Environmental Pollution 317 (2023) 120773

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Association of urinary and ambient black carbon, and other ambient air pollutants with risk of prediabetes and metabolic syndrome in children and adolescents☆

Rajini Nagrani [a,*], Manuela Marron [a], Eva Bongaerts [b], Tim S. Nawrot [b,c], Marcel Ameloot [d], Kees de Hoogh [e,f], Danielle Vienneau [e,f], Emeline Lequy [g], Bénédicte Jacquemin [h], Kathrin Guenther [a], Thaïs De Ruyter [b,i], Kirsten Mehlig [j], Dénes Molnár [k], Luis A. Moreno [l], Paola Russo [m], Toomas Veidebaum [n], Wolfgang Ahrens [a,o], Christoph Buck [a], on behalf of on behalf of IDEFICS and I.Family consortia

[a] Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany
[b] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[c] Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium
[d] Biomedical Research Institute, Hasselt University, Hasselt, Belgium
[e] Swiss Tropical and Public Health Institute, Kreuzenstrasse 2, 4123 Allschwil, Switzerland
[f] University of Basel, Petersplatz 1, 4001 Basel, Switzerland
[g] Unité "Cohortes en Population" UMS 011 Inserm/Université Paris-Cité/Université Paris Saclay/UVSQ Villejuif, France
[h] Univ Rennes, Inserm, EHESP, Irset (Institut de Recherché en Santé, Environnement et Travail) – UMR_S 1085,Rennes, France
[i] Department of Public Health and Primary Care, Ghent University, 9000, Ghent, Belgium
[j] School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[k] Department of Paediatrics, Medical School, University of Pécs, Pécs, Hungary
[l] GENUD (Growth, Exercise, Nutrition and Development) Research Group, University of Zaragoza, Instituto Agroalimentario de Aragón (IA2), Instituto de Investigación Sanitaria de Aragón (IIS Aragón) Zaragoza, Spain and Centro de Investigación Biomédica en Red de Fisiopatología de La Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain
[m] Institute of Food Sciences, National Research Council, Avellino, Italy
[n] National Institute for Health Development, Tallinn, Estonia
[o] Institute of Statistics, Faculty of Mathematics and Computer Science, Bremen University, Bremen, Germany

ARTICLE INFO

Keywords:
Children cohort
Air pollution
Black carbon
Prediabetes
Metabolic syndrome
Urine biomarker

ABSTRACT

The effects of exposure to black carbon (BC) on various diseases remains unclear, one reason being potential exposure misclassification following modelling of ambient air pollution levels. Urinary BC particles may be a more precise measure to analyze the health effects of BC. We aimed to assess the risk of prediabetes and metabolic syndrome (MetS) in relation to urinary BC particles and ambient BC and to compare their associations in 5453 children from IDEFICS/I. Family cohort. We determined the amount of BC particles in urine using label-free white-light generation under femtosecond pulsed laser illumination. We assessed annual exposure to ambient air pollutants (BC, $PM_{2.5}$ and NO_2) at the place of residence using land use regression models for Europe, and we calculated the residential distance to major roads (≤250 m vs. more). We analyzed the cross-sectional relationships between urinary BC and air pollutants (BC, $PM_{2.5}$ and NO_2) and distance to roads, and the associations of all these variables to the risk of prediabetes and MetS, using logistic and linear regression models. Though we did not observe associations between urinary and ambient BC in overall analysis, we observed a positive association between urinary and ambient BC levels in boys and in children living ≤250 m to a major road compared to those living >250 m away from a major road. We observed a positive association between log-transformed urinary BC particles and MetS ($OR_{per\ unit\ increase}$ = 1.72, 95% CI = 1.21; 2.45). An association between ambient BC and MetS was only observed in children living closer to a major road. Our findings suggest that exposure to BC (ambient and biomarker) may contribute to the risk of MetS in children. By measuring the

☆ This paper has been recommended for acceptance by Payam Dadvand.

* Corresponding author. Leibniz Institute for Prevention Research and Epidemiology—BIPS, Achterstrasse 30, Bremen, D-28359, Germany.
E-mail addresses: nagrani@leibniz-bips.de, sec-epi@leibniz-bips.de (R. Nagrani).

https://doi.org/10.1016/j.envpol.2022.120773
Received 17 August 2022; Received in revised form 10 November 2022; Accepted 26 November 2022
Available online 28 November 2022

internal dose, the BC particles in urine may have additionally captured non-residential sources and reduced exposure misclassification. Larger studies, with longitudinal design including measurement of urinary BC at multiple time-points are warranted to confirm our findings.

1. Introduction

Ambient air pollution is a major contributor to the global burden of the disease accounting for more than 3.4 million deaths in 2017 and attributable to approximately 90 million disability-adjusted life-years (Stanaway et al., 2018). As ambient air pollution is a global problem and no "safe limits" have been identified (Schwartz et al., 2012), even a very modest increase in risk represents an important disease burden. Air pollution has the largest impact on human health in low- and middle-income countries, particularly in Southeast Asia, but it also constitutes a major health risk in high-income countries. Approximately 5–25% of the urban population in the European Union are exposed to air pollutants above EU standards which are much lenient compared to the World Health Organization recommendations (Guerreiro et al., 2018).

Children are at greater risk than adults for the many adverse health effects of air pollution, owing to a combination of behavioral, environmental and physiological factors (World Health Organization, 2018). They are especially susceptible throughout prenatal development and in their early years, when their lungs, brains, and other organs are still developing. They breathe faster than adults, taking in more air and, with it, more pollutants (World Health Organization, 2018).

Accumulation of evidence suggests that ambient air pollution increases the risks of type 2 diabetes mellitus and metabolic syndrome (MetS) (Eze et al., 2015; Thiering and Heinrich, 2015; Zhang et al., 2021a). Insulin resistance is considered an independent predictor for type 2 diabetes (Cameron et al., 2008; Morris et al., 2013) and has been shown to be positively associated with air pollution (Brook et al., 2016; Thiering et al., 2013; Thiering et al., 2016). Studies have also indicated that ambient air pollution may be detrimentally related to individual components of MetS: hypertension (Sanders et al., 2018; Yang et al., 2018a), obesity (Wang et al., 2021), elevated fasting glucose (FG) (Ma et al., 2020) and dyslipidemia (Gaio et al., 2019). The possible biological pathways might include autonomic nervous system imbalances (Rajagopalan and Brook, 2012), oxidative stress, adipose tissue inflammation (Andersen et al., 2012; Fleisch et al., 2014), endothelial dysfunction, and alterations in insulin sensitivity, glucose metabolism, and glycosylated hemoglobin metabolism (Liu et al., 2016; Rajagopalan and Brook, 2012).

However, the exposure assessment for air pollutants, including black carbon (BC) in epidemiological studies generally rely on spatial-temporal models using land cover data and other spatial data to represent multiple primary sources (i.e., road networks, line and point locations of potential emission sources, building density) with ground-based and satellite-based measurements to evaluate the monthly or annual residential exposure levels (Dang et al., 2018; Eze et al., 2015; Liu et al., 2016; Thiering et al., 2013). Such exposure assessment methods focus on residential addresses, and less often on workplace addresses, and therefore cannot capture exposure indoors, or during commuting thus, inevitably leading to some degree of misclassification. In addition, these exposure assessment methods are based on the estimation of ambient air exposures, which does not necessarily equate to the amount of air pollutants inhaled by individuals over an extended period of time (Bai et al., 2018). On the other hand, biomarkers have the potential to improve research on the health impacts of air pollution by improving exposure measurement, expanding knowledge of mechanisms, and allowing for the exploration of individual susceptibility (Demetriou and Vineis, 2015; Kim et al., 2020). Previous studies have included the use of biomarkers in the measurement of air pollution, most of which are either non-specific or reflect short-term exposure (Demetriou and Vineis, 2015; Lettieri Barbato et al., 2010). Recently, Saenen et al. have devised a label-free method to quantify BC particles in children's urine which reflected medium-term to chronic exposure to combustion-related air pollution (Saenen et al., 2017). The present study thus comprehensively investigated the chronic exposure to BC primarily assessed by urinary BC and additionally by ambient exposure assessment, and its association with markers of metabolic dysfunction among children and adolescents.

2. Methods

2.1. Study population

The study population was selected from the pan-European, multicenter, prospective cohort based on the Identifications and prevention of dietary and lifestyle-induced health effects in children and infants (IDEFICS) study and its extension: the I.Family study. A total of 16,229 children aged between 2 and 9.9 years, from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, and Sweden) were examined for the first time in 2007–08 (T_0), with follow-up examinations after two (T_1; 2009–10) and six (T_3; 2013–14, I.Family study) years. In each country two or more communities were selected whose socio-demographic profile and infrastructure were similar and typical for their region. Within each community all children attending kindergartens and primary schools were eligible (Ahrens et al., 2011; Ahrens et al., 2014). Risk factors for lifestyle-related outcomes were assessed in young children in the IDEFICS/I.Family study, and anthropometric and clinical examinations were performed at each examination wave. Blood samples were considered fasting if the last meal or drink (other than water) was consumed >8 h before drawing blood. Morning urine was collected and stored at 4 °C until the examination at the survey center (where it was aliquoted) and frozen at −80 °C for long-term storage. Parents gave written informed consent before their children participated in the study. In addition, children aged 12 years and above provided simple written consent. Younger children verbally consented to the tests and sample collection. All eight study centres' institutional review boards granted ethics approval. For this paper, we performed a cross-sectional analysis using study participants and urine samples collected at the last follow-up examination (T_3).

2.2. Outcome variables

We used outcomes that were assessed at the last follow-up examination (T_3) in 2013–14. For FG analysis an enzymatic UV test (Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany) was used from NaF plasma. Serum insulin was analyzed (at the University of Bremen, Center for Biomolecular Interactions Bremen) by multiplex analysis with electrochemiluminescence technology from Meso Scale Discovery (MSD) using a MULTI-SPOT® Assay System; Human Leptin, Insulin Assay Kit. The hemoglobin A1c (HbA_{1c}) was analyzed in K2-EDTA venous blood by high-performance liquid chromatography (AUTOGA variant, Biorad, Munich, Germany) in a central laboratory. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin ($\mu IU\ ml^{-1}$) × FG (mg/dl)/405. Prediabetes was defined as FG between 100 mg/dL to 125 mg/dL or HbA_{1c} between 5.7 and 6.4% or both (American Diabetes Association, 2020).

The continuous MetS score was calculated summing age and sex-specific z-scores of waist circumference (WC), HOMA-IR, high-density lipoprotein (HDL), triglyceride (TG), systolic and diastolic blood pressure (SBP and DBP). The age- and sex-specific z-scores of these components were derived using previously described methods (Barba et al., 2014; De Henauw et al., 2014; Nagy et al., 2014; Peplies et al., 2014), in

children and adolescents using the data collected in the IDEFICS/I. Family cohort.

The formula for continuous MetS score by Ahrens et al. (2014) is given below:

$$\text{MetS score} = z_{WC} + \frac{z_{SBP} + z_{DBP}}{2} + \frac{z_{TG} - z_{HDL}}{2} + z_{HOMA-IR}$$

A higher score was associated with an unfavorable metabolic profile (Ahrens et al., 2014). Additionally, children were categorized as cases of MetS if at least three of the components of MetS exceeded the 90th percentile. A detailed description of the measurements of components of MetS has been published previously (Ahrens et al., 2014).

2.3. Exposure assessment

Urinary BC which reflects chronic exposure to combustion-related air pollution (Saenen et al., 2017) was measured in samples collected at T_3 (2013–14). The detection method is based on the non-incandescence related white light generation of BC under femtosecond pulsed illumination as previously reported (Bové et al., 2016; Saenen et al., 2017). Each urine sample was aliquoted at 100 μl per imaging chamber constructed by placing a glass coverslip (24 × 24 mm, #1.5, VWR, The Netherlands) on a microscopic glass slide (75 × 25, VWR, The Netherlands) merged with 100 μm thick double-sided tape (4959, Tesa, Germany). The urine-filled imaging chambers were air-sealed to prevent drying. Images of the urine samples were collected at room temperature using a Zeiss LSM510 (Carl Zeiss, Germany) equipped with a femtosecond pulsed laser (810 nm, 120 fs, 80 MHz, MaiTai DeepSee, Spectra-Physics, USA) tuned to a central wavelength of 810 nm using an EC Plan-Neofluar 20x/0.50 M27 objective (Carl Zeiss, Germany). The white light generated by the BC particles naturally present in the urine was detected via analog photomultiplier detection in epi-configuration in non-descanned mode after the signal passed through a 405/10 nm and 550/200 nm band-pass filters. Five 3 × 3 tile scans were collected 5 μm inwards from the bottom of the imaging chamber. The resulting tile scans had a field of view of 1350 × 1350 μm^2 with a 1536 × 1536 pixel resolution, and a pixel dwell time of 1.6 μs. The images were acquired by ZEN Black 2.0 Software (Carl Zeiss, Germany). To determine the number of BC particles in the images, a peak-find algorithm counting connected pixels above a threshold value of 99.5% and 50% from the highest pixel intensity of the narrow second harmonic generation channel (400–410 nm) and two-photon excited autofluorescence channel (450–650 nm), respectively, was used. These thresholds resulted in highly reproducible values, which were checked manually using Fiji (ImageJ v2.0, open source software, http://fiji.sc/Fiji). The average amount of particles detected in the different tile scans were normalized to the image volume using the focal volume estimated from the point spread function of the optical system. Finally, the result was expressed as the number of detected BC particles per milliliter urine.

Modelled air pollution exposures (ambient BC, $PM_{2.5}$, NO_2) were assigned to the participants' residential addresses provided at cohort entry. First, the addresses in the IDEFICS/I.Family cohort were geocoded, with a ~95% success rate using automatic matching. The remaining ~5% were manually geocoded using Google Maps©. Due to data protection regulations, geocodes in Germany could only be used after adding white noise error (average of 50 m to the x,y coordinates) (Buck et al., 2015). The ambient BC, $PM_{2.5}$, and NO_2 data were derived from existing and validated 100 × 100 m land use regression (LUR) models for Europe developed for the year 2010, see supplementary methods for details (de Hoogh et al., 2018). Finally, the value of the 2010 exposure assigned to the residential address was rescaled annually via back-and forward extrapolation using the ratio method according to the approach by Beelen et al., (2014) (Beelen et al., 2014). This calculation was facilitated by annual average estimates from the 26 × 26 km Danish Eulerian Hemispheric Model (Brandt et al., 2012), and applied by the NUTS1 region (European Nomenclature of Territorial Units for Statistics-1, administrative regions within countries) in Italy, Belgium, Sweden, Germany, Hungary and Spain. The annual average estimates were calculated for each year from cohort entry to the end of follow-up examination i.e. the entire study period that each participant could be followed-up for (median follow-up duration = 6 years). We also calculated the residential distance to major roads using OpenStreetMap (OSM) within QGIS. Major roads were defined according to the OSM classification of highways using line types classified as motorways, trunks, primary, and secondary roads. Since there was no change in residential addresses for almost all study participants we used the same residential address throughout the study period.

2.4. Covariables

The osmolality of urine at T_3 was measured by the advanced Cryptomatic Osmometer (Fiske, Norwood, MA). Urine creatinine was assessed using immunoturbidimetric protein determination (COBAS INTEGRA 400 plus, Roche Diagnostics Ltd.) at Institute of Laboratory Medicine University of Pécs, Hungary. Height [cm] of the children was measured to the nearest 0.1 cm with a calibrated stadiometer (Seca 225 stadiometer, Birmingham, UK), body weight [kg] was measured in fasting state in light clothing on a calibrated scale accurate to 0.1 kg (Tanita BC 420 SMA, Tanita Europe GmbH, Sindelfingen, Germany). BMI was computed by dividing measured weight [kg] by measured height [m] squared. The alcohol questionnaire was completed at T_3 by study participants who were 12 years of age or older at the time of examination. We used the number of occasions reported for alcohol intake in their lifetime to create a binary indicator variable for alcohol intake. Sports club membership (yes/no) served as an indicator of physical activity (Buck et al., 2019). Daily TV, DVD, video, computer or games-console use in hours were summed to obtain the total screen time for the whole week. The screen time was categorized in tertiles for its use as a proxy for sedentary behavior. In T_3 these proxy measures were reported by parents if the child was younger than 12 years, or self-reported if the child was 12 years or older. Parents self-reported their history of diabetes which was categorized as positive (at least one parent with diabetes), negative (both parents without diabetes), or unknown (if diabetes status of mother and father were unknown). Parents were categorized as smokers if they were identified as current smokers or if they reported smoking after index childbirth. The highest educational attainment of parents was classified as a proxy indicator for socio-economic status (SES) according to the International Standard Classification of Education (ISCED) (low: ISCED levels 0–2; medium: ISCED levels 3–4; high: ISCED levels 5 and higher) using the maximum educational level of both parents (UNESCO Institute for Statistics, 2012).

2.5. Analysis dataset

Our analysis dataset included study participants with at least one available metabolic measurement of HbA_{1c}, HOMA-IR, FG, MetS, HDL, WC, SBP, DBP or TG at T_3 (n = 9142). Children who reported cigarette smoking at least on one occasion (n = 370) or those taking anti-diabetic drugs (ATC codes: A10) within the last 14 days of cohort entry or follow-up examination (n = 51) were excluded from the analysis. Further, children with a history of diabetes (n = 16) or with missing residential address (n = 3252) were excluded from the analysis, thus leading to a final analysis dataset of 5453 children. The information on residential distance to a major road was available for 5442 children as the distances could not be derived for 11 children. The ambient air pollution data were available for 4315 children as the LUR model was not available for Estonia (n = 1138). The urinary biomarker assay for BC was performed on 435 randomly selected urine samples collected at T_3 after excluding children for whom urine samples were not available (n = 1318). After excluding two samples due to assay failure, the analysis dataset for urinary BC included 433 study participants. The study population and

exclusion criteria are shown in Supplementary Fig. 1.

2.6. Statistical analysis

Descriptive statistics of study characteristics included median with an interquartile range or numbers and percentages as appropriate. To improve the normality of the distributions we used natural log-transformed urinary BC for all analyses. To account for the dispersion pattern of air pollution with decreasing distance from a major road, we calculated proximity to major roads as the inverse of the distance to the nearest major road. We also analyzed the data using categorized distance to a major road (≤250 m vs. >250 m).

We included the mean of annual average ambient air pollutants (BC, $PM_{2.5}$ and NO_2) for the entire study period of each participant separately as a single pollutant in our main model. For e.g.: if a participant entered the study in 2008 and could be followed-up until 2013, then the mean for years 2008–2013 were calculated. Similarly, if the participant entered the study in 2010 and followed up until 2014, then the mean for years 2010–2014 was calculated and so on. For the present analysis, since we used outcomes that were assessed at the last follow-up examination (T_3) in 2013–14, the period of modelled ambient pollutants estimation either included or preceded the outcome assessment. In the analysis dataset, ambient air pollutants $PM_{2.5}$ and BC were correlated (r = 0.65) and including both exposure variables in one regression model may have distorted the true effects of one or both variables. Therefore, we attempted to isolate the effect of BC from that of $PM_{2.5}$ by regressing BC (dependent variable) on $PM_{2.5}$ (independent variable). The residuals of this regression represent the variations of BC independently of $PM_{2.5}$ such that the resulting residuals are uncorrelated with $PM_{2.5}$ (Mostofsky et al., 2012). The coefficient in the models that use BC residuals as exposure indicates the risk associated with increasing levels of BC exposure while maintaining a $PM_{2.5}$ exposure constant. We constructed study region-specific quartiles and interquartile range (IQR) for all variables of exposure to ambient air pollution, BC residuals and the proximity to major roads variable to explore any non-linear association.

Multiple linear regressions were performed to compare the levels of urinary BC with ambient BC and other ambient air pollutants, BC residuals, distance and residential proximity to major roads while adjusting for potential confounders - age, sex, study region, body mass index (BMI), parental education, parental smoking, urine osmolality, urinary creatinine concentration and month of urine collection. To investigate whether the associations of urinary BC are stronger with the recent exposure to annual average ambient air pollutants, we additionally limited our analysis to annual average ambient air pollutants 1 year before urine sample collection i.e., for urine samples collected in 2014 we used annual average pollutant values of 2013.

We used linear regression to cross-sectionally assess the association between ambient air pollutants, urinary BC, residential distance as well as proximity to major roads, and prediabetes and metabolic markers at T_3. We further dichotomized the outcome variables (prediabetes and MetS) and performed multiple logistic regressions to cross-sectionally analyze its association with urinary or ambient BC, $PM_{2.5}$ and NO_2 as a single pollutant or residential distance or proximity to major roads, separately at T_3. In previous studies differences in association were reported w.r.t sex, obesity (normal weight vs. overweight/obese) or residential distance to major road (≤250 m vs. >250 m) (Clementi et al., 2019; Mann et al., 2021; Zhang et al., 2021a). We therefore performed stratified analysis on these variables to investigate for possible effect modification. We performed sensitivity analysis by limiting the analysis to non-smoker parents to rule out confounding effects of second-hand smoking. Crude models included age and sex. The adjusted models additionally included study region, lifetime alcohol status, family history of diabetes, membership in a sports club, screen time per week, parental education and parental smoking.

To account for missingness in the covariables screen time per week, membership in a sports club, parental education and parental smoking we introduced a missing category. All results were reported as regression coefficients or odds ratios and their 95% confidence intervals. The level of significance was set to $\alpha = 0.05$. Statistical analyses were performed using Stata 16 and R 4.1.0.

3. Results

3.1. Characteristics of the study population

The analysis dataset consisted of 5453 children. Their characteristics at the last follow-up examination (T_3) are shown in Table 1 with a median age of 11.2 years. The prevalence of obesity was 24%. Fifteen percent (n = 807) children were prediabetic and almost 6% (n = 303) of children had MetS (Table 1). The overall study population consisted of almost 50% females. Almost 11% of study participants reported ever consuming alcohol. At least one of the parents of 30% of the children reported being an ex-/current smoker. The characteristics of the samples selected for urinary BC measurement (n = 433) were similar to the analysis dataset of 5453 participants (Table 1).

The distribution of ambient BC, $PM_{2.5}$ and NO_2 concentrations in median (IQR) between 2007 and 2014 at residential addresses of 4315 study participants across different study regions of IDEFICS/I.Family cohort are depicted in Supplementary Fig. 2.

The annual average ambient $PM_{2.5}$ and NO_2 exposures in year 2010 were well above the 2021 WHO guideline values (5 μg/m^3 and 10 μg/m^3, respectively) for all study participants, and for $PM_{2.5}$ many also exceeded the former 2005 guideline values (10 μg/m^3). Though a considerable heterogeneity was observed for ambient annual average BC levels between study participants residing in different study regions, this heterogeneity wasn't reflected in the urinary BC levels which showed comparable median values across study regions (Fig. 1).

3.2. Association between urinary and ambient BC

We did not observe significant associations between urinary BC and ambient BC in the overall analysis or when stratified on study regions (Table 2, Supplementary Table 1). However, the stratified analysis by sex showed an association between urinary and ambient BC in boys ($\beta_{boys\ Q2} = 0.66$, 95% CI = 0.07; 1.25, $\beta_{girls\ Q2} = -0.22$, 95% CI = −0.76; 0.31, Supplementary Table 2). A similar association was observed in boys with BC residuals (Supplementary Table 2). We also observed a positive association between urinary BC and BC residuals in children living away from a major road (Supplementary Table 3). Finally, the urinary BC concentrations were higher in children living ≤250 m from a major road compared to those living >250 m from a major road (Table 2, Supplementary Table 4).

3.3. Association between urinary BC and metabolic outcomes

We observed a positive association between urinary BC and MetS ($OR_{per\ log\ unit\ increase} = 1.72$, 95% CI = 1.21; 2.45, Fig. 2) with a stronger association in girls compared to boys (Supplementary Table 5). The association remained even after exclusion of children with smoking parents (Supplementary Table 6). On stratifying the analysis by BMI, the association between urinary BC and MetS was limited only to overweight/obese children ($OR_{per\ log\ unit\ increase} = 2.22$, 95% CI = 1.24; 3.95, Supplementary Table 7). Due to the limited number of children with prediabetes and MetS in each study region, we couldn't perform a stratified analysis on the study region for binary outcomes prediabetes and MetS (Supplementary Table 8).

3.4. Chronic exposure to ambient air pollutants/residential distance to major roads and its association with metabolic outcomes

Using the single pollutant model for chronic ambient BC exposure, we did not observe any statistically significant association with

Table 1
Study characteristics of participants included in the analysis dataset.

Parameters		All children at T_3 (n = 5453)		Children at T_3 with urinary BC measurement (n = 433)	
Year of examination		2013–14		2013–14	
		n	%/median (IQR)	n	%/median (IQR)
Age, years		5453	11.2 (9.7–13.1)	433	12.2 (10.6–13.4)
Sex, female		2735	50.2	205	47.3
Parental history of diabetes	Yes	135	2.5	15	3.5
	No	5318	97.5	418	96.5
	missing	–	–	–	–
Parental education/SES	Low	294	5.4	23	5.3
	Medium	2301	42.2	201	46.4
	High	2738	50.2	206	47.6
	missing	120	2.2	3	0.7
Parental smoking (Current/Ex-smokers)	Yes	1628	29.9	127	29.3
	missing	845	15.5	43	9.9
Membership in a sports club	Yes	3573	65.5	307	70.9
	No	1636	30.0	111	25.6
	missing	244	4.47	15	3.5
Screen time per week (hours)		5061	14 (8.5–21.0)	410	13.5 (9.3–20.5)
Ever consumed alcohol[a]	Yes	586	10.8	52	12.0
	missing	207	3.8	23	5.0
BMI category by Cole & Lobstein (2012)	Thinness grade 1-3	469	8.6	35	8.1
	Normal weight	3671	67.3	288	66.5
	Overweight/obese	1313	24.1	110	25.4
	missing	–	–	–	–
WC (cm)		5399	63.6 (58.0–71.0)	428	65.4 (59.9–72.0)
SBP (mm Hg)		5242	106.0 (100.0–112.5)	430	107 (101.0–112.5)
DBP (mm Hg)		5241	64.5 (60.5–69.0)	430	65 (60.0–69.0)
TG (mg/dL)		3719	59.0 (46.0–80.0)	428	56 (44.5–74.0)
HDL (mg/dL)		3719	59.0 (50.0–69.0)	428	58 (50.0–69.0)
HOMA-IR		2607	1.2 (0.8–1.9)	433	1.2 (0.8–1.9)
HbA_{1c} (%)		3655	5.0 (4.8–5.2)	433	5 (4.8–5.2)
FG (mg/dL)		3084	94.0 (90.0–98.0)	433	94.0 (90.0–99.0)
HOMA-IR >2.5		528	9.7	67	15.5
HbA_{1c} 5.7–6.4%		21	0.4	4	0.9
FG 100 mg/dL-125 mg/dL		798	14.6	87	20.1
Prediabetes	Yes	807	14.8	88	20.3
	No	2796	51.3	344	79.5
	missing	1850	34.0	1	0.2
Metabolic Syndrome	Yes	303	5.6	31	7.2
	No	2999	55.0	389	89.8
	missing	2151	39.5	13	3.0
Urine osmolality (mOsmol/kg)		426	590.5 (699.0–1042.0)	426	890.5 (699.0–1042.0)
Urine creatinine (μmol/l)		3945	10629.0 (7459.0–14433.0)	413	11,690 (8275.0–15912.0)

Abbreviations: BC, black carbon; BMI, body mass index; DBP, diastolic blood pressure, FG, fasting glucose; HbA_{1c}, hemoglobin A_{1c}; HDL, high density lipoprotein, HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

[a] Information collected only from participants who were aged 12 years or older at T_3. Children below 12 years were considered non-drinkers. Characteristics of the study participants are presented as number (percentages) for categorical variables and median (25th and 75th percentiles) for continuous variables.

prediabetes or MetS (Fig. 2, Supplementary Table 6). However, in stratified analysis on residential distance to a major road, we observed an association between ambient BC and MetS in children living closer to a major road ($\beta_{\text{residential distance } \leq 250\text{m to a major road Q3}} = 3.12$, 95% CI = 1.47; 6.64, Supplementary Table 9). When assessing the association with metabolic components, we observed ambient $PM_{2.5}$ to be associated with HOMA-IR ($\beta_{\text{per IQR increase}} = 0.06$, CI = 0.01; 0.12) and HbA_{1c} ($\beta_{\text{per IQR increase}} = 0.06$, CI = 0.01; 0.10; Supplementary Table 10). Concerning chronic ambient NO_2 levels, we mostly observed null or inverse associations with prediabetes, components of MetS (Fig. 2, Supplementary Tables 5, 6, 7, 9 and 10). Living ≤250 m from a major road was associated with higher levels of HbA_{1c} and DBP (Supplementary Table 10).

4. Discussion

In our analysis dataset of children and adolescents from the IDEFICS/I.Family study we observed a positive association between urinary BC and MetS. In stratified analysis, these associations remained significant in both sexes and in overweight/obese children. To confirm that the urinary BC mirrors the accumulation of chronic exposure to combustion related air pollution, we ran linear regressions of log urinary BC on region specific quartiles of annual average ambient air pollutants and observed non-linear associations between urinary and ambient BC in boys. This sex-specific association maybe attributed to the differences in lung function growth rates and lower respiratory volumes and greater airway resistance among boys (Clougherty, 2010). Since traffic-related emissions are one of the major sources of BC particles in the study region (von Schneidemesser et al., 2017), our observation of stronger association of urinary BC with children living closer to a major road seems plausible. This is the first epidemiological study to assess the association of the newly identified novel biomarker of internal dose (urinary carbon load) with a disease outcome.

4.1. Comparison with previous studies

Observational studies have demonstrated that air pollution contributes to higher FG, insulin resistance, diabetes and MetS in adults (Eze et al., 2015; Hou et al., 2020; Lee et al., 2019; Matthiessen et al., 2018; Shamy et al., 2017; Yang et al., 2018b; Yu et al., 2020; Zhang et al., 2021b). Furthermore, studies have indicated that children are more vulnerable to the negative health consequences of air pollution due to their increased minute ventilation, greater levels of physical activity, and dynamic developmental physiology (Sly and Flack, 2008). However, very few studies were able to assess the association of ambient BC

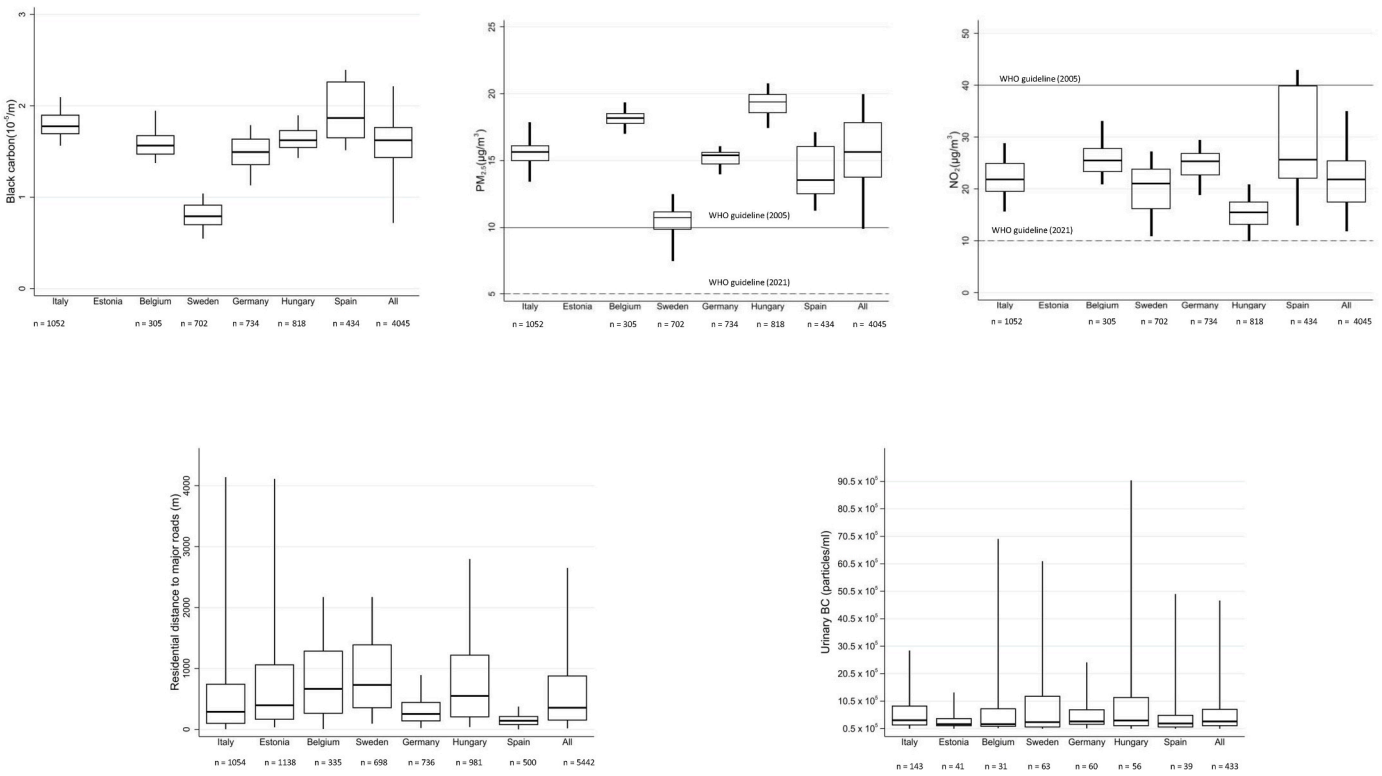

Fig. 1. Distribution of urinary black carbon, ambient air pollution exposure as 2010 annual average concentrations (Black carbon, $PM_{2.5}$, NO_2) and residential distance to major roads stratified by study region, median (IQR); whiskers extend to 5% and 95% points of the distribution. Residential air pollution exposures were not evaluated for Estonia.

with metabolic health particularly in children (Prunicki et al., 2020). Indeed, only a few epidemiological studies focused on long-term exposure to BC and its association with metabolic health (Curto et al., 2019a; Du et al., 2021). A previous study conducted on rural Indian adults did not observe an association of ambient BC with prediabetes or metabolic outcomes (Curto et al., 2019a; Curto et al., 2019b). Other studies which explored long-term levels of $PM_{2.5}$ absorbance, a comparable measure to BC (Renzi et al., 2018; Strak et al., 2017; Wolf et al., 2016) also observed weak and modest associations with higher FG or diabetes prevalence. These weak or null associations were partly attributed to the inability to capture the complex mixture of sources (Curto et al., 2019a). We speculate that the previous and the present study may have underestimated the risk associated with BC due to non-differential exposure misclassification inherent to the modelling of ambient air pollution levels. Therefore, in the present study, the inclusion of a biomarker of exposure to quantify the chronic exposure to BC in addition to spatial models may have helped in capturing the association with metabolic dysfunction better. This association was robust such that it persisted even after limiting the analysis to children without exposure to second-hand smoke. Our observation of the association between urinary BC levels and MetS in overweight/obese children is consistent with the mechanism/pathway that BC and other air pollutants contribute to the development of metabolic dysfunction via its association with obesity (Clementi et al., 2019; de Bont et al., 2019; Sun et al., 2015).

4.2. Chronic exposure to ambient air pollutants/residential distance to major roads and its association with metabolic outcomes

We did not observe consistent associations of ambient BC, $PM_{2.5}$, or NO_2 exposures with metabolic parameters, although there were a few sporadic associations. In the present study we observed a positive association between ambient BC and MetS in children living closer to a major road. Similar to our observations, based on the limited literature on MetS, both short- and long-term exposure studies observed positive associations between ambient BC or living in close proximity to major roads with adverse metabolic outcomes (Mann et al., 2021; Rajkumar et al., 2019).

Further, the findings of our current study suggest that living closer to major road (≤250 m) increases the HbA_{1c} and DBP levels in children. This observation is consistent with the existing literature (Li et al., 2018; Pindus et al., 2015). Pindus et al. investigated the association of distance to a major road with blood pressure and showed that living closer than 150 m to a busy road can increase the odds of having cardiac disease and hypertension (Pindus et al., 2015). Analysis from the Framingham Heart Study also reported an association between living closer to a major road and glucose dysregulation (Li et al., 2018).

We observed null or non-significant inverse associations between ambient NO_2 and metabolic outcomes. This is inconsistent with previous studies which observed significant positive associations (Matthiessen et al., 2018) or non-significantly elevated estimates (Fuks et al., 2017) which could be attributed to the relatively moderate sample size for ambient air pollutant data compared to the above mentioned studies. Furthermore, though we observed a weak inverse association between BC residuals and HDL, we did not observe associations between other ambient air pollutants and HDL or TG. Consistent with our current findings, no significant associations for air pollutants ($PM_{2.5}$ and NO_2) with TG and HDL were observed in a recent Chinese study of children and adolescents (Zhang et al., 2021a).

4.3. Sex-related differences

Our observation of sex-related differences in the association with urinary BC may potentially be associated with sex-specific biological, social, or behavioral traits that could affect the deposition rate of pollutants and exposure patterns. We observed a stronger association in girls compared to boys which is inconsistent with a previous report by

Table 2
Association between urinary BC and exposure to ambient BC, $PM_{2.5}$, NO_2 & residential proximity to major roads (using linear regression).

Exposure		Parsimonious	Fully adjusted
		β (95% CI)	β (95% CI)
n		406	406
Proximity to major roads	Q1	ref	ref
	Q2	0.04 (−0.32; 0.40)	0.00 (−0.36; 0.36)
	Q3	0.35 (−0.01; 0.71)	0.32 (−0.04; 0.68)
	Q4	0.28 (−0.08; 0.63)	0.35 (0.00; 0.71)
	per IQR increase	0.00 (0.00; 0.01)	0.01 (0.00; 0.01)
Residential distance ≤250 m to major roads		0.19 (−0.07; 0.45)	**0.40 (0.11; 0.69)**
Annual average ambient pollutants 1 year before urine sample collection			
n		366	366
Ambient BC	Q1	ref	ref
	Q2	0.27 (−0.13; 0.66)	0.21 (−0.18; 0.61)
	Q3	0.18 (−0.20; 0.57)	0.16 (−0.25; 0.57)
	Q4	0.09 (−0.28; 0.47)	0.19 (−0.24; 0.61)
	per IQR increase	0.04 (−0.04; 0.11)	0.16 (−0.06; 0.37)
Ambient $PM_{2.5}$	Q1	ref	ref
	Q2	0.05 (−0.36; 0.46)	0.02 (−0.39; 0.43)
	Q3	−0.15 (−0.52; 0.22)	−0.14 (−0.54; 0.26)
	Q4	0.11 (−0.27; 0.48)	0.25 (−0.16; 0.66)
	per IQR increase	0.02 (−0.01; 0.04)	0.10 (−0.06; 0.26)
Ambient NO_2	Q1	ref	ref
	Q2	0.36 (−0.04; 0.77)	0.28 (−0.13; 0.70)
	Q3	0.15 (−0.24; 0.53)	0.11 (−0.29; 0.51)
	Q4	0.15 (−0.23; 0.53)	0.28 (−0.13; 0.69)
	per IQR increase	0.07 (−0.04; 0.17)	0.14 (−0.05; 0.32)
BC residuals	Q1	ref	ref
	Q2	−0.11 (−0.50; 0.28)	−0.09 (−0.48; 0.30)
	Q3	0.21 (−0.18; 0.60)	0.23 (−0.16; 0.62)
	Q4	−0.03 (−0.41; 0.36)	−0.07 (−0.47; 0.33)
	per IQR increase	−0.06 (−0.13; 0.01)	0.05 (−0.14; 0.24)
Annual average ambient pollutants for the entire study period[a]			
n		366	366
Ambient BC	Q1	ref	ref
	Q2	0.34 (−0.5; 0.73)	0.31 (−0.08; 0.69)
	Q3	0.06 (−0.33; 0.46)	0.06 (−0.35; 0.46)
	Q4	0.17 (−0.20; 0.55)	0.31 (−0.10; 0.73)
	per IQR increase	0.03 (−0.04; 0.10)	0.13 (−0.07; 0.32)
Ambient $PM_{2.5}$	Q1	ref	ref
	Q2	−0.13 (−0.54; 0.28)	−0.10 (−0.52; 0.31)
	Q3	−0.13 (−0.52; 0.26)	−0.14 (−0.54; 0.25)
	Q4	0.03 (−0.36; 0.41)	0.24 (−0.18; 0.67)
	per IQR increase	0.02 (−0.01; 0.05)	0.14 (−0.04; 0.31)
Ambient NO_2	Q1	ref	ref
	Q2	0.09 (−0.32; 0.50)	−0.01 (−0.42; 0.41)
	Q3	0.19 (−0.20; 0.59)	0.13 (−0.27; 0.53)
	Q4	0.05 (−0.34; 0.44)	0.17 (−0.24; 0.58)
	per IQR increase	0.06 (−0.04; 0.16)	0.14 (−0.05; 0.32)
BC residuals	Q1	ref	ref
	Q2	−0.19 (−0.59; 0.21)	−0.12 (−0.52; 0.29)
	Q3	−0.15 (−0.55; 0.24)	−0.07 (−0.47; 0.33)
	Q4	−0.30 (−0.71; 0.11)	−0.23 (−0.65; 0.19)
	per IQR increase	−0.07 (−0.14; 0.004)	0.02 (−0.18; 0.21)

Abbreviations: BC, black carbon; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤2.5 μm. [a]Parsimonious models were adjusted for age, sex, urine osmolality and creatinine. [b]Fully adjusted models were additionally adjusted for the study region, body mass index, parental education, parental smoking, and month of examination. [a]Mean of annual average ambient air pollutants (BC, $PM_{2.5}$ and NO_2) are calculated for the entire study period that each participant could be followed-up for. Associations are represented for each quartile of ambient BC/$PM_{2.5}$/NO_2/BC residuals/proximity to major roads vs. Q1 or per quartile increase in ambient BC/$PM_{2.5}$/NO_2/BC residuals/proximity to major roads or for residential distance ≤250 m to major roads vs. >250 m (ref). The quartiles for the exposures are study region specific. BC residuals were calculated as the residuals of the regression of annual average BC against annual average $PM_{2.5}$. Significant associations at $p < 0.05$ are shown in bold.

Zhang et al. where the associations were more robust in boys (Zhang et al., 2021a). Given the currently mixed evidence regarding the effect modification by sex (Clougherty, 2010), further investigation is needed to elucidate possible mechanisms.

4.4. Suggested biological mechanisms

Several biological mechanisms by which BC and other air pollutants may be associated with metabolic dysfunction have been suggested in previous experimental studies (Li et al., 2016; Sun et al., 2009; Xu et al., 2010). One plausible hypothesis is that the inhalation of air pollutants may induce the generation of endogenous pro-inflammatory mediators and vasculo-active molecules, leading to alterations in the insulin signaling pathway and impaired vaso-relaxation, resulting in insulin resistance and detrimental vascular effects (Houstis et al., 2006; Miller, 2014). Further, some particulate matter constituents (e.g. nano-sized particles and soluble metals) may have the potential to pass through the alveolar-capillary membrane, entering the bloodstream and directly inducing systemic inflammation and oxidative stress within the pulmonary tissue and causing "spillover" into the systemic circulation, then having detrimental effects on the cardiovascular system or other organs like adipose tissue (Brook et al., 2008). The second plausible explanation is that air pollutants may disrupt the autonomic nervous system by activating afferent pulmonary autonomic reflexes, which may raise blood pressure (Brook et al., 2008; Franklin et al., 2015). In addition, previous studies have linked air pollution exposure to abnormal methylation levels of global DNA and candidate genes involved in blood pressure regulation, glucose-homeostasis, and lipid metabolism pathways (Breton et al., 2016; Peng et al., 2016). To disentangle the complexity of the associations between metabolic outcomes and urinary BC, there is a need for multiple measurements of the biomarker to facilitate longitudinal analysis and confirm temporality. Overall, this study adds new insights into the potential role of urinary biomarkers in the associations between long-term exposure to BC and metabolic

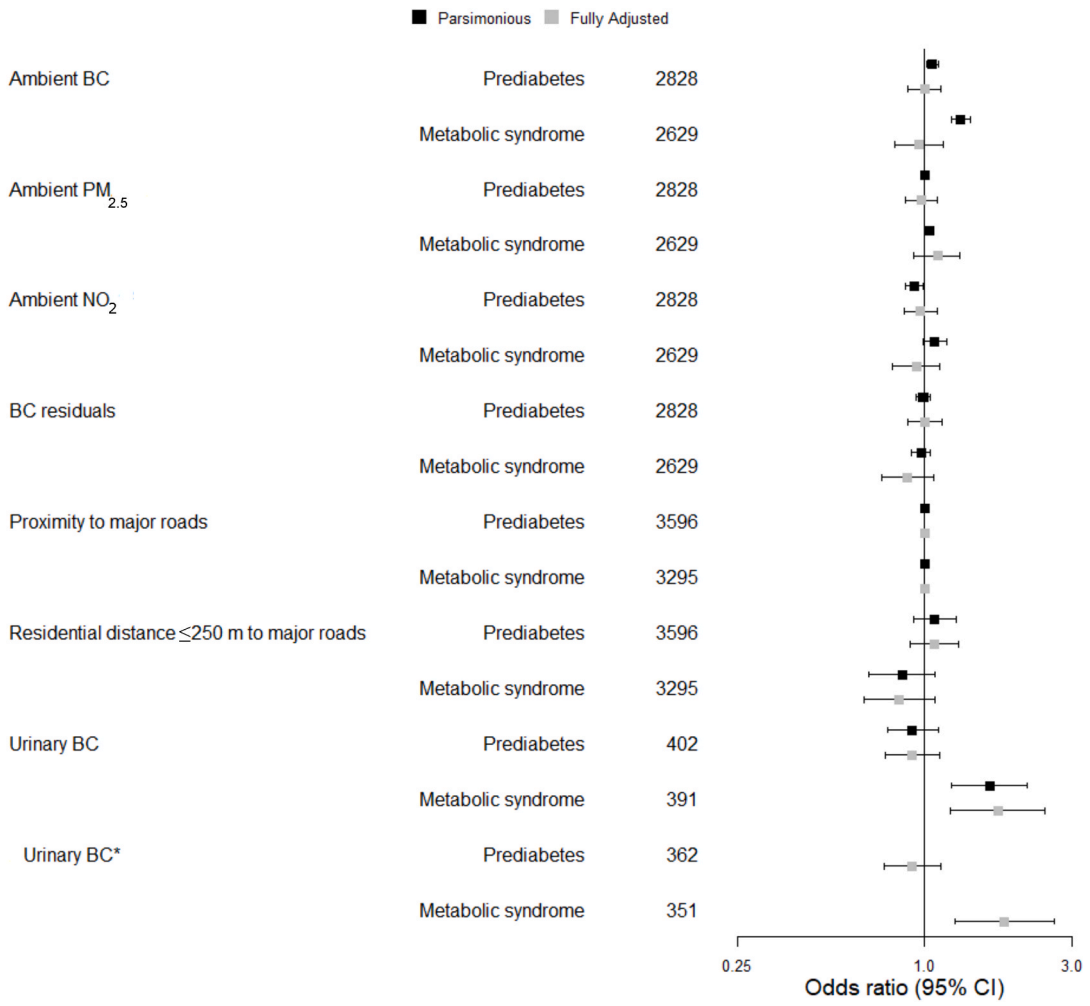

Fig. 2. Association of urinary BC, ambient pollutants and proximity to major roads with Prediabetes and Metabolic syndrome in children and adolescents of the IDEFICS/I. Family cohort. Abbreviations: BC, black carbon; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ≤2.5 μm. Parsimonious models were adjusted for age and sex. Fully adjusted models were additionally adjusted for the study region, lifetime alcohol status, membership in a sports club, screen time/week, parental education status, parental smoking and family history of diabetes. Parsimonious and fully adjusted models for urinary BC were additionally adjusted for urine osmolality and creatinine. [a]Mean of annual average ambient air pollutants (BC, $PM_{2.5}$ and NO_2) are calculated for the entire study period that each participant could be followed-up for. Associations represent per unit increase in log urinary BC or per IQR increase in ambient BC/$PM_{2.5}$/NO_2/BC residuals/proximity to major roads or for residential distance ≤250 m to a major road vs. >250 m (ref). The IQR for the exposures are study region specific. BC residuals were calculated as the residuals of the regression of mean of annual average BC against mean of annual average $PM_{2.5}$. *Additionally adjusted for ambient BC.

dysfunction in children.

4.5. Strengths and limitations

The strength of the study is that it takes advantage of the novel urinary biomarker for BC in addition to the ambient exposure assessment using European-wide LUR models. Our study utilizes careful outcome assessment using several biomarkers for assigning prediabetes and MetS to the study participants. The study includes the non-smoking vulnerable population of children from the well-characterized pan-European IDEFICS/I.Family cohort combined with objective information on ambient air pollutants and outcomes.

Despite these strengths, our analyses may have suffered from limited statistical power for ambient air pollutants/stratified analysis which may have precluded us from finding small (perhaps clinically important) associations. Selection bias may have occurred in the analysis dataset; nevertheless, it is unlikely that selection/participation was impacted by both exposure and disease status as previous attrition analyses from our cohort showed only marginally affect exposure-outcome associations (Langeheine et al., 2018). Given the cross-sectional study design, we could not establish temporality between the biomarker and the health effects examined. Though both the ambient LUR models and urinary BC reflect chronic exposure to BC, the ambient air pollution concentrations may have limitations as they were estimated only based on participants' residential addresses whereas the biomarker additionally captured indoor, at school, or other non-residential sources of BC. This may explain the observed differences in associations between ambient and biomarker models with outcomes of interest and also the considerable heterogeneity in the ambient air pollutants observed across study regions compared to urinary BC levels. In addition, some residual confounding factors (e. g., noise, green space, average time activity patterns) were not considered in the current study.

Conclusion: Based on a detailed analysis of BC, one of the most important components of $PM_{2.5}$, and by applying a new biomarker for urinary BC particle load, we conclude that exposure to BC may contribute to the risk of MetS in children and adolescents. By additionally capturing non-residential sources and measuring the internal dose of BC, the novel urinary biomarker has probably reduced exposure misclassification in case of long-term BC exposure and subsequently achieved a higher precision of the effect estimates for metabolic outcomes. Larger studies and studies with longitudinal design may further confirm our findings with measurement of the urinary biomarker at

multiple time-points.

Author statement

Conceptualization – RN; Data curation – RN, CB; Formal analysis – RN; Funding acquisition – DM, LM, TV, WA; Investigation – RN, EB, TN, MA, CB,; Methodology – RN, DV, EL, BJ, KdH; Project administration – KG, DM, LM, PR, TV; Resources - BJ, KG, KdH DM, LM, PR, TV, WA; Supervision – KdH, DV, EL, DV, WA; Validation – EB, TN, MA; Roles/ Writing - original draft – RN, EB, DV, CB; Writing - review & editing – RN, MM, EB, TN, DV, EL, BJ, TdR, KM, WA, CB.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Marcel Ameloot, Tim Nawrot has patent Method for detecting or quantifying carbon black and/or black carbon particles issued to Marcel Ameloot, Tim Nawrot.

Data availability

Data will be made available on request.

Acknowledgments

We thank the IDEFICS and I. Family children and their parents for taking the time to participate in this extensive examination program. This work was done as part of the IDEFICS/I. Family studies.We are grateful for the support provided by school boards, headmasters, teachers, school staff and communities, and for the effort of all study nurses and our data managers, especially Claudia Brünings-Kuppe, Willempje Hummel-Bartenschlager, and Sandra Israel-Georgii. We are thankful to Nada El Jundi and Philine Betker for their support in literature search and data entry.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.120773.

References

Ahrens, W., Moreno, L.A., Mårild, S., Molnár, D., Siani, A., De Henauw, S., Böhmann, J., Günther, K., Hadjigeorgiou, C., Iacoviello, L., Lissner, L., Veidebaum, T., Pohlabeln, H., Pigeot, I., 2014. Metabolic syndrome in young children: definitions and results of the IDEFICS study. Int. J. Obes. 38, S4–S14.

American Diabetes Association, 2020. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care 44, S15–S33.

Andersen, Z.J., Raaschou-Nielsen, O., Ketzel, M., Jensen, S.S., Hvidberg, M., Loft, S., Tjonneland, A., Overvad, K., Sorensen, M., Diabetes incidence and long-term exposure to air pollution: a cohort study, 2012. Diabetes Care 35, 92–98.

Bai, Y., Bové, H., Nawrot, T.S., Nemery, B., 2018. Carbon load in airway macrophages as a biomarker of exposure to particulate air pollution; a longitudinal study of an international Panel. Part. Fibre Toxicol. 15, 14.

Barba, G., Buck, C., Bammann, K., Hadjigeorgiou, C., Hebestreit, A., Marild, S., Molnar, D., Russo, P., Veidebaum, T., Vyncke, K., Ahrens, W., Moreno, L.A., 2014. Blood pressure reference values for European non-overweight school children: the IDEFICS study. Int. J. Obes. 38, S48–S56.

Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., Wolf, K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A.S., Lanki, T., Turunen, A., Oftedal, B., Nystad, W., Nafstad, P., De Faire, U., Pedersen, N.L., Östenson, C.G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Sugiri, D., Krämer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin, H., Nagel, G., Ineichen, A., Schaffner, E., Probst-Hensch, N., Künzli, N., Schindler, C., Schikowski, T., Adam, M., Phuleria, H., Vilier, A., Clavel-Chapelon, F., Declercq, C., Grioni, S., Krogh, V., Tsai, M.Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Katsoulis, M., Trichopoulou, A., Brunekreef, B., Hoek, G., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383, 785–795.

Bové, H., Steuwe, C., Fron, E., Slenders, E., D'Haen, J., Fujita, Y., Uji-i, H., vandeVen, M., Roeffaers, M., Ameloot, M., 2016. Biocompatible label-free detection of carbon black particles by femtosecond pulsed laser microscopy. Nano Lett. 16, 3173–3178.

Brandt, J., Silver, J.D., Frohn, L.M., Geels, C., Gross, A., Hansen, A.B., Hansen, K.M., Hedegaard, G.B., Skjøth, C.A., Villadsen, H., Zare, A., Christensen, J.H., 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos. Environ. 53, 156–176.

Breton, C.V., Yao, J., Millstein, J., Gao, L., Siegmund, K.D., Mack, W., Whitfield-Maxwell, L., Lurmann, F., Hodis, H., Avol, E., Gilliland, F.D., 2016. Prenatal air pollution exposures, DNA methyl transferase genotypes, and associations with newborn LINE1 and alu methylation and childhood blood pressure and carotid intima-media thickness in the children's health study. Environ. Health Perspect. 124, 1905–1912.

Brook, R.D., Jerrett, M., Brook, J.R., Bard, R.L., Finkelstein, M.M., 2008. The relationship between diabetes mellitus and traffic-related air pollution. J. Occup. Environ. Med. 50, 32–38.

Brook, R.D., Sun, Z., Brook, J.R., Zhao, X., Ruan, Y., Yan, J., Mukherjee, B., Rao, X., Duan, F., Sun, L., Liang, R., Lian, H., Zhang, S., Fang, Q., Gu, D., Sun, Q., Fan, Z., Rajagopalan, S., 2016. Extreme air pollution conditions adversely affect blood pressure and insulin resistance: the air pollution and cardiometabolic disease study. Hypertension 67, 77–85.

Buck, C., Dreger, S., Pigeot, I., 2015. Anonymisation of Address Coordinates for Microlevel Analyses of the Built Environment: a Simulation Study. BMJ Open 5, p. e006481.

Buck, C., Eiben, G., Lauria, F., Konstabel, K., Page, A., Ahrens, W., Pigeot, I., on behalf of the, I., the, I.F.c, 2019. Urban Moveability and physical activity in children: longitudinal results from the IDEFICS and I.Family cohort. Int. J. Behav. Nutr. Phys. Activ. 16, 128.

Cameron, A.J., Magliano, D.J., Zimmet, P.Z., Welborn, T.A., Colagiuri, S., Tonkin, A.M., Shaw, J.E., 2008. The metabolic syndrome as a tool for predicting future diabetes: the AusDiab study. J. Intern. Med. 264, 177–186.

Clementi, E.A., Talusan, A., Vaidyanathan, S., Veerappan, A., Mikhail, M., Ostrofsky, D., Crowley, G., Kim, J.S., Kwon, S., Nolan, A., 2019. Metabolic Syndrome and Air Pollution: A Narrative Review of Their Cardiopulmonary Effects. Toxics 7.

Clougherty, J.E., 2010. A growing role for gender analysis in air pollution epidemiology. Environ. Health Perspect. 118, 167–176.

Curto, A., Ranzani, O., Milà, C., Sanchez, M., Marshall, J.D., Kulkarni, B., Bhogadi, S., Kinra, S., Wellenius, G.A., Tonne, C., 2019a. Lack of association between particulate air pollution and blood glucose levels and diabetic status in peri-urban India. Environ. Int. 131, 105033.

Curto, A., Wellenius, G.A., Milà, C., Sanchez, M., Ranzani, O., Marshall, J.D., Kulkarni, B., Bhogadi, S., Kinra, S., Tonne, C., 2019b. Ambient particulate air pollution and blood pressure in peri-urban India. Epidemiology 30, 492–500.

Dang, J., Yang, M., Zhang, X., Ruan, H., Qin, G., Fu, J., Shen, Z., Tan, A., Li, R., Moore, J., 2018. Associations of exposure to air pollution with insulin resistance: a systematic review and meta-analysis. Int. J. Environ. Res. Publ. Health 15, 2593.

de Bont, J., Casas, M., Barrera-Gómez, J., Cirach, M., Rivas, I., Valvi, D., Álvarez, M., Dadvand, P., Sunyer, J., Vrijheid, M., 2019. Ambient air pollution and overweight and obesity in school-aged children in Barcelona, Spain. Environ. Int. 125, 58–64.

De Henauw, S., Michels, N., Vyncke, K., Hebestreit, A., Russo, P., Intemann, T., Peplies, J., Fraterman, A., Eiben, G., de Lorgeril, M., Tornaritis, M., Molnar, D., Veidebaum, T., Ahrens, W., Moreno, L.A., 2014. Blood lipids among young children in Europe: results from the European IDEFICS study. Int. J. Obes. 38, S67–S75.

de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., Bauwelinck, M., van Donkelaar, A., Hvidtfeldt, U.A., Katsouyanni, K., Klompmaker, J., Martin, R.V., Samoli, E., Schwartz, P.E., Stafoggia, M., Bellander, T., Strak, M., Wolf, K., Vienneau, D., Brunekreef, B., Hoek, G., 2018. Spatial PM2.5, NO2, O3 and BC models for western Europe – evaluation of spatiotemporal stability. Environ. Int. 120, 81–92.

Demetriou, C.A., Vineis, P., 2015. Carcinogenicity of ambient air pollution: use of biomarkers, lessons learnt and future directions. J. Thorac. Dis. 7, 67–95.

Du, X., Zhang, Y., Liu, C., Fang, J., Zhao, F., Chen, C., Du, P., Wang, Q., Wang, J., Shi, W., van Donkelaar, A., Martin, R.V., Bachwenkizi, J., Chen, R., Li, T., Kan, H., Shi, X., 2021. Fine particulate matter constituents and sub-clinical outcomes of cardiovascular diseases: a multi-center study in China. Sci. Total Environ. 759, 143555.

Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M., 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect. 123, 381–389.

Fleisch, A.F., Gold, D.R., Rifas-Shiman, S.L., Koutrakis, P., Schwartz, J.D., Kloog, I., Melly, S., Coull, B.A., Zanobetti, A., Gillman, M.W., Oken, E., Air pollution exposure and abnormal glucose tolerance during pregnancy: the project Viva cohort, 2014. Environ. Health Perspect. 122, 378–383.

Franklin, B.A., Brook, R., Arden Pope, C., 2015. Air pollution and cardiovascular disease. Curr. Probl. Cardiol. 40, 207–238.

Fuks, K.B., Weinmayr, G., Basagaña, X., Gruzieva, O., Hampel, R., Oftedal, B., Sørensen, M., Wolf, K., Aamodt, G., Aasvang, G.M., Aguilera, I., Becker, T., Beelen, R., Brunekreef, B., Caracciolo, B., Cyrys, J., Elosua, R., Eriksen, K.T., Foraster, M., Fratiglioni, L., Hilding, A., Houthuijs, D., Korek, M., Künzli, N., Marrugat, J., Nieuwenhuijsen, M., Östenson, C.G., Penell, J., Pershagen, G., Raaschou-Nielsen, O., Swart, W.J.R., Peters, A., Hoffmann, B., Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of

the European study of cohorts for air pollution effects (ESCAPE), 2017. Eur. Heart J. 38, 983–990.
Gaio, V., Roquette, R., Dias, C.M., Nunes, B., 2019. Ambient air pollution and lipid profile: systematic review and meta-analysis. Environ. Pollut. 254, 113036.
Guerreiro, C.d.L., Viana, Frank, Colette, Mar, Augustin, 2018. Air Quality in Europe: 2018 Report.
Hou, J., Liu, X., Tu, R., Dong, X., Zhai, Z., Mao, Z., Huo, W., Chen, G., Xiang, H., Guo, Y., Li, S., Wang, C., 2020. Long-term exposure to ambient air pollution attenuated the association of physical activity with metabolic syndrome in rural Chinese adults: a cross-sectional study. Environ. Int. 136, 105459.
Houstis, N., Rosen, E.D., Lander, E.S., 2006. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 440, 944–948.
Kim, J.B., Prunicki, M., Haddad, F., Dant, C., Sampath, V., Patel, R., Smith, E., Akdis, C., Balmes, J., Snyder, M.P., Wu, J.C., Nadeau, K.C., 2020. Cumulative lifetime burden of cardiovascular disease from early exposure to air pollution. J. Am. Heart Assoc. 9, e014944.
Langeheine, M., Pohlabeln, H., Lauria, F., Veidebaum, T., Tornaritis, M., Molnar, D., Eiben, G., de Henauw, S., Moreno, L.A., Williams, G., Ahrens, W., Rach, S., 2018. Attrition in the European Child Cohort IDEFICS/I.Family: Exploring Associations Between Attrition and Body Mass Index. Frontiers in Pediatrics 6.
Lee, S., Park, H., Kim, S., Lee, E.-K., Lee, J., Hong, Y.S., Ha, E., 2019. Fine particulate matter and incidence of metabolic syndrome in non-CVD patients: A nationwide population-based cohort study. Int. J. Hyg Environ. Health 222, 533–540.
Lettieri Barbato, D., Tomei, G., Tomei, F., Sancini, A., 2010. Traffic air pollution and oxidatively generated DNA damage: can urinary 8-oxo-7,8-dihydro-2-deoxiguanosine be considered a good biomarker? A meta-analysis. Biomarkers 15, 538–545.
Li, W., Dorans, K.S., Wilker, E.H., Rice, M.B., Kloog, I., Schwartz, J.D., Koutrakis, P., Coull, B.A., Gold, D.R., Meigs, J.B., Fox, C.S., Mittleman, M.A., 2018. Ambient air pollution, adipokines, and glucose homeostasis: the Framingham Heart Study. Environ. Int. 111, 14–22.
Li, W., Wilker, E.H., Dorans, K.S., Rice, M.B., Schwartz, J., Coull, B.A., Koutrakis, P., Gold, D.R., Keaney Jr., J.F., Lin, H., Vasan, R.S., Benjamin, E.J., Mittleman, M.A., 2016. Short-Term Exposure to Air Pollution and Biomarkers of Oxidative Stress: the Framingham Heart Study. J Am Heart Assoc 5.
Liu, C., Yang, C., Zhao, Y., Ma, Z., Bi, J., Liu, Y., Meng, X., Wang, Y., Cai, J., Chen, R., Kan, H., 2016. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. Environ. Int. 92–93, 416–421.
Ma, R., Zhang, Y., Sun, Z., Xu, D., Li, T., 2020. Effects of ambient particulate matter on fasting blood glucose: a systematic review and meta-analysis. Environ. Pollut. 258, 113589.
Mann, J.K., Lutzker, L., Holm, S.M., Margolis, H.G., Neophytou, A.M., Eisen, E.A., Costello, S., Tyner, T., Holland, N., Tindula, G., Prunicki, M., Nadeau, K., Noth, E.M., Lurmann, F., Hammond, S.K., Balmes, J.R., 2021. Traffic-related air pollution is associated with glucose dysregulation, blood pressure, and oxidative stress in children. Environ. Res. 195, 110870.
Matthiessen, C., Lucht, S., Hennig, F., Ohlwein, S., Jakobs, H., Jöckel, K.-H., Moebus, S., Hoffmann, B., 2018. Long-term exposure to airborne particulate matter and NO2 and prevalent and incident metabolic syndrome – results from the Heinz Nixdorf Recall Study. Environ. Int. 116, 74–82.
Miller, M.R., 2014. The Role of Oxidative Stress in the Cardiovascular Actions of Particulate Air Pollution.
Morris, D.H., Khunti, K., Achana, F., Srinivasan, B., Gray, L.J., Davies, M.J., Webb, D., 2013. Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia 56, 1489–1493.
Mostofsky, E., Schwartz, J., Coull, B.A., Koutrakis, P., Wellenius, G.A., Suh, H.H., Gold, D.R., Mittleman, M.A., 2012. Modeling the association between particle constituents of air pollution and health outcomes. Am. J. Epidemiol. 176, 317–326.
Nagy, P., Kovacs, E., Moreno, L.A., Veidebaum, T., Tornaritis, M., Kourides, Y., Siani, A., Lauria, F., Sioen, I., Claessens, M., Marild, S., Lissner, L., Bammann, K., Intemann, T., Buck, C., Pigeot, I., Ahrens, W., Molnar, D., 2014. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. Int. J. Obes. 38, S15–S25.
Peng, C., Bind, M.-A.C., Colicino, E., Kloog, I., Byun, H.-M., Cantone, L., Trevisi, L., Zhong, J., Brennan, K., Dereix, A.E., Vokonas, P.S., Coull, B.A., Schwartz, J.D., Baccarelli, A.A., 2016. Particulate air pollution and fasting blood glucose in nondiabetic individuals: associations and epigenetic mediation in the normative aging study, 2000–2011. Environ. Health Perspect. 124, 1715–1721.
on behalf of the, I.c Peplies, J., Jiménez-Pavón, D., Savva, S.C., Buck, C., Günther, K., Fraterman, A., Russo, P., Iacoviello, L., Veidebaum, T., Tornaritis, M., De Henauw, S., Mårild, S., Molnár, D., Moreno, L.A., Ahrens, W., 2014. Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in pre-pubertal normal weight European children from the IDEFICS cohort. Int. J. Obes. 38, S39–S47.
Pindus, M., Orru, H., Modig, L., 2015. Close proximity to busy roads increases the prevalence and onset of cardiac disease – results from RHINE Tartu. Publ. Health 129, 1398–1405.
Prunicki, M., Cauwenberghs, N., Ataam, J.A., Movassagh, H., Kim, J.B., Kuznetsova, T., Wu, J.C., Maecker, H., Haddad, F., Nadeau, K., 2020. Immune biomarkers link air pollution exposure to blood pressure in adolescents. EH (Environ. Health) (Lond.) 19, 108.
Rajagopalan, S., Brook, R.D., 2012. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 61, 3037–3045.
Rajkumar, S., Young, B.N., Clark, M.L., Benka-Coker, M.L., Bachand, A.M., Brook, R.D., Nelson, T.L., Volckens, J., Reynolds, S.J., L'Orange, C., Good, N., Koehler, K., Africano, S., Osorto Pinel, A.B., Peel, J.L., 2019. Household air pollution from biomass-burning cookstoves and metabolic syndrome, blood lipid concentrations, and waist circumference in Honduran women: a cross-sectional study. Environ. Res. 170, 46–55.
Renzi, M., Cerza, F., Gariazzo, C., Agabiti, N., Cascini, S., Di Domenicantonio, R., Davoli, M., Forastiere, F., Cesaroni, G., 2018. Air pollution and occurrence of type 2 diabetes in a large cohort study. Environ. Int. 112, 68–76.
Saenen, N.D., Bové, H., Steuwe, C., Roeffaers, M.B.J., Provost, E.B., Lefebvre, W., Vanpoucke, C., Ameloot, M., Nawrot, T.S., 2017. Children's urinary environmental carbon load. A novel marker reflecting residential ambient air pollution exposure? Am. J. Respir. Crit. Care Med. 196, 873–881.
Sanders, A.P., Saland, J.M., Wright, R.O., Satlin, L., 2018. Perinatal and childhood exposure to environmental chemicals and blood pressure in children: a review of literature 2007–2017. Pediatr. Res. 84, 165–180.
Schwartz, J., Alexeeff, S.E., Mordukhovich, I., Gryparis, A., Vokonas, P., Suh, H., Coull, B.A., 2012. Association between long-term exposure to traffic particles and blood pressure in the Veterans Administration Normative Aging Study. Occup. Environ. Med. 69, 422–427.
Shamy, M., Alghamdi, M., Khoder, M.I., Mohorjy, A.M., Alkhatim, A.A., Alkhalaf, A.K., Brocato, J., Chen, L.C., Thurston, G.D., Lim, C.C., Costa, M., 2017. Association between exposure to ambient air particulates and metabolic syndrome components in a Saudi arabian population. Int. J. Environ. Res. Publ. Health 15.
Sly, P.D., Flack, F., 2008. Susceptibility of children to environmental pollutants. Ann. N. Y. Acad. Sci. 1140, 163–183.
Stanaway, J.D., Afshin, A., Gakidou, E., Lim, S.S., Abate, D., Abate, K.H., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R.S., Abebe, M., Abebe, Z., Abera, S.F., Abil, O.Z., Abraha, H.N., Abrham, A.R., Abu-Raddad, L.J., Abu-Rmeileh, N.M.E., Accrombessi, M.M.K., Acharya, D., Acharya, P., Adamu, A.A., Adane, A.A., Adebayo, O.M., Adedoyin, R.A., Adekanmbi, V., Ademi, Z., Adetokunboh, O.O., Adib, M.G., Admasie, A., Adsuar, J.C., Afanvi, K.A., Afarideh, M., Agarwal, G., Aggarwal, A., Aghayan, S.A., Agrawal, A., Agrawal, S., Ahmadi, A., Ahmadi, M., Ahmadieh, H., Ahmed, M.B., Aichour, A.N., Aichour, I., Aichour, M.T.E., Akbari, M. E., Akinyemiju, T., Akseer, N., Al-Aly, Z., Al-Eyadhy, A., Al-Mekhlafi, H.M., Alahdab, F., Alam, K., Alam, S., Alam, T., Alashi, A., Alavian, S.M., Alene, K.A., Ali, K., Ali, S.M., Alijanzadeh, M., Alizadeh-Navaei, R., Aljunid, S.M., Alkerwi, A.a., Alla, F., Alsharif, U., Altirkawi, K., Alvis-Guzman, N., Amare, A.T., Ammar, W., Anber, N.H., Anderson, J.A., Andrei, C.L., Androudi, S., Animut, M.D., Anjomshoa, M., Ansha, M.G., Antó, J.M., Antonio, C.A.T., Anwari, P., Appiah, L.T., Appiah, S.C.Y., Arabloo, J., Aremu, O., Ärnlöv, J., Artaman, A., Aryal, K.K., Asayesh, H., Ataro, Z., Ausloos, M., Avokpaho, E.F.G.A., Awasthi, A., Ayala Quintanilla, B.P., Ayer, R., Ayuk, T.B., Azzopardi, P.S., Babazadeh, A., Badali, H., Badawi, A., Balakrishnan, K., Bali, A.G., Ball, K., Ballew, S.H., Banach, M., Banoub, J. A.M., Barac, A., Barker-Collo, S.L., Bärnighausen, T.W., Barrero, L.H., Basu, S., Baune, B.T., Bazargan-Hejazi, S., Bedi, N., Beghi, E., Behzadifar, M., Behzadifar, M., Béjot, Y., Bekele, B.B., Bekru, E.T., Belay, E., Belay, Y.A., Bell, M.L., Bello, A.K., Bennett, D.A., Bensenor, I.M., Bergeron, G., Berhane, A., Bernabe, E., Bernstein, R.S., Beuran, M., Beyranvand, T., Bhala, N., Bhalla, A., Bhattarai, S., Bhutta, Z.A., Biadgo, B., Bijani, A., Bikbov, B., Bilano, V., Bililign, N., Bin Sayeed, M.S., Bisanzio, D., Biswas, T., Bjørge, T., Blacker, B.F., Bleyer, A., Borschmann, R., Bou-Orm, I.R., Boufous, S., Bourne, R., Brady, O.J., Brauer, M., Brazinova, A., Breitborde, N.J.K., Brenner, H., Briko, A.N., Britton, G., Brugha, T., Buchbinder, R., Burnett, R.T., Busse, R., Butt, Z.A., Cahill, L.E., Cahuana-Hurtado, L., Campos-Nonato, I.R., Cárdenas, R., Carreras, G., Carrero, J.J., Carvalho, F., Castañeda-Orjuela, C.A., Castillo Rivas, J., Castro, F., Catalá-López, F., Causey, K., Cercy, K.M., Cerin, E., Chaiah, Y., Chang, H.-Y., Chang, J.-C., Chang, K.-L., Charlson, F.J., Chattopadhyay, A., Chattu, V.K., Chee, M.L., Cheng, C.-Y., Chew, A., Chiang, P.P.-C., Chimed-Ochir, O., Chin, K.L., Chitheer, A., Choi, J.-Y.J., Chowdhury, R., Christensen, H., Christopher, D.J., Chung, S.-C., Cicuttini, F.M., Cirillo, M., Cohen, A. J., Collado-Mateo, D., Cooper, C., Cooper, O.R., Coresh, J., Cornaby, L., Cortesi, P.A., Cortinovis, M., Costa, M., Cousin, E., Criqui, M.H., Cromwell, E.A., Cundiff, D.K., Daba, A.K., Dachew, B.A., Dadi, A.F., Damasceno, A.A.M., Dandona, L., Dandona, R., Darby, S.C., Dargan, P.I., Daryani, A., Das Gupta, R., Das Neves, J., Dasa, T.T., Dash, A.P., Davitoiu, D.V., Davletov, K., De la Cruz-Góngora, V., De La Hoz, F.P., De Leo, D., De Neve, J.-W., Degenhardt, L., Deiparine, S., Dellavalle, R.P., Demoz, G.T., Denova-Gutiérrez, E., Deribe, K., Dervenis, N., Deshpande, A., Des Jarlais, D.C., Dessie, G.A., Deveber, G.A., Dey, S., Dharmaratne, S.D., Dhimal, M., Dinberu, M.T., Ding, E.L., Diro, H.D., Djalalinia, S., Do, H.P., Dokova, K., Doku, D.T., Doyle, K.E., Driscoll, T.R., Dubey, M., Dubljanin, E., Duken, E.E., Duncan, B.B., Duraes, A.R., Ebert, N., Ebrahimi, H., Ebrahimpour, S., Edvardsson, D., Effiong, A., Eggen, A.E., El Bcheraoui, C., El-Khatib, Z., Elyazar, I.R., Enayati, A., Endries, A.Y., Er, B., Erskine, H.E., Eskandarieh, S., Esteghamati, A., Estep, K., Fakhim, H., Faramarzi, M., Fareed, M., Farid, T.A., Farinha, C.S.E.s., Farioli, A., Faro, A., Farvid, M.S., Farzaei, M.H., Fatima, B., Fay, K.A., Fazaeli, A.A., Feigin, V.L., Feigl, A.B., Fereshtehnejad, S.-M., Fernandes, E., Fernandes, J.C., Ferrara, G., Ferrari, A.J., Ferreira, M.L., Filip, I., Finger, J.D., Fischer, F., Foigt, N.A., Foreman, K.J., Fukumoto, T., Fullman, N., Fürst, T., Furtado, J.M., Futran, N.D., Gall, S., Gallus, S., Gamkrelidze, A., Ganji, M., Garcia-Basteiro, A.L., Gardner, W.M., Gebre, A.K., Gebremedhin, A.T., Gebremichael, T.G., Gelano, T.F., Geleijnse, J.M., Geramo, Y.C. D., Gething, P.W., Gezae, K.E., Ghadimi, R., Ghadiri, K., Ghasemi Falavarjani, K., Ghasemi-Kasman, M., Ghimire, M., Ghosh, R., Ghoshal, A.G., Giampaoli, S., Gill, P. S., Gill, T.K., Gillum, R.F., Ginawi, I.A., Giussani, G., Gnedovskaya, E.V., Godwin, W. W., Goli, S., Gómez-Dantés, H., Gona, P.N., Gopalani, S.V., Goulart, A.C., Grada, A., Grams, M.E., Grosso, G., Gugnani, H.C., Guo, Y., Gupta, R., Gupta, R., Gupta, T., Gutiérrez, R.A., Gutiérrez-Torres, D.S., Haagsma, J.A., Habtewold, T.D., Hachinski, V., Hafezi-Nejad, N., Hagos, T.B., Hailegiyorgis, T.T., Hailu, G.B., Haj-Mirzaian, A., Haj-Mirzaian, A., Hamadeh, R.R., Hamidi, S., Handal, A.J., Hankey, G. J., Hao, Y., Harb, H.L., Harikrishnan, S., Haro, J.M., Hassankhani, H., Hassen, H.Y.,

Havmoeller, R., Hawley, C.N., Hay, S.I., Hedayatizadeh-Omran, A., Heibati, B., Heidari, B., Heidari, M., Hendrie, D., Henok, A., Heredia-Pi, I., Herteliu, C., Heydarpour, F., Heydarpour, S., Hibstu, D.T., Higazi, T.B., Hilawe, E.H., Hoek, H.W., Hoffman, H.J., Hole, M.K., Homaie Rad, E., Hoogar, P., Hosgood, H.D., Hosseini, S. M., Hosseinzadeh, M., Hostiuc, M., Hostiuc, S., Hoy, D.G., Hsairi, M., Hsiao, T., Hu, G., Hu, H., Huang, J.J., Hussen, M.A., Huynh, C.K., Iburg, K.M., Ikeda, N., Ilesanmi, O.S., Iqbal, U., Irvani, S.S.N., Irvine, C.M.S., Islam, S.M.S., Islami, F., Jackson, M.D., Jacobsen, K.H., Jahangiry, L., Jahanmehr, N., Jain, S.K., Jakovljevic, M., James, S.L., Jassal, S.K., Jayatilleke, A.U., Jeemon, P., Jha, R.P., Jha, V., Ji, J.S., Jonas, J.B., Jonnagaddala, J., Jorjoran Shushtari, Z., Joshi, A., Jozwiak, J.J., Jürisson, M., Kabir, Z., Kahsay, A., Kalani, R., Kanchan, T., Kant, S., Kar, C., Karami, M., Karami Matin, B., Karch, A., Karema, C., Karimi, N., Karimi, S. M., Kasaeian, A., Kassa, D.H., Kassa, G.M., Kassa, T.D., Kassebaum, N.J., Katikireddi, S.V., Kaul, A., Kawakami, N., Kazemi, Z., Karyani, A.K., Kefale, A.T., Keiyoro, P.N., Kemp, G.R., Kengne, A.P., Keren, A., Kesavachandran, C.N., Khader, Y.S., Khafaei, B., Khafaie, M.A., Khajavi, A., Khalid, N., Khalil, I.A., Khan, G., Khan, M.S., Khan, M.A., Khang, Y.-H., Khater, M.M., Khazaei, M., Khazaie, H., Khoja, A.T., Khosravi, A., Khosravi, M.H., Kiadaliri, A.A., Kiirithio, D.N., Kim, C.-I., Kim, D., Kim, Y.-E., Kim, Y.J., Kimokoti, R.W., Kinfu, Y., Kisa, A., Kissimova-Skarbek, K., Kivimäki, M., Knibbs, L.D., Knudsen, A.K.S., Kochhar, S., Kokubo, Y., Kolola, T., Kopec, J.A., Kosen, S., Koul, P.A., Koyanagi, A., Kravchenko, M.A., Krishan, K., Krohn, K.J., Kromhout, H., Kuate Defo, B., Kucuk Bicer, B., Kumar, G.A., Kumar, M., Kuzin, I., Kyu, H.H., Lachat, C., Lad, D.P., Lad, S.D., Lafranconi, A., Lalloo, R., Lallukka, T., Lami, F.H., Lang, J.J., Lansingh, V.C., Larson, S.L., Latifi, A., Lazarus, J.V., Lee, P.H., Leigh, J., Leili, M., Leshargie, C.T., Leung, J., Levi, M., Lewycka, S., Li, S., Li, Y., Liang, J., Liang, X., Liao, Y., Liben, M.L., Lim, L.-L., Linn, S., Liu, S., Lodha, R., Logroscino, G., Lopez, A.D., Lorkowski, S., Lotufo, P.A., Lozano, R., Lucas, T.C.D., Lunevicius, R., Ma, S., Macarayan, E.R.K., Machado, Í.E., Madotto, F., Mai, H.T., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mamun, A.A., Manda, A.-L., Manguerra, H., Mansournia, M.A., Mantovani, L.G., Maravilla, J.C., Marcenes, W., Marks, A., Martin, R.V., Martins, S.C. O., Martins-Melo, F.R., März, W., Marzan, M.B., Massenburg, B.B., Mathur, M.R., Mathur, P., Matsushita, K., Maulik, P.K., Mazidi, M., McAlinden, C., McGrath, J.J., McKee, M., Mehrotra, R., Mehta, K.M., Mehta, V., Meier, T., Mekonnen, F.A., Melaku, Y.A., Melese, A., Melku, M., Memiah, P.T.N., Memish, Z.A., Mendoza, W., Mengistu, D.T., Mensah, G.A., Mensink, G.B.M., Mereta, S.T., Meretoja, A., Meretoja, T.J., Mestrovic, T., Mezgebe, H.B., Miazgowski, B., Miazgowski, T., Millear, A.I., Miller, T.R., Miller-Petrie, M.K., Mini, G.K., Mirarefin, M., Mirica, A., Mirrakhimov, E.M., Misganaw, A.T., Mitiku, H., Moazen, B., Mohajer, B., Mohammad, K.A., Mohammadi, M., Mohammadifard, N., Mohammadnia-Afrouzi, M., Mohammed, S., Mohebi, F., Mokdad, A.H., Molokhia, M., Momeniha, F., Monasta, L., Moodley, Y., Moradi, G., Moradi-Lakeh, M., Moradinazar, M., Moraga, P., Morawska, L., Morgado-Da-Costa, J., Morrison, S.D., Moschos, M.M., Mouodi, S., Mousavi, S.M., Mozaffarian, D., Mruts, K.B., Muche, A.A., Muchie, K.F., Mueller, U.O., Muhammed, O.S., Mukhopadhyay, S., Muller, K., Musa, K.I., Mustafa, G., Nabhan, A.F., Naghavi, M., Naheed, A., Nahvijou, A., Naik, G., Naik, N., Najafi, F., Nangia, V., Nansseu, J.R., Nascimento, B.R., Neal, B., Neamati, N., Negoi, I., Negoi, R.I., Neupane, S., Newton, C.R.J., Ngunjiri, J.W., Nguyen, A.Q., Nguyen, G., Nguyen, H.T., Nguyen, H.L.T., Nguyen, H.T., Nguyen, M., Nguyen, N.B., Nichols, E., Nie, J., Ningrum, D.N.A., Nirayo, Y.L., Nishi, N., Nixon, M.R., Nojomi, M., Nomura, S., Norheim, O.F., Noroozi, M., Norrving, B., Noubiap, J.J., Nouri, H.R., Nourollahpour Shiadeh, M., Nowroozi, M.R., Nsoesie, E.O., Nyasulu, P. S., Obermeyer, C.M., Odell, C.M., Ofori-Asenso, R., Ogbo, F.A., Oh, I.-H., Oladimeji, O., Olagunju, A.T., Olagunju, T.O., Olivares, P.R., Olsen, H.E., Olusanya, B.O., Olusanya, J.O., Ong, K.L., Ong, S.K., Oren, E., Orpana, H.M., Ortiz, A., Ota, E., Otstavnov, S.S., Øverland, S., Owolabi, M.O., P A, M., Pacella, R., Pakhare, A.P., Pakpour, A.H., Pana, A., Panda-Jonas, S., Park, E.-K., Parry, C.D.H., Parsian, H., Patel, S., Pati, S., Patil, S.T., Patle, A., Patton, G.C., Paudel, D., Paulson, K.R., Paz Ballesteros, W.C., Pearce, N., Pereira, A., Pereira, D.M., Perico, N., Pesudovs, K., Petzold, M., Pham, H.Q., Phillips, M.R., Pillay, J.D., Piradov, M.A., Pirsaheb, M., Pischon, T., Pishgar, F., Plana-Ripoll, O., Plass, D., Polinder, S., Polkinghorne, K.R., Postma, M.J., Poulton, R., Pourshams, A., Poustchi, H., Prabhakaran, D., Prakash, S., Prasad, N., Purcell, C.A., Purwar, M.B., Qorbani, M., Radfar, A., Rafay, A., Rafiei, A., Rahim, F., Rahimi, Z., Rahimi-Movaghar, A., Rahimi-Movaghar, V., Rahman, M., Rahman, M.H.u., Rahman, M.A., Rai, R.K., Rajati, F., Rajsic, S., Raju, S.B., Ram, U., Ranabhat, C.L., Ranjan, P., Rath, G.K., Rawaf, D.L., Rawaf, S., Reddy, K.S., Rehm, C.D., Rehm, J., Reiner, R.C., Reitsma, M. B., Remuzzi, G., Renzaho, A.M.N., Resnikoff, S., Reynales-Shigematsu, L.M., Rezaei, S., Ribeiro, A.L.P., Rivera, J.A., Roba, K.T., Rodríguez-Ramírez, S., Roever, L., Román, Y., Ronfani, L., Roshandel, G., Rostami, A., Roth, G.A., Rothenbacher, D., Roy, A., Rubagotti, E., Rushton, L., Sabanayagam, C., Sachdev, P. S., Saddik, B., Sadeghi, E., Saeedi Moghaddam, S., Safari, H., Safari, Y., Safari-Faramani, R., Safdarian, M., Safi, S., Safiri, S., Sagar, R., Sahebkar, A., Sahraian, M. A., Sajadi, H.S., Salam, N., Salamati, P., Saleem, Z., Salimi, Y., Salimzadeh, H., Salomon, J.A., Salvi, D.D., Salz, I., Samy, A.M., Sanabria, J., Sanchez-Niño, M.D., Sánchez-Pimienta, T.G., Sanders, T., Sang, Y., Santomauro, D.F., Santos, I.S., Santos, J.V., Santric Milicevic, M.M., Sao Jose, B.P., Sardana, M., Sarker, A.R., Sarmiento-Suárez, R., Sarrafzadegan, N., Sartorius, B., Sarvi, S., Sathian, B., Satpathy, M., Sawant, A.R., Sawhney, M., Saylan, M., Sayyah, M., Schaeffner, E., Schmidt, M.I., Schneider, I.J.C., Schöttker, B., Schutte, A.E., Schwebel, D.C., Schwendicke, F., Scott, J.G., Seedat, S., Sekerija, M., Sepanlou, S.G., Serre, M.L., Serván-Mori, E., Seyedmousavi, S., Shabaninejad, H., Shaddick, G., Shafieesabet, A., Shahbazi, M., Shaheen, A.A., Shaikh, M.A., Shamah Levy, T., Shams-Beyranvand, M., Shamsi, M., Sharafi, H., Sharafi, K., Sharif, M., Sharif-Alhoseini, M., Sharifi, H., Sharma, J., Sharma, M., Sharma, R., She, J., Sheikh, A., Shi, P., Shibuya, K., Shiferaw, M.S., Shigematsu, M., Shin, M.-J., Shiri, R., Shirkoohi, R., Shiue, I., Shokraneh, F., Shoman, H., Shrime, M.G., Shupler, M.S., Si, S., Siabani, S., Sibai, A. M., Siddiqi, T.J., Sigfusdottir, I.D., Sigurvinsdottir, R., Silva, D.A.S., Silva, J.P., Silveira, D.G.A., Singh, J.A., Singh, N.P., Singh, V., Sinha, D.N., Skiadaresi, E., Skirbekk, V., Smith, D.L., Smith, M., Sobaih, B.H., Sobhani, S., Somayaji, R., Soofi, M., Sorensen, R.J.D., Soriano, J.B., Soyiri, I.N., Spinelli, A., Sposato, L.A., Sreeramareddy, C.T., Srinivasan, V., Starodubov, V.I., Steckling, N., Stein, D.J., Stein, M.B., Stevanovic, G., Stockfelt, L., Stokes, M.A., Sturua, L., Subart, M.L., Sudaryanto, A., Sufiyan, M.a.B., Sulo, G., Sunguya, B.F., Sur, P.J., Sykes, B.L., Szoeke, C.E.I., Tabarés-Seisdedos, R., Tabuchi, T., Tadakamadla, S.K., Takahashi, K., Tandon, N., Tassew, S.G., Tavakkoli, M., Taveira, N., Tehrani-Banihashemi, A., Tekalign, T.G., Tekelemedhin, S.W., Tekle, M.G., Temesgen, H., Temsah, M.-H., Temsah, O., Terkawi, A.S., Tessema, B., Teweldemedhin, M., Thankappan, K.R., Theis, A., Thirunavukkarasu, S., Thomas, H.J., Thomas, M.L., Thomas, N., Thurston, G.D., Tilahun, B., Tillmann, T., To, Q.G., Tobollik, M., Tonelli, M., Topor-Madry, R., Torre, A.E., Tortajada-Girbés, M., Touvier, M., Tovani-Palone, M.R., Towbin, J.A., Tran, B.X., Tran, K.B., Truelsen, T.C., Truong, N.T., Tsadik, A.G., Tudor Car, L., Tuzcu, E.M., Tymeson, H.D., Tyrovolas, S., Ukwaja, K.N., Ullah, I., Updike, R. L., Usman, M.S., Uthman, O.A., Vaduganathan, M., Vaezi, A., Valdez, P.R., Van Donkelaar, A., Varavikova, E., Varughese, S., Vasankari, T.J., Venkateswaran, V., Venketasubramanian, N., Villafaina, S., Violante, F.S., Vladimirov, S.K., Vlassov, V., Vollset, S.E., Vos, T., Vosoughi, K., Vu, G.T., Vujcic, I.S., Wagnew, F.S., Waheed, Y., Waller, S.G., Walson, J.L., Wang, Y., Wang, Y., Wang, Y.-P., Weiderpass, E., Weintraub, R.G., Weldegebreal, F., Werdecker, A., Werkneh, A.A., West, J.J., Westerman, R., Whiteford, H.A., Widecka, J., Wijeratne, T., Winkler, A.S., Wiyeh, A. B., Wiysonge, C.S., Wolfe, C.D.A., Wong, T.Y., Wu, S., Xavier, D., Xu, G., Yadgir, S., Yadollahpour, A., Yahyazadeh Jabbari, S.H., Yamada, T., Yan, L.L., Yano, Y., Yaseri, M., Yasin, Y.J., Yeshaneh, A., Yimer, E.M., Yip, P., Yisma, E., Yonemoto, N., Yoon, S.-J., Yotebieng, M., Younis, M.Z., Yousefifard, M., Yu, C., Zaidi, Z., Zaman, S. B., Zamani, M., Zavala-Arciniega, L., Zhang, A.L., Zhang, H., Zhang, K., Zhou, M., Zimsen, S.R.M., Zodpey, S., Murray, C.J.L., 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1923–1994.

Strak, M., Janssen, N., Beelen, R., Schmitz, O., Vaartjes, I., Karssenberg, D., van den Brink, C., Bots, M.L., Dijst, M., Brunekreef, B., Hoek, G., 2017. Long-term exposure to particulate matter, NO(2) and the oxidative potential of particulates and diabetes prevalence in a large national health survey. Environ. Int. 108, 228–236.

Sun, Q., Yue, P., Deiuliis, J.A., Lumeng, C.N., Kampfrath, T., Mikolaj, M.B., Cai, Y., Ostrowski, M.C., Lu, B., Parthasarathy, S., Brook, R.D., Moffatt-Bruce, S.D., Chen, L. C., Rajagopalan, S., 2009. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 119, 538–546.

Sun, Y., Song, X., Han, Y., Ji, Y., Gao, S., Shang, Y., Lu, S.E., Zhu, T., Huang, W., 2015. Size-fractioned ultrafine particles and black carbon associated with autonomic dysfunction in subjects with diabetes or impaired glucose tolerance in Shanghai, China. Part. Fibre Toxicol. 12, 8.

Thiering, E., Cyrys, J., Kratzsch, J., Meisinger, C., Hoffmann, B., Berdel, D., von Berg, A., Koletzko, S., Bauer, C.-P., Heinrich, J., 2013. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts. Diabetologia 56, 1696–1704.

Thiering, E., Heinrich, J., 2015. Epidemiology of air pollution and diabetes. Trends Endocrinol. Metabol. 26, 384–394.

Thiering, E., Markevych, I., Bruske, I., Fuertes, E., Kratzsch, J., Sugiri, D., Hoffmann, B., von Berg, A., Bauer, C.P., Koletzko, S., Berdel, D., Heinrich, J., 2016. Associations of residential long-term air pollution exposures and satellite-derived greenness with insulin resistance in German adolescents. Environ. Health Perspect. 124, 1291–1298.

UNESCO Institute for Statistics, 2012. International Standard Classification of Education: ISCED 2011. UNESCO Institute for Statistics, Montreal.

von Schneidemesser, E., Mar, K.A., Saar, D., 2017. Black Carbon in Europe – Targeting an Air Pollutant and Climate Forcer. Institute for Advanced Sustainability Studies (IASS) Potsdam, Germany.

Wang, Z., Zhao, L., Huang, Q., Hong, A., Yu, C., Xiao, Q., Zou, B., Ji, S., Zhang, L., Zou, K., Ning, Y., Zhang, J., Jia, P., 2021. Traffic-related environmental factors and childhood obesity: a systematic review and meta-analysis. Obes. Rev. 22, e12995.

Wolf, K., Popp, A., Schneider, A., Breitner, S., Hampel, R., Rathmann, W., Herder, C., Roden, M., Koenig, W., Meisinger, C., Peters, A., 2016. Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation, and adipokines. Diabetes 65, 3314–3326.

World Health Organization, 2018. Air Pollution and Child Health: Prescribing Clean Air: Summary. World Health Organization.,.

Xu, X., Yavar, Z., Verdin, M., Ying, Z., Mihai, G., Kampfrath, T., Wang, A., Zhong, M., Lippmann, M., Chen, L.C., Rajagopalan, S., Sun, Q., 2010. Effect of early particulate air pollution exposure on obesity in mice: role of p47phox. Arterioscler. Thromb. Vasc. Biol. 30, 2518–2527.

Yang, B.-Y., Qian, Z., Howard, S.W., Vaughn, M.G., Fan, S.-J., Liu, K.-K., Dong, G.-H., 2018a. Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. Environ. Pollut. 235, 576–588.

Yang, B.-Y., Qian, Z., Li, S., Fan, S., Chen, G., Syberg, K.M., Xian, H., Wang, S.-Q., Ma, H., Chen, D.-H., Yang, M., Liu, K.-K., Zeng, X.-W., Hu, L.-W., Guo, Y., Dong, G.-H., 2018b. Long-term exposure to ambient air pollution (including PM1) and metabolic syndrome: the 33 Communities Chinese Health Study (33CCHS). Environ. Res. 164, 204–211.

Yu, G., Ao, J., Cai, J., Luo, Z., Martin, R., Donkelaar, A.V., Kan, H., Zhang, J., 2020. Fine particular matter and its constituents in air pollution and gestational diabetes mellitus. Environ. Int. 142, 105880.

Zhang, J.-S., Gui, Z.-H., Zou, Z.-Y., Yang, B.-Y., Ma, J., Jing, J., Wang, H.-J., Luo, J.-Y., Zhang, X., Luo, C.-Y., Wang, H., Zhao, H.-P., Pan, D.-H., Bao, W.-W., Guo, Y.-M., Ma, Y.-H., Dong, G.-H., Chen, Y.-J., 2021a. Long-term exposure to ambient air pollution and metabolic syndrome in children and adolescents: a national cross-sectional study in China. Environ. Int. 148, 106383.

Zhang, S., Mwiberi, S., Pickford, R., Breitner, S., Huth, C., Koenig, W., Rathmann, W., Herder, C., Roden, M., Cyrys, J., Peters, A., Wolf, K., Schneider, A., 2021b. Longitudinal associations between ambient air pollution and insulin sensitivity: results from the KORA cohort study. Lancet Planet. Health 5, e39–e49.