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# Longitudinal associations of air pollution and green space with cardiometabolic risk factor clustering among children in the Netherlands

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ABSTRACT

*Background:* This study examines longitudinal associations of air pollution and green space with cardiometabolic risk among children in the Netherlands.
*Methods:* Three Dutch prospective cohorts with a total of 13,822 participants aged 5 to 17 years were included: (1) the Amsterdam Born Children and their Development (ABCD) study from Amsterdam (n = 2,547), (2) the Generation R study from Rotterdam (n = 5,431), and (3) the Lifelines study from northern Netherlands (n = 5,844). Air pollution ($PM_{2.5}$, $PM_{10}$, $NO_2$, and elemental carbon (EC)) and green space exposures (density in multiple Euclidean buffer sizes) from 2006 to 2017 at home address level were used. Cardiometabolic risk factor clustering was assessed by a MetScore, which was derived from a confirmatory factor analysis of six cardiometabolic risk factors to assess the overall risk. Linear regression models with change in Metscore as the dependent variable, adjusted for multiple confounders, were conducted for each cohort separately. Meta-analyses were used to pool cohort-specific estimates.
*Results:* Exposure to higher levels of $NO_2$ and EC was significantly associated with increases in MetScore in Lifelines (per SD higher exposure: $\beta_{NO2} = 0.006$, 95 % CI = 0.001 to 0.010; $\beta_{EC} = 0.008$, 95 % CI = 0.002 to 0.014). In the other two cohort studies, these associations were in the same direction but these were not significant. Higher green space density in 500-meter buffer zones around participants' residential addresses was not significantly associated with decreases of MetScore in all three cohorts. Higher green space density in 2000-meter buffer zones was significantly associated with decreases of MetScore in ABCD and Lifelines (per SD higher green space density: $\beta_{ABCD} = -0.008$, 95 % CI = -0.013 to −0.003; $\beta_{Lifelines} = -0.002$, 95 % CI = -0.003 to −0.00003). The pooled estimates were $\beta_{NO2} = 0.003$ (95 % CI = -0.001 to 0.006) for $NO_2$, $\beta_{EC} = 0.003$ (95 % CI = -0.001, 0.007) for EC, and $\beta_{500m\ buffer} = -0.0014$ (95 % CI = -0.0026 to −0.0001) for green space.
*Conclusions:* More green space exposure at residence was associated with decreased cardiometabolic risk in children. Exposure to more $NO_2$ and EC was also associated with increased cardiometabolic risk.

## 1. Introduction

Cardiometabolic risk factors are the largest contributors to the global disease burden (GBD 2017 Risk Factor Collaborators, 2018). In terms of disability-adjusted life-years, high systolic blood pressure (SBP), high fasting plasma glucose, high Body Mass Index (BMI), and high low-density lipoprotein cholesterol (LDL-C) were among the top 10 risk factors in 2017 (GBD 2017 Risk Factor Collaborators, 2018). Although

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cardiometabolic diseases (CMDs) occur most frequently among middle-aged and older adults, cardiometabolic risk factor clustering has been shown to be stable from childhood into adulthood (Camhi and Katzmarzyk, 2010), which emphasizes that risk factors in early life have later life consequences (Hoffman et al., 2017).

Exposure to environmental characteristics, such as air pollution and green space, may be important factors of cardiometabolic alterations among children (Araujo, 2011; Giorgini et al., 2016; Kuo, 2015; Markevych et al., 2017a). Exposure to higher levels of air pollution may negatively impact cardiometabolic health through autonomic nervous system imbalance, pulmonary and systemic inflammation, and oxidative stress (Araujo, 2011; Giorgini et al., 2016). Children are suggested to be more vulnerable to the harmful effects of air pollutants than adults, because their immune system is still evolving and because they inhale a higher volume of air pollutants per body weight than adults (Salvi, 2007). On the contrary, green space may improve cardiometabolic health by its restoration and building capacities (Kuo, 2015; Markevych et al., 2017a). For restoration, green space relieves psychological stress (Kuo, 2015), which is associated with cardiometabolic diseases (Turner et al., 2020). For building, green space releases certain chemical agents with cardiometabolic health implications (e.g., phytoncides) (Kuo, 2015). It also has an indirect effect on cardiometabolic health. Specifically, green space can reduce harm from exposure to air pollution, heat, and noise, and can encourage healthy lifestyle like outdoor physical activity (Markevych et al., 2017a).

Previous evidence on the associations of air pollution and green space with cardiometabolic risk among children is limited and inconsistent. A nationwide school-based study in Iran investigated the association between air quality and individual cardiometabolic risk factors, and found significant positive associations for SBP, total cholesterol, and triglycerides (TG) (Poursafa et al., 2014). A study in Spain showed that the distance from home to green spaces was not significantly associated with cardiometabolic risk in primary students (Gutiérrez-Zornoza et al., 2015). Another study did not provide evidence for beneficial effects of green space or adverse effects of air pollution on cardiometabolic health in Dutch adolescents (Bloemsma et al., 2019). These three studies are all based on cross-sectional designs, thus a longitudinal study to provide evidence of a temporal relationship is merited.

Previous studies focused on individual cardiometabolic risk factors or sum of standardized scores (z-scores) (Bloemsma et al., 2019; Gutiérrez-Zornoza et al., 2015; Poursafa et al., 2014), which are not ideal indicators of overall cardiometabolic risk (Magge et al., 2017). An alternative indicator is metabolic syndrome (MetS), which is a standard measure in adults referring to the presence of at least three of the following five conditions: abdominal obesity, high blood pressure (BP), high blood glucose, high serum TG, and low serum high-density lipoprotein (HDL-C) (Kaur, 2014). More than 40 unique definitions of MetS have been identified in literature (Ford and Li, 2008). However, to date, there is no consensus on whether MetS should be defined in pediatric populations and, if defined, which definition to use (Magge et al., 2017). Furthermore, studies found that the diagnosis of MetS is highly unstable and fluctuates throughout childhood (Goodman et al., 2007; Stanley et al., 2014). Thus its predictive value of future risk is unclear (Magge et al., 2017).

To address these issues, it has been recommended to focus on cardiometabolic risk clustering, and to use a continuous latent variable of cardiometabolic risk score, such as MetScore (Magge et al., 2017). The MetScore as a continuum has been demonstrated to better predict adult risk from early adolescence as compared to MetS or summed z-scores (Camhi and Katzmarzyk, 2010; Kelly et al., 2011; Magge et al., 2017). To our knowledge, this new approach has not been previously used to analyse the association of air pollution and green space with cardiometabolic risk. The current study aimed to examine the prospective associations of air pollution and green space density with cardiometabolic risk factor clustering among children in the Netherlands. It was hypothesized that higher exposure levels of air pollution and green space are associated with a higher and lower MetScore among children in the Netherlands, respectively.

## 2. Methods

### 2.1. Study populations

Data were derived from three Dutch population-based prospective cohort studies: Amsterdam Born Children and their Development (ABCD) study, Generation R study, and Lifelines. All three cohort studies have been described in detail previously (Kooijman et al., 2016; Scholtens et al., 2015; Van Eijsden et al., 2011). The three cohort studies were approved by the Ethical Review Boards of the respective institutions, and written informed consent from participants were obtained by each cohort study.

The ABCD study is a prospective cohort study with the aim to examine the associations of maternal and early-life conditions with children's health (Van Eijsden et al., 2011). In brief, between January 2003 and March 2004, all pregnant women (n = 12,373) in Amsterdam attending their first prenatal visit were invited to participate in the study. Mothers of singleton infants were contacted for follow-up measurements. The current study included data from two follow-up waves when children from this pregnancy were about five (2009) and eleven (2015–2016) years old, respectively.

The Generation R study is a population-based prospective cohort study from early pregnancy onwards in Rotterdam, aiming to identify early environmental and genetic determinants of growth, development and health from foetal life until young adulthood. (Kooijman et al., 2016). All pregnant women living in the study area with a delivery date between April 2002 and January 2006 were invited to participate, resulting in 9,778 mothers and their children enrolled in the study. The current study included data from two follow-up waves when children were about five (2007–2011) and nine (2011–2015) years old, respectively.

The Lifelines study is a multi-disciplinary prospective cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in three northern provinces of the Netherlands (Groningen, Friesland and Drenthe) (Scholtens et al., 2015). It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The current study included data from baseline (2007–2013) – with children aged 8 to 17 years – and the first follow-up wave (2014–2017).

Combining the three cohorts resulted in a study sample size of 14,097 (ABCD: 2,811; Generation R: 5,431; and Lifelines: 5,855) children aged 5 to 17 years who attended both surveys. Of those participants, 18 (ABCD: 7; and Lifelines: 11) participants were excluded because they had a history of diabetes, hypertension, stroke, heart disease, or disease precocious puberty, and 257 (ABCD: 257) participants were excluded because they used certain medication that may influence the cardiometabolic risk factor levels (medication with ATC codes (ATC Code, 2023): B01, C01, *H*01, H02, J01, D06, H03, and M01). The analytical sample included 13,822 participants (ABCD: 2,547; Generation R: 5,431; and Lifelines: 5,844).

### 2.2. Exposure assessment

Data on air pollution and green space were obtained from the Geoscience and Health Cohort Consortium (GECCO) (Lakerveld et al., 2020; Timmermans et al., 2018). The environmental exposure data at the home address-level were linked to participants.

Data on annual average outdoor concentrations of particulate matter with diameters < 2.5 μm ($PM_{2.5}$) and < 10.0 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), and elemental carbon (EC) were modeled by the Institute for Public Health and the Environment (Velders et al., 2011; Wesseling et al., 2015). These data were based on a combination of dispersion and chemical transport model calculations and measurements from National Air Quality monitoring locations. Data were available on 1 × 1 km resolution from 2006 to 2017 annually, and on 25 × 25 m resolution from 2013 to 2017 annually. The data in 1 × 1 km resolution were used to back-extrapolate data in 25 × 25 m resolution for years before 2013 (Chen et al., 2010). We scaled 25 × 25 m map in 2013 by ratio of the 1 × 1 km map of the years prior to 2013 to the 1 × 1 km map in 2013, and assumed this to be applicable to all 25*25 m grids in a 1*1 km grid.

Residential green space exposure was assessed by green space density. This refers to the percentage of area devoted to green space (i.e., parks, public gardens, forests, graveyards, and agriculture) within a Euclidean buffer (radii of 150, 250, 350, 500, 750, 1000, 1650, and 2000 m) around residential addresses. These data were based on the land area coverage statistics from Statistics Netherlands (Statistics Netherlands, 2024), and were available for 2006, 2008, 2010, 2012, and 2015. Applying situational interpretation on all available sources, a minimum lower limit of 1 ha was used for green space (Statistics Netherlands, 2024). Both air pollution and green space data were used by averaging over the study period corresponding to each cohort.

### 2.3. Assessment of cardiometabolic risk factors

Assessed cardiometabolic risk factors for deriving the MetScore consisted of total cholesterol, HDL-C, TG, BMI, SBP, and diastolic blood pressure (DBP) (Fig. 1). The measurement methods for each cohort are described in **Appendix 1**.

### 2.4. Calculation of MetScore

A consistent confirmatory factor analysis (CFA) was conducted in a pooled dataset to derive the MetScore across all cohorts. CFA allows for the testing of hypotheses or theories about the relationships between observed variables and their underlying latent constructs (Harrington, 2009). In the current study, it was used to validate the MetScore, ensuring that MetScore adequately represents the six component cardiometabolic risk factors (Harrington, 2009). BMI was standardized by age and sex using LMS tables (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation (Cole, 1990)) from a Dutch nationwide growth study (Schönbeck et al., 2011) and a German cohort study (Rönnecke et al., 2019), respectively. The SBP and DBP were standardized by age and sex using LMS tables from a reference for Caucasian children (Wühl et al., 2002). TG was log-transformed because its distribution was skewed. The reciprocal of HDL-C was used when standardizing so that the interpretation of higher factor loading scores is the same with other measures. Subsequently, the z-scores for all CFA components were created.

The goodness of fit indices included the Comparative Fit Index (good fit: CFI, ≥0.90), the Tucker-Lewis Index (good fit: TLI, ≥0.90), the Root Mean Square Error of Approximation (good fit: RMSEA, ≤0.06), and the Standardized Root Mean Square Residual (good fit: SRMR, <0.08) (Hu and Bentler, 1999). The standardized factor loadings were used to calculate the factor score of MetScore for each participant, separately. This score can be interpreted as a z-score, the value is positively correlated with cardiometabolic risk and where zero indicates the population mean.

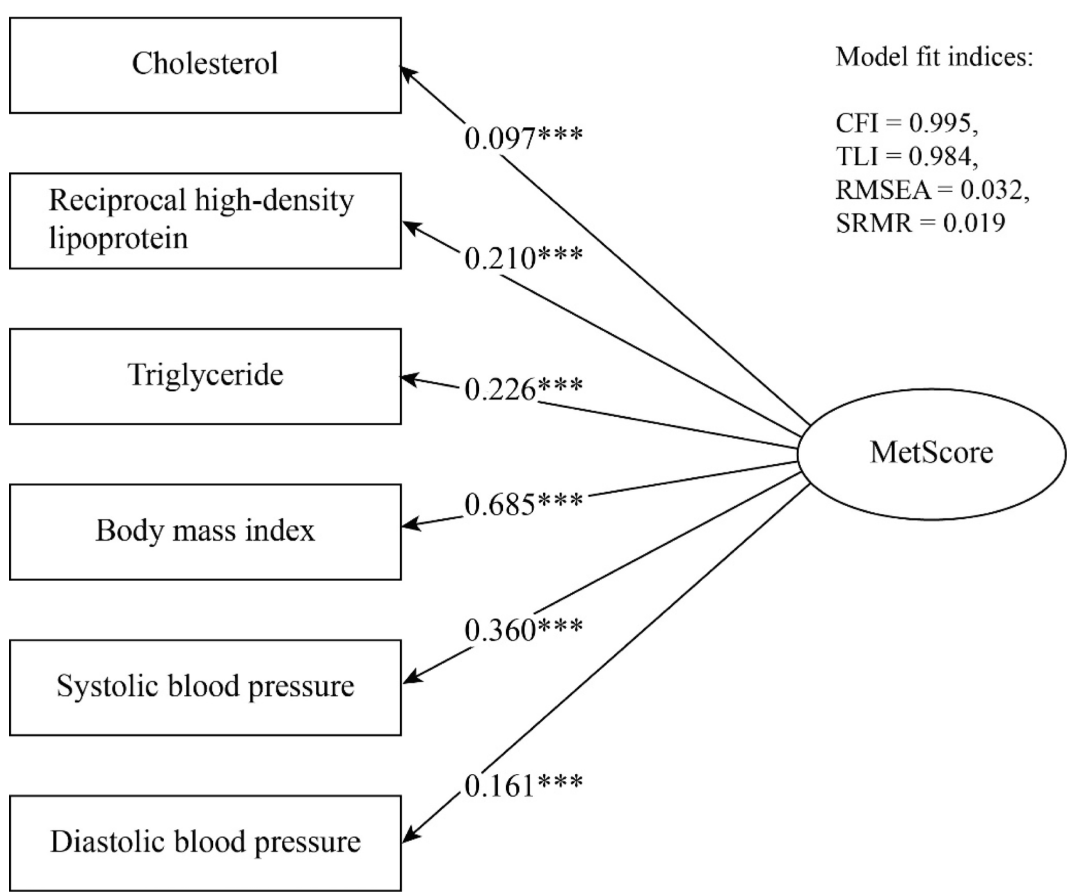


**Fig. 1.** Factor loadings for cardiometabolic risk factor clustering (MetScore), combing data from the first waves of three cohorts: ABCD, Generation R and Lifelines. All components are standardized into z-scores. Abbreviations: CFI = Comparative Fit Index, TLI = Tucker-Lewis Index, RMSEA = Root Mean Square Error of Approximation, SRMR = Standardized Root Mean Square Residual.

### 2.5. Covariates

Based on confounders used in previous studies (Bloemsma et al., 2019; Poursafa et al., 2014; Shenassa and Williams, 2020), a directed acyclic graph was created to choose confounders (**Appendix Figure S1**). At two surveys of each cohort, participants' parents provided information about age, sex (male, female), ethnicity (Dutch, Non-western other, Western other), parental education level (low to low-intermediate, high-intermediate, high), maternal smoking during pregnancy (no, <1 a day, ≥1 a day), child screen time (<1 h a day, 1 to 2 h a day, >2 h a day), child leisure time physical activity (<1 h a week, 1 to 2 h a week, 2 to 4 h a week, >4 h a week), parental marital status (married / live together, divorced / don't live together), and year of birth. The duration between these two surveys was also obtained. Urbanization degree within a Euclidean buffer of 1 km around each address was obtained from GECCO (Lakerveld et al., 2020; Timmermans et al., 2018). Objectively measured neighborhood socioeconomic status (SES) scores were obtained from the Netherlands Institute for Social Research (Netherlands Institute for Social Research, 2023). These scores are based on the average income, the percentage of residents with a low income, the percentage of residents with a low level of education, and the percentage of unemployed residents in the neighborhood (Netherlands Institute for Social Research, 2023). Higher scores indicate higher area-level SES.

### 2.6. Statistical analysis

Characteristics of the study sample and the area-level exposure measures were presented using descriptive statistics for each cohort, separately. The relative variability between exposures was compared by coefficient of variation, which is calculated by dividing the standard deviation by the mean and then multiplying by 100. The average of environmental exposures across years (air pollution with 25 × 25 m resolution and green space density in 500 m, 1000 m, and 2000 m buffers) were calculated and used in longitudinal analyses. Since all three cohorts have two waves of measurements, the change of MetScore between the two waves was used as dependent variable. Linear regression models were conducted for the association between average environmental exposure over time and change of MetScore over time. Models were adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood SES score, and urbanization degree. For sensitivity analyses, mutual confounding between air pollution and green space exposure was further considered in models by adjusting for each other. Air pollution with 1 × 1 km resolution across all years and green space density in other Euclidean buffer sizes (radii of 150, 250, 350, 750, and 1650 m) were also modelled in sensitivity analyses. In all analyses, unit of air pollution and green space were per standard deviation (SD).

Within each cohort, multiple imputation was conducted to deal with missing data. For each variable with missing values, the specified imputation model replaced missing values with values randomly drawn from the predictive distribution of the variable conditional on other observed data. This process created multiple imputed datasets with no missing values that reflected the uncertainty of missing data. All variables in the analytical model were included in the imputation model. We generated twenty imputed datasets that were analysed separately and pooled the estimates based on Rubin's rules (Van Buuren, 2018). Lastly, random-effect *meta*-analyses were conducted to synthesize the results from the three cohorts. The $I^2$ statistic was obtained as a measure of heterogeneity across cohorts. All analyses were performed using R software (Liu et al., 2021). Statistical significance was defined as $P <$ 0.05 (2-sided).

## 3. Results

The characteristics at baseline of the study sample and the area-level exposure measures for each cohort are presented in Table 1. The mean ages at baseline were 5.5 ± 0.5 years for ABCD, 6.1 ± 0.5 years for Generation R, and 9.5 ± 2.7 years for Lifelines, respectively. The percentages of male participants were 50.4 % for ABCD, 49.9 % for Generation R, and 48.6 % for Lifelines. Participants in Lifelines were mostly ethnically Dutch (96.6 %), while Generation R had more ethnical diversity (Dutch: 58.0 %). Participants in ABCD had more children with high parental education level (75.9 %) and more parents divorced or not living together (17.4 %). Participants in Generation R had more events of maternal smoking during pregnancy. Children in Lifelines had more screen time and underwent more physical activities during leisure time. Participants in ABCD had higher neighborhood SES score. Participants in ABCD and Generation R mostly lived in urban areas while participants in Lifelines mostly lived in rural areas. Participants in Lifelines were generally exposed to less air pollution and more green space at residence. The coefficient of variations ranged from 5.5 % to 8.2 % for particulate matter, and ranged from 13.9 % to 20 % for $NO_2$ and EC. **Appendix Figure S1** shows the Spearman correlations between green space and air pollutants in the three cohorts, respectively. Green space density was moderately, negatively correlated with air pollutants (r = -0.39 to −0.62), expect for particulate matter in Lifelines (r = -0.10 to −0.12).

Fig. 1 presents the model fit indices and factor loadings of the CFA model of MetScore. The model fit indices overally showed good fit. All components were significantly contributing to the MetScore. The variance in MetScore was mostly explained by BMI z score (46.9 %, the square of the standardized factor loadings). The associations of air pollution and green space exposure with change of MetScore for each separate cohort are shown in Table 2. There is no multicollinearity problem in the models. After adjusting for multiple confounders, exposures to higher levels of $NO_2$ and EC were significantly associated with increases of MetScore in Lifelines (per SD higher exposure: $\beta_{NO2} = 0.006$, 95 % CI = 0.001 to 0.010; $\beta_{EC} = 0.008$, 95 % CI = 0.002 to 0.014). In ABCD and Generation R, these associations were in the same direction, but these were not statistically significant. The associations of $PM_{2.5}$ and $PM_{10}$ with change of MetScore were not significant in all three cohorts. Higher green space density in 500-meter buffer zones around participants' residential address was significantly associated with decreases of MetScore in ABCD and Lifelines (per SD higher green space: $\beta_{ABCD} =$ -0.003, 95 % CI = -0.011 to 0.005; $\beta_{Lifelines} =$ -0.001, 95 % CI = -0.003 to 0.00004). All observed associations were not significant in Generation R. In sensitivity analyses, after considering mutual confounding between air pollution and green space, or modeling in another resolution (i.e., 1 × 1 km) and other buffer sizes (i.e., 150, 250, 350, 750, and 1650 m), models showed similar results (**Appendix Table S1-S3**).

Fig. 2 presents the *meta*-analyses of results from three cohorts. The pooled estimates were 0.003 (95 % CI = -0.001 to 0.006; $P = 0.13$) for $NO_2$, 0.003 (95 % CI = -0.001, 0.007; $P = 0.13$) for EC, and −0.0014 (95 % CI = -0.0026 to −0.0001; $P = 0.03$) for green space in 500-meter buffer zones. The pooled estimates were marginally significant for green space in other buffer zones, but were not significant for particulate matter.

## 4. Discussion

More green space exposure at residence was associated with decreased cardiometabolic risk as measured by MetScore over time among children. Results for air pollution were inconsistent among pollution indicators. Higher concentrations of $NO_2$ and EC were associated with increased cardiometabolic risk in Lifelines. The pooled estimates were marginally significant for $NO_2$ and EC. There was no statistical evidence found for the association of $PM_{2.5}$ and $PM_{10}$ with cardiometabolic risk. Results are robust after considering mutual

**Table 1**
Characteristics of participants by cohorts.

| Variables[1] | Cohorts | | |
|---|---|---|---|
| | ABCD 2009–2016 | Generation R 2007–2015 | Lifelines 2007–2017 |
| N | 2,547 | 5,431 | 5,844 |
| Age at baseline (year) | 5.5 ± 0.5 | 6.1 ± 0.5 | 9.5 ± 2.7 |
| Male (%) | 50.4 | 49.9 | 48.6 |
| Ethnicity (%) | | | |
| Dutch | 73.7 | 58.0 | 96.6 |
| Non-western other | 13.0 | 15.2 | 2.0 |
| Western other | 13.4 | 26.8 | 1.4 |
| Highest parental education level (%) | | | |
| Low to Low-intermediate | 7.7 | 15.2 | 8.4 |
| High-intermediate | 16.5 | 26.8 | 41.7 |
| High | 75.9 | 58.1 | 49.9 |
| Maternal smoking during pregnancy (%) | | | |
| No | 93.0 | 73.2 | 90.4 |
| < 1 a day | 2.3 | 4.5 | 0.9 |
| ≥ 1 a day | 4.7 | 22.4 | 8.7 |
| Child Screen time (%) | | | |
| < 1 h a day | 38.1 | 42.7 | 15.8 |
| 1 to 2 h a day | 46.2 | 40.1 | 36.8 |
| > 2 h a day | 15.7 | 17.3 | 47.5 |
| Child Leisure time physical activity (%) | | | |
| < 1 h a week | 10.5 | 5.3 | 2.5 |
| 1 to 2 h a week | 19.4 | 27.7 | 3.5 |
| 2 to 4 h a week | 33.1 | 44.1 | 60.2 |
| > 4 h a week | 37.0 | 22.8 | 33.9 |
| Parental marital status (%) | | | |
| Married / live together | 82.6 | 88.9 | 93.7 |
| Divorced / don't live together | 17.4 | 11.1 | 6.3 |
| Neighborhood socio-economic status score[2] | 0.6 (−0.5, 1.3) | −0.4 (−1.3, 1.2) | −0.5 (−1.4, 0.2) |
| Residence density (addresses per km$^2$) | 2,529 (1,566, 5,698) | 2,629 (1,604, 4,605) | 449 (171, 913) |
| Urbanicity degree (%) | | | |
| Non-urban (<500 addresses per km$^2$) | 4.5 | 2.8 | 53.6 |
| Limited urban (500–1000 addresses per km$^2$) | 7.7 | 7.9 | 25.4 |
| Moderately urban (1000–1500 addresses per km$^2$) | 10.4 | 11.5 | 12.4 |
| Strong urban (1500–2500 addresses per km$^2$) | 26.8 | 25.0 | 6.2 |
| Very strong urban (≥2500 addresses per km$^2$) | 50.7 | 52.8 | 2.5 |
| Duration between two surveys (years) | 6.1 ± 0.5 | 3.7 ± 0.5 | 2.9 ± 0.8 |
| Average $PM_{2.5}$ concentration (μg/m$^3$) | 15.1 ± 1.2 | 15.8 ± 1.3 | 9.5 ± 0.7 |
| Average $PM_{10}$ concentration (μg/m$^3$) | 23.4 ± 1.7 | 24.3 ± 1.7 | 16.3 ± 0.9 |
| Average $NO_2$ concentration (μg/m$^3$) | 25.5 ± 4.5 | 31.2 ± 4.5 | 12.2 ± 1.7 |
| Average elemental carbon concentration (μg/m$^3$) | 1.1 ± 0.2 | 1.3 ± 0.2 | 0.5 ± 0.1 |
| Average Green space density in 1 km buffer (percentage)[3] | 18.8 ± 15.9 | 16.5 ± 13.7 | 54.1 ± 26.8 |
| Average Agriculture density in 1 km buffer (percentage) | 8.7 ± 16.0 | 7.4 ± 12.9 | 46.9 ± 29.2 |
| Baseline MetScore[4] | −0.03 ± 0.06 | 0.01 ± 0.06 | −0.01 ± 0.07 |
| Total cholesterol (mmol/L) | 4.0 ± 0.7 | 4.2 ± 0.6 | 4.1 ± 0.7 |
| High-density lipoprotein (mmol/L) | 1.3 ± 0.3 | 1.4 ± 0.3 | 1.6 ± 0.3 |
| Triglyceride (mmol/L) | 0.7 ± 0.3 | 1.0 ± 0.5 | 0.7 ± 0.4 |
| Body mass index (kg/m$^2$) | 15.5 ± 1.4 | 16.2 ± 1.9 | 18.7 ± 3.2 |
| Systolic blood pressure (mmHg) | 98.4 ± 8.5 | 103.3 ± 8.0 | 106.4 ± 10.8 |
| Diastolic blood pressure (mmHg) | 59.1 ± 8.2 | 61.4 ± 6.7 | 59.5 ± 6.3 |
| Change of MetScore | 0.01 ± 0.06 | −0.01 ± 0.05 | 0.01 ± 0.05 |

[1] Values are mean ± SD or median (first quartile, third quartile) for continuous variables and % for categorical variables. The values for environmental exposures have been averaged over the study period corresponding to each cohort.

[2] This score is based on the average income, the percentage of residents with a low income, the percentage of residents with a low level of education, and the percentage of unemployed residents in the neighborhood.

[3] Green space are aggregates of parks, public gardens, forests, graveyards, and agriculture.

[4] Cardiometabolic risk factor clustering, derived from a factor analysis of six components: total cholesterol, HDL-C, TG, BMI, SBP, and DBP. All in z-scores.

confounding between air pollution and green space, or modeling in other resolution and buffer sizes.

The current results strengthen the evidence of a protective effect of green space exposure against cardiometabolic risk among children. Several previous studies reported associations between green space exposure and individual cardiometabolic risk factors among children, like lower BMI (Bell et al., 2008; Wolch et al., 2011) and lower BP (Zhao et al., 2022). However, to the best of our knowledge, this is the first study that found a significant association for overall cardiometabolic risk. A previous study in The Netherlands did not find an association between green space and overall cardiometabolic risk at ages 12 and 16 years, respectively (Bloemsma et al., 2019). Neither a Spanish study in rural areas found an association between distance from children's home to green space and overall risk (Gutiérrez-Zornoza et al., 2015). Both studies applied a cross-sectional design, and both studies measured the overall risk by summing the z-scores of individual risk factors, which gives equal weight to components. Instead, the current study used a prospective design and derived a MetScore by a CFA of component risk factors, which takes the weight of separate components into account, as recommended (Magge et al., 2017). Therefore, the present study expands the current literature and strengthens the evidence base on the association between green space and cardiometabolic risk among children.

For air pollution, there was large heterogeneity among the current study and previous ones. A study in the Netherlands investigated the associations of $PM_{2.5}$, $PM_{10}$, and $NO_2$ at residence with overall cardiometabolic risk (summed z-scores), and found no significant results (Bloemsma et al., 2019). A national study in the US used residential concentrations of volatile organic compounds as indicator of air pollution and found an elevated overall risk (summed z-scores) (Shenassa and Williams, 2020). A study in China investigated the $PM_{2.5}$ constituents at school in relation to MetS and indicated a robust association for EC (Li et al., 2023). All of them were cross-sectional studies among children. The current prospective study found evidence for $NO_2$ and EC, but not for particulate matter.

Even when using the same exposure and overall risk measures in the current study, there was large heterogeneity among the three cohorts (Table 1). For example, Generation R was more ethnically diverse while Lifelines is predominantly Dutch. Children in Generation R were more predisposed to cardiometabolic risk because more mothers smoked during pregnancy. Children in ABCD lived in neighborhoods characterized by a substantially higher SES. Children in Lifelines mostly lived in rural areas, while children in ABCD and Generation R mostly lived in strong urban areas. However, this heterogeneity cannot be addressed by *meta*-regression since there is a small number of studies. The credibility of the current results from *meta*-analysis is low. We therefore emphasize to interpret the results of the *meta*-analyses with caution.

Literature has proposed several mechanisms that green space exposure may decrease cardiometabolic risk. As discussed earlier, green space can release certain chemical agents like phytoncides that directly inhibit inflammation (Day, 2012), which is associated with cardiometabolic health in the long term. Apart from direct effect, green space may indirectly benefit cardiometabolic health by releasing stress, encouraging physical activity and depositing air pollution (Markevych

**Table 2**
Linear relation between air pollution, green space exposure and change of cardiometabolic risk factor clustering (MetScore)[1,2].

| Exposure | Change of MetScore in ABCD, n = 2,547 | | Change of MetScore in Generation R, n = 5,431 | | Change of MetScore in Lifelines, n = 5,844 | |
|---|---|---|---|---|---|---|
| | β (95 % CI) | *P* | β (95 % CI) | *P* | β (95 % CI) | *P* |
| $PM_{2.5}$ concentration | 0.0001 (−0.006, 0.006) | 0.98 | 0.001 (−0.001, 0.004) | 0.25 | −0.0003 (−0.004, 0.003) | 0.86 |
| $PM_{10}$ concentration | 0.0005 (−0.005, 0.006) | 0.86 | 0.001 (−0.001, 0.003) | 0.31 | −0.001 (−0.005, 0.002) | 0.50 |
| $NO_2$ concentration | 0.003 (−0.003, 0.009) | 0.39 | 0.001 (−0.001, 0.003) | 0.43 | **0.006 (0.001, 0.010)*** | **0.02** |
| Elemental carbon concentration | 0.003 (−0.004, 0.009) | 0.42 | 0.001 (−0.002, 0.004) | 0.48 | **0.008 (0.002, 0.014)*** | **0.01** |
| Green space density in 500 m buffer | −0.003 (−0.011, 0.005) | 0.46 | −0.001 (−0.004, 0.002) | 0.46 | −0.001 (−0.003, 0.00004) | 0.06 |
| Green space density in 1000 m buffer | **−0.007 (−0.013, −0.0005)*** | **0.04** | −0.001 (−0.004, 0.003) | 0.64 | −0.001 (−0.003, 0.0002) | 0.08 |
| Green space density in 2000 m buffer | **−0.008 (−0.013, −0.003)**** | **0.003** | −0.001 (−0.004, 0.002) | 0.45 | **−0.002 (−0.003, −0.00003)*** | **0.048** |

[1] Unit of air pollution is per standard deviation (SD) based on data of a resolution of 25 × 25 m raster. Unit of green space is per SD. The SDs were 1.1, 1.4, 3.6, 0.2, 21.1, 20.6, and 19.0 for $PM_{2.5}$, $PM_{10}$, $NO_2$, elemental carbon, and green space in 500 m buffer, 1000 m buffer, and 2000 m buffer, respectively.
[2] Models adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood socioeconomic status score, and residence density.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

et al., 2017b). Therefore, air pollution may play a role as a mediator in the association between green space and cardiometabolic risk. It has been recommended in a recent review that primary study should consider interrelationships between these built environment aspects in relation to cardiometabolic risk (Liu et al., 2023). The current study included mutual confounding of air pollution and green space in models and found their independent associations with cardiometabolic risk. However, simply adjusting for each other does not address the interrelationship since there could partially be a mediation effect, a moderation effect, or both. Future studies should investigate the mediation and moderation effects, while taking into account the types of green space, because vegetation of different heights may interact with air pollution differently (Jim and Chen, 2008).

The current study found an increasing risk for $NO_2$ and EC, but not for $PM_{2.5}$ and $PM_{10}$. Statistic description showed that particulate matter exposures had small variation within cohorts while $NO_2$ and EC exposures had larger variation. This small variation within cohorts could impede the finding of significant associations. Another potential explanation is that particulate matter comprises a wide range of particles. Some particles may be less associated with cardiometabolic health, but may be more related to allergy and respiratory issues, like pollen and spores (Idrose et al., 2022; Tham et al., 2014). Other particles, such as EC, are more strongly associated with cardiometabolic risk (Song et al., 2022). Both $NO_2$ and EC are primarily produced by combustion processes, particularly in vehicles, power plants, and industrial facilities. EC is generated by the incomplete combustion of carbon-based fuels (Niranjan and Thakur, 2017). In the context of the Netherlands, $NO_2$ and EC are mostly traffic-related diesel exhaust. Randomized trials showed that their exposures are associated with acute endothelial dysfunction and vasoconstriction in vivo (Mills et al., 2005; Peretz et al., 2008), which in turn can increase cardiometabolic risk.

### *4.1. Strengths and limitations*

The current study has several strengths, including a relatively large sample size as compared to previous studies, use of a longitudinal design and applying a recommended MetScore to assess overall cardiometabolic risk among children. There are also several limitations to consider when interpreting the results. First, there was little variability in the environmental exposures which impede the finding of significance. Second, the exposures were only measured at residence in the current study. The mobility of individuals should be considered in future study including exposures at school and commute (Ntarladima et al., 2019). Third, due to data availability across three cohorts, the MetScore was constructed based on an incomplete list of components. Future study should add other components like fasting glucose and HbA1c. Lastly, due to the small number of studies included, heterogeneity cannot be addressed via a *meta*-regression.

## 5. Conclusion

Among children, more green space exposure at residence was associated with decreased cardiometabolic risk over time. Some evidence was found for the association between air pollution and increased cardiometabolic risk. Exposure to higher concentrations of $NO_2$ and EC was associated with increased cardiometabolic risk in the Lifelines cohort. No evidence was found for $PM_{2.5}$ and $PM_{10}$, probably due to the small variations in exposures. More research is needed to investigate the longitudinal effect of air pollution and green space on cardiometabolic risk among children; this should involve application of the MetScore and consideration of the interrelationship between exposure measures.


## CRediT authorship contribution statement

**Mingwei Liu:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ilonca Vaartjes:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization. **Gerard Hoek:** Writing – review & editing, Validation, Supervision, Methodology. **Vincent W.V. Jaddoe:** Writing – review & editing, Validation, Resources, Data curation. **Susana Santos:** Writing – review & editing, Validation, Resources, Data curation. **Anton Schreuder:** Writing – review & editing, Validation, Resources, Data curation. **Tanja G.M. Vrijkotte:** Writing – review & editing, Validation, Resources, Data curation. **Diederick E. Grobbee:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition. **Erik J. Timmermans:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Erik J. Timmermans reports financial support was provided by NWO Gravitation Grant (Exposome-NL, 024.004.017). Mingwei Liu reports financial support was provided by China Scholarships Council. Ilonca Vaartjes reports financial support was provided by NWO Gravitation Grant (Exposome-NL, 024.004.017). Gerard Hoek reports financial support was provided by NWO Gravitation Grant (Exposome-NL, 024.004.017). Diederick E. Grobbee reports financial support was provided by NWO Gravitation Grant (Exposome-NL, 024.004.017). Susana Santos reports financial support was provided by Marie Sklodowska-Curie Postdoctoral Fellowship Grant Agreement No. 101109136 (URBANE). Vincent W.V. Jaddoe reports financial support was provided by European Research Council (ERC Consolidator Grant, ERC-2014-CoG-648916). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could

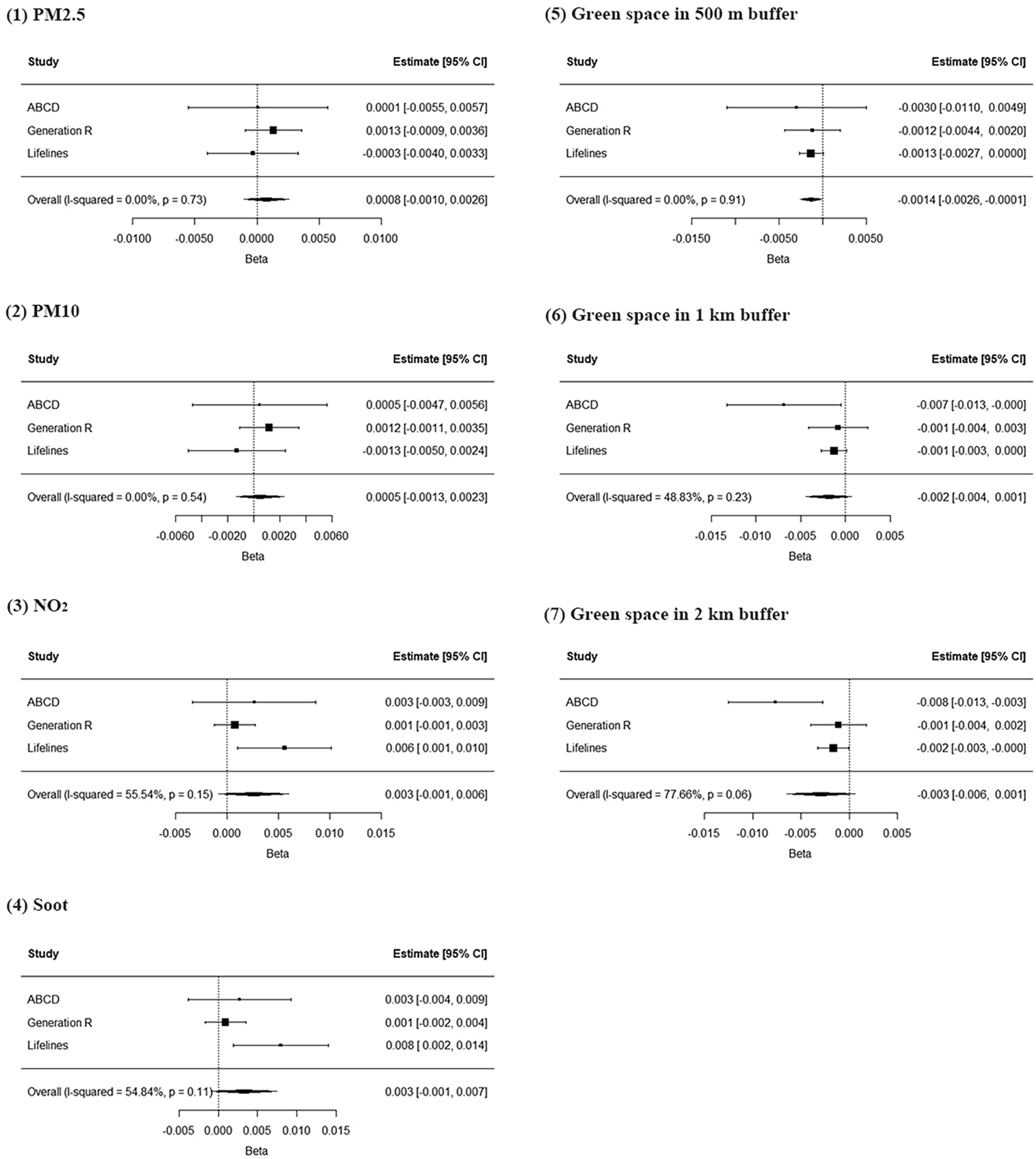


**Fig. 2.** Meta-analyses of linear associations of air pollution and green space exposure with change of cardiometabolic risk factor clustering in children participating in three Dutch cohort studies. Unit of air pollution is per standard deviation (SD) based on data of a resolution of 25 × 25 m raster. Unit of green space is per SD. The SDs were 1.1, 1.4, 3.6, 0.2, 21.1, 20.6, and 19.0 for $PM_{2.5}$, $PM_{10}$, $NO_2$, elemental carbon, and green space in 500 m buffer, 1000 m buffer, and 2000 m buffer, respectively.

have appeared to influence the work reported in this paper.

## Data availability

The data that has been used is confidential.

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## Appendix A. Supplementary material

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