



Spatial variation in nitrogen dioxide concentrations and cardiopulmonary hospital admissions

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ABSTRACT

Background: Air pollution episodes are associated with increased cardiopulmonary hospital admissions. Cohort studies showed associations of spatial variation in traffic-related air pollution with respiratory and cardiovascular mortality. Much less is known in particular about associations with cardiovascular morbidity. We explored the relation between spatial variation in nitrogen dioxide (NO₂) concentrations and cardiopulmonary hospital admissions.

Methods: This ecological study was based on hospital admissions data (2001–2004) from the National Medical Registration and general population data for the West of the Netherlands (population 4.04 million). At the 4-digit postcode area level (n=683) associations between modeled annual average outdoor NO₂ concentrations and hospital admissions for respiratory and cardiovascular causes were evaluated by linear regression with the log of the postcode-specific percentage of subjects that have been admitted at least once during the study period as the dependent variable. All analyses were adjusted for differences in composition of the population of the postcode areas (age, sex, income).

Results: At the postcode level, positive associations were found between outdoor NO₂ concentrations and hospital admission rates for asthma, chronic obstructive pulmonary disease (COPD), all cardiovascular causes, ischemic heart disease and stroke (e.g. adjusted relative risk (95% confidence interval) for the second to fourth quartile relative to the first quartile of exposure were 1.87 (1.46–2.40), 2.34 (1.83–3.01) and 2.81 (2.16–3.65) for asthma; 1.44 (1.19–1.74), 1.50 (1.24–1.82) and 1.60 (1.31–1.96) for COPD). Associations remained after additional (indirect) adjustment for smoking (COPD admission rate) and degree of urbanization.

Conclusions: Our study suggests an increased risk of hospitalization for respiratory and cardiovascular causes in areas with higher levels of NO₂. Our findings add to the currently limited evidence of a long-term effect of air pollution on hospitalization. The ecological design of our study is a limitation and more studies with individual data are needed to confirm our findings.

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1. Introduction

There is consistent evidence from epidemiologic studies that short-term air pollution exposure (e.g. over several hours to days) is associated with respiratory and cardiovascular effects such as increases in respiratory symptoms, emergency room visits and hospital admissions for asthma and/or COPD; myocardial infarction, heart failure and stroke (Brook et al., 2010; Mills et al., 2015; Health Effects Institute (HEI), 2010; Shah et al., 2015; Wang et al.,

2014). The associations of short-term air pollution exposure with hospitalization and death were found to be stronger in elderly subjects (age ≥ 65 years) than in younger subjects (Bell et al., 2013). In the past two decades, the focus has shifted from the acute health effects towards the chronic health effects of air pollution exposure (e.g. over several months to years) (Brunekreef and Holgate, 2002). In cohort studies, spatial contrasts in air pollution levels have been linked to mortality, onset and presence of respiratory disease. From these cohort studies, there is increasing evidence for an effect of long-term exposure to air pollution on all-cause and cardiovascular mortality, (Hoek et al., 2013; Health Effects Institute (HEI), 2010) atherosclerosis, (Health Effects Institute (HEI), 2010) and the development of asthma in children and to a

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lesser extent in adults (Bowatte et al., 2015; Health Effects Institute (HEI), 2010).

Besides mortality and disease, hospital admissions due to (non-fatal) respiratory or cardiovascular events present an additional facet of the long-term air pollution-health relationship. Especially for cardiovascular diseases, the evidence for morbidity effects of air pollution is still limited. Only a few studies so far have investigated the relationship between long-term air pollution exposure and hospital admissions and findings are mixed. A cohort study among adults in Denmark reported increasing incidence of hospital admissions for asthma, COPD, and stroke with increasing 35-year mean residential nitrogen dioxide (NO₂) level (Andersen et al., 2012a, 2011, 2012b). Moreover, several case-control studies on chronic exposure to air pollution and hospital admissions have been conducted. Lin et al. (2002) reported an association of traffic density within 200 m of the residential address with childhood asthma hospital admissions in North America, in absence of a dose-response relationship. No association was found between hospital admissions for asthma among children and living close to busy roads in London (Wilkinson et al., 1999). Neupane et al. (2010) reported significant increases in hospitalization for community acquired pneumonia with increased exposures to NO₂ and particulate matter with a diameter of less than 2.5 µm (PM_{2.5}) among the elderly. No clear associations were found between nitrogen oxides (NO_x) and hospital admissions for ischemic stroke in Sweden (Oudin et al., 2009). Likewise, no clear association was found between hospital admissions for coronary heart disease and NO₂ in an English ecological study among subjects aged 45 and older (Maheswaran et al., 2005b); but hospital admission rates for stroke were increased among subjects in the highest exposure category (Maheswaran et al., 2005a).

Registries present an ideal framework for the assessment of the long-term effects of air pollution on hospital admissions in large populations. For the present population-based study, we linked hospital admissions data for four million inhabitants of the Western part of the Netherlands to spatial contrasts in NO₂ concentrations and explored associations with hospital admission rates for respiratory and cardiovascular causes.

2. Materials and methods

2.1. Study area and population

The study was conducted among inhabitants (4.04 million) of the western part of the Netherlands (Supplementary Fig. 1). The study area (approx. 7,300 km²) consists of rural and (sub)urban areas including the cities of Amsterdam and Rotterdam. The population was studied by four-position postcode (PC4) area. Residential location data of the patients was not available at a more detailed spatial scale since hospitals do not record the full address in the National Medical Registration due to privacy protection laws. In the Netherlands, PC4 areas typically represent small villages or neighborhoods. The city of Amsterdam (740,000 inhabitants), for instance, consists of 78 PC4 areas. In this study area, the total number of PC4 areas is 683 with an average population size of 5,916 inhabitants.

2.2. Air pollution exposure assessment

Annual average NO₂ concentrations for the PC4 areas were estimated using a land use regression model that has been developed specifically for the study area and has been described elsewhere (Dijkema et al., 2011). In brief, an air pollution monitoring campaign was performed in 2007 in the study area. At each of a total of 60 rural, urban, and traffic dominated sites four

1-week measurements of NO₂ were performed in the different seasons (one measurement per season). Results from the four measurements were averaged to estimate the annual average concentration. Traffic and land use data were evaluated as predictors of the spatial variability in NO₂ concentrations. Data on traffic were obtained from local authorities in the study area responsible for traffic management in the study area. The national government is responsible for the freeways; the provinces for the highways, main connection routes, and other country roads in rural areas; and the municipalities for all other roads and streets. In the study area, there were 93 sources of traffic data: the national department of traffic, 3 provinces, and 89 municipalities. Data on land use were obtained from geographic information system (GIS) databases. A regression model was fitted to maximize the adjusted explained variance using a supervised forward step-wise approach that has been described elsewhere (Dijkema et al., 2011). In brief, the variable with the highest R² based on simple linear regression analysis was selected first. Variables with the second, third, etc. highest R² were then added one by one and included in the multiple regression model if the adjusted R² improved by at least 1% and if the sign of each of the regression coefficients remained as expected. After all available variables had been tested, the resulting model was reexamined. We excluded variables with the highest *p*-values one at a time if the adjusted R² remained unchanged (difference in adjusted R² < 1%). The reduced model was preferred. The final model included regional background NO₂ concentration, traffic volume at the nearest road, distance to the nearest busy road and the percentage of residential land use within a circular buffer with a radius of 5 km. Leave one out cross-validation of the model resulted in an R² of 84%. For this study, first NO₂ concentration were estimated for the centroids of all six-position postcode (PC6, consisting of four numbers followed by two letters) areas (consisting of approximately 20 addresses) in the study area. Then, for each PC4 area (defined as all PC6 with the same four numbers), the mean of the PC6 concentrations was calculated (average number of PC6 areas per PC4 area: 141, range 4–378).

2.3. Hospital admissions data

Hospital admissions data were obtained from the National Medical Registration (Borghans et al., 2008). For the period of January 1, 2001 to December 31, 2004, all hospital admissions of inhabitants of the study area were registered. The registration consists of cause (ICD-9), dates of admission and discharge, and whether the admission was planned or an emergency. Furthermore, registration of a limited number of personal characteristics (sex, date of birth, residential postcode) took place. In this study we focused on all hospital admissions (that is the total of emergency and planned) and emergency hospital admissions separately for a number of *a priori* selected admission causes: all respiratory (ICD-9: 460–519), asthma (ICD-9: 493), COPD (ICD-9: 490–492 and 494–496), all cardiovascular (ICD-9: 390–429), ischemic heart disease (IHD, ICD-9: 410–414) and stroke (ICD-9: 430–438) during the study period, i.e. 2001–2004. The main outcome for the present analysis is the risk of being hospitalized during the study period defined as the number of subjects that have been admitted at least once for any (specific) respiratory or cardiovascular causes per total number of inhabitants in a postcode (PC4) area. This means that subsequent admissions for the same cause are ignored. We analyzed emergency hospital admissions in addition to all hospital admissions to get some insights into the role of acute and chronic exposures in the observed associations with hospital admissions. We hypothesize that emergency hospital admissions, in contrast to scheduled hospital admissions, are primarily weather driven short-term air pollution episodes rather than with chronic

exposure. Ethical approval was obtained from the authorized Institutional Review Board of Prismaant.

2.4. Confounding variables

Statistics Netherlands (CBS, Heerlen/Den Haag, the Netherlands) provided data on the total population and population by sex and age group (categorized as 0–20 years old, 20–65 years old and older than 65 years), mean income (Euro per month) and urbanization (addresses per km²) for each PC4 area. For our analyses, the average values of the population data for the period 2001–2004 were used. Adjustment for sex and age at hospital admission at the individual instead of at the PC4 level was not possible as age and sex were available for subjects who were admitted to the hospital only and not for subjects who were not admitted to the hospital.

2.5. Statistical analysis

We analyzed the association between modeled NO₂ concentrations and the risk of hospitalization (defined as the number of persons admitted at least once during the study period for respiratory and cardiovascular causes per total number of inhabitants in a postcode (PC4) area) by linear regression with the log of the PC4 specific risk of hospitalization as the dependent variable. PC4 areas with no admissions for a specific cause during the study period were assigned a value of one-half of the smallest observed non-zero value. Smoothing splines (GAM procedure, mgcv-package, R version 2.8.0, R foundation for Statistical Computing, Vienna, Austria) were used to explore the functional relationship between the risk of hospital admissions and air pollution. Since associations between risk of hospital admissions and NO₂ concentration were generally non-linear (Supplementary Fig. 2), NO₂ levels were divided into quartiles. The lowest exposure quartile was used for reference. Results of regression analyses are presented as relative risks (RR), calculated from the estimated regression coefficients β as e^{β} with 95% confidence intervals (95% CI), with and without adjustment for confounders.

We adjusted for the following *a priori* selected confounders: age, sex and income. Age was included in the regression models using two variables: the percentage of young (< 20 years) people per postcode area and the percentage of elderly (> 65 years) people per postcode area. Sex was included as the percentage of men and income as mean income per month per postcode area. We performed all analyses for all hospital admissions (the total of emergency and planned) and emergency hospital admissions, separately. As there is evidence for hospitalization being associated with urbanization, (Uijen et al., 2010; van Hooijdonk et al., 2007) we performed sensitivity analyses with additional adjustment for the number of addresses per km² as an indicator for urbanization. No information on smoking was available for the full population. Adjustment for diseases such as COPD and lung-cancer has been suggested in studies where information on smoking is not available (Best and Hansell, 2009; Richardson, 2010). We therefore performed sensitivity analyses for all hospital admissions with additional adjustment for COPD. We calculated Moran's I statistics for the model residuals to assess the presence of spatial autocorrelation.

In addition, we explored the association between smoking and NO₂ concentrations using 2001–2004 questionnaire derived data from the CBS for 8,433 subjects living in the study area (Permanent Quality of Life (Permanent Onderzoek LeefSituatie, POLS)-questionnaire). POLS is performed yearly among a sample of the Dutch population and contains questions on active smoking for all participants aged 12 years and older. For this analysis, we assigned exposure quartiles to all postcodes in the study area using the

LUR-model described above and the same cut-offs for exposure categories as in the main analysis and sent it to CBS, where upon our request, CBS linked exposure quartiles to the home address of the 8,433 participants and compared smoking prevalence between quartiles of exposure. Data were not directly available to us due to privacy regulations.

All analyses were done using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

The distributions of population characteristics and estimated outdoor NO₂ concentrations for the PC4 areas are shown in Table 1. Although the range in concentrations was large, for the majority of the postcode areas concentrations were between 17 and 32 $\mu\text{g}/\text{m}^3$. The size of the population was 0.5, 0.9, 1.2 and 1.4 million for the first, second, third and fourth quartile of exposure, respectively.

Table 2 shows the distribution of the population characteristics for the four quartiles of NO₂ exposure. The highest NO₂ concentrations occurred at urban locations. Differences in percentages of male subjects, subjects younger than 20 years or older than 65 years, and differences in mean income between exposure quartiles were statistically significant (p -value < 0.05), but small. There was no trend of increasing or decreasing percentages of male subjects, subjects younger than 20 years or older than 65 years, and mean income with increasing exposure.

Table 3 shows the distribution of the number of the number of hospital admission per cause (247,351 in total) and the distribution of the percentage of inhabitants that was hospitalized at least once per PC4 area. The percentage of persons that has been admitted to a hospital at least once was not correlated with the total number of inhabitants per PC4 area ($r=0.19$ and 0.01 for all respiratory and all cardiovascular causes, respectively).

For all respiratory causes, for all hospital admissions and for emergency hospital admissions, the relative risks for the second, third and fourth quartile were elevated relative to the reference quartile in crude analyses, with no increase in relative risk with increasing exposure (Table 4). Adjustment for age, sex and income did not change these findings. For asthma and COPD, however, increasing relative risks with increasing exposure were observed for all hospital admissions (Table 4). An increase in relative risk with increasing exposure was also observed for emergency hospital admissions for asthma (Table 4).

For all cardiovascular hospital admissions, relative risks were significantly increased for the three highest quartiles of exposure compared to the lowest quartile (Table 4). Adjustment for

Table 1

Distribution of population characteristics per postcode area ($n=683$) in the study area (West of the Netherlands) during 2001–2004.

Characteristic	Minimum	25th percentile	Median	75th percentile	Maximum
Inhabitants per PC4 area (n)	25	1,605	5,178	9,059	22,934
Male (%)	36	49	50	51	99
Age < 20 yrs (%)	0	21	25	27	43
Age > 65 yrs (%)	0	9	12	17	80
Average income (€/month)	900	1,849	2,045	2,298	4,633
Urbanization (addresses/km ²)	7	341	1,342	2,305	11,439
NO ₂ ($\mu\text{g}/\text{m}^3$)	7.7	17.4	24.0	31.2	82.5

Table 2
Distribution of population characteristics by quartile of NO₂ exposure.

Characteristic	Q1: < 17.4 µg/m ³		Q2: 17.4–24.0 µg/m ³		Q3: 24.0–31.2 µg/m ³		Q4: > 31.2 µg/m ³	
	Median	(25th–75th percentile)	Median	(25th–75th percentile)	Median	(25th–75th percentile)	Median	(25th–75th percentile)
Inhabitants per PC4 area (n)	1,556	(526–3,794)	5,565	(2,208–8,203)	6,673	(3,133–9,431)	8,439	(4,785–12,179)
Male (%)	51	(50–52)	50	(49–51)	49	(48–50)	50	(50–52)
Age < 20 yrs (%)	26	(23–28)	25	(22–28)	23	(21–27)	22	(18–26)
Age > 65 yrs (%)	11	(10–14)	13	(8–17)	14	(10–19)	11	(8–16)
Average income (€/month)	1,981	(1,823–2,175)	2,126	(1,933–2,335)	2,125	(1,866–2,387)	1,942	(1,752–2,269)
Urbanization (addresses/km ²)	184	(66–465)	1,066	(481–1,647)	1,780	(1,038–2,406)	2,847	(1,831–5,508)

Table 3
Number of inhabitants admitted at least once to a hospital in the study area (West of the Netherlands) during 2001–2004.

Cause of admission		Total number of admissions (N)	Inhabitants admitted at least once per postcode area (%)			PC4 areas without admissions (n)
			25th percentile	Median	75th percentile	
All Respiratory	All	134,235	2.6	3.1	3.7	10
	Emergency	42,184	0.7	1.0	1.2	24
Asthma	All	5,252	< 0.1	0.1	0.2	119
	Emergency	3,912	< 0.1	0.1	0.1	142
COPD	All	10,769	0.1	0.2	0.3	77
	Emergency	6,741	0.1	0.1	0.2	101
All Cardiovascular	All	113,116	2.1	2.7	3.3	6
	Emergency	73,524	1.3	1.7	2.2	8
IHD	All	55,794	1.0	1.3	1.6	16
	Emergency	34,801	0.6	0.8	1.0	28
Stroke	All	28,600	0.4	0.6	0.8	28
	Emergency	20,161	0.3	0.5	0.6	41

potential confounders reduced the effect estimates somewhat, but most remained (borderline) significantly elevated. For emergency hospital admissions for ‘all cardiovascular causes’ and IHD, increased relative risks were found for the second, third and fourth exposure quartile with no consistent increase in relative risk with increasing NO₂ concentrations. Moran's I coefficients of the residuals of the adjusted models were small for all outcomes (ranging from 0.00 to 0.02).

Supplementary Figs 3 and 4 show the result of the sensitivity analysis exploring the effect of additional adjustment for urbanization. Adjustment for urbanization reduced effect estimates for all hospital admissions for ‘all respiratory causes’, asthma, COPD and stroke (Supplementary Fig. 3). However, risks remained significantly elevated relative to the reference quartile. The effect estimates for ‘all cardiovascular causes’ and IHD admissions increased somewhat and the relative risk tended to increase with increasing exposure for these outcomes after adjustment for urbanization. The same adjustment reduced effect estimates for emergency hospital admissions for all causes studied (Supplementary Fig. 4).

Results of sensitivity analyses with additional adjustment for COPD as a proxy for smoking were very similar to those from analyses without adjustment for COPD. The COPD-adjusted relative risks (95% confidence intervals) for all hospital admissions for asthma, for instance, were 1.82 (1.42–2.33), 2.27 (1.77–2.91) and 2.75 (2.12–3.57), for the second, third and fourth quartile, respectively. For all hospital admissions for ‘all cardiovascular causes’, these relative risks (95% confidence intervals) were 1.06 (0.98–1.15), 1.07 (0.99–1.16) and 1.10 (1.01–1.19).

Data from the CBS indicated that smoking was somewhat more

prevalent among respondents living in areas with NO₂-levels in the highest quartile (35%) compared to the reference quartile (29%). However, no statistically significant difference was observed between the second and third quartiles and the reference quartile (30% and 31%, respectively, see Supplementary Table 1 for more details).

4. Discussion

This study shows that the community risk of hospitalization for respiratory and cardiovascular causes is positively associated with NO₂ levels.

NO₂ concentrations were modeled by land use regression. For less than ten percent of the postcodes estimated NO₂ concentrations were above the annual European Air Quality Limit Value, which is 40 µg/m³ (European Commission, 2013). Elevated risks for hospital admissions were thus seen at levels well below the EU Limit Value. The use of NO₂ as the single exposure metric is a limitation of the current study. In outdoor air, NO₂ is often highly correlated with other combustion products, in particular fine particulate matter (Eeftens et al., 2012). In the past, it has been suggested that NO₂ is a marker for a complex mixture of traffic-related air pollutants in studies such as ours (Brown et al., 2007). A recent review, however, concluded that NO₂ individually or in combination with other pollutants may cause adverse health effects (WHO Regional Office for Europe, 2013).

We assigned the average concentration of all six-position postcode-coordinates to the four-position postcode (PC4) area. Since six-position postcode areas consist of approximately 20

Table 4

Crude and adjusted associations between residential postcode area NO₂-concentration (in quartiles) and hospital admissions per postcode area in the West of the Netherlands during 2001–2004 expressed as relative risks (RR) with 95% confidence intervals (CI).

Outcome	Exposure category	All admissions				Emergency admissions			
		Crude		Adjusted ^a		Crude		Adjusted ^a	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
All Respiratory	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.17	(1.07, 1.28)	1.16	(1.07, 1.27)	1.27	(1.10, 1.45)	1.24	(1.09, 1.41)
	Q3: 24.0–31.2 µg/m ³	1.15	(1.05, 1.26)	1.14	(1.04, 1.24)	1.32	(1.15, 1.52)	1.23	(1.08, 1.39)
	Q4: > 31.2 µg/m ³	1.16	(1.06, 1.27)	1.18	(1.08, 1.29)	1.35	(1.17, 1.55)	1.27	(1.11, 1.46)
Asthma	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.83	(1.41, 2.36)	1.87	(1.46, 2.40)	1.65	(1.28, 2.12)	1.70	(1.33, 2.17)
	Q3: 24.0–31.2 µg/m ³	2.30	(1.78, 2.98)	2.34	(1.83, 3.01)	1.95	(1.51, 2.51)	2.00	(1.57, 2.57)
	Q4: > 31.2 µg/m ³	2.83	(2.19, 3.66)	2.81	(2.16, 3.65)	2.46	(1.90, 3.18)	2.47	(1.90, 3.20)
COPD	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.50	(1.20, 1.86)	1.44	(1.19, 1.74)	1.39	(1.11, 1.75)	1.34	(1.09, 1.65)
	Q3: 24.0–31.2 µg/m ³	1.76	(1.41, 2.18)	1.50	(1.24, 1.82)	1.49	(1.19, 1.87)	1.29	(1.05, 1.59)
	Q4: > 31.2 µg/m ³	1.84	(1.48, 2.29)	1.60	(1.31, 1.96)	1.52	(1.21, 1.90)	1.31	(1.06, 1.63)
All Cardiovascular	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.11	(1.00, 1.23)	1.07	(0.99, 1.15)	1.15	(1.03, 1.28)	1.12	(1.03, 1.22)
	Q3: 24.0–31.2 µg/m ³	1.22	(1.11, 1.35)	1.08	(1.00, 1.17)	1.32	(1.18, 1.48)	1.17	(1.28, 1.08)
	Q4: > 31.2 µg/m ³	1.18	(1.07, 1.30)	1.10	(1.01, 1.19)	1.14	(1.02, 1.27)	1.07	(0.98, 1.18)
IHD	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.15	(1.02, 1.28)	1.08	(0.98, 1.20)	1.21	(1.21, 1.38)	1.18	(1.05, 1.33)
	Q3: 24.0–31.2 µg/m ³	1.27	(1.13, 1.42)	1.12	(1.01, 1.23)	1.37	(1.20, 1.57)	1.24	(1.10, 1.40)
	Q4: > 31.2 µg/m ³	1.24	(1.10, 1.39)	1.13	(1.02, 1.25)	1.18	(1.03, 1.36)	1.14	(1.01, 1.30)
Stroke	Q1: < 17.4 µg/m ³	Reference		Reference		Reference		Reference	
	Q2: 17.4–24.0 µg/m ³	1.13	(0.98, 1.29)	1.11	(0.98, 1.25)	1.15	(0.95, 1.39)	1.12	(0.94, 1.33)
	Q3: 24.0–31.2 µg/m ³	1.25	(1.09, 1.44)	1.12	(0.99, 1.26)	1.28	(1.06, 1.55)	1.12	(0.94, 1.33)
	Q4: > 31.2 µg/m ³	1.32	(1.15, 1.51)	1.28	(1.13, 1.45)	1.18	(0.97, 1.43)	1.14	(0.95, 1.36)

^a Adjusted for age, sex and income.

addresses, no weighting based on residential density was performed. Estimation of residential NO₂-exposure at PC4 level instead of the individual street address may have caused some misclassification. Moreover, by defining exposure as residential exposure we hypothesize that residential exposure is a good representative for an individual's total personal exposure, which may have introduced further exposure misclassification (Aguilera et al., 2009; Nethery et al., 2008), especially for those subjects who live in rural areas and who commute to and from work in urban areas. Residential mobility, on which no information was available, may have been another source of misclassification. Such misclassifications may have made it more difficult to see exposure-response relationships in our data. This is supported by studies that reported associations of long-term air pollution exposure with asthma development in children (Gehring et al., 2010) and mortality (Beelen et al., 2008) separately for subjects who did and did not change residence during the follow-up, and that found stronger associations for those who did not change residence as compared to those who changed residence. Another limitation of the exposure assessment may be that the land-use regression model was developed based on measurement data for 2007, which is after the period for which hospitalization data were available (2000–2004). Recent studies, however, showed reasonable long-term validity of LUR models for periods of up to almost 10 years (Cesaroni et al., 2012; Eeftens et al., 2011; Madsen et al., 2011; Wang et al., 2013). Eeftens and co-workers (Eeftens et al., 2011) documented a very high correlation between NO₂ concentrations measured in 2007 and 1999–2000 across the Netherlands. Further support for the validity of the estimated air pollution levels over

time comes from the National Air Quality Monitoring Network: annual average NO₂ levels were relatively stable between 2000 and 2007 (Beijk et al., 2008).

The degree of urbanization is associated with cardiovascular and respiratory hospital admission, and air pollution is among the possible explanations for this associations (Uijen et al., 2010; van Hooijdonk et al., 2007). Urbanization, however, is also associated with differences in life-style and, for instance, access to hospitals. We therefore additionally adjusted our analyses for the number of addresses per km² as an indicator of urbanization. Adjustment for urbanization indeed reduced the effect estimates for the associations of NO₂ with respiratory admissions (particularly asthma) and stroke. Nevertheless, these associations remained statistically significant. In contrast, effect estimates for IHD and 'all cardiovascular causes' increased slightly after adjustment for urbanization. As one of the predictors in the land use regression model for NO₂ was the percentage of residential land use in a 5 km buffer, which is correlated with the number of addresses per km² (r=0.60), adjustment for urbanization likely resulted in overcorrection.

In the present analysis, we analyzed associations of NO₂ with the risk of hospitalization in the general population defined as the number of persons admitted at least once during the study period for a number of cardiorespiratory causes. This means that we assigned the same weight to subjects with single and multiple hospital admissions during the study period. We acknowledge that is only one possible way to analyze the present data. Alternatively, we could for example have analyzed associations of NO₂ with the risk of repeated hospitalization (more than once, twice etc.) for the

same cause, representing associations within a more susceptible subgroup of our study population or more severe diseases.

The risk of ecological bias is a limitation of the present study that used regionally aggregated data (at the PC4 level) and not individual data (e.g. Richardson et al., 1987). Ecological bias refers to the fact that factors associated with disease rates at the geographical level may not be associated with disease at the individual level. Ecological bias is caused by regional differences in disease rates due to variation in confounding factors across regions. It has been shown that under special assumptions, ecological studies can provide individual risk estimates (Beral et al., 1979). However, the evaluation of the extent of bias is usually difficult and therefore further exploration of the exposure-health relationship using individual data is needed (Greenland and Robins, 1994).

Furthermore, in this study, adjustment was only possible for a limited number of covariates. The distribution of the population per postcode area based on age and sex differed between quartiles of exposure, but overall differences were small. The analysis of questionnaire-based smoking data from the Statistics Netherlands for the study area showed that smoking prevalence was somewhat elevated in the highest air pollution quartile only. This could indicate that the elevated risk in the group with the highest exposure to NO₂ may be partly attributable to smoking. For several causes of hospital admission, however, we observed increased risks in the second and third quartile of NO₂ concentrations also, for which the smoking prevalence was comparable to the first quartile of NO₂ concentrations. Furthermore, adjustment for COPD as proxy for smoking did not change the effect estimates in our study. Due to the nature of our study, we cannot exclude that other unmeasured variables related to occupation, diet, lifestyle or other environmental exposures such as noise may have confounded our results, although no noteworthy confounding was found in cohort studies on similar associations (Andersen et al., 2012a, 2011; Mills et al., 2015).

Only few studies so far investigated the effect of chronic air pollution exposure on hospitalizations for asthma. Delfino et al. (Delfino et al., 2009) found significant positive associations between residential exposure to traffic-related air pollution (NO_x and CO) and risk of repeated hospitalization for asthma in children aged 0–18 years living in Orange County, California. A case-control study by Lin and colleagues (Lin et al., 2002) in Erie County, New York, in which exposure was estimated at the residential address, indicated that children aged 0–14 years, who were hospitalized for asthma, were more likely to live in close proximity to heavy traffic as compared to children who were not hospitalized. However, no clear exposure-response relation was found (Lin et al., 2002). A similar case-control study among children aged 5–14 years living in London was done by Wilkinson et al. (Wilkinson et al., 1999). Proximity to traffic was assessed at the postcode centroid level, and showed no association with hospital admissions for asthma. A clear association between air pollution and hospital admissions for asthma (all hospital admissions as well as emergency hospital admissions) was seen in our study. The ecological design of our study allowed us to incorporate a higher number of asthma hospital admissions than in the studies by Lin et al. (Lin et al., 2002) and Wilkinson et al. (Wilkinson et al., 1999) (5,252 vs. 417 and 2,131 respectively). Both aforementioned studies furthermore used proximity to traffic as main measure of exposure. A limitation proximity measures is that usually have not been directly validated for their use as exposure measure (Brauer et al., 2003). Our findings are consistent with the findings of Andersen et al. (Andersen et al., 2012a), who reported a hazard ratio of 1.12 (95% CI: 1.04–1.22) per 5.8 µg/m³ increase in 35-year mean NO₂ level and risk of hospitalization for asthma and found no significant associations with traffic proximity at the baseline residence as

surrogates of long-term exposure. Andersen et al. also presented analyses similar to the approach followed in our study: Relative to the first quartile of exposure (< 13.4 µg/m³ NO₂), hazard ratios for the second, third and fourth quartile of exposure 13.4–15.2, 15.2–19.2 and > 19.2 µg/m³, respectively were 1.28 (95% CI: 1.05–1.54), 1.20 (0.99–1.46) and 1.38 (1.14–1.66), respectively (Andersen et al., 2012a).

In the same cohort of 50–64 year-olds, Andersen et al. (Andersen et al., 2011) showed that long-term exposure to NO₂ was associated with hospital admissions for COPD (hazard ratio: 1.08 (95% CI: 1.02–1.14) per 5.8 µg/m³ increase in 35-year mean NO₂-levels). We also found the risk of hospital admission for COPD to increase with increasing exposure to NO₂. Our study furthermore showed elevated risks, albeit no increase in risk with increasing exposure, for all and emergency hospital admissions for 'all respiratory causes'.

In their study of 50–64 year old Danish adults, Andersen et al. also reported an increased risk of stroke hospitalization followed by death in relation to residential NO₂ exposure (Andersen et al., 2012b). These associations were observed for ischemic strokes, but not for hemorrhagic stroke. Another study presented a rate ratio of 1.13 for the highest (> 57.7 µg/m³ NO_x) relative to the lowest (< 49.6 µg/m³ NO_x) exposed subjects aged 45 years and over (Maheswaran et al., 2005a), while no association with coronary heart disease was seen in the same population (Maheswaran et al., 2005b). We found an increased risk with increased exposure for hospital admissions for 'all cardiovascular causes', IHD and stroke. Like Maheswaran et al. (Maheswaran et al., 2005a, 2005b) we did the analyses at an area-level rather than at the individual level. The underlying total number of hospital admissions in our study, however, was much larger (e.g. 28,600 vs. 5,122 hospital admissions for stroke). A possible limitation of our study is that we were not able to distinguish different subtypes of stroke and fatal from non-fatal events.

For asthma and COPD, but not for the other outcomes studied, the effects were clearer for all hospital admissions than for emergency hospital admissions. This could be due to an effect of chronic exposure to air pollution above that of short-term effects of air pollution episodes. Such episodes, which lead to elevated numbers of emergency hospital admissions, are primarily weather driven and may affect all study areas in the same way. Consistently our effect estimates are substantially larger than typical effect estimates of short-term exposure studies over the same concentration range. This is in agreement with the substantially higher associations of mortality with long-term exposure as compared to equivalent short-term associations that have been reported previously (Beverland et al., 2012).

5. Conclusion

Our study suggests an increased risk of hospitalization for respiratory and cardiovascular causes in areas with higher levels of NO₂. Our findings add to the currently limited evidence of a long-term effect of air pollution on hospitalization. The ecological design of our study is a limitation and more studies with individual data are needed to confirm our findings.

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Ethical approval

Ethical approval was obtained from the authorized Institutional Review Board of Prismant.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2016.09.008>.

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