



Respiratory symptoms, asthma and levels of fractional exhaled nitric oxide in schoolchildren in the industrial areas of Estonia

Idavain J.^{a,b,*}, Julge K.^{c,d}, Rebane T.^e, Lang A.^f, Orru H.^{a,g}

^a University of Tartu, Institute of Family Medicine and Public Health, Ravila 19, 50411 Tartu, Estonia

^b National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia

^c Tartu University Hospital Children's Clinic, N. Lunini 6, 51014 Tartu, Estonia

^d University of Tartu, Institute of Clinical Medicine, Department of Pediatrics, N. Lunini 6, 51014 Tartu, Estonia

^e Tartu University Hospital United Laboratories, L. Puusepa 8, 51014 Tartu, Estonia

^f University of Tartu, Institute of Biomedicine and Translational Medicine, Ravila 19, 50411 Tartu, Estonia

^g Umea University, Department of Public Health and Clinical Medicine, SE-901 87, Sweden

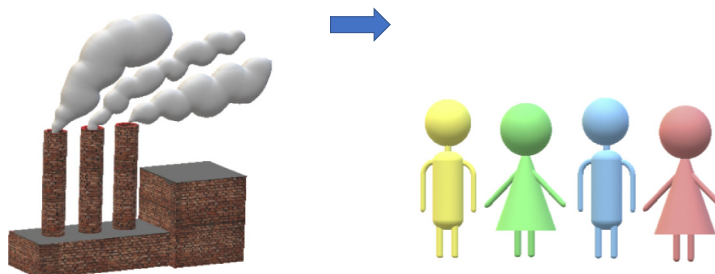
HIGHLIGHTS

- Industrial areas have increased levels of benzene, phenol, formaldehyde and NMHC.
- Children living in industrial area have higher prevalence of respiratory symptoms and asthma.
- Children living near shale oil industry and power plants have more often high FeNO levels.
- Children exposed to industrial pollutants have higher odds of respiratory diseases.

GRAPHICAL ABSTRACT

Benzene, phenol, formaldehyde, NMHC

Rhinitis, dry cough, high FeNO, asthma



ARTICLE INFO

Article history:

Received 28 April 2018

Received in revised form 26 August 2018

Accepted 27 August 2018

Available online 28 August 2018

Keywords:

Oil shale

Children

Asthma

Respiratory symptoms

Air pollution

FeNO

ABSTRACT

Objectives: Exposure to air pollutants in the ambient environment has been associated with various respiratory symptoms, and with increased asthma diagnosis, in both children and adults. Most research to date has focussed on core pollutants, such as PM₁₀, PM_{2.5}, SO₂ and NO₂, and less attention has been given to the effects of industry-specific contamination. The current study aimed to examine the associations between respiratory symptoms, asthma, increased levels of fractional exhaled nitric oxide (FeNO) (as a marker of eosinophilic airway inflammation) and ambient levels of industrial pollutants (such as benzene, phenol, formaldehyde and non-methane hydrocarbons) for schoolchildren living near oil shale industries in Ida-Viru County, Estonia.

Methods: A total of 1326 schoolchildren from Ida-Viru, Lääne-Viru and Tartu Counties participated in a cross-sectional study, consisting of questionnaires on respiratory symptoms and asthma, as well as clinical examinations to measure FeNO. Dispersion modelling was used to characterize individual-level exposure to industrial air pollutants at each subject's home address. Associations between exposure and respiratory health were investigated using logistic regression analysis, and differences in results between regions were analysed using the Chi-squared test.

Results: The prevalence of respiratory symptoms ($p < 0.05$) in children living near (i.e. within 5 km) of an oil shale industry site in Ida-Viru County was 2–4 times higher than in children living in the reference area of Tartu County. Children exposed to 1 µg/m³ higher levels of benzene and formaldehyde had a higher odds ratio (OR) of having rhinitis without a cold (OR 1.03, 95% confidence interval (CI) 1.01–1.06), of ever having had attacks of asthma

* Corresponding author at: University of Tartu, Institute of Family Medicine and Public Health, Ravila 19, 50411 Tartu, Estonia.

E-mail addresses: Jane.Idavain@ut.ee (J. Idavain), Kaja.Julge@kliinikum.ee (K. Julge), Tiina.Rebane@kliinikum.ee (T. Rebane), Aavo.Lang@ut.ee (A. Lang), Hans.Orru@ut.ee (H. Orru).

(OR 1.05, 95% CI 1.01–1.10) and of having a dry cough a few days per year (OR 1.05, 95% CI 1.01–1.10). Children exposed to 1 $\mu\text{g}/\text{m}^3$ higher levels of benzene, formaldehyde, phenol and non-methane hydrocarbons had a higher odds ratio of having high FeNO levels (≥ 30 ppb): OR and 95% CI of 1.05, 1.01–1.09; 1.22, 1.06–1.41; 1.01, 1.00–1.01; and 1.75, 1.75–2.62, respectively.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

Industrial areas have often high concentrations of air pollutants, which may lead to increased morbidity and mortality; depending on the types of pollutants, and the concentration to which the population living in the region is exposed (Martuzzi et al., 2014). Children are particularly susceptible to air pollution exposure, as their pulmonary metabolic capacity has not yet fully developed (Kurt et al., 2016). Lifelong exposure to air pollution could therefore have adverse effects on the lung development of children (Rice et al., 2016).

There is evidence that children living near (i.e. within 5 km) of industrial sites, or exposed to industrial pollutants, have an increased risk of adverse health outcomes when compared with those living far away (i.e. >20 km), or those less exposed (Alwahaibi and Zeka, 2016; Bergstra et al., 2018; Lewin et al., 2013; Nirel et al., 2015; Smargiassi et al., 2014; Wichmann et al., 2009; Wilhelm et al., 2007; Wong et al., 2016; Yang et al., 1997). However, studies investigating associations between industry-related air pollution and health among younger populations are rare, as was highlighted by Pascal et al. in a recent review (Pascal et al., 2013).

Industrial activity in Ida-Viru County, in North-Eastern Estonia, consists mainly of oil shale extraction, power generation and shale oil production (OECD/ECLAC, 2016). Several previous studies have indicated that the activities of the oil shale sector may affect the respiratory health of children (Etlin, 1989; Tefanova et al., 1993; Vasar et al., 2011). According to surveys conducted between 1971 and 1981, children living in the Ida-Viru area had 1.1 times smaller lung capacity, and higher morbidity, than children living in the reference areas (also in Estonia). The studies of Etlin (1989) showed that the overall number of doctor's appointments was 1.3 times higher in Ida-Viru County than in other regions of Estonia, and the frequency of abnormal birth weight was also 60% higher (Etlin, 1989). During the 1990s, several complex surveys were conducted on preschool children living in two cities in North-Eastern Estonia (Kohtla-Järve and Jõhvi), examining the clinical-immunological parameters of their health condition, and the impact of air pollution on the level and structure of their morbidity. The results indicated that children aged between 3 and 6 years and living in Kohtla-Järve had a higher overall risk of morbidity, and a higher morbidity risk for respiratory diseases (Tefanova et al., 1993). Children living in Narva (a city in North-Eastern Estonia) have also been found to have more respiratory and asthma-like symptoms than those living in Tallinn, Pärnu, or Elva (Bjorksten et al., 1998; Vasar et al., 2006). According to Vasar et al. (2011), in the early 2000s there was more diagnosed asthma, and more respiratory symptoms indicative of asthma in the Ida-Viru region than in other parts of Estonia.

During the past decade, the pattern of oil shale usage has transformed, resulting in significant changes in the amounts and locations of air pollution emissions. Shale oil factory Enefit 280 commenced operation near Narva in 2012; and two Petroter factories at Kohtla-Järve (2014/2015) and the 300 MW Auvere Power Plant (2015) were opened with lower stacks, which change the dynamics of air pollution dispersion. However, despite the measures taken to reduce the emission of air pollutants, the health status of residents in oil shale industry region is still worse in many aspects than elsewhere in Estonia (Orru et al., 2018).

The aim of the current study was to detect whether the levels of respiratory problems among children living in oil shale industry areas

remain higher than elsewhere, even though air pollution emissions have decreased and the oil shale usage pattern has changed. The primary focus was on the possible health effects of industry-specific pollutants, such as benzene, phenol, formaldehyde and non-methane hydrocarbons.

2. Materials and methods

The study population consisted of participants in two different studies: SINPHONIE (Schools Indoor Pollution and Health: Observatory Network in Europe) (Csobod et al., 2014) and SOHOS (Study of the Health Impact of Oil-Shale Sector) (Orru et al., 2016). SINPHONIE was a multi-disciplinary research project covering the areas of health, environment, transport and climate change, aimed at improving air quality in schools and kindergartens. Twenty-four countries across Europe participated in the SINPHONIE project, and the data collection in Tartu County took place during January–February 2012. The SOHOS study focused on the possible health effects of the oil shale sector; data was collected from children in Ida-Viru and Lääne-Viru Counties between November 2014 and January 2015. This data also formed part of the material for the Estonian National Development Plan for the Use of Oil Shale 2016–2030. In total, the study population consisted of 1326 randomly selected schoolchildren from twenty-five schools, aged between 8 and 12 years and living in North-Eastern Estonia (in Ida-Viru and Lääne-Viru Counties) or South-Eastern Estonia (Tartu County) (Fig. 1, Table 1). Tartu and Lääne-Viru Counties are non-industrially-polluted regions and were included as reference areas. Schools were selected randomly, according to socioeconomic status and levels of industrial pollution. All clinical examinations were approved by the Research Ethics Committee of the University of Tartu.

2.1. Questionnaire study and clinical examinations

Questionnaires on health and socio-demographics were distributed to subjects by teachers, and were completed by parent and child together. The questionnaire concentrated on respiratory health, and included questions on physician-diagnosed asthma; the frequency of attacks of asthma; and allergies. The following questions were included in the study:

1. “Has your child ever had wheezing or whistling in the chest at any time in the past?” Yes/No
2. “Has your child ever had a problem with sneezing, or a runny nose, or blocked nose when he/she did not have a cold or flu?” Yes/No
3. “Has your child ever had asthma diagnosed by physician?” Yes/No
4. “Has your child ever had attacks of asthma?” Yes/No
5. “Has your child had wheezing or whistling in the chest without cold in the past 12 months?” Yes/No
6. “In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?” Yes/No
7. “Does your child have dry cough without cold on some days during a year?”
8. “Does your child have phlegm without cold on some days during a year?”

Survey respondents were then invited to a clinical examination, during which the content of fractional exhaled nitric oxide (FeNO) was



Fig. 1. Map of Estonia. Counties studied (shaded areas), locations of the study populations (dark grey areas), and the location of oil shale industry facilities and power plants (black dots).

determined, with NIOX MINO®, as a marker of eosinophilic airway inflammation. Values of fractional exhaled nitric oxide differ individually, but for children, 20–35 ppb (parts per billion) (Dweik et al., 2011) and 20–30 ppb (Wang et al., 2017) are considered intermediate levels of FeNO. In the current study, based on the clinical expertise of Estonian paediatric allergists, FeNO values of ≥ 30 ppb in children were defined as ‘high’.

2.2. Exposure assessment

For the purpose of ecological analysis, all respondents living in the three cities of Kohtla-Järve (Järve district), Kiviõli and Püssi (termed the ‘Chemical industry region’) were considered to be highly exposed to industrial pollutants. Respondents from ‘Chemical industry region’ and from the city of Narva, which has two electricity generation plants

using fuel extracted from oil shale, located nearby (termed the ‘Chemical industry and power plant region’) were considered to be highly exposed to industrial pollutants as well.

The annual mean concentrations in 2013 of phenol, benzene, formaldehyde, non-methane hydrocarbons, particulate matter (PM₁₀) and fine particles (PM_{2.5}) were modelled in 1×1 km grids in Ida-Viru County, using an Eulerian air quality dispersion model that formed part of the Airviro Air Quality Management System (SMHI, Sweden; <http://airviro.smhi.se>); see the detailed description in the Airviro Documentation (Airviro, 2010). Industrial pollutant emission levels were retrieved from the ambient air emission database OSIS2013, which consists of annual emissions (tons per year), as reported by companies and confirmed by the Estonian Environmental Board. Transport-sector emissions came from the database Traffic 2007, and domestic heating emissions from the local heating database. The modelled concentrations were validated with monitored emission levels from the monitoring stations in Ida-Viru County; see details in Orru et al. (2018). For visualization, the model output was generalized and classified into five classes, using the ArcGIS scripting environment ArcPy. The obtained annual concentrations of modelled pollutants per grid cell were linked with the geo-code of each respondent’s home address, in ArcGIS.

2.3. Statistical analysis

Statistical analyses were performed using the statistical program Stata/SE 14.2 (StataCorp, College Station, TX, USA). The Chi-squared test was used to compare the prevalence of respiratory symptoms and asthma among schoolchildren living in the different counties. A *p*-value of <0.05 was considered statistically significant.

The multivariate analysis was based on regression, using a logarithmic function. Independent variables in the model were: ‘Chemical industry region’, ‘Chemical industry and power plant region’ and pollutants such as benzene, phenol, formaldehyde, NMHC, PM₁₀, and PM_{2.5}. The regression models were adjusted for such possible confounders as gender, age, BMI (by WHO BMI-for-age (5–19 years) (WHO, 2007)), parent’s highest education and family income.

3. Results

3.1. Sociodemographic variables of the respondents

A total of 1208 subjects completed the questionnaires and 1098 participated in the clinical examinations. The majority (98%) of the children

Table 1
Characteristics of the study population.

	Ida-Viru County n (%)	Lääne-Viru County n (%)	Tartu County n (%)
Total	910	181	235
Schools	18	3	4
Respondents			
Questionnaires	827	173	208
Clinical examinations	871	181	46
Age (years)			
8	39 (4.3)	0	0
9	431 (47.5)	82 (45.3)	79 (35.0)
10	412 (45.4)	85 (47.0)	103 (45.5)
11	24 (2.6)	13 (7.2)	44 (19.5)
12	1 (0.1)	1 (0.5)	0
Gender			
Male	430 (47.3)	81 (44.8)	120 (51.1)
Female	479 (52.7)	100 (55.2)	115 (48.9)
BMI			
Male			
Underweight ($<-2SD$)	6 (1.4)	0	0
Normal weight ($-2SD > n < 1SD$)	255 (61.2)	55 (67.9)	77 (67.0)
Overweight/obese ($>1SD$)	156 (37.4)	26 (32.1)	38 (33.0)
Female			
Underweight ($<-2SD$)	4 (0.9)	1 (1.0)	1 (0.9)
Normal weight ($-2SD > n < 1SD$)	314 (68.9)	74 (74.0)	79 (71.2)
Overweight/obese ($>1SD$)	138 (30.2)	25 (25.0)	31 (27.9)

were 9–10 years old. There were slightly more girls (52%) than boys (48%). Overall, 32% of the schoolchildren (36% of boys and 29% of girls) were overweight or obese. There were no significant differences in the sociodemographic characteristics of subjects from different regions. Table 1 presents the characteristics of the study population.

3.2. Prevalence of respiratory symptoms, asthma and high FeNO levels

Of the study locations, the prevalence of the different respiratory symptoms was highest in Ida-Viru County. Symptoms such as ever having had wheezing, rhinitis without a cold, nocturnal dry cough without a cold during the past year, dry cough without a cold and phlegm were significantly more prevalent in Ida-Viru County than in Tartu County (Table 2). The prevalence of physician-diagnosed asthma in the different counties was: 12.8% in Ida-Viru County; 10.1% in Lääne-Viru County; and 7.2% in Tartu County (which was significantly lower ($p < 0.05$) than in Ida-Viru County). Approximately 11% of the children in Ida-Viru County had experienced attacks of asthma, whereas in Lääne-Viru County the prevalence was 6.6%.

The prevalence of high fractional exhaled NO (FeNO) values (≥ 30 ppb) among students in grades three and four was more than three times higher in Ida-Viru County (15.0%) than in Tartu County (4.2%), and two times higher than in Lääne-Viru County (8.3%); these differences were statistically significant. Moreover, 11.2% of children in Ida-Viru County had high values of FeNO, but no previous asthma diagnosis by a physician. This was significantly higher than in Lääne-Viru County (4.2%).

3.3. Multivariate relationships

3.3.1. Association between residence in an oil shale industry area and respiratory health

There were no differences in the sociodemographic characteristics of children living within a 5 km radius of shale oil industry site, or a power plant, compared to subjects living in the rest of Ida-Viru County (Appendix A). The overall prevalence of the different respiratory symptoms was lower in each of the oil shale industry reference regions compared to Ida-Viru County. The combined level of high FeNO values was highest for 'Chemical industry region' and 'Chemical industry and power plant region' together was 15.9%, compared to the rest of the Ida-Viru County. The prevalence of high FeNO values (≥ 30 ppb) was

Table 2
Prevalence (%) of respiratory symptoms and asthma in the different counties of Estonia.

	Ida-Viru County	Lääne-Viru County	Tartu County
Questionnaire			
<i>Ever had</i>			
Wheezing	21.5 ¹	23.3	10.3
Rhinitis without cold	35.3 ^{1,2}	24.6	13.8
Asthma diagnosis by physician	12.8 ¹	10.1	7.2
Asthma attack	10.8	6.6	N/A
<i>During last 12 months</i>			
Wheezing without cold	20.0	20.0	N/A
Nocturnal dry cough without cold	23.7 ^{1,2}	16.0	5.9
<i>Some days during a year</i>			
Dry cough without cold	16.9 ^{1,2}	7.8	5.0
Phlegm	9.5 ¹	6.1	2.0
Clinical examination			
FeNO ≥ 30 ppb	15.0 ^{1,2}	8.3	4.2
FeNO ≥ 30 ppb and no asthma diagnosis	11.2 ^{1,2}	04.2	4.9

N/A not included in the questionnaire for Tartu County.

¹ Significant difference ($p < 0.05$) between results for Ida-Viru County and Tartu County.

² Significant difference ($p < 0.05$) between results for Ida-Viru County and Lääne-Viru County.

0.9% higher in the 'Chemical industry region' (12.1%) and 0.6% higher in the 'Chemical industry and power plant region' (11.8%) than in Ida-Viru County overall (Appendix B).

In the ecological analysis, the crude unadjusted model for schoolchildren living in the 'Chemical industry and power plant region' showed a 1.57 (95% CI 1.22–2.02) higher odds ratio of having rhinitis without a cold; a 1.46 (95% CI 1.22–2.02) higher odds ratio of having high exhaled nitric oxide values; and a 1.57 (95% CI 1.02–2.41) higher odds ratio of having high levels of FeNO without an asthma diagnosis. The adjusted model for subjects living in the 'Chemical industry region' and/or 'Chemical industry and power plant region' showed a 1.63 (95% CI 1.03–2.60) higher odds ratio of having high levels of FeNO without an asthma diagnosis (Table 3).

3.3.2. Association between air pollution exposure and respiratory health

Children exposed to higher levels of industry-specific air pollutants, such as benzene (Fig. 2), had significantly ($p < 0.05$) higher odds ratios (OR) for most of the tested symptoms: rhinitis without a cold, attacks of asthma, dry cough during the night over the last 12 months, dry cough without a cold and phlegm some days during the year; as well as increased prevalence of high values of FeNO (≥ 30 ppb).

Schoolchildren living in the areas with the highest levels of formaldehyde had higher odds ratios for most of the respiratory symptoms, including physician-diagnosed asthma. These subjects also showed the highest odds ratios (1.22, 95% CI 1.06–1.41) for high FeNO levels; these were higher again (1.26, 95% CI 1.06–1.50) for those subjects without a concurrent asthma diagnosis. Children living in the areas with the highest levels of phenol and non-methane hydrocarbons (NMHC) had 1.01 (95% CI 1.00–1.01) and 1.75 (95% CI 1.75–2.62) higher

Table 3

Relationships between respiratory symptoms, asthma and high FeNO levels for subjects living in an (oil shale) Chemical industry region or in a Chemical industry and power plant region (odds ratios (OR), 95% CI).

	Model 1		Model 2	
	Chemical industry region	Chemical industry and power plant region	Chemical industry region	Chemical industry and power plant region
Questionnaire				
<i>Ever had</i>				
Wheezing	0.91 (0.64–1.29)	1.14 (0.84–1.53)	0.78 (0.53–1.15)	0.88 (0.62–1.22)
Rhinitis without cold	1.40 (0.05–1.87)	1.57 (1.22–2.02)	1.18 (0.85–1.62)	1.25 (0.93–1.67)
Asthma diagnosis by physician	0.89 (0.58–1.38)	0.87 (0.60–1.26)	0.79 (0.49–1.27)	0.71 (0.46–1.07)
Asthma attack	0.92 (0.57–1.49)	0.89 (0.58–1.36)	0.83 (0.49–1.40)	0.75 (0.47–1.18)
<i>During last 12 months</i>				
Wheezing without cold	0.62 (0.31–1.24)	0.74 (0.41–1.34)	0.57 (0.27–1.21)	0.68 (0.35–1.32)
Nocturnal dry cough without cold	1.21 (0.87–1.70)	1.38 (1.03–1.84)	1.02 (0.71–1.47)	1.01 (0.73–1.41)
<i>Some days during a year</i>				
Dry cough	1.14 (0.76–1.70)	1.36 (0.96–1.92)	1.04 (0.68–1.60)	1.09 (0.74–1.62)
Phlegm	1.32 (0.81–2.13)	1.52 (0.99–2.35)	1.17 (0.70–1.94)	1.19 (0.75–1.91)
Clinical examination				
FeNO ≥ 30 ppb	1.33 (0.90–1.97)	1.46 (1.01–2.09)	1.29 (0.84–1.97)	1.44 (0.97–2.15)
FeNO ≥ 30 ppb and no asthma diagnosis	1.43 (0.91–2.24)	1.57 (1.02–2.41)	1.43 (0.89–2.31)	1.63 (1.03–2.60)

Model 1 – unadjusted model.

Model 2 – adjusted for sex, age, BMI, parents' education and family income. The odds ratios in bold italics differ significantly ($p < 0.05$).

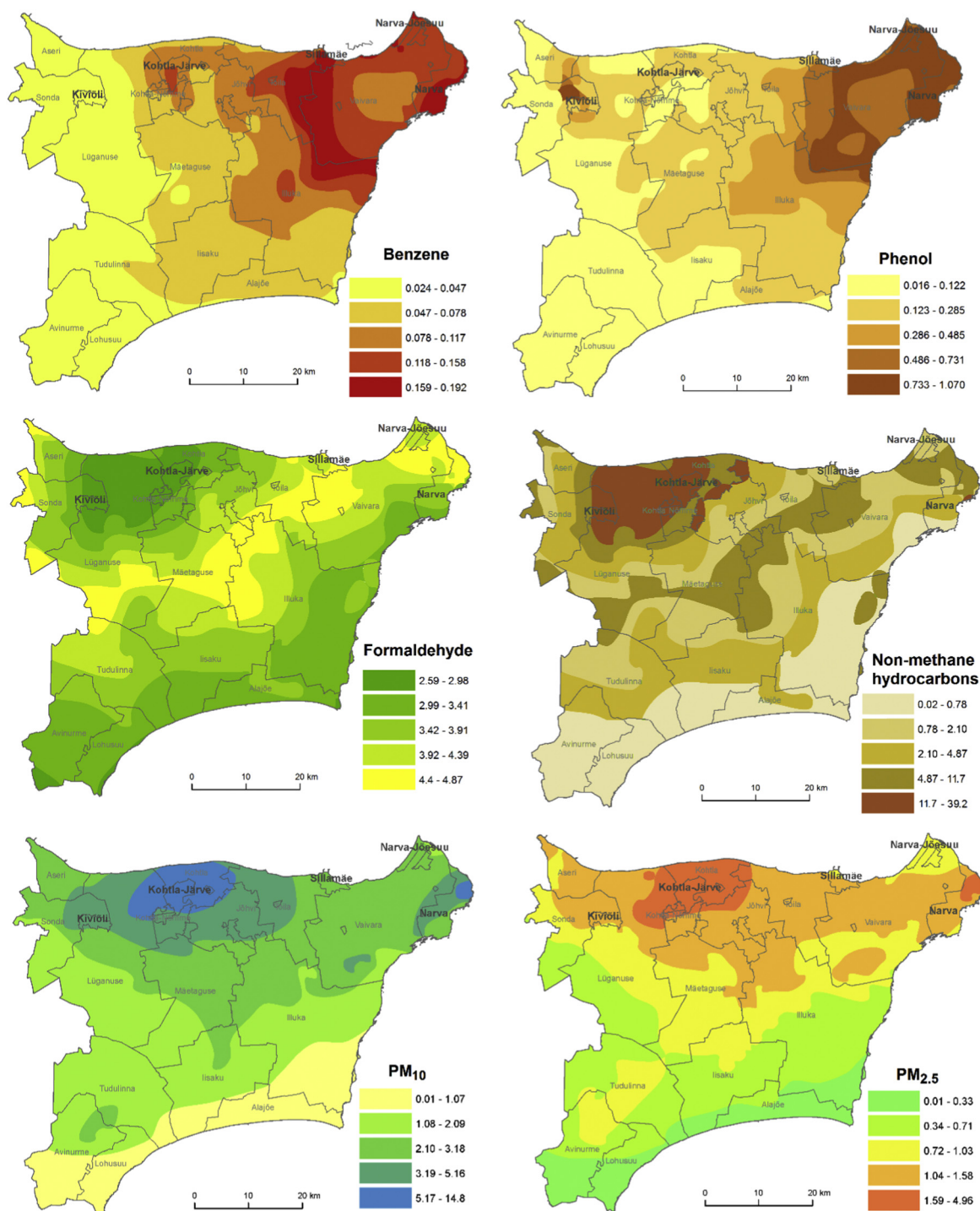


Fig. 2. Oil shale industry facilities, air quality monitoring station locations and annual (2013) average concentrations ($\mu\text{g}/\text{m}^3$) of benzene, phenol, formaldehyde, NMHC, coarse particles (PM_{10}), and fine particles ($\text{PM}_{2.5}$) in the ambient air of Ida-Viru County.

odds ratios, respectively, of having high FeNO levels (Table 4). Lower levels of fine particles ($\text{PM}_{2.5}$) were also associated with high FeNO levels, both with and without an asthma diagnosis.

4. Discussion

The impact of localised industrial air pollution on population health is a major concern in many areas worldwide (Mudu et al., 2014). This study aimed to identify possible relationships between (oil shale) industry-specific air pollutants and the respiratory health of children.

Research on chemical exposure to the oil shale industry is still quite rare. There is little information, therefore, on possible health outcomes for children living close to shale oil extraction industry sites. In the current study, the prevalence of symptoms commonly associated with asthma, and asthmatic symptoms, were higher among 8–12-year-old children in industrially-exposed Ida-Viru County, compared to the non-industrially-polluted Tartu region. Despite the relatively small number of studies focussing on the respiratory symptoms of children living near petrochemical industries, it has been shown that exposure even to low levels of atmospheric pollutants such as benzene, NO_2 and

Table 4

Association (odds ratios and 95% confidence intervals) of respiratory symptoms with oil shale associated pollutants.

	Benzene	Phenol	Formaldehyde	NMHC	PM ₁₀	PM _{2.5}
OR* (95% CI), per 1 µg/m ³ increase in exposure (benzene and phenol per 1 ng/m ³)						
Questionnaire						
Ever had						
Wheezing	1.01 (0.98–1.04)	1.00 (0.99–1.01)	1.01 (0.90–1.13)	0.95 (0.92–0.99)	1.00 (0.95–1.06)	1.04 (0.95–1.14)
Rhinitis without cold	1.03 (1.01–1.06)	1.00 (0.99–1.01)	1.13 (1.02–1.25)	1.01 (0.98–1.03)	1.00 (0.95–1.05)	0.93 (0.86–1.01)
Asthma diagnosis by physician	1.04 (0.99–1.08)	1.00 (0.99–1.01)	1.17 (1.00–1.36)	0.96 (0.92–1.01)	0.978 (0.91–1.05)	0.94 (0.83–1.06)
Asthma attack	1.05 (1.01–1.10)	1.00 (0.99–1.00)	1.21 (1.04–1.42)	0.97 (0.92–1.01)	0.98 (0.92–1.05)	0.91 (0.81–1.03)
During last 12 months						
Wheezing without cold	1.04 (0.98–1.10)	1.00 (0.99–1.01)	1.18 (0.94–1.49)	0.96 (0.90–1.03)	0.96 (0.86–1.07)	0.93 (0.77–1.12)
Nocturnal dry cough without cold	1.01 (1.04–1.07)	1.00 (0.99–1.01)	1.14 (1.01–1.27)	1.00 (0.97–1.02)	0.97 (0.93–1.04)	0.92 (0.84–1.01)
Some days during a year						
Dry cough	1.05 (1.01–1.10)	1.00 (0.99–1.01)	1.23 (1.06–1.45)	1.00 (0.97–1.03)	0.98 (0.92–1.05)	0.89 (0.79–1.00)
Phlegm	1.06 (1.01–1.11)	1.00 (0.99–1.01)	1.17 (0.99–1.39)	0.97 (0.93–1.02)	1.02 (0.94–1.10)	0.93 (0.81–1.07)
Clinical examination						
FeNO ≥ 30 ppb	1.05 (1.01–1.09)	1.01 (1.00–1.01)	1.22 (1.06–1.41)	1.75 (1.17–2.62)	0.94 (0.88–1.01)	0.85 (0.75–0.96)
FeNO ≥ 30 ppb and no asthma diagnosis	1.05 (1.00–1.10)	1.01 (1.00–1.01)	1.26 (1.06–1.50)	1.04 (1.01–1.07)	0.93 (0.86–1.01)	0.81 (0.69–0.94)

Adjusted model for sex, age, BMI, parents' education and family income.

NMHC - non-methane hydrocarbons.

PM₁₀ - particulate matter with a diameter between 2.5 and 10 micrometers (µm)PM_{2.5} - particulate matter with a diameter of 2.5 micrometers (µm) or less.The odds ratios in bold italics differ significantly ($p < 0.05$)

PM₁₀ is associated with an increase in wheezing symptoms, decrease in lung function, a nocturnal cough and a higher prevalence of respiratory hospitalizations (Rusconi et al., 2011; Moraes et al., 2010; Rovira et al., 2014).

In the current study, a similar trend for benzene was observed, but there was no association for PM₁₀ and the reverse trend was seen for PM_{2.5}. The main reason for this could be the different sources of the pollutants. Benzene, phenol, formaldehyde and non-methane hydrocarbons are mainly industry-based, whereas a large proportion of particulates come from traffic (Maasikmets et al., 2013). The different pattern of results may be due to more industry-specific pollutants being near industrial areas, and more traffic-specific pollutants being in larger cities (Fig. 2). Bergstra et al. (2018) also noted the difficulty of disentangling the effects of traffic exposure from those of exposure to industry. More accurate investigation of industry-specific pollutants might help to characterize this exposure in more detail. It also appears that the children with asthma, and with a high risk of air pollution, are those who live near the sources of industrial pollutants; they often have the least access to medical care, due to poverty (Gold and Wright, 2005). Whereas those children living in larger cities, with higher levels of fine particles, have better access to medical care and may therefore have lower FeNO values (Petsky et al., 2016).

The analysis also showed that the prevalence of asthma and asthmatic symptoms in Estonia have increased over time, compared to earlier studies (Meren et al., 2001; Vasar et al., 2011). According to questionnaire-based studies on children's health, the prevalence of asthma diagnosis by a physician after the collapse of the Soviet Union in the 1990s was only 2.4% in Narva (the largest city in Ida-Viru County) (Meren et al., 2001); however these studies also reported numerous respiratory symptoms indicative of mild asthma. By 2003, the prevalence of asthma in Narva among preadolescent children had increased to 5.2% (Vasar et al., 2011). The SOHOS study showed that, since 2003, the prevalence of asthma in Narva had doubled, and the overall prevalence in Ida-Viru County was approximately 2.5 times higher. However, some

of the differences between time periods may be the result of differences in asthma diagnosis. Until the beginning of the 1990s, the definitions of chronic respiratory diseases accepted in the Soviet Union were used in Estonia; the definition of asthma was characterized by symptoms such as bronchospasm, hypersecretion, breathlessness and swelling of bronchial mucosa (Jannus-Pruljan et al., 1975). Asthma was often considered to be a complication of a chronic bronchitis, or even chronic pneumonia (Ado, 1978). Whereas, in recent decades, only the principles of the Global Initiative for Asthma (GINA) have been applied in Estonia; milder symptoms, such as a cough, are now taken into account (Reddel et al., 2015). As well as the prevalence of asthma being higher in Ida-Viru County, compared to the two reference regions, the children there also showed more respiratory symptoms (Table 2).

In the current study, one of the established biomarkers of airway inflammation, FeNO (Ricciardolo et al., 2015; van Amsterdam et al., 2000) was measured during clinical examinations. The prevalence in Ida-Viru County of high FeNO levels (i.e. ≥30 ppb) was 3.8 times higher than in Tartu, and 1.8 times higher than in Lääne-Viru County. These differences were statistically significant ($p < 0.05$). The number of children having high values of FeNO was also significantly higher in Ida-Viru County. Children living within a 5 km radius of shale oil chemical plant, and/or a power plant using fuel extracted from oil shale, also had 1.63 (95% CI 1.03–2.60) higher combined odds of having high FeNO values than children living further away. Several studies (Fischer et al., 2002) investigating associations between fractional exhaled nitric oxide, ambient air pollution and respiratory health in schoolchildren confirm the observation of an association between air pollution and higher levels of FeNO in children (Fischer et al., 2002; Flamant-Hulin et al., 2009). Furthermore, a large proportion of children had high FeNO values, but no (self-reported) asthma diagnosis by a physician. This is a major public health concern, as high levels of FeNO are the indicators for bronchodilator responsiveness and probable asthma (Malmberg et al., 2003).

In the current analysis, high FeNO levels were defined as ≥30 ppb, as previously described by Pijnenburg et al. (2005) and Wang et al. (2017).

Recent reviews (Jones et al., 2018; Petsky et al., 2016) note that high FeNO in children may vary between 20 and 50 ppb. Levels of fractional exhaled nitric oxide as high as 30 ppb may indicate insufficient control of asthma, or possible subsequent exacerbations (Wang et al., 2017).

The main strength of the current study was the air pollution dispersion modelling, with a large number of different industry- (including oil shale industry) specific pollutants, such as benzene, phenol, formaldehyde and NMHC. Usually, only core pollutants, such as PM_{2.5}, SO₂ and NO_x are studied (Bergstra et al., 2018; Brand et al., 2016; Saric-Tanaskovic et al., 2006; Wong et al., 2016). Dispersion modelling takes into account stack height, annual weather conditions and the exact location of subject children's home addresses. Many studies of industrially-contaminated areas have only compared resident populations with control areas; or have relied on emission information instead of modelled exposure patterns.

The limitations of the current study were as follows. Firstly, the emission-based exposures were only calculated for one year (2013), as no information was available on subjects' previous residences. Secondly, the emission data in some cases was of low quality, which caused the heterogeneous deviation of some concentrations of pollutants, even in the chemical industry region (Orru et al., 2018). Thirdly, living in an industrial area may be viewed as a health threat (Orru et al., 2018); families with asthmatic children may avoid living near contaminated sites, or may move away. Finally, the data on health symptoms and diseases was self-reported. Nevertheless, oil shale associated air pollutants (especially for exposure to benzene and formaldehyde) association with respiratory symptoms, self-reported physician diagnosed asthma with clinically measured FeNO values were statistically significant.

5. Conclusions

In this study, the prevalence of respiratory symptoms, asthma and high levels of fractional exhaled nitric oxide (FeNO) (as a marker of eosinophilic airway inflammation) was significantly higher for school-aged children living in an oil shale industrial area than for the reference group living in a non-industrialised area. There was a significant association for children exposed to benzene, phenol, formaldehyde and NMHC with respiratory health and airway inflammation. Respiratory symptoms and airway inflammation among children in Ida-Viru County could therefore be associated with industrial pollution.

Acknowledgments

“Study of the health impact of oil shale sector—SOHOS” was financed by the Estonian Environmental Investment Centre (KIK). Additional funding was provided by the Estonian Ministry of Education and Research grant IUT34-17.

Appendix A. Characteristics of the study population and response rates in the ‘Chemical industry region’, ‘Chemical industry and power plant region’ and in Ida-Viru County

	Chemical industry region	Chemical industry and power plant region	Ida-Viru County
	n (%)	n (%)	n (%)
Total	282	476	910
Schools	10	13	18
Respondents			
Questionnaires	275	471	827
Clinical examinations	276	459	871
Age (years)			
8	11 (2.9)	24 (5.1)	39 (4.3)
9	132 (47.1)	217 (45.8)	431

(continued)

	Chemical industry region	Chemical industry and power plant region	Ida-Viru County
	n (%)	n (%)	n (%)
10	129 (46.1)	214 (45.1)	(47.5)
11	8 (2.9)	19 (4.0)	412
12	0	0	(45.4)
Gender			24 (2.6)
Male	131 (46.5)	222 (46.6)	1 (0.1)
Female	151 (53.5)	254 (53.4)	430
			(47.3)
BMI			479
Male			(52.7)
Underweight (<−2SD)	4 (3.1)	5 (2.3)	6 (1.4)
Normal weight (−2SD > n < 1SD)	78 (60.9)	127 (59.1)	255
Overweight/obese (>1SD)	46 (35.9)	83 (38.6)	(61.2)
Female			156
Underweight (<−2SD)	1 (0.7)	1 (0.4)	(37.4)
Normal weight (−2SD > n < 1SD)	99 (66.9)	167 (68.4)	4 (0.9)
Overweight/obese (>1SD)	48 (32.4)	76 (31.1)	314
			(68.9)
			138
			(30.2)

Appendix B. Prevalence of respiratory symptoms and asthma in different types of industrial region in Ida-Viru County (%)

	Chemical industry region	Chemical industry and power plant region	Ida-Viru County
Questionnaire			
Ever had			
Wheezing	18.7	21.1	21.5
Rhinitis without cold	35.6	35.7	35.3
Asthma diagnosis	10.7	10.7	12.8
Asthma attack	9.7	9.7	10.8
During last 12 months			
Wheezing without cold	15.6	18.3	20.0
Nocturnal dry cough without cold	21.9	22.6	23.7
Some days during a year			
Dry cough without cold	14.7	15.7	16.7
Phlegm	9.4	9.6	9.5
Clinical examination			
FeNO ≥ 30 ppb	15.9	15.9	15.0
FeNO ≥ 30 ppb and no asthma diagnosis	12.1	11.8	11.2

References

- Ado, A.D., 1978. *Общая аллергология*, second ed. Медицина, Москва.
- AirViro, 2010. Working With the Dispersion Module. How to Simulate the Dispersion of Pollutants. SMHI Airviro User's Reference, p. 2.
- Alwahaibi, A., Zeka, A., 2016. Respiratory and allergic health effects in a young population in proximity of a major industrial park in Oman. *J. Epidemiol. Community Health* 70, 174–180.
- Bergstra, A.D., Brunekreef, B., Burdorf, A., 2018. The effect of industry-related air pollution on lung function and respiratory symptoms in school children. *Environ. Health* 17, 30.
- Bjorksten, B., Dumitrascu, D., Foucard, T., Khetsuriani, N., Khaitov, R., Leja, M., Lis, G., Pekkanen, J., Priftanji, A., Riikjarv, M.A., 1998. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. *Eur. Respir. J.* 12 (2), 432.
- Brand, A., McLean, K.E., Henderson, S.B., Fournier, M., Liu, L., Kosatsky, T., et al., 2016. Respiratory hospital admissions in young children living near metal smelters, pulp mills and oil refineries in two Canadian provinces. *Environ. Int.* 94, 24–32.
- Csobod, E., Annesi-Maesano, I., Carrer, P., Kephelopoulou, S., Madureira, J., Rudnai, P., et al., 2014. SINFONIE Schools Indoor Pollution and Health Observatory Network in

- Europe Final Report. The Regional Environmental Centre for Central and Eastern Europe, Hungary.
- Dweik, R.A., Boggs, P.B., Erzurum, S.C., Irvin, C.G., Leigh, M.W., Lundberg, J.O., et al., 2011. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am. J. Respir. Crit. Care Med.* 184, 602–615.
- Etlín, S., 1989. Гигиенические основы охраны атмосферного воздуха в районе размещения предприятий станционной химии и энергетики (Moscow).
- Fischer, P., Steerenberg, P., Snelder, K., van Loveren, H., van Amsterdam, J., 2002. Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. *Int. Arch. Occup. Environ. Health* 75 (5), 348–353.
- Flamant-Hulin, M., Caillaud, D., Sacco, P., Pénard-Morand, C., Annesi-Maesano, I., 2009. Air pollution and increased levels of fractional exhaled nitric oxide in children with no history of airway damage. *J. Toxic. Environ. Health A* 73 (4), 272–283.
- Gold, D.R., Wright, R., 2005. Population disparities in asthma. *Annu. Rev. Public Health* 26, 89–113.
- Jannus-Pruljan, L., Karusoo, J., Maser, L., Raukas, E., Reinvald, A., Sauemägi, L., 1975. *Pulmonoloogia: kroonilised mitespetsiifilised kopsuhaigused*. Valgus, Tallinn.
- Jones N, Wang K, Heneghan C, Price CP, Van den Bruel A, Plüddemann A. C. Primary Care Diagnostic Horizon Scanning Centre Oxford, Oxford, 2018.
- Kurt, O.K., Zhang, J., Pinkerton, K.E., 2016. Pulmonary health effects of air pollution. *Curr. Opin. Pulm. Med.* 22, 138–143.
- Lewin, A., Buteau, S., Brand, A., Kosatsky, T., Smargiassi, A., 2013. Short-term risk of hospitalization for asthma or bronchiolitis in children living near an aluminum smelter. *J. Expo. Sci. Environ. Epidemiol.* 23, 474–480.
- Maasikmets, M., Saare, K., Arumäe, T., Lehes, L., Viidik, A., Ebber, A., 2013. Analysis of Complex Assessment of the Quality of Ambient Air in Estonian towns. Estonian Environmental Research Centre, Tallinn.
- Malmberg, L.P., Pelkonen, A.S., Hahtela, T., Turpeinen, M., 2003. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax* 58, 494–499.
- Martuzzi, M., Pasetto, R., Martin-Olmedo, P., 2014. Industrially contaminated sites and health. *J. Environ. Public Health* 2014, 2.
- Meren, M., Jannus-Pruljan, L., Loit, H.M., Pölluste, J., Jönsson, E., Kiviloog, J., Lundbäck, B., 2001. Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire. *Respir. Med.* 95 (12), 954–964.
- Moraes, A.C., Ignotti, E., Netto, P.A., Jacobson, L.D., Castro, H., Hacon, S.D., 2010. Wheezing in children and adolescents living next to a petrochemical plant in Rio Grande do Norte, Brazil. *J. Pediatr.* 86 (4), 337–344.
- Mudu, P., Terracini, B., Martuzzi, M. (Eds.), 2014. *Human Health in Areas With Industrial Contamination*. WHO Regional Office for Europe, Copenhagen.
- Nirel, R., Maimon, N., Fireman, E., Agami, S., Eyal, A., Peretz, A., 2015. Respiratory hospitalizations of children living near a hazardous industrial site adjusted for prevalent dust: a case-control study. *Int. J. Hyg. Environ. Health* 218, 273–279.
- OECD/ECLAC, 2016. *OECD Environmental Performance Reviews: Estonia 2016*. OECD Publishing, Paris.
- Orru, H., Tomasova, J., Idavain, J., Julge, K., Rebane, T., Ruut, J., et al., 2016. Health impacts of the oil shale sector in Eastern Estonia. *Rapporti Istisan.* 16, pp. 54–57.
- Orru, H., Idavain, J., Pindus, M., Orru, K., Kesanurm, K., Lang, A., et al., 2018. Residents' self-reported health effects and annoyance in relation to air pollution exposure in an industrial area in Eastern-Estonia. *Int. J. Environ. Res. Public Health* 15.
- Pascal, M., Pascal, L., Bidondo, M.L., Cochet, A., Sarter, H., Stempfelet, M., et al., 2013. A review of the epidemiological methods used to investigate the health impacts of air pollution around major industrial areas. *J. Environ. Public Health* 2013, 737926.
- Petsky, H.L., Kew, K.M., Turner, C., Chang, A.B., 2016. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst. Rev.* 9, 1–53.
- Pijnenburg, M.W., Bakker, E.M., Hop, W.C., De Jongste, J.C., 2005. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am. J. Respir. Crit. Care Med.* 172, 831–836.
- Reddel, H.K., Bateman, E.D., Becker, A., Boulet, L.-P., Cruz, A.A., Drazen, J.M., et al., 2015. A summary of the new GINA strategy: a roadmap to asthma control. *Eur. Respir. J.* 46, 622–639.
- Ricciardolo, F.L.M., Sorbello, V., Ciprandi, G., 2015. A pathophysiological approach for FeNO: a biomarker for asthma. *Allergol. Immunopathol.* 43 (6), 609–616.
- Rice, M.B., Rifas-Shiman, S.L., Litonjua, A.A., Oken, E., Gillman, M.W., Kloog, I., et al., 2016. Lifetime exposure to ambient pollution and lung function in children. *Am. J. Respir. Crit. Care Med.* 193, 881–888.
- Rovira, E., Cuadras, A., Aguilar, X., Esteban, L., Borrás-Santos, A., Zock, J.P., Sunyer, J., 2014. Asthma, respiratory symptoms and lung function in children living near a petrochemical site. *Environ. Res.* 133 (August), 156–163.
- Rusconi, F., Catelan, D., Accetta, G., Peluso, M., Pistelli, R., Barbone, F., Di Felice, E., et al., 2011. Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. *J. Asthma* 48 (1), 84–90.
- Saric-Tanaskovic, M., Nikolovski, D., Belojovic, G., 2006. Air quality and respiratory health of school children in Pancevo. *Srp. Arh. Celok. Lek.* 134 (Suppl. 2), 108–112.
- Smargiassi, A., Goldberg, M.S., Wheeler, A.J., Plante, C., Valois, M.F., Mallach, G., et al., 2014. Associations between personal exposure to air pollutants and lung function tests and cardiovascular indices among children with asthma living near an industrial complex and petroleum refineries. *Environ. Res.* 132, 38–45.
- Tefanova, V., Kremerman, I., Priimägi, L., Redko, L., Kurvinen, E., Mordvinova, H., et al., 1993. Eesti põlvkivibasseini laste tervise kliinilis-immunoloogiline iseloomustus. *Eesti arst. pp.* 168–171.
- van Amsterdam, J.G.C., Nierkens, S., Vos, S.G., Opperhuizen, A., Loveren, H., Steerenberg, P.A., 2000. Exhaled nitric oxide: a novel biomarker of adverse respiratory health effects in epidemiological studies. *Arch. Environ. Health* 55 (6), 418–423.
- Vasar, M., Julge, K., Kivivare, M., Otter, K., 2006. Astma ja teiste allergiahaiguste sõeluuring Eesti kooliõpilastel. *Eesti Arst* 85 (8), 488–493.
- Vasar, M., Julge, K., Kivivare, M., Otter, K., 2011. Regional differences in diagnosing asthma and other allergic diseases in Estonian schoolchildren. *Medicina (Kaunas)* 47, 661–666.
- Wang, Z., Pianosi, P., Keogh, K., Zaiem, F., Alsawas, M., Alahdab, F., Almasri, J.M., Mohammed, K., Larrea-Mantilla, L., Farah, W., Daraz, L., Barrionuevo, P., Gunjal, S., Prokop, L.J., Murad, M.H., 2017. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197 (Prepared by the Mayo Clinic Evidence-based Practice Center Under Contract No. 290-2015-00013-1). AHRQ Publication No.17(18)-EHC030-EF. Agency for Healthcare Research and Quality, Rockville, MD www.effectivehealthcare.ahrq.gov/reports/final.cfm.
- WHO, 2007. BMI-for-ages (5–19 years). http://www.who.int/growthref/who2007_bmi_for_age/en/.
- Wichmann, F.A., Müller, A., Busi, L.E., Cianni, N., Massolo, L., Schlink, U., et al., 2009. Increased asthma and respiratory symptoms in children exposed to petrochemical pollution. *J. Allergy Clin. Immunol.* 123, 632–638.
- Wilhelm, M., Eberwein, G., Holzer, J., Gladtko, D., Angerer, J., Marczyński, B., et al., 2007. Influence of industrial sources on children's health—hot spot studies in North Rhine Westphalia, Germany. *Int. J. Hyg. Environ. Health* 210, 591–599.
- Wong, S.L., Coates, A.L., To, T., 2016. Exposure to industrial air pollutant emissions and lung function in children: Canadian Health Measures Survey, 2007 to 2011. *Health Rep.* 27, 3–9.
- Yang, C.Y., Wang, J.D., Chan, C.C., Chen, P.C., Huang, J.S., Cheng, M.F., 1997. Respiratory and irritant health effects of a population living in a petrochemical-polluted area in Taiwan. *Environ. Res.* 74, 145–149.