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A comparison of associations with childhood lung function between air pollution exposure assessment methods with and without accounting for time-activity patterns

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ABSTRACT

Background: To investigate associations between annual average air pollution exposures and health, most epidemiological studies rely on estimated residential exposures because information on actual time-activity patterns can only be collected for small populations and short periods of time due to costs and logistic constraints. In the current study, we aim to compare exposure assessment methodologies that use data on time-activity patterns of children with residence-based exposure assessment. We compare estimated exposures and associations with lung function for residential exposures and exposures accounting for time activity patterns.
Methods: We compared four annual average air pollution exposure assessment methodologies; two rely on residential exposures only, the other two incorporate estimated time activity patterns. The time-activity patterns were based on assumptions about the activity space and make use of available external data sources for the duration of each activity. Mapping of multiple air pollutants (NO_2, NO_X, $PM_{2.5}$, $PM_{2.5}$absorbance, PM_{10}) at a fine resolution as input to exposure assessment was based on land use regression modelling. First, we assessed the correlations between the exposures from the four exposure methods. Second, we compared estimates of the cross-sectional associations between air pollution exposures and lung function at age 8 within the PIAMA birth cohort study for the four exposure assessment methodologies.
Results: The exposures derived from the four exposure assessment methodologies were highly correlated ($R > 0.95$) for all air pollutants. Similar statistically significant decreases in lung function were found for all four methods. For example, for NO_2 the decrease in FEV_1 was −1.40% (CI; −2.54, −0.24%) per IQR (9.14 μg/m^3) for front door exposure, and −1.50% (CI; −2.68, −0.30%) for the methodology which incorporates time activity pattern and actual school addresses.
Conclusions: Exposure estimates from methods based on the residential location only and methods including time activity patterns were highly correlated and associated with similar decreases in lung function. Our study illustrates that the annual average exposure to air pollution for 8-year-old children in the Netherlands is sufficiently captured by residential exposures.

1. Introduction

Outdoor air pollution is an important determinant of health, and has been estimated to be related to 4.2 million premature deaths annually (World Health Organization, 2018). A large number of studies have demonstrated associations between air pollution and health. The

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evidence has been summarized in several review papers (Landrigan et al., 2018; Schlesinger et al., 2006; Thurston et al., 2017). Specifically, outdoor air pollution has been shown to have short- and long-term impacts on the lung function of children (Götschi et al., 2008; Paulin and Hansel, 2016; Schultz et al., 2017), which is an objective measure of respiratory health and predictor of cardio-respiratory morbidity and mortality (Sin et al., 2005).

A potential limitation of most of the epidemiological studies that have been performed so far is the exposure assessment approach they followed. Actual personal exposure can be described as the time-weighted average air pollution concentration across all activities of a person (Sexton and Barry, 1988). However, most epidemiological studies mainly rely on residential exposures to characterize individual exposure and more specifically on annual average air pollution at typically the front door or at the centre of the parcel of the residence (Clark et al., 2010; Gehring et al., 2013; Krämer et al., 2009; Nordling et al., 2008). This approach assumes that the between person differences in exposures are only due to differences in residential concentrations. Although most people spend most of their time at home (Klepeis et al., 2001), this remains an approximation as people visit various spaces during the day with potentially different air pollution levels (Park and Kwan, 2017).

Most epidemiological studies are based upon residential exposures, because direct personal measurements of air pollution concentrations are not feasible for large study populations (Larkin and Hystad, 2017). Moreover, estimated personal exposure based on actual personal activity patterns are difficult to acquire for extended periods because it is a costly procedure (Larkin and Hystad, 2017; Pekkanen and Pearce, 2001). Furthermore, individual time activity data cannot be obtained for past exposures.

We therefore developed a method to estimate individual time activity patterns of children that can be applied to large populations (Ntarladima et al., 2019). This approach is based on buffers, which represent typical activity spaces around the residential addresses. The exposures derived from each buffer were weighted with the estimated time spent on specific activities from an external database (Ntarladima et al., 2019). Enriching residential exposures with estimated activity pattern gives the potential to capture the spatial variation in air pollution exposure amongst several microenvironments that children visit daily (home, school, playing ground and street network).

We developed our approach in a population of children aged 5 years living in a fairly small quarter of the city of Utrecht with limited spatial variation in outdoor air pollution (Ntarladima et al., 2019). The current paper extends our approach and evaluates the methodology in the Dutch prospective PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study. Participants of the PIAMA cohort live spread over three large parts of the Netherlands, in large urban areas and small towns. Associations between (residential) air pollution exposure and health have been reported for the PIAMA study, including lung function at age 8 (Gehring et al., 2013).

2. Subjects and methods

2.1. Design

This study compares four air pollution exposure assessment methodologies by calculating and comparing the correlation of estimated exposures and their associations with lung function at age 8 years in a large Dutch birth cohort study. Two of the methodologies are based on the residential exposures only. The third and fourth methodologies use estimated time activity patterns to calculate a time-weighted average individual exposure of residential, school, neighborhood and commuting exposures. The difference between the third and fourth methodology is the use of the estimated versus actual school locations. The third methodology has been applied before in a cohort where information on the actual school locations was not available (Ntarladima et al., 2019). Comparing methodologies three and four allows us to assess whether the simulated school exposures are a good representation of the exposures at the actual school locations.

2.2. Study population

This study uses data from the Dutch prospective Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study (Wijga et al., 2013). The PIAMA study has been selected for this study for several reasons. First, this cohort has already examined the associations between air pollution and lung function (Gehring et al., 2013). Second, the PIAMA cohort recruited participants from three different regions of the Netherlands (North, Southwest and Central) including urban and rural areas which ensures contrasts in air pollution exposure. Third, information on the school location was available to be used in one of the exposure assessment methodologies. Participants were born in 1996/97 in the Netherlands.

The current analysis included participants with successful lung function measurements at 8 years of age, complete information on sex, age, height, and weight at the time of lung function measurement as in a previous study (Gehring et al., 2013) and for whom in addition a valid school address was available (n = 668). We have compared the population included in the analysis with the full PIAMA population and the population of all participants with successful measurements of lung function (Table S1). Children with allergic mothers were over-represented by design among the participants with lung function data and the current sample. Apart from that, the characteristics of the different populations were very similar. Due to missing values on potential confounders, 638 participants were included in the models.

Data were obtained by questionnaires which were completed by parents. Parents reported home and school addresses at each round of follow up (Wijga et al., 2013).

The lung function measurements were performed by obtaining at least three acceptable maneuvers by trained personnel when children were 8 years as described previously (Gehring et al., 2013). The lung function measurement used in this study are the commonly used measures: forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).

2.3. Air pollution exposure assessment

To assess air pollution levels at home, at school and at other locations we used land use regression (LUR) models. LUR models are used in many epidemiological studies for estimating annual average outdoor air pollution concentrations at the home addresses of cohort subjects as the performance of the method in urban areas is typically better or equivalent to geo-statistical methods, such as kriging, and dispersion models (Hoek et al., 2008). The models were originally developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project and described elsewhere (Beelen et al., 2013; Eeftens et al., 2012). Following the original paper on air pollution and lung function (Gehring et al., 2013), we used the annual average concentrations of the same year (2009) as in the original analysis. Air pollution levels were calculated at any location (5*5 m grids) in the study area for several air pollutants including nitrogen oxides (NO_2, NO_x) and particulate matter (PM_{10}, $PM_{2.5}$ and $PM_{2.5}$absorbance) (Schmitz et al., 2018).

To calculate air pollution exposures, we followed four methodologies. Two of the methodologies were based on the residential location only and the two other methods included both home and school location and integrated activity patterns. The activity patterns have been estimated for weekdays only. An overview of the methodologies that have been applied in the current analysis is presented in Table 1 and an example of how the exposures were calculated using GIS is illustrated in Fig. 1. Information about the specific datasets used for the calculation can be found in Table S2.

The first methodology applied is the conventional residential

Table 1
Overview of the exposure assessment methodologies.

Activity areas	Method 1: Residential exposure (point estimate)	Method 2: Residential exposure (20 m buffer)	Method 3: Time- activity weighted exposure using estimated school address	Method 4: Time- activity weighted exposure using actual school address
Staying at home	Air pollution level at front door of home address (point estimate)	Average air pollution level within a 20 m buffer around front door of home address	Average air pollution level within a 20 m buffer around front door of home address	Average air pollution level within a 20 m buffer around front door of home address
Playing in the neighborhood	–	–	Average air pollution level for open public and private spaces within a 500 m buffer around home address	Average air pollution levels for open public and private spaces within a 500 m buffer around home address
Travelling to school	–	–	Average air pollution level on the road network within a 2000m buffer around home address	Average air pollution level on the road network between actual home location and actual school location (based on shortest route). For passive commuters we used the car road network and for active commuters the cycling network.
Being at school	–	–	Average air pollution level for all schools within a 2000m buffer around home address. The number of school addresses within a 2000m buffer can be found in Table S2.	Average air pollution level within a 20 m buffer around the actual school address

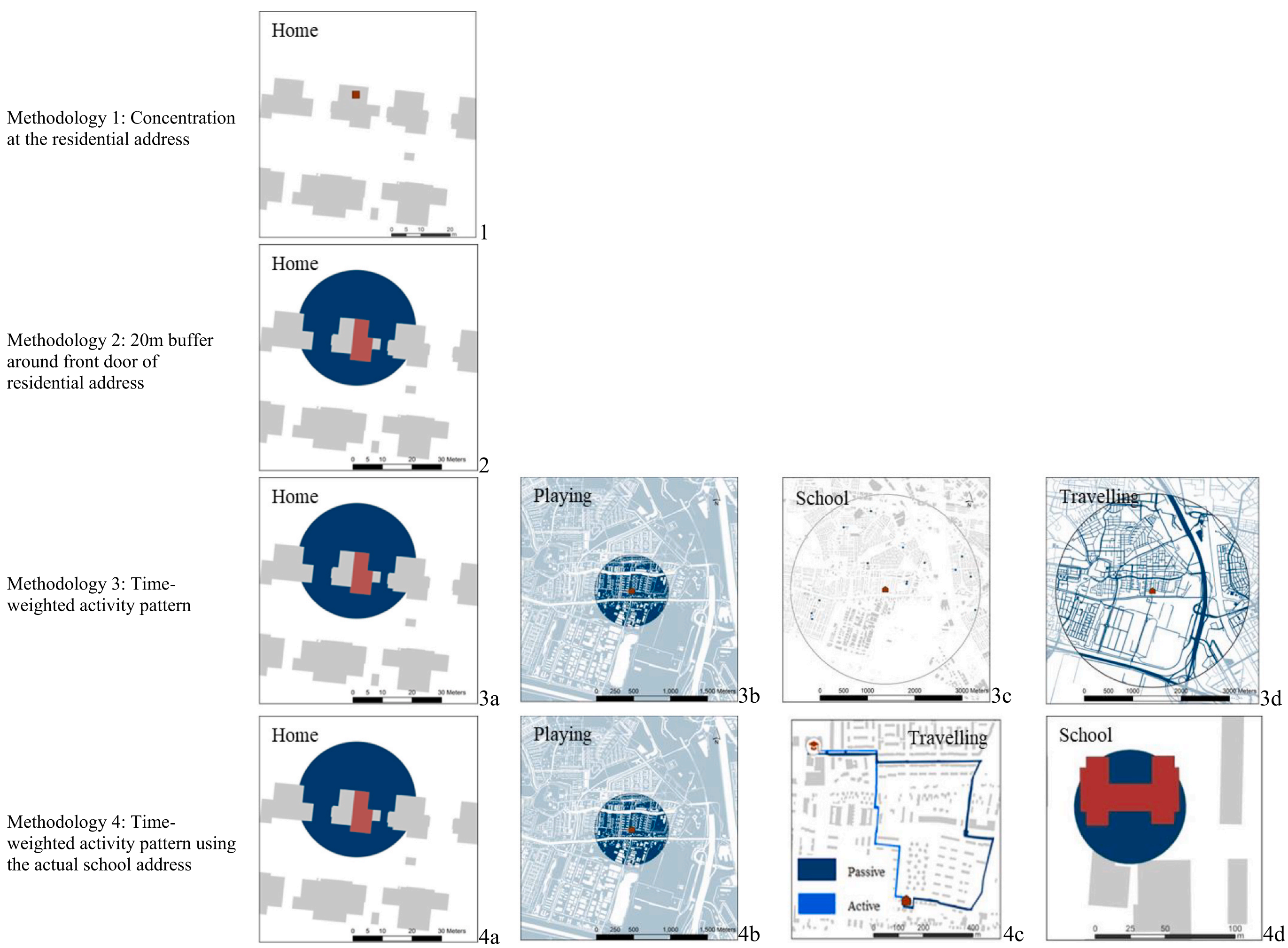

Fig. 1. Representation of the four methodologies, depicted for a single (arbitrarily chosen) residential address (red square) within the area of interest. Blue indicates the land use related to each activity space (dark blue: actual activity area). 1, first methodology: concentration at the residential address (front door coordinate); 2, second approach: 20 m buffer around residential address; 3, third approach; 3a, same as 2; 3 b, 500 m buffer including open public and private space around residential address to represent playing in the neighborhood activity; 3c, 2000m buffer including road network to represent travelling, 3 d 20 m around all schools included within a 2000m buffer around the residential address; 4a, same as 2; 4 b, same as 3 b; 4c, travelling from residential address to school address for children where dark blue represents passive travelling and bright blue active travelling; 4 d, 20 m buffer around the actual school address to represent the activity being at school. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exposure (Fig. 1, panel 1). This methodology is applied in most air pollution epidemiological studies and makes use of the air pollution level at the home address only. More specifically, the exposure estimate relies on estimated air pollution level within the 5*5 raster cell around the front door coordinate. For the second methodology we applied a 20 m buffer around the front door coordinate and averaged the concentrations within this buffer (Fig. 1, panel 2). This approach aims to cover the complete home footprint and not only the front door as in the previous methodology. The third and fourth methodologies aim to estimate the children's exposure over the course of a day. These methodologies were also based on the residential addresses, but in addition they incorporate simulated children's activity patterns for schooldays. The activities we assumed as major daily activities were being at home, playing in the neighborhood, travelling to/from school, and being at school. The activity spaces are based on assumptions of how far the activities would take place from home and on which land uses. To estimate the average time spent at each activity we used an external dataset which includes data on mobility in the Netherlands for the year 2010 (CBS, 2015). The assumptions and the calculations for each activity are presented in Table 1.

In methodology 3 all activity spaces were calculated using buffers around the residential address and all activity durations were based on the external mobility dataset (CBS, 2015). The choice of the buffer-sizes was based on educated guesses of the children's activities considering the age of the children, the average degree of urbanization and the average time needed to reach a place. Specifically, we observed that within 500 m of most homes, playgrounds exist. 500 m correspond to a 5 min' walk which is a reasonable time to reach an activity space. Therefore, we used a 500 m buffer for the playing activity in the neighborhood. We used a 2000m buffer for travelling to school and being at school activity as (within our datasets) this was the maximum distance between the participants' homes and the nearest school. In methodology 4, the exact school addresses available from the PIAMA questionnaire have been utilized for the activity being at school and for the travelling from/to school activity instead of estimated school addresses (Fig. 1). For the activity travelling from/to school we used the shortest-path algorithm between the home and actual school address on the car road network for the children who travel passively (i.e. by bus or by car, Figs. 1 and 4c) and on the cycling road network for the children travelling actively (i.e. on foot or by bike, Figs. 1 and 4c). The duration of travelling was calculated based on the shortest road network distance between home and school, the average biking speed for children (Hummer et al., 2006) and the car average speed in urban streets with moderate congestion levels (Svyk, 2020). The information about active or passive travel of a child was derived from parental-completed questionnaires included in PIAMA. The estimated exposure for child i for methodologies 3 and 4 has been calculated as:

$$E_i = \frac{T_h\, C_{h(i)} + T_p\, C_{p(i)} + \; T_s\, C_{s(i)} + T_t\, C_{t(i)}}{1440} \tag{1}$$

where E_i is the personal exposure for child i (μg/m^3), $C_{h(i)}$ the air pollution concentration (μg/m^3) representative for home activity, and T_h the time (minutes) spent at home; $C_{p(i)}$ the air pollution concentration for playing in the neighborhood, T_p the time spent playing in the neighborhood, $C_{s(i)}$ the air pollution concentration at school, T_s the time spent at school, $C_{t(i)}$ the air pollution concentration at the road network, T_t the time spent travelling. The denominator represents the total number of minutes per day.

All spatial computations based on vector files were performed using ArcGIS Pro and the raster calculations were performed in PCRaster environment (Karssenberg et al., 2010).

2.4. Covariates

The participants' height and weight were measured by trained during the medical examination at age 8 years. Also, information on recent respiratory infections (during the 3 weeks prior to the lung function measurement, yes/no) was collected during the medical examination. Information on other important covariates such as sex, Dutch nationality (defined as both parents being born in the Netherlands, yes/no), maternal and paternal education (defined as the maximum educational level attained by the mother or father; low: primary school, lower vocational, or lower secondary education; medium: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education and university), maternal and paternal allergies (asthma, hay fever allergies to house dust mites or pets, yes/no yes/no), breastfeeding at age 12 weeks (yes/no), maternal smoking during pregnancy (defined as maternal smoking in at least the first 4 weeks of pregnancy, yes/no), smoking in the child's home (yes/no), mold/damp spots in the living room and/or child's bedroom (yes/no), and furry pets in the child's home (cats, dogs, and/or rodents, yes/no) was obtained from the parent-completed questionnaires. For time-varying covariates, we used information from the questionnaire that coincided best with the air pollution exposure.

2.5. Data analyses

To assess the correlations between the four exposure assessment methodologies we used Pearson's correlation coefficients. As the correlation for the full cohort is affected by regional variation and within-region variation, we also assessed the correlations for the Northern region and the remaining regions (Central, Southwest) of the Netherlands separately. The Northern region has lower air pollution levels than the other parts of the country (Schmitz et al., 2019). We also performed stratified analysis to study whether urban and rural areas showed different correlations between methodologies. The distinction between urban and rural was based on the CBS categorization (Centraal Bureau voor de Statistiek, 2015), that defines 5 categories based on the number of addresses per km^2, ranging from $<$500 addresses/km^2 to $>$2500 addresses/km^2. Urban areas were classified as areas with $>$1000 addresses per km^2, rural areas as areas with $<$1000 addresses per km^2. Finally, we assessed correlations between the exposures at the simulated school location and actual school location, to test how well we estimated school-based exposures, an important micro-environment.

To investigate the associations between lung function and air pollution, we fitted separate linear regression models for the two lung function variables (FEV_1 and FVC) and all pollutants (NO_2, NO_x, PM_{10}, $PM_{2.5}$ and $PM_{2.5}$absorbance) derived from the four exposure-assessment methodologies. As in previous analyses (Gehring et al., 2013), we applied natural log-transformation to the lung function variables. We adjusted for the potential confounders described above. Age, height and weight were natural-log transformed and entered as continuous variables. All other potential confounders were entered as binary variables apart from age, weight and height which were entered as continuous variables. As recent respiratory infections we included participants which have symptoms three weeks prior to the lung-function measurement.

The exposures were entered as continuous variables without transformation assuming linear exposure-response relationships. The associations are presented as the percent-change in each lung function parameter and expressed per interquartile range (IQR) increase in exposure, to facilitate comparison of effect estimates between air pollutants and methodologies.

The statistical analysis was performed using R version 3.5.1.

3. Results

3.1. Characteristics of the study population

Data on 668 children (mean age, 8.1 years) were used in the analyses. Characteristics of the study population and lung function parameters are presented in Table 2.

Table 2
Population characteristics and lung function measurements (N = 668).

Population characteristics	n (%) or mean (SD)	missings (count)
Age (years)	8.08 (0.29)	0
Female sex	339 (50.7)	0
Weight (kg)	28.85 (4.72)	0
Height (cm)	132.96 (5.55)	0
Recent respiratory infections[a]	159 (24.1)	9
Dutch nationality	632 (96.0)	10
High maternal SES	266 (39.8)	0
High paternal SES	299 (45.2)	0
Allergic mother	409 (61.2)	0
Allergic father	214 (32.1)	1
Breast-feeding (≥12 weeks)	357 (53.4)	0
Mother smoking during pregnancy	96 (14.5)	6
Smoking at home	158 (23.7)	1
Mold/dampness at home	181 (27.3)	6
Furry pets at home	267 (40.0)	0
Living in urban areas	481 (72.0)	0
Living in the North	167 (25.0)	0
Lung function measurements		
FEV_1 (L)	1.78 (0.25)	0
FVC (L)	1.97 (0.29)	0

[a] 3 weeks prior to the lung function measurement.

3.2. Exposure to air pollution

The distributions of the estimated annual average air pollution concentrations for the four different exposure assessment methodologies are presented in Table 3. In method 3, we assumed that children spent on average 964 min per day at home, 399 min at school, 28 min playing in the neighborhood, and 49 min travelling to school. In method 4 we used the same durations for all activities, except for travelling. For travelling we calculated each child's travelling time based on the distance between home and school and on average was 5 min.

Variation in exposures was much larger for NO_2, NO_x and $PM_{2.5}$absorbance than for $PM_{2.5}$ and PM_{10} for which the variation was limited in all four approaches. The mean levels and variation did not differ much between the residential exposure approaches (M1, M2) and the time-weighted activity pattern methodologies (M3, M4). Correlations between the four methodologies are presented in Fig. 2 for NO_2 and Figure S1 for the remaining pollutants. Air pollution exposures derived from the four methodologies were highly correlated (R between 0.95 and 1) and correlations between the two residence only methods (M1 and M2) were generally highest (0.99 for all the pollutants).

We explored several causes for the high correlation between exposures estimated with the four methodologies (M1-M4). One possible explanation is that variation in exposure between children is mainly caused by large contrasts in air pollution levels between regions of the country or between urban and rural areas. In this case, the differences in exposures assessed by different methodologies would be overshadowed by contrasts occurring at the larger scale. However, stratified analyses revealed high correlations between the four exposures also within the urban areas and rural areas and within the northern and central/southwestern parts of the Netherlands (Fig. 3, Fig. 4, Figure S2; Figure S3). A second possible explanation for the high correlation between exposures calculated with different methodologies is a high correlation between exposures during different activities, which are the components of our exposure assessment calculations for the different methods. We found strong correlations between air pollution exposures at home and in the different activity spaces that we used in the four methodologies (home –front door estimate-, home –20 m buffer-, playing in the neighborhood, travelling –simulated-, school –simulated-, travelling by bike –based on shortest path-, travelling by car –based on shortest path-, school –actual location-) as shown in Table 4.

Table 3
Estimated air pollution exposure levels from the different methodologies. M1 is the residential exposure derived from front-door estimate, M2 is the residential exposure in a 20 m buffer, M3 is the time-weighted activity approach using estimated time activity – and M4 is the time weighted activity methodology using the actual school location. The unit of NO_2, NO_x, $PM_{2.5}$ and PM_{10} is μg/m^3 and of $PM_{2.5}$abs it is (10^{-5}/m).

		Mean	Std	Median	Minimum	Maximum
M1	NO_2	22.9	6.6	23.0	10.4	53.2
	NO_X	33.1	11.9	31.9	17.0	99.6
	$PM_{2.5}$	16.3	0.6	16.5	14.9	18.4
	$PM_{2.5}$abs	1.2	0.2	1.2	0.8	2.1
	PM_{10}	24.8	1.0	24.5	23.7	29.9
M2	NO_2	23.7	6.7	23.8	10.7	52.3
	NO_X	33.2	12.1	31.9	17.0	104.5
	PM_{25}	16.3	0.6	16.5	14.9	18.3
	PM_{25}abs	1.2	0.2	1.2	0.8	2.1
	PM_{10}	24.8	1.0	24.5	23.7	29.9
M3	NO_2	23.7	6.5	24.0	10.8	44.6
	NO_X	33.3	10.7	32.9	17.4	87.3
	$PM_{2.5}$	16.3	0.6	16.5	14.9	17.9
	$PM_{2.5}$abs	1.2	0.2	1.2	0.9	2.0
	PM_{10}	24.8	0.9	24.6	23.7	29.0
M4	NO_2	23.5	6.5	23.7	11.2	44.4
	NO_X	33.1	11.0	32.3	17.3	85.0
	$PM_{2.5}$	16.3	0.6	16.4	14.8	17.9
	$PM_{2.5}$abs	1.3	0.2	1.3	0.9	2.2
	PM_{10}	24.8	1.0	24.5	23.7	30.0

3.3. Associations between air pollution and lung function

Most associations between air pollution exposures and lung function were negative, indicating a decrease in lung function with increasing exposures. The associations were significant for FVC for all exposures and for FEV_1 for NO_2, $PM_{2.5}$ and PM_{10} whereas for NO_x a significant association was observed only when using methodology 3 (Table 5). Associations between air pollution exposures and lung function were very similar for all exposure assessment methodologies. The association estimates were slightly higher for the two methodologies which incorporate the time activity patterns.

Estimates are adjusted for ln (age), sex, ln (height), ln (weight), recent respiratory infections, ethnicity/nationality, parental education, allergic mother, allergic father, breastfeeding, mother smoking during pregnancy, smoking at home, mold/dampness at home, furry pets at home. In bold are the significant associations. The effect estimates are presented per IQR increase in exposure: 9.14 μg/m^3 for NO_2, 12.37 μg/m^3 for NO_x, 1.15 μg/m^3 for $PM_{2.5}$, 0.32 10^{-5}/m for $PM_{2.5}$ absorbance, 0.99 μg/m^3 for PM_{10}

4. Discussion

Our study among 8-year-old children, living spread over the Netherlands, showed small differences in estimated exposure between the four air pollution assessment methodologies. Exposures from all four methods were highly correlated. Consistently, associations with lung function were very similar for the four exposure assessment methods.

4.1. Interpretation of the high correlation between exposures

First, the exposure estimates for all activity-spaces were highly correlated with the exposure at home. This is probably because all major activities of young children were assumed to take place around the home address. Second, children undergo activities with different, exposures from those at home for limited time. For example, children commute for limited time, which is usually the activity with the highest exposure (Chaney et al., 2017), while they spend 16 h at home based on our calculations.

The correlations between activity spaces indicate that the correlations between the exposures at school and at home were lower than the

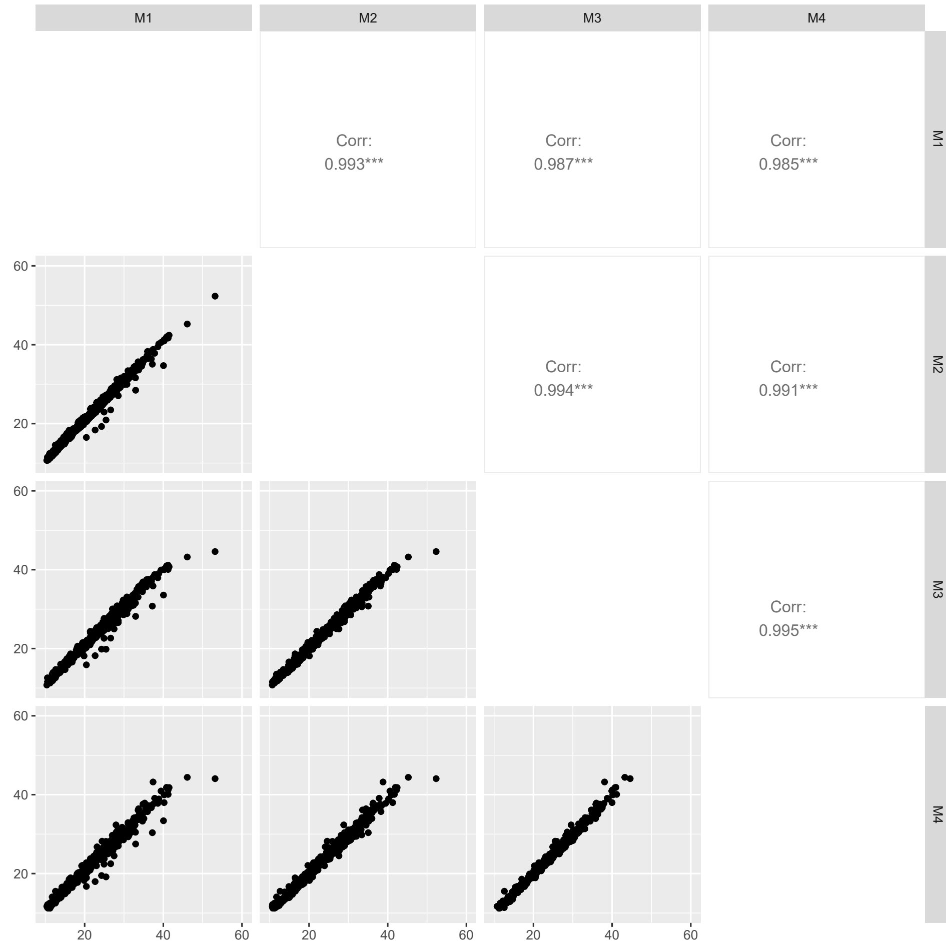

Fig. 2. Scatterplot matrix and correlations for NO_2 exposures for the four exposure assessment methodologies.

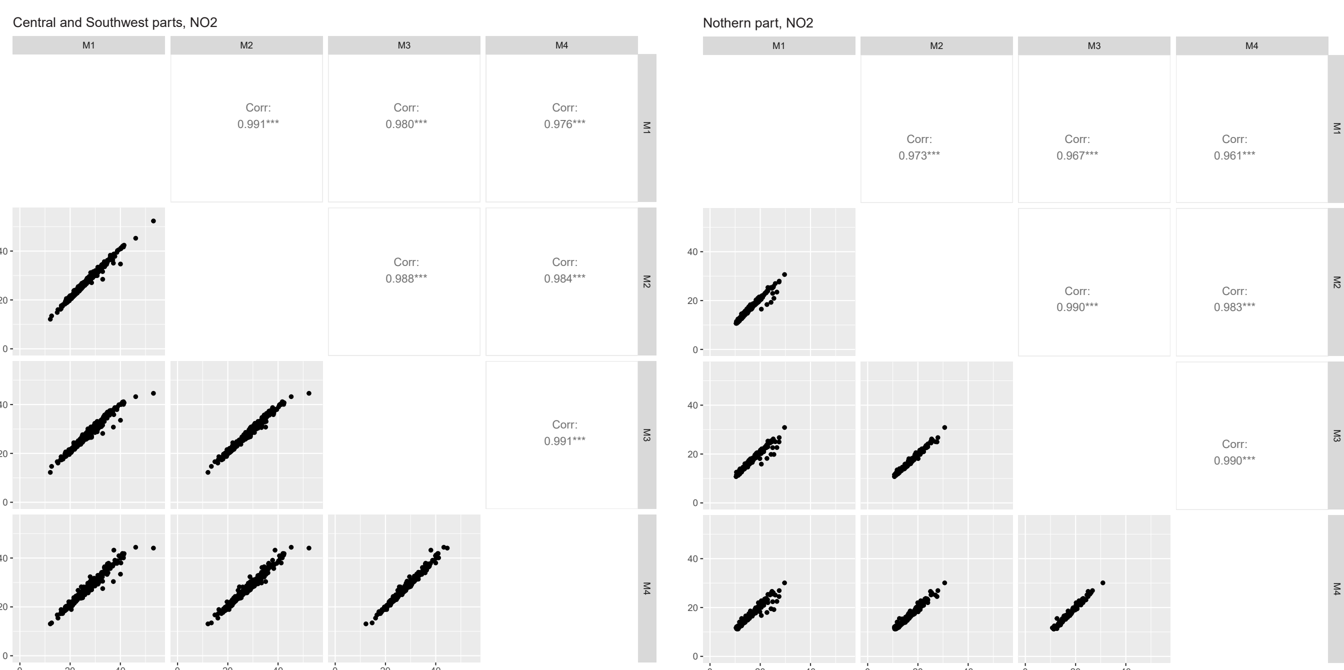

Fig. 3. Scatterplot matrix for NO_2 of correlations between the four exposure assessment methodologies by region (left panel: Central/Southwest, right panel: North).

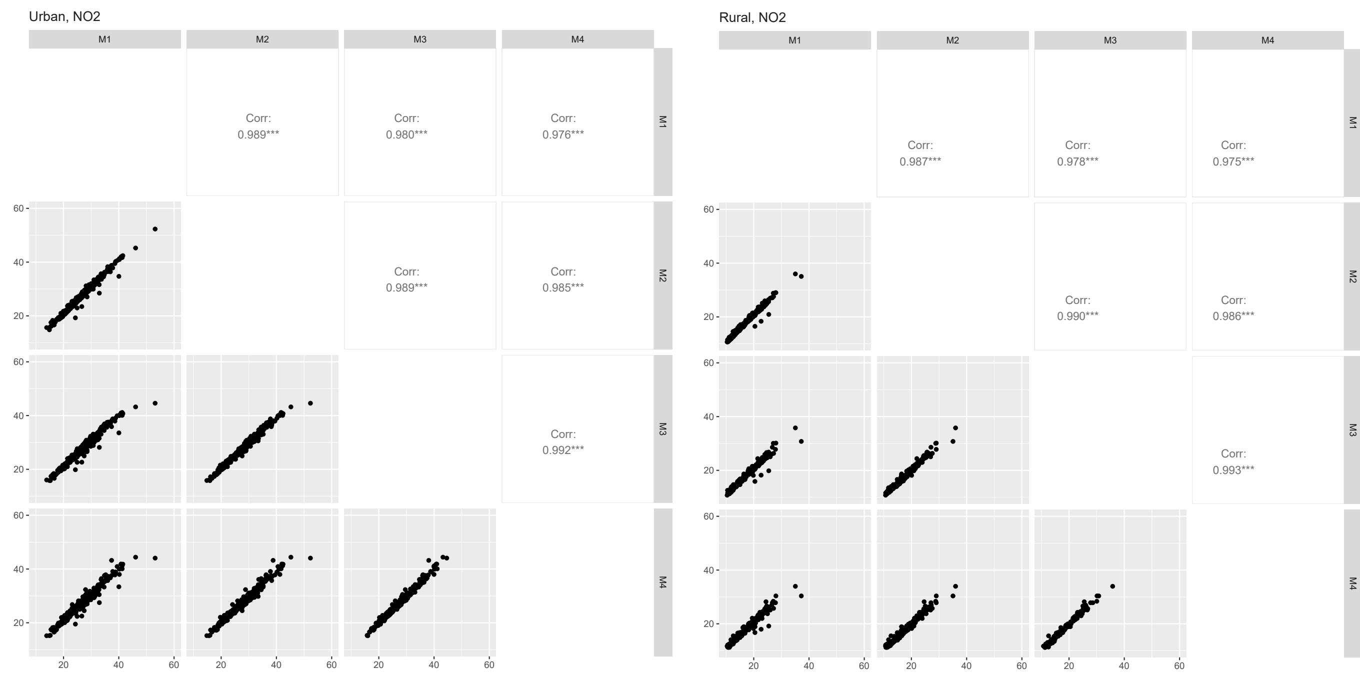

Fig. 4. Scatterplot matrix for NO_2 and correlations between the four exposure assessment methodologies for urban (left panel) and rural area (right panel).

Table 4
Correlation between exposure estimates for different activity spaces for all air pollutants.

		Home (20 m average)	Playing	Travelling (estimated)	School (estimated)	Travelling by bike (shortest path)	Travelling by car (shortest path)	School (actual location)
NO_2	Home (front-door)	0.99	0.96	0.92	0.92	0.93	0.91	0.89
	School (estimated)							0.93
	Travel (estimated)					0.92	0.90	
NO_X	Home (front-door)	0.99	0.95	0.77	0.76	0.83	0.75	0.68
	School (estimated)							0.81
	Travel (estimated)					0.77	0.72	
$PM_{2.5}$	Home (front-door)	0.99	0.91	0.88	0.90	0.84	0.76	0.84
	School (estimated)							0.91
	Travel (estimated)					0.83	0.77	
$PM_{2.5}$ abs	Home (front-door)	0.99	0.94	0.86	0.88	0.87	0.82	0.84
	School (estimated)							0.91
	Travel (estimated)					0.84	0.80	
PM_{10}	Home (front-door)	0.99	0.95	0.80	0.80	0.85	0.79	0.73
	School (estimated)							0.82
	Travel (estimated)					0.79	0.77	

correlations between the exposure at home and during other activities (i.e., commuting and playing). Specifically, the correlations were between 0.68 and 0.89 for the exposures between at home and at school. As a result, home exposures contain the least information about school exposure, which is the second most important activity in terms of time spent after staying at home. Furthermore, the high correlation between the exposure at the estimated school and the actual school locations ($0.81 < R < 0.94$) suggests that the simulated school exposures are good estimates of "true" school exposures. Importantly, the correlation was higher for the estimated school exposure than with the residential

Table 5
% Difference in lung function (with 95% confidence intervals) per IQR increase in exposure.

		M1: Front door		M2: Home		M3: Activity pattern using estimated school address		M4: Activity pattern using actual school address	
FEV_1	NO_2	**−1.40**	**(-2.54, -0.24)**	**−1.39**	**(-2.53, -0.23)**	**−1.59**	**(-2.77, -0.39)**	**−1.50**	**(-2.68, -0.30)**
	NO_X	−0.74	(-1.59, 0.12)	−0.73	(-1.57, 0.12)	**−1.05**	**(-2.00, -0.08)**	−0.90	(-1.82, 0.04)
	$PM_{2.5}$	**−2.11**	**(-3.58, -0.62)**	**−2.07**	**(-3.54, -0.58)**	**−2.38**	**(-3.91, -0.82)**	**−2.20**	**(-3.71, -0.66)**
	$PM_{2.5}$abs	**−0.61**	**(-1.03, -0.18)**	**−0.59**	**(-1.02, -0.16)**	**−0.68**	**(-1.13, -0.23)**	**−0.63**	**(-1.07, -0.19)**
	PM_{10}	−0.51	(-1.32, 0.32)	−0.49	(-1.31, 0.33)	−0.71	(-1.61, 0.2)	−0.55	(-1.4, 0.32)
FVC	NO_2	**−2.78**	**(-3.91, -1.63)**	**−2.78**	**(-3.91, -1.64)**	**−3.07**	**(-4.23, -1.89)**	**−2.97**	**(-4.14, -1.8)**
	NO_X	**−1.51**	**(-2.36, -0.65)**	**−1.50**	**(-2.34, -0.66)**	**−2.01**	**(-2.97, -1.05)**	**−1.84**	**(-2.76, -0.91)**
	$PM_{2.5}$	**−3.85**	**(-5.30, -2.38)**	**−3.8**	**(-5.25, -2.33)**	**−4.22**	**(-5.72, -2.69)**	**−4.03**	**(-5.52, -2.53)**
	$PM_{2.5}$abs	**−1.11**	**(-1.54, -0.68)**	**−1.1**	**(-1.52, -0.67)**	**−1.22**	**(-1.66, -0.77)**	**−1.17**	**(-1.60, -0.73)**
	PM_{10}	**−1.05**	**(-1.87, -0.22)**	**−1.03**	**(-1.85, -0.21)**	**−1.33**	**(-2.24, -0.42)**	**−1.15**	**(-2.01, -0.29)**

address, documenting that our procedure provided additional information that better explained actual school. As a result, methodologies which do not incorporate the exact school location can also be relevant for countries like the Netherlands. However, this may not apply for other countries or specific areas where the distance and the exposure contrast between home and school is larger and children may travel from rural homes to more urban school locations. Given the small differences between the correlations of all exposure activity spaces it is hard to make solid conclusions other than that the inclusion of time activity patterns and exposures at non-residential locations adds little information to the conventional residential exposure in settings similar to the one examined here.

4.2. Comparison with previous studies

Several studies have compared static exposures with exposures which integrate activities (Blanchard et al., 2018; Dhondt et al., 2012; Ragettli et al., 2015; Setton et al., 2011; Strand et al., 2006). Only one of them was carried out in children (Strand et al., 2006) while the remaining studies included either adults (Blanchard et al., 2018; Setton et al., 2011) or a mixed population of adults and children (Dhondt et al., 2012; Ragettli et al., 2015).

Blanchard et al. (2018) compared the static approach with an approach which also includes commuting of pregnant women and concluded that air pollution exposure can be underestimated when mobility and commuting mode are not integrated in the exposure estimates (around 0.5–1.5 $\mu g/m^3$ for NO_2) (Blanchard et al., 2018). Similarly, in our study the underestimation was also very small in absolute terms (between 0.6 and 0.8 $\mu g/m^3$).

Setton et al. (2011) used paired individual residence and mobility exposure estimates and calculated bias in epidemiological analyses when mobility is not included. They concluded that ignoring daily mobility patterns can contribute to bias towards the null (bias range: 0.63–0.77; SD: 0.02) in exposure-health analyses (Setton et al., 2011). They additionally found that the bias was depended on the amount of time spent away from home and the distance between the home and work address (Setton et al., 2011). The same bias estimation method used in another study (Ragettli et al., 2015) where they used time-activity data, including travel data in Basel. Despite the relative small contributions of travelling exposure to the total exposure they found significant (12%) underestimation of health effects. Similarly, Dhondt et al. (2012) developed an exposure modelling framework to assess population-based air pollution exposure and the relation with health. They found a significant 1.2% increase in respiratory mortality for NO_2 by incorporating time-activity patterns compared to a static exposure (Dhondt et al., 2012). Our analyses did not reveal significant increase in lung function by incorporating time-activity patterns as in the aforementioned studies. This could be a result of the young age (8 years) of our cohort participants. Young children usually spent more time at home or around home location compared to adults.

An epidemiological study which studied the association between FEV_1 and personal exposure to sulphate in children aged 6–12 years with asthma, indicated that the use of personal exposure estimates enhance sensitivity for detecting associations with health outcomes (Strand et al., 2006). Specifically, they found that a 10 mg/m^3 increase in $PM_{2.5}$ was associated with a 2.2% decrease in FEV_1 at a 1-day lag of the pollutant (95% CI: 0.0–4.3% decrease) compared to a 1.0% (95% CI: 0.0–2.0% decrease by using a fixed monitor. The same study showed that personal exposure to sulphate was highly correlated with home exposure ($R = 0.94$) and school exposure ($R = 0.92$) (Strand et al., 2006), those high correlations are in agreement with our very high correlations between the exposures.

4.3. Strengths and limitations

The major strength is that we systematically compared methods of exposure assessments that can be scaled to large populations. One of the strengths of the present study is the spatial distribution of the PIAMA home addresses that are well dispersed geographically both in urban and rural areas ensuring variability in exposure. Additionally, the maps of the air pollutants and especially of NO_2, NO_x and $PM_{2.5}$ absorbance exhibit substantial small-scale spatial variation. Furthermore, we were able to investigate the associations between air pollution exposures and lung function with exposure assessment methodologies applicable to large populations. We were able to incorporate within the daily activity pattern of one of our methodologies the actual school addresses; while such information is not often available in cohort studies.

A limitation is that our method is based upon estimated time activity patterns, which may deviate from actual time activity patterns for individual children. We only had individual information about the location of the home and school locations. We note however that for a scalable solution to the problem of including time activity data in epidemiological studies, estimation of time activity patterns is inevitable. Additionally, we were not able to validate our exposure assessment methodologies against “true” exposures from personal monitoring. We did observe that the estimated school exposures calculated as the average exposure at all schools within 2 km of a participant’s home were highly correlated with exposures at the actual school location. The number of hours spent at school does not differ between children, because this is regulated in the Netherlands and therefore it is easier to account for it when no information on the duration of activities is available. Another limitation is that we did not take into account weekends and (school) holidays. For weekend days and holidays, time activity patterns likely differ more between children and are less predictable. We note that we covered five of seven days, the majority of time. Furthermore, we assigned estimated annual average concentrations to all activities, we expect that the error will differ among the activities which are related to lifestyle and weather conditions such as playing in the neighborhood.

4.4. Generalizability of findings

The added value of including exposure at non-residential locations in the air pollution exposure assessment was rather limited for this specific age-group and setting. Hence, for this age group, residential exposures may be sufficient to capture the air pollution exposures. This is an important finding for air pollution epidemiology studies on children in the Netherlands and possibly for other European countries. However, the findings of this study may not be generalizable to other countries which have different urban structure as the assumptions about distances of activity spaces from home were designed using Dutch datasets. Furthermore, the findings may differ in an adult population whose activities would take place for longer durations and further away from the home addresses (e.g., working activity and related commute trips).

5. Conclusions

Air pollution exposure estimates for 8-year-old children in the Netherlands, from methods based on the residential location only and methods including time activity patterns, were highly correlated and associated with similar decreases in lung function. Our study illustrates that the contrast in annual average exposure to air pollution for school children across the Netherlands was sufficiently captured by residential exposures.

Credit author statement

Anna-Maria Ntarladima, conceived the manuscript. Anna-Maria Ntarladima, Oliver Schmitz, Meng Lu, prepared and checked the geo data. Anna-Maria Ntarladima, wrote the initial draft and had the responsibility for submitting for publication. Ulrike Gehring, Derek Karssenberg, Ilonca Vaartjes, Gerard Hoek, Diederick E. Grobbee, Jolanda Boer, Gerard Koppelman, Judith Vonk, Roel Vermeulen, performed a critical revision of the manuscript. Anna-Maria Ntarladima, conducted the analyses. Ulrike Gehring, Derek Karssenberg, Ilonca Vaartjes, Gerard Hoek, provided important feedback on how the study can be improved. Ulrike Gehring, Jolanda Boer, Gerard Hoek, Roel Vermeulen, contributed with offering the PIAMA data. All authors read and approved the final manuscript.

Declaration of competing interest

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

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Appendix A. Supplementary data

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References

Beelen, Rob, Hoek, Gerard, Vienneau, Danielle, Eeftens, Marloes, Dimakopoulou, Konstantina, Pedeli, Xanthi, Tsai, Ming-Yi, Künzli, Nino, Schikowski, Tamara, Marcon, Alessandro, 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in europe – the ESCAPE project. Atmos. Environ. 72, 10–23. https://doi.org/10.1016/j.atmosenv.2013.02.037.

Blanchard, Olivier, Deguen, Séverine, Kihal-Talantikite, Wahida, François, Romain, Zmirou-Navier, Denis, 2018. Does residential mobility during pregnancy induce exposure misclassification for air pollution? Environ. Health : A Global Access Science Source 17 (1), 1–16. https://doi.org/10.1186/s12940-018-0416-8.

CBS, 2015. Onderzoek Verplaatsingen in Nederland 2014 july):39. doi: https://doi.org/10.17026/dans-x95-5p7y.

Centraal Bureau voor de Statistiek, 2015. Gemeentegrootte En Stedelijkheid. *CBS*. https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/overig/gemeentegrootte-en-stedelijkheid. (Accessed 23 October 2018).

Chaney, Robert A., Sloan, Chantel D., Cooper, Victoria C., Robinson, Daniel R., Hendrickson, Nathan R., Mccord, Tyler A., Johnston, James D., 2017. Personal exposure to fine particulate air pollution while commuting: an examination of six transport modes on an urban arterial roadway. https://doi.org/10.1371/journal.pone.0188053.

Clark, Nina Annika, Demers, Paul A., Karr, Catherine J., Koehoorn, Mieke, Lencar, Cornel, Tamburic, Lillian, Brauer, Michael, 2010. Effect of early life exposure to air pollution on development of childhood asthma. Environ. Health Perspect. 118 (2), 284–290. https://doi.org/10.1289/ehp.0900916.

Dhondt, Stijn, Beckx, Carolien, Degraeuwe, Bart, Lefebvre, Wouter, Kochan, Bruno, Bellemans, Tom, Int Panis, Luc, Macharis, Cathy, Putman, Koen, 2012. Health impact assessment of air pollution using a dynamic exposure profile: implications for exposure and health impact estimates. Environ. Impact Assess. Rev. 36, 42–51. https://doi.org/10.1016/j.eiar.2012.03.004.

Eeftens, Marloes, Beelen, Rob, de Hoogh, Kees, Bellander, Tom, Cesaroni, Giulia, Cirach, Marta, Declercq, Christophe, Dėdelė, Audrius, Dons, Evi, de Nazelle, Audrey, Dimakopoulou, Konstantina, Eriksen, Kirsten, Falq, Grégoire, Fischer, Paul, Galassi, Claudia, Gražulevičienė, Regina, Heinrich, Joachim, Hoffmann, Barbara, Jerrett, Michael, Keidel, Dirk, Korek, Michal, Lanki, Timo, Lindley, Sarah, Madsen, Christian, Mölter, Anna, Nádor, Gizella, Nieuwenhuijsen, Mark, Nonnemacher, Michael, Pedeli, Xanthi, Raaschou-Nielsen, Ole, Patelarou, Evridiki, Quass, Ulrich, Ranzi, Andrea, Schindler, Christian, Stempfelet, Morgane, Stephanou, Euripides, Sugiri, Dorothea, Tsai, Ming-Yi, Yli-Tuomi, Tarja, Varró, Mihály J., Vienneau, Danielle, von Klot, Stephanie, Wolf, Kathrin, Brunekreef, Bert, Hoek, Gerard, 2012. Development of land use regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. Environ. Sci. Technol. 46 (20), 11195–11205. https://doi.org/10.1021/es301948k.

Gehring, Ulrike, Gruzieva, Olena, Agius, Raymond M., Beelen, Rob, Custovic, Adnan, Cyrys, Josef, Eeftens, Marloes, Flexeder, Claudia, Fuertes, Elaine, Heinrich, Joachim, Hoffmann, Barbara, de Jongste, Johan C., Kerkhof, Marjan, Klümper, Claudia, Korek, Michal, Mölter, Anna, Schultz, Erica S., Simpson, Angela, Sugiri, Dorothea, Svartengren, Magnus, von Berg, Andrea, Wijga, Alet H., Pershagen, Göran, Brunekreef, Bert, 2013. Air pollution exposure and lung function in children: the ESCAPE project. Environ. Health Perspect. 121 (11–12), 1357–1364. https://doi.org/10.1289/ehp.1306770.

Götschi, Thomas, Heinrich, Joachim, Jordi, Sunyer, Nino, Künzli, 2008. Long-term effects of ambient air pollution on lung function: a review. Epidemiology 19 (5), 690–701. https://doi.org/10.1097/EDE.ObO.

Hoek, Gerard, Beelen, Rob, de Hoogh, Kees, Vienneau, Danielle, Gulliver, John, Fischer, Paul, Briggs, David, 2008. A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmos. Environ. 42 (33), 7561–7578. https://doi.org/10.1016/J.ATMOSENV.2008.05.057.

Hummer, J.E., Rouphail, N.M., Toole, J.L., Patten, R.S., Schneider, R.J., Green, J.S., Hughes, R.G., Fain, S.J., 2006. Evaluation of safety, design, and operation of shared-use paths - final report.

Karssenberg, Derek, Schmitz, Oliver, Salamon, Peter, De Jong, Kor, Bierkens, Marc F.P., 2010. Environmental modelling & software A software framework for construction of process-based stochastic spatio-temporal models and data assimilation. Environ. Model. Software 25 (4), 489–502. https://doi.org/10.1016/j.envsoft.2009.10.004.

Klepeis, Neil E., Nelson, William C., Ott, Wayne R., Robinson, John P., Tsang, Andy M., Switzer, Paul, Behar, Joseph V., Hern, Stephen C., Engelmann, William H., 2001. The national human activity pattern survey (NHAPS): a resource for assessing exposure to environmental pollutants. J. Expo. Anal. Environ. Epidemiol. 11 (3), 231–252. https://doi.org/10.1038/sj.jea.7500165.

Krämer, Ursula, Sugiri, Dorothea, Ranft, Ulrich, Krutmann, Jean, von Berg, Andrea, Berdel, Dietrich, Behrendt, Heidrun, Kuhlbusch, Thomas, Hochadel, Matthias, Erich Wichmann, Heinz, Heinrich, Joachim, 2009. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. J. Dermatol. Sci. 56 (2), 99–105. https://doi.org/10.1016/j.jdermsci.2009.07.014.

Landrigan, Philip J., Fuller, Richard, Acosta, Nereus J.R., Adeyi, Olusoji, Arnold, Robert, Basu, Niladri (Nil), Bibi Baldé, Abdoulaye, Bertollini, Roberto, Bose-O'Reilly, Stephan, Boufford, Jo Ivey, Breysse, Patrick N., Chiles, Thomas, Mahidol, Chulabhorn, Coll-Seck, Awa M., Cropper, Maureen L., Fobil, Julius, Fuster, Valentin, Greenstone, Michael, Haines, Andy, Hanrahan, David, Hunter, David, Khare, Mukesh, Krupnick, Alan, Lanphear, Bruce, Lohani, Bindu, Martin, Keith, Mathiasen, Karen V., McTeer, Maureen A., Murray, Christopher J.L., Ndahimananjara, Johanita D., Perera, Frederica, Potočnik, Janez, Preker, Alexander S., Ramesh, Jairam, Rockström, Johan, Salinas, Carlos, Samson, Leona D., Sandilya, Karti, Sly, Peter D., Smith, Kirk R., Steiner, Achim, Stewart, Richard B., Suk, William A., van Schayck, Onno C.P., Yadama, Gautam N., Yumkella, Kandeh, Zhong, Ma, 2018. The lancet commission on pollution and health. Lancet 391 (10119), 462–512. https://doi.org/10.1016/S0140-6736(17)32345-0.

Larkin, A., Hystad, P., 2017. Towards personal exposures: how technology is changing air pollution and health Research. Curr. Environ. Health Rep. https://doi.org/10.1007/s40572-017-0163-y.

Nordling, Emma, Berglind, Niklas, Melén, Erik, Emenius, Gunnel, Hallberg, Jenny, Nyberg, Fredrik, Pershagen, Göran, Svartengren, Magnus, Wickman, Magnus, Bellander, Tom, 2008. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 19, 401–408. https://doi.org/10.1097/EDE.0b013e31816a1ce3.

Ntarladima, Anna-Maria, Vaartjes, Ilonca, Grobbee, Diederick E., Dijst, Martin, Schmitz, Oliver, Uiterwaal, Cuno, Dalmeijer, Geertje, van der Ent, Cornelis, Hoek, Gerard, Karssenberg, Derek, 2019. Relations between air pollution and vascular development in 5-year old children: a cross-sectional study in The Netherlands. Environ. Health 18 (1), 50. https://doi.org/10.1186/s12940-019-0487-1.

Park, Yoo Min, Kwan, Mei Po, 2017. Individual exposure estimates may Be erroneous when spatiotemporal variability of air pollution and human mobility are ignored. Health Place 43, 85–94. https://doi.org/10.1016/j.healthplace.2016.10.002.

Paulin, Laura, Hansel, Nadia, 2016. Particulate air pollution and impaired lung function. F1000Research 5, 1–9. https://doi.org/10.12688/f1000research.7108.1, 0.

Pekkanen, J., Pearce, N., 2001. Environmental epidemiology: challenges and opportunities. Environ. Health Perspect. 109 (1), 1–5. https://doi.org/10.2307/3434913.

Ragettli, Martina S., Phuleria, Harish C., Tsai, Ming Yi, Schindler, Christian, De Nazelle, Audrey, Ducret-Stich, Regina E., Ineichen, Alex, Perez, Laura, Braun-Fahrländer, Charlotte, Probst-Hensch, Nicole, Künzli, Nino, 2015. The relevance of commuter and work/school exposure in an epidemiological study on traffic-related air pollution. J. Expo. Sci. Environ. Epidemiol. 25 (5), 474–481. https://doi.org/10.1038/jes.2014.83.

Schlesinger, R.B., Kunzli, N., Hidy, G.M., Gotschi, T., Jerrett, M., 2006. The health relevance of ambient particulate matter characteristics: coherence of toxicological and epidemiological inferences. Inhal. Toxicol. 18 (2), 95–125. https://doi.org/10.1080/08958370500306016.

Schmitz, O., Beelen, R., Strak, M., Hoek, G., Soenario, I., Brunekreef, B., Vaartjes, I., Dijst, M., Grobbee, R., Karssenberg, D., 2018. High resolution air pollution concentration maps for The Netherlands. Scientific Data 1–17.

Schmitz, Oliver, Beelen, Rob, Strak, Maciej, Hoek, Gerard, Soenario, Ivan, Brunekreef, Bert, Vaartjes, Ilonca, Dijst, Martin J., Grobbee, Diederick E., Karssenberg, Derek, 2019. Data descriptor: high resolution annual average air pollution concentration maps for The Netherlands. Scientific Data 6, 1–12. https://doi.org/10.1038/sdata.2019.35.

Schultz, Erica S., Litonjua, Augusto A., Melén, Erik, 2017. Effects of long-term exposure to traffic-related air pollution on lung function in children. Curr. Allergy Asthma Rep. 17 (6).

Setton, Eleanor, Marshall, Julian D., Brauer, Michael, Lundquist, Kathryn R., Hystad, Perry, Keller, Peter, Cloutier-Fisher, Denise, 2011. The impact of daily mobility on exposure to traffic-related air pollution and health effect estimates. J. Expo. Sci. Environ. Epidemiol. 21 (1), 42–48. https://doi.org/10.1038/jes.2010.14.

Sexton, Ken, Barry, Ryan, 1988. Assessment of human exposure to air pollution. In: Air Pollution, the Automobile and Public Health, 208–32.

Sin, Don D., Wu, Lie Ling, Man, S. F. Pau, 2005. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. Chest 127 (6), 1952–1959. https://doi.org/10.1378/chest.127.6.1952.

Strand, Matthew, Vedal, Sverre, Rodes, Charles, Dutton, Steven J., Gelfand, Erwin W., Rabinovitch, Nathan, 2006. Estimating effects of ambient PM 2.5 exposure on health using PM 2.5 component measurements and regression calibration. J. Expo. Sci. Environ. Epidemiol. 16, 30–38. https://doi.org/10.1038/sj.jea.7500434.

Svyk, Bogna, 2020. Car vs. Bike calculator - omni. https://www.omnicalculator.com/ecology/car-vs-bike. (Accessed 24 February 2020).

Thurston, G.D., Kipen, H., AnnesiMaesano, I., Balmes, J., Brook, R.D., Cromar, K., De Matteis, S., Forastiere, F., Forsberg, B., Frampton, M.W., Grigg, J., Heederik, D., Kelly, F.J., Kuenzli, N., Laumbach, R., Peters, A., Rajagopalan, S.T., Rich, D., Ritz, B., Samet, J.M., Sandstrom, T., Sigsgaard, T., Sunyer, J., Brunekreef, B., 2017. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur. Respir. J. 49 (1) (pagination):Arte Number: 1600419. ate of Pubaton: 01 Jan 2017.

Wijga, Alet H., Kerkhof, Marjan, Gehring, Ulrike, De jongste, Johan C., Postma, Dirkje S., Aalberse, Rob C., Wolse, Ada P.H., Koppelman, Gerard H., Van rossem, Lenie, Oldenwening, Marieke, Brunekreef, Bert, Smit, Henriëtte A., 2013. Cohort profile: the prevention and incidence of asthma and mite Allergy (PIAMA) birth cohort. Int. J. Epidemiol. 43 (2), 527–535. https://doi.org/10.1093/ije/dys231.

World Health Organization, 2018. WHO | Ambient Air Pollution. *WHO*.