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Long-term exposure to particulate matter and all-cause and cause-specific mortality in an analysis of multiple Asian cohorts

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A B S T R A C T

Background: Exposure to ambient air pollution is associated with a significant number of deaths. Much of the evidence associating air pollution with adverse effects is from North American and Europe, partially due to incomplete data in other regions limiting location specific examinations. The aim of the current paper is to leverage satellite derived air quality data to examine the relationship between ambient particulate matter and all-cause and cause-specific mortality in Asia.
Methods: Six cohorts from the Asia Cohort Consortium provided residential information for participants, recruited between 1991 and 2008, across six countries (Bangladesh, India, Iran, Japan, South Korea, and Taiwan). Ambient particulate material ($PM_{2.5}$) levels for the year of enrolment (or 1998 if enrolled earlier) were assigned utilizing satellite and sensor-based maps. Cox proportional models were used to examine the association between ambient air pollution and all-cause and

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cause-specific mortality (all cancer, lung cancer, cardiovascular and lung disease). Models were additionally adjusted for urbanicity (representing urban and built characteristics) and stratified by smoking status in secondary analyses. Country-specific findings were pooled via random-effects *meta*-analysis.

Findings: More than 300,000 participants across six cohorts were included, representing more than 4-million-person years. A positive relationship was observed between a 5 μg/m (Dockery et al., 1993) increase in $PM_{2·5}$ and cardiovascular mortality (HR: 1·06, 95 % CI: 0.99, 1·13). The additional adjustment for urbanicity resulted in increased associations between $PM_{2.5}$ and mortality outcomes, including all-cause mortality (1·04, 95 % CI: 0·97, 1·11). Results were generally similar regardless of whether one was a current, never, or ex-smoker.

Interpretation: Using satellite and remote sensing technology we showed that associations between $PM_{2.5}$ and all-cause and cause-specific Hazard Ratios estimated are similar to those reported for U.S. and European cohorts.

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1. Research in context

1.1. Evidence before this study

There is a large evidence base reporting that exposure to ambient (outdoor) air pollution causes between 3 and 4 million deaths globally per year. However, much of this evidence base comes from studies based in high-income nations – specifically North America and Western Europe. Evidence from Asia however, where exposures are typically much higher than North America and Europe (and many countries are low or middle income – resulting in higher disease burden secondary to heightened vulnerability and limited infrastructure) is lacking. This lack of evidence is largely a consequence there being relatively few standardized exposure metrics or models to base analysis on. However, recent developments in models derived from satellite and ground-based data provide opportunities to examine the effects of air quality in areas previously considered inaccessible.

1.2. Added value of this study

The current study highlights the utility of using global models to examine exposures to ambient particulate matter and its associated effects in a variety of locations. A main pooled finding of an association between ambient air pollution and cardiovascular disease is consistent with that seen elsewhere in the literature and further highlights the health risks of ambient air pollution.

1.3. Implications of all the available evidence

Ambient particulate matter is a risk factor for non-communicable diseases – notably cardiovascular disease. The combined use of satellite & remote sensing technology provides a powerful tool in the evaluation of environmental risks among hard to reach and hard to monitor communities.

1.4. Background

Ambient air pollution represents a significant cause of morbidity and mortality world-wide. According to the 2019 GBD study, ambient air pollution was responsible for approximately 4 million deaths and 120 million lost disability adjusted life years. (GBD, 2019) Much of this evidence is derived from high-income nations, especially Europe and North America where studies such as the ESCAPE, ELAPSE, Six City, and American Cancer Society studies have provided major insights into the role air pollution makes to human health. (Beelen et al., 2014; Dockery et al., 1993; Pope et al., 2002; Strak et al., 2021).

Of the 4 million deaths attributed to ambient air pollution, nearly three quarters are predicted to have occurred in Asia, where air pollution levels are typically higher than in Europe and North America. This, coupled with infrastructural and economical limitations in many low-and—middle-income-countries, can exacerbate overall disease burden. However, despite this high disease burden, the health effects of air pollution within the Asia region overall remain relatively understudied. A systematic review and *meta*-analysis performed by Chen & Hoek (2020) identified 107 studies examining ambient particulate matter exposure around the world. (Chen and Hoek, 2020) Of these 107, more than 80% (n = 87) examined the North American or European setting but only 19 examined Asia. Therefore, despite the higher exposures, the overall amount which is known about the area specific effects of ambient air pollution in many Asian countries remains limited.

Linking air pollution to health studies in Asia and many low-and-middle-income countries has been a major challenge due to a lack of standardized, wide-scale information on air pollution exposure, such as that used in the ESCAPE and ELAPSE projects. (Beelen et al., 2014; Strak et al., 2021) A resource which has been gaining increasing attention for addressing this research gap has been the development of global models, built using a combination of satellite information and ground-based measurements (where available). These provide a powerful tool for examining air pollution and its effects in areas where this was previously impossible. For example, the Prospective Urban and Rural Epidemiology (PURE) study utilized such models to examine exposure to ambient $PM_{2·5}$ using satellite-based estimates for over 150,000 individuals living in 747 communities in 21 countries. This study reported that a 5 μg/m (Dockery et al., 1993) increase in $PM_{2·5}$ exposure was associated with an increase in cardiovascular disease mortality (hazard ratio [HR]: 1·01, 95% CI: 1·00, 1·03). (Hystad et al., 2020).

The aim of the current paper is to use satellite and model-based estimates of ambient particulate matter with aerodynamic diameter smaller than 2·5 μm ($PM_{2·5}$) to assess the association between long-term exposure and all-cause and mortality from cancer, lung cancer, cardiovascular and respiratory disease in an analysis of diverse cohorts across Asia.

2. Methods

2.1. Study population

Levels of ambient $PM_{2·5}$ were assigned to the residential information of participants within the Asia Cohort Consortium (ACC). The ACC is a multi-centre epidemiology project, formed in 2008 to explore the relationship between genetics, environmental factors, and disease across a broad geographic scope, consisting of (to date) more than one million people from ten Asian countries. (Chen et al., 2017; Zheng et al., 2011; Song et al., 2012) Participating cohorts share data related to demographics, activities, and mortality outcomes. To ensure data consistency across the various cohorts, covariates are standardized via iterative internal harmonization procedures, involving multiple rounds of data review between the ACC and contributing cohorts to ensure that data was comparable across cohorts and the completion of logic and missing data checks. Conflicts and queries regarding data are resolved by active discussion with contributing cohorts.

The principal investigators for each individual cohort were invited to participate in the current study. Of the 23 cohorts invited, six consented, representing over 340,000 participants and more than 4 million person-years from six countries. The participating cohorts were the Community-based Cancer Screening Program (CBCSP, Taiwan, n = 23,759), the

Golestan Cohort Study (Golestan, Iran, n = 49,985), the Health Effects for Arsenic Longitudinal Study (HEALS, Bangladesh, n = 19,990), the Japan Public Health Centre-based Prospective Study (JPHC, n = 87,600), the Korean Multi-centre Cancer Cohort Study (KMCC, South Korea, n = 18,529), and the Mumbai Cohort Study (MCS, India, n = 141,238). (Chen et al., 2006; Liao et al., 2012; Pourshams et al., 2010; Ahsan et al., 2006; Tsugane and Sobue, 2001; Tsugane and Sawada, 2014; Yoo et al., 2002; Pednekar et al., 2009) The CBCSP, JPHC, and KMCC cohorts included participants from multiple areas across their respective countries. The Golestan cohort recruited from the Golestan region in Iran, HEALS from the Araihazar in Bangladesh, and MCS from Mumbai, India.

Data on cause of death was collected by each individual cohort, typically through linkage to death/cancer registries and/or active follow-up. Specific causes of death were coded via either the International Classification of Diseases (ICD) 9 or 10 coding system depending on the year of death.

2.2. Air pollution metrics

Levels of $PM_{2.5}$ were assigned from global satellite and LUR models which had been derived from the application of a geographically weighted regression model of satellite, chemical transport, and ground-based data. The full details are described elsewhere. (van Donkelaar et al., 2016) Briefly, values from the Moderate Resolution Imaging Spectroradiometer, Multi-angle Imaging SpectroRadiometer and Sea-Viewing Wide Field-of-View Sensor were integrated, giving a near continuous planetary surface of $PM_{2.5}$. Through the application of the GEOS-Chem chemical transport model and ground-based sun photometer observations, these values were converted to near-ground concentrations at an approximate resolution of 1km x 1km for the years of 1998 to 2016. Generated values correlated well with available ground-based data with an overall out-of-sample validated R^2 of 0·81 and calculated bias and global variance of 1·3 and 7·9 $\mu g/m^3$ respectively (for the year 2010). Within the Asia region, bias varied from 3.2 (Central region) to 11.6 (Eastern). Variance ranged from 15.9 (Southeast Asia) 33.9 (South Asia).

Concentrations of ambient air pollution for the year in which participants were recruited (or 1998 if they were recruited before this year) were assigned to their residential coordinates. For the CBCSP, HEALS, JPHC, and KMCC cohorts, precise residential (address) coordinates were used. For Golestan, community level coordinates were used to assign exposure. As communities were typically within the resolution of the model, community centroids were used to assign exposures. Within MCS, the average exposure within Mumbai post-codes were used to assign exposure (median area of each postcode was 2·7 km^2). Owing to incomplete coverage, not all locations were able to have predictions generated, in which case the number of valid predictions was reported. For quality control purposes, a subset of assigned exposures (maximum 200 per cohort) was manually reviewed and found complete agreement with assigned exposures.

2.3. Statistical analysis

Cohort demographics and values of $PM_{2.5}$ were explored through descriptive statistics. Cox proportional hazard models, with age as the time scale, were developed to examine the relationship between exposure to $PM_{2.5}$ at recruitment (treated as a linear variable) and all-cause, cardiovascular, cancer, and lung cancer mortality. Models were constructed for each cohort separately and then combined via random-effects *meta*-analysis. Model construction and confounder/covariate selection was intended to replicate the analytical approach and covariate selection utilized in the ESCAPE project. (Beelen et al., 2014) Initial models (model 1) utilized pollution and outcomes. Recruitment year and sex were subsequently added (model 2). Finally, these were supplemented by the addition of smoking (ever/never/current status and pack-years), BMI (<18.5, 18–25, 25–30, and >30), socio-economic status (categories of education and/or occupation), and (where available) dietary factors such as caloric or alcohol intake (model 3). Summary descriptions of each covariate are provided in the supplement. Further, within the Golestan Cohort, information on the domestic use of fuel was available. As this is an Important contributor to personal exposure and health this was additionally included for this group. Analysis was only performed on those with complete data on variables included in the models – see the Supplement for information on missing data. To be consistent with previous reporting in the ELAPSE and ESCAPE projects, derived hazard ratios were reported for a 5 μg/m (Dockery et al., 1993) increment in $PM_{2.5}$. (Beelen et al., 2014; Strak et al., 2021).

Model robustness was evaluated through several levels of sensitivity and secondary analysis. First, given the potential for temporal misalignment of findings (e.g. assigning $PM_{2.5}$ for 1998 to those recruited before that year), analysis was repeated by restricting to those alive during the period in which satellite information was available. Second, the assumption for proportional hazards was evaluated for each individual cohort through the examination of Schoenfeld residuals. Variables which showed evidence of violating the assumption had a time interaction term (Zhang et al., 2018) added for repeat analysis.

Urban features represent a variety of environmental and community components, including socioeconomics, pollution sources, and infrastructure. As these urban features may be relevant for health, we performed a secondary analysis, examining any additional effect of urbanicity on estimates. Urbanicity, on a scale of 0 (completely non-urban), to 1 (completely urban) were assigned through the application of the global gradient for relative urbanicity as described by Gao and Pesaresi where global urban land projections were generated at a 1km ground resolution (note: MCS was considered completely urban and thus not included in this analysis). (Gao and Pesaresi, 2021) Additionally, as a high number of non-smokers (73%) was observed, analysis was repeated after restricting to non-smokers and non-smoking females in order to evaluate whether air pollution had a more pronounced effect within this group. Finally, to examine relative differences at different levels of exposures, analysis was repeated utilizing quartiles of exposure as opposed to a single linear gradient.

The findings from model 3 were considered the a priori "main" models for the current paper. Further adjustment for urbanicity was included as an additional analysis to examine any effect of urban features on the effect of $PM_{2.5}$. Results for smoking status and quartile analysis will be described briefly with full figures and tables available in the supplement.

All statistical analysis was performed in R (version 3·5) utilizing the Survival package.

2.4. Ethical considerations

This project was reviewed and approved by both the ACC executive committee and the University Medical Center Utrecht IRB prior to its initiation. Cohorts were approved by their local IRBs and only included in the current study following the assent of the PIs of each respective cohort.

2.5. Role of the funding source

The funders of the current study had no role in the current study design, data collection, analysis, writing, or decision to submit for publication.

3. Results

A total of six cohorts provided participant data, representing 341,098 individuals. The number of participants in each cohort varied from 18,529 (KMCC, South Korea) to 141,238 (MCS, India). Selected demographics for each cohort are provided in Table 1 (more detailed

Table 1
Mean (sd) or n (%) Key Population Demographics at Recruitment.

	CBCSCP	Golestan	HEALS	JPHC	KMCC	MCS
Country	Taiwan	Iran	Bangladesh	Japan	Korea	India
Total *N*	23,759	49,982	19,990	87,653	18,529	141,238
Age	47 (10)	52 (9)	37 (10)	52 (8)	55 (14)	51 (11)
% Male	50 %	42 %	41 %	47 %	40 %	58 %
Recruitment years	1991–1992	2004–2008	2000–2008	1990–1995	1993–2005	1991–1997
Follow-up	23 (6)	11 (2)	10(3)	20 (5)	13 (5)	5 (2)
Total person-years	555,781	533,658	199,518	1,742,722	247,437	732,082
Smoking status						
Never	16,858 (71 %)	39,141 (78 %)	13,483 (67 %)	51,994 (60 %)	11,456 (63 %)	115,340 (82 %)
Former	6,861 (29 %)[a]	3,318 (7 %)	1,249 (6 %)	10,791 (12 %)	1,971 (11 %)	5,126 (4 %)
Current		7,523 (15 %)	5,250 (26 %)	24,551 (28 %)	4,893 (27 %)	20,772 (15 %)
Pack-years[b]	24 (20)	17 (18)	15 (15)	30 (21)	27 (23)	7 (15)
BMI	24 (3)	27 (5)	20 (3)	23 (3)	24 (3)	22 (4)
<18.5	756 (3 %)	2,408 (5 %)	7,780 (39 %)	2,842 (3 %)	725 (4 %)	25,851 (18 %)
18.5–25	14,428 (61 %)	17,938 (36 %)	10,532 (53 %)	60,513 (70 %)	11,029(64 %)	80,915 (57 %)
25–30	7,374 (31 %)	16,917 (34 %)	1,266 (6 %)	21,150 (24 %)	4,830 (28 %)	28,114 (20 %)
>30	1,145 (5 %)	12,711 (25 %)	132 (1 %)	2,136 (2 %)	603 (4 %)	6,328 (4 %)
Number of deaths	6,295 (26 %)	7,060 (14 %)	1,532 (8 %)	17,931 (20 %)	3,411 (18 %)	12,934 (9 %)
Causes of death:						
Nonaccidental	5,821	5,966	1,467	–	2,983	8,689
All cancer	2,189	1,401	268	7,331	1,072	793
Lung cancer	466	94	63	1,462	282	78
Cardiovascular	1,089	3,022	513	4,318	666	3,306
Nonmalignant lung	587	403	219	1,196	285	1,255

Study cohorts: CBCSCP = Community-based Cancer Screening Project (Taiwan); Golestan = Golestan region, Iran; HEALS = Health Effects for Arsenic Longitudinal Study (Bangladesh); JPHC = Japan Public Health Centre-based Prospective Study; KMCC = Korean Multi-centre Cancer Cohort Study; MCS = Mumbai Cohort Study (India).
Missing values not shown (available in the Appendix). Percentage calculations are rounded to the nearest whole number and calculated with missing values excluded.
[a] CBCSCP only supplied ever/never smoking information.
[b] Former and current smokers only.

information is provided in the Supplement). Cohorts tended to have a higher proportion of female than male participants (range 50 to 40% male) and mean ages at recruitment ranged from late thirties (37) to early/mid-fifties (55). There was a wide range of follow-up time, ranging from 5 (MCS) to 23 (CBCSCP) years. Participants' BMIs tended to be in the range of 18.5–25 (58%). The highest proportion of participants with a BMI greater than 30 was in the Golestan cohort (25%) whereas the highest proportion with a BMI less than 18.5 was in HEALS (39%). Participants were generally non-smokers (73% overall were never smokers).

Descriptions of the predicted pollutants and urbanicity score are provided in Table 2. Overall, a wide range in exposure across the different cohorts was observed. Cohort-specific mean exposures to $PM_{2·5}$ ranged from 7·9 μg/m (Dockery et al., 1993) (CBCSCP) to 57·9 μg/m^3 (HEALS). Mean urbanicity scores tended to be less than 0·5, ranging from 0·03 (HEALS) to 0·30 (JPHC). $PM_{2.5}$ and urbanicity tended to be positively correlated (except for HEALS with a correlation coefficient of – 0·20) and was strongest for CBCSCP (0·63) and KMCC (0·69).

Graphical depictions of the estimated hazard ratios for each cohort (model 3 and additional adjustment for urbanicity), and their respective contribution to the performed *meta*-analyses are shown in Fig. 1. The numerical values for these findings, including unadjusted findings, are provided in the Supplement. Overall, high levels of variation in HRs were observed between the different cohorts, including both increased and reduced likelihoods for mortality. Within the JPHC, positive relationships between ambient $PM_{2·5}$ and all-cause (HR: 1·06, 95% CI: 1·03, 1·09), cancer (HR: 1·10, 95% CI: 1·05, 1·15), and cardiovascular (HR: 1.07, 95% CI: 1.01, 1.13) mortality was observed. When examining quartiles (Table S21), the HR for all-cause and cancer mortality gradually increased over quartile groups (e.g. the all-cause mortality HR for the second quartile versus the first was 1.07, 95% CI: 1.02, 1.12 and 1.14, 95% CI: 1.07, 1.20 for the fourth). However, the HR for cardiovascular mortality was similar in the second and third quartiles (1.26, 95% CI: 1.14, 1.38 and 1.33, 95% CI 1.19, 1.49 respectively) but lower

Table 2
Particulate matter ($PM_{2.5}$) concentrations and Urbanicity Characteristics for Each Cohort at Recruitment.

	CBCSCP		Golestan		HEALS		JPHC		KMCC		MCS	
	n[a]	Mean (sd) [P5, P95]	*n*[a]	Mean (sd) [P5, P95]	*n*[a]	Mean (sd) [P5, P95]	*n*[a]	Mean (sd) [P5, P95]	*n*[a]	Mean (sd) [P5, P95]	*n*[a]	Mean (sd) [P5, P95]
$PM_{2.5}$	23,390	7·9 (6·5) [1·2, 24·7]	49,982	32·2 (3·7) [27·1, 38·4]	19,990	57·9 (2·4) [55·2, 61·4]	87,600	10·9 (3·3) [6·1, 16·9]	18,529	22·8 (3·1) [19·9, 28·8]	126,377	34 (1·3) [32·7, 37·8]
Urbanicity[b]	23,193	0·23 (0·21) [0·01, 0·67]	49,982	0·07 (0·15) [0·00, 0·42]	19,990	0·03 (0·02) [0·01, 0·08]	87,619	0·30 (0·33) [0·00, 0·97]	18,529	0·12 (0·21) [0·00, 0·63]	NA[c]	
Pearson's Correlation $PM_{2.5}$/Urbanicity	0·63		0·51		−0·20		0·36		0·69		NA	

Study cohorts: CBCSCP = Community-based Cancer Screening Project (Taiwan); Golestan = Golestan region, Iran; HEALS = Health Effects for Arsenic Longitudinal Study (Bangladesh); JPHC = Japan Public Health Centre-based Prospective Study; KMCC = Korean Multi-centre Cancer Cohort Study; MCS = Mumbai Cohort Study (India).
P5 = 5th centile; P95 = 95th centile.
[a] *n* represents the total number for whom predictions could be made.
[b] Score from 0 (fully rural) to 1 (fully urban). Based on urbanicity score in 2000. (Gao and O'Neill, 2020).
[c] As participants were only recruited from Mumbai, assumed to be completely urban.

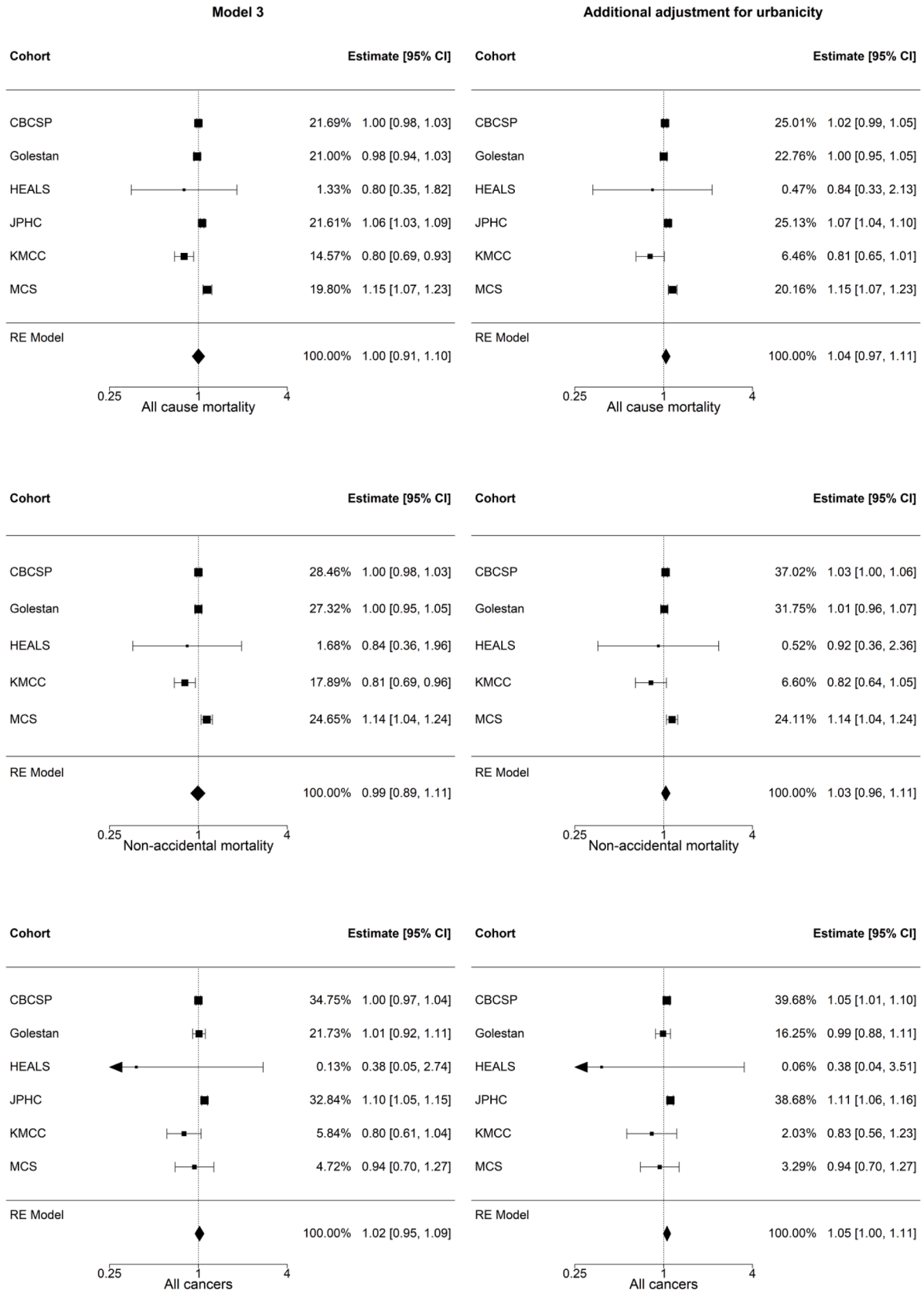

Fig. 1. Random effects *meta*-analysis for association between 5-μg/m^3 increase in $PM_{2.5}$ and all-cause and cause-specific mortality. Models adjusted for sex, recruitment year, smoking status and pack-years, body mass index, socioeconomic status, alcohol intake, and diet. Golestan cohort was additionally adjusted for domestic fuel use. Percentage weights based on variance value. Study cohorts: CBCSCP = Community-based Cancer Screening Project (Taiwan); Golestan = Golestan region, Iran; HEALS = Health Effects for Arsenic Longitudinal Study (Bangladesh); JPHC = Japan Public Health Centre-based Prospective Study; KMCC = Korean Multi-centre Cancer Cohort Study; MCS = Mumbai Cohort Study (India).

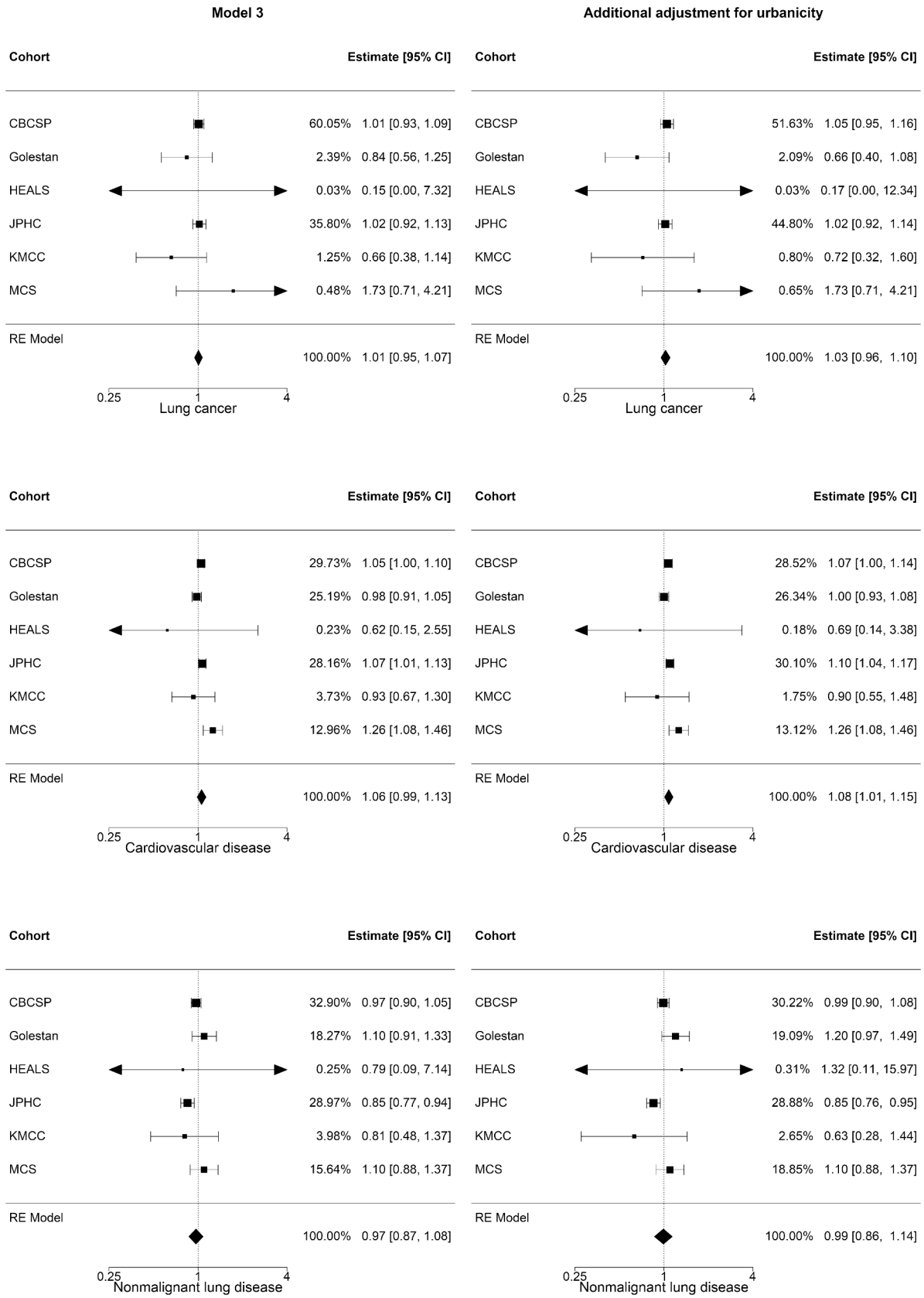

Fig. 1. (*continued*).

in the highest quartile of $PM_{2.5}$ (1.13, 95% CI 1.00, 1.27). Within the MCS, $PM_{2.5}$ was associated with all-cause (HR: 1·15, 95% CI: 1·07, 1·23), non-accidental (HR: 1·14, 95% CI: 1·04, 1·24) and cardiovascular (HR: 1·26, 95% CI: 1·08, 1·46) mortality with HRs remaining generally consistent across quartiles of exposure (Table S33). A positive association between $PM_{2.5}$ and cardiovascular mortality was also observed in

CBCSCP (HR: 1·05, 95% CI: 1·00, 1·10), which was strongest when comparing the highest quartile of exposure to the lowest (HR: 1.28, 95% CI: 1.07, 1.54, Table S5). In addition to positive associations, negative associations were also observed – most notably for KMCC where $PM_{2·5}$ was negatively associated with all-cause mortality (HR: 0·80, 95% CI: 0·69, 0·93) and JPHC where $PM_{2·5}$ was negatively associated with non-malignant lung mortality (HR: 0·85, 95% CI: 0·77, 0·94).

Additional adjustment for urbanicity tended to result in higher HRs for $PM_{2·5}$, with negative associations becoming null and null associations becoming positive. This was most notable for CBCSCP, where null findings for non-accidental (1·00, 95% CI: 0·98, 1·03) and cancer (1·00, 95% CI: 0·97, 1·04) mortality became positive (HRs: 1·03, 95% CI: 1·00, 1·06 and 1·05, 95% CI: 1·01, 1·10 respectively).

The findings from each cohort were subsequently combined via random effects *meta*-analysis (Fig. 1). When examining the pooled estimates for model 3 and $PM_{2·5}$, a positive relationship was observed between $PM_{2.5}$ exposure and cardiovascular mortality, where a 5 $\mu g/m^3$ increase in $PM_{2·5}$ was associated with a pooled HR of 1·06 (95% CI: 0·99, 1·13), including after additional adjustment for urbanicity (1·08, 95% CI: 1·01, 1·15). The pooled analysis for the remaining outcomes and $PM_{2·5}$ tended towards null findings with pooled HRs consistently approximating 1 for both models with and without adjustment for urbanicity. The only exception was that for all cancer mortality, which was null in Model 3 (HR: 1·02, 95% CI: 0·95, 1·09) but positive after additional adjustment for urbanicity (HR: 1·05, 95% CI: 1·00, 1·11).

Findings were generally consistent across a variety of sensitivity analyses. Minimally adjusted models (i.e. models 1 and 2) showed directionally consistent findings with those of model 3 (see Supplement). Restricting to those alive during the time period in which satellite data was available showed no appreciable change in findings. The usage of polluting fuels (especially kerosene) in the Golestan cohort was found to be positively associated with all-cause (HR for Kerosene: 1·12, 95% CI: 1·06, 1·20) and cancer (HR for kerosine: 1·12, 95% CI: 1·11, 1·48) mortality (Table S7). The inclusion of a time-varying term for variables which potentially violated the proportional hazards assumption had no appreciable impact on the directionality of findings.

Examining non-smokers and non-smoking females showed overall similar findings as per the main analysis. This included cancer mortality where, after additionally adjusting for urbanicity, non-smokers, and non-smoking females had a higher likelihoods of cancer mortality (HR: 1·10, 95% CI: 1·03, 1·18 and 1·07, 95% CI: 1·03, 1·12). Similarly, the likelihood of cardiovascular mortality was increased among female non-smokers (HR: 1·09, 95% CI: 1·01, 1·17).

4. Discussion

The current study examined the relationship between ambient air pollution and all-cause and cause-specific mortality in six cohorts from across Asia. Exposures to $PM_{2.5}$ ranged from being broadly comparable to those of North America and Western Europe (e.g. JPHC with a mean $PM_{2.5}$ of 10.9 $\mu g/m^3$) to being many times higher than the WHO recommended level (e.g. MCS with a mean $PM_{2.5}$ of 34.0). Overall, we observed limited evidence for an association at the all-cause mortality level, with a pooled HR of 1·00 (95% CI: 0·91, 1·10) – although this became positive after additional adjustment for urbanicity (HR: 1·04, 95% CI: 0·97, 1·11). We also observed a positive relationship between ambient $PM_{2.5}$ and cardiovascular mortality in pooled *meta*-analysis (pooled HR: 1·06, 95% CI: 0·99, 1·13), including after additional adjustment for urbanicity (1·08, 95% CI: 1·01, 1·15). This finding is matched by the *meta*-analysis of Chen & Hoek (2020) who reported a *meta*-RR of 1·05 (95% CI: 1·04, 1·07) for cardiovascular mortality when examining a 5 $\mu g/m^3$ increase of $PM_{2·5}$. (Chen and Hoek, 2020) These findings are higher than those reported by Hystad et.al. where, through the application of the same global LUR models used here, a 5 $\mu g/m^3$ increase in $PM_{2·5}$ was associated with an HR of 1·01 (95% CI: 1·00, 1·03) for cardiovascular mortality. (Hystad et al., 2020) We also observed a positive association between $PM_{2·5}$ and cancer mortality (after additionally adjusting for urbanicity, HR: 1·05, 95% CI: 1·00, 1·11) – which is also consistent with the *meta*-analysis of Chen & Hoek.

Despite these positive associations, we also observed a variety of null associations in our pooled analysis, including for all-cause (and non-accidental) mortality and lung cancer mortality – all of which are associated with $PM_{2·5}$ elsewhere. (Chen and Hoek, 2020) This is reflected by the range of exposures, outcomes, and various markers of heterogeneity in *meta*-analysis observed. While exposures tended to follow a pattern of lower income countries having higher exposures than higher income countries, the socioeconomic status of the underlying nation did not appear to directly contribute to the degree of effect between air pollution and outcome. For example, the strongest positive relationships we observed were for the JPHC and MCS cohorts, which represent high and (low-) middle-income countries respectively. Further, null or negative associations were observed for the other countries in the current study with no discernible pattern. While the number of countries available to properly evaluate this is small, this may reflect important underlying features between different countries such as differences in the sources and constituents of pollutants. It may also reflect historical profiles in exposure as differing rates of urbanization across the contributing countries may mean that long-term exposures may differ between sites.

An additional consideration is that physical restriction of healthcare access can be detrimental to health. (Joseph et al., 2020) Therefore, those living in rural centres or with limited access to health care can be expected to have worse outcomes than those living in urban centres where, despite higher exposures, the more readily accessible health-care results in improved outcomes overall. When adjusting for the effect of urbanicity we tended to observe a more positive effect for $PM_{2·5}$. This may reflect the added importance of urbanicity in general when evaluating disease risk. However, as we tended to observe positive correlations $PM_{2·5}$ and urbanicity, and urban features can contribute to air pollution, these findings should be interpreted with caution.

4.1. Strengths and weaknesses

The current paper represents a large-scale examination of the health effects of air pollution across multiple diverse populations. Cohorts were well-defined and with harmonized data. A particular strength was the presence of well-defined smoking information which in other larger multi-national studies required indirect adjustment. (Stafoggia et al., 2022) In the current study we observed similar HRs for non-smokers and non-smoking women as for our main analysis, suggesting that ambient air quality may play an important role in disease aetiology regardless of smoking status. Other lifestyle factors, such as exercise, are also important predictors of disease. While we were able to include factors such as BMI and diet as covariates, information on physical activity was unavailable.

The pollution maps used in this paper represent a series of robust tools which can be applied in a variety of settings, especially those lacking routine monitoring data of their own. Despite their strength, some limitations of these models need to be considered. The validation of satellite models is dependent upon available ground-based data. Therefore, in those regions with poorer monitoring, poorer performance may be expected. (van Donkelaar et al., 2016) A related limitation is that geocoded information was provided in a non-uniform manner, with some cohorts giving precise geo-location whereas for others community or post-code level information was the only available information source. These limitations will likely introduce "noise" to the assignment of air pollution, increasing uncertainty. However, given the positive findings with MCS – which was the only cohort where the geographical area was larger than the resolution of the maps used – the impact of this limitation may be small. Regardless, further refinement in both pollution prediction and residential location will be required to better apply these models in the future. A similar limitation is that residential

coordinates were only utilized for the assigning of pollution and not for any additional analysis such as adjustment for area, which may contribute spatial confounding.

Additional limitations include the fact that many participants were recruited outside of the time in which pollutant data was available. In addition, for diseases with prolonged latency periods, relevant exposure periods may extend many decades into the past. We attempted to evaluate any impact of exposure misclassification due to recruitment period through repeating analysis on those only alive from 1998 onwards, which provided similar results to our main findings. An additional limitation was that we did not explicitly examine longitudinal changes in exposure or residential mobility (i.e. moving home during the follow-up period) in the current paper, presenting a potential source of exposure misclassification.

In addition to ambient air pollution, many people are also exposed to significant levels of household air pollution (HAP), typically generated through the combustion of solid (or other similarly polluting) fuels for domestic cooking and heating. The absolute levels of this pollution can be orders of magnitude higher than ambient pollution, meaning that only examining ambient pollution in regions with frequent solid fuel use will give an incomplete picture. This is reflected in the Golestan cohort where 66% of the population used some form of polluting fuel which, even after adjusting for ambient $PM_{2.5}$, had a higher likelihood of death from any cause (e.g. HR for kerosene use: 1·12, 95% CI: 1·06, 1·20, Table S7). This is also reflected in an arm of the PURE study which reported that solid fuel use was associated with a higher likelihood of death (HR: 1·12, 95% CI: 1·05, 1·19) than those not using solid fuels. (Hystad et al., 2019) In India and Bangladesh, large portions of the community continue to depend on solid fuels, (World Bank, 2016) meaning that for the HEALS and MCS cohorts, additional information may be gained by examining the interplay between household and ambient air pollution. (Hosgood HD,3rd, Klugman M, Matsuo K, et al. The establishment of the household air pollution consortium (HAPCO). Atmosphere (Basel)., et al., 2019).

5. Conclusion

In this study of ambient air pollution and mortality within several Asian countries we observed a positive association between ambient $PM_{2.5}$ and cardiovascular mortality. These findings, matched by those with the wider evidence base, indicate the utility of applying global models of ambient air pollution and provide further evidence of the detrimental effects of air pollution on health.

CRediT authorship contribution statement

G.S. Downward: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **P. Hystad:** Writing – review & editing, Data curation. **S. Tasmin:** Writing – review & editing, Formal analysis, Data curation. **S.K. Abe:** Writing – review & editing, Software, Resources, Data curation. **E Saito:** Writing – review & editing, Data curation. **M.S. Rahman:** Writing – review & editing, Software, Data curation. **M.R. Islam:** Writing – review & editing, Data curation. **P. C. Gupta:** Writing – review & editing, Data curation. **N. Sawada:** Writing – review & editing, Data curation. **R. Malekzadeh:** Writing – review & editing, Data curation. **S.L. You:** Writing – review & editing, Data curation. **H. Ahsan:** Writing – review & editing, Data curation. **S.K. Park:** Writing – review & editing, Data curation. **M.S. Pednekar:** Writing – review & editing, Data curation. **S. Tsugane:** Writing – review & editing, Data curation. **A. Etemadi:** Writing – review & editing, Data curation. **C.J. Chen:** Writing – review & editing, Data curation. **A. Shin:** Writing – review & editing, Data curation. **Y. Chen:** Writing – review & editing, Data curation. **P. Boffetta:** Writing – review & editing, Data curation. **K.S. Chia:** Writing – review & editing, Data curation. **K. Matsuo:** Writing – review & editing, Data curation. **Y.L. Qiao:** Writing – review & editing, Data curation. **N. Rothman:** Writing – review & editing, Supervision. **W. Zheng:** Writing – review & editing, Data curation. **M. Inoue:** Writing – review & editing, Data curation. **D. Kang:** Writing – review & editing, Data curation. **Q. Lan:** Writing – review & editing, Supervision, Methodology. **R.C.H Vermeulen:** Writing – review & editing, Validation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Investigators who are interested in using Asia Cohort Consortium data can apply for committee review. Upon reasonable request and with the approval of the both the ACC committee and Institutional Review Board, access may be granted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108803.

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