ITEMS

AERONET	AErosol RObotic NETwork
ACC	Asia Cohort Consortium
CBCSCP	Community-based Cancer Screening Program
CI	confidence interval
DALYs	disability adjusted life years
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Cohorts for Air Pollution Effects
GBD	Global Burden of Disease
GEMM	Global Exposure Mortality Model
HEALS	Health Effects for Arsenic Longitudinal Study
HIC	high-income country
HR	hazard ratio
ICD	International Classification of Diseases
IER	integrated exposure–response
JPHC	Japan Public Health Center-based Prospective Study
KMCC	Korean Multi-center Cancer Cohort Study
LMIC	low-and-middle-income countries
LUR	land use regression
MCS	Mumbai Cohort Study
NO_2	nitrogen dioxide
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
ppb	parts per billion
PURE	Prospective Urban and Rural Epidemiology
R^2	coefficient of determination
RR	relative risk
sd	standard deviation
WHO	World Health Organization

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