

# Methodology for defining the effects of outdoor air pollution on children's health at the population level – a systematic review

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## ABSTRACT

Outdoor air pollution is an important determinant of health. Children are one of the most sensitive population groups due to their yet underdeveloped respiratory system. Methodology for linkage environmental and health data at population level had been initiated by the World Health Organization about twenty years ago. The aim of our study is an overview of methods with which the effects of outdoor air pollution on children's health have been investigated at the population level. Literature overview was made systematically. Health effects of outdoor air pollution at the population level were firstly investigated after 1990. Simultaneously with the most common outdoor air pollutants (NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub> and CO) monitoring of health effects was measured. Poisson regression analysis was the most frequently used method of ecological time-series studies and spatial studies. Exposure misclassification was in this research field the most common limitation of ecological studies. This study supports the need of future research on outdoor air pollution's effects on the at population level from an engineering and public health view.

**Key words:** outdoor air pollution, children health, time-series study, spatial study, methodology

## INTRODUCTION

In Europe in 2012 482,000 people died of outdoor air pollution-related causes. Outdoor air pollution occurs when the concentration of pollutants in air exceeds the level which has adverse health effects or adverse effects on environment [1]. In average, people daily breathe between 10 to 20 m<sup>3</sup> of air, depending on their physical constitution and physical activity [2, 3]. Excessive outdoor air pollution represents a health hazard for population [4].

One of the first evidences of adverse health effects of air pollution at the population level is so called the Great Smog during December 1952 in London. Thousands of people have died because of the high levels of sulphur dioxide (SO<sub>2</sub>) and particles of different diameter present in outdoor air. The main reason for the incident was associated with temperature inversion which had trapped (and formed a thick layer of) SO<sub>2</sub> and smoke. Since then many epidemiological studies have confirmed that short-term exposure to outdoor air pollution is connected with morbidity and mortality [5].

There are about 200 different pollutants present in urban outdoor air. The most common outdoor air pollutants are particulate matter of different diameters, ozone (O<sub>3</sub>), nitrogen oxides (NO<sub>x</sub>), sulphur dioxide (SO<sub>2</sub>), carbon monoxide (CO), heavy metals, volatile organic compounds and pesticides [6].

Both short- and long-term exposure is associated with high risk of respiratory and heart diseases, stroke and lung cancer. The exposure has stronger effect on children, elderly, poor and ill [1]. Outdoor air pollution is strongly associated with chronic respiratory diseases which often appear in childhood. Asthma and other lower respiratory system diseases are in children strongly associated with exposure to NO<sub>2</sub>, SO<sub>2</sub> and PM<sub>10</sub> [7-9]. Outdoor air pollution is also associated with daily visit of primary care health system and hospital admissions [10-14].

The association between outdoor air pollution and its effects on human health can be examined at the individual or at the population level [15, 16]. Studies at the population level were firstly initiated by the World Health Organization (WHO) about twenty years ago, when the usage of so called "linkage methods for environment and health analysis" was recommended [17, 18] as a useful tool in determining the association between environmental pollution and its health effects. Time-trend studies are studies that compare disease rates over time in one population (Morgenstern, 1982; Morgenstern and Thomas, 1993). Spatial studies, usually referred to as multi-group studies, are studies that compare disease rates among many spatial units during the same period [19, 20].

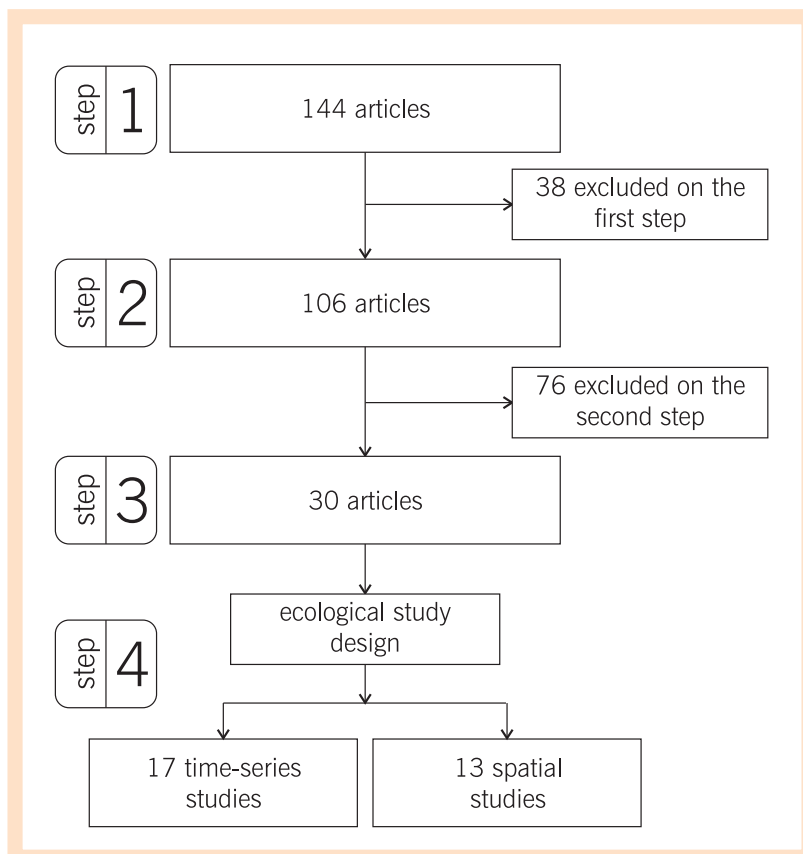
The aim of our systematic review is an overview of methods of epidemiological studies with which the effects of outdoor air pollution on children's health have been investigated at the population level. The specific goal of this review is the presentation of the progress in new findings of the effects of outdoor air pollution on children's health. For

this purpose the overview of scientific articles on this field was made, with the emphasis on methods of defining the association between pollution and effect health effects at population level with the view of the opportunity for future research.

## METHODS

Overview of articles on the topic of outdoor air pollution's effects on children's health was arranged chronologically in database PubMed Central. Overview of articles was made in four steps. In each next step new inclusion and exclusion criteria were added.

In the first step we included original and review scientific articles in English language with free full text available and with the publication date between January 1<sup>st</sup> 1977 (publication year of first article on this topic) and October 17<sup>th</sup> 2015. In the second step we have excluded the articles which did not include the topic of outdoor air pollutions effect's on children's health. In the third step articles were divided into the groups depending on study design. In the last, fourth step epidemiological ecological studies were analysed precisely. Observed health outcome, exposure to outdoor air pollution and methods of defining the association between outdoor air pollution and health effects at the population level are displayed in tabular form. In databases epidemiological ecological studies that were made in Slovenian area were looked for, the results of this search is also displayed in tabular form (Figure 1).

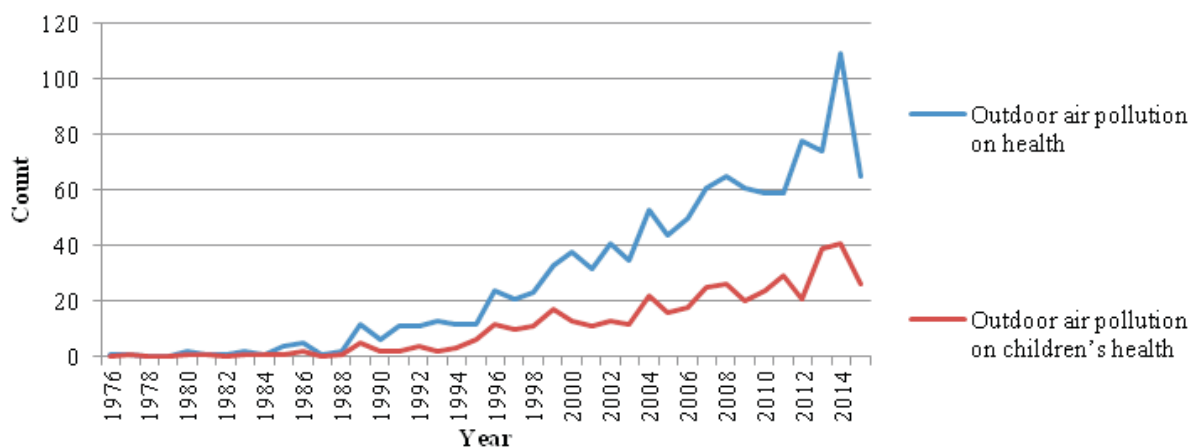


**Picture 1:**  
Flow diagram of the search process

## RESULTS

### The progress in new findings of the effects of outdoor air pollution on children's health

The first epidemiological article on the health effects of outdoor air pollution was published in 1976. Already in the next year, in 1977, the same effects were investigated on children. Picture 2 shows number of original scientific articles (epidemiological and toxicological study design) and review articles.



**Picture 2:**

Publication trends for the effect of outdoor air pollution on health (blue) and the effect of outdoor air pollution on children's health (red) at the population level from January 1<sup>st</sup> 1976 to October 17<sup>th</sup> 2015 [21].

### Methods of association between outdoor air pollution and children's health effects at the population level

In our systematic review we focused on ecological study designs; time-series studies and spatial studies. Overview of time-series studies is displayed in Table 1 and spatial studies in Table 2.

**Table 1:** Overview of ecological time-series studies at the population level included in systematical analysis

Research	Period of observation	Observed health outcome	Exposure to outdoor air pollution		Meteorological parameters	Methods
			Pollutants	Lag [day]		
Buchdahl et al., 1996 [22]	Mar. 1992 – Feb. 1993	Daily incidence of acute wheezy episodes	Daily av. conc.: O <sub>3</sub> , SO <sub>2</sub> , NO <sub>2</sub>	1, 2, 3, 4, 5, 6, 7	T, wind speed	Poisson regression analysis
Morgan et al., 1998 [10]	Jan. 1990 – Dec. 1994	Daily hospital admission of asthma	Particulates <sub>0.01 to 2.00 μm</sub> (daily av. conc.), NO <sub>2</sub> (daily av. conc., daily max. 1-hr conc.); O <sub>3</sub> (daily max. 1-hour)	0, 1, 2	T (mean, dew point)	Poisson regression analysis
Segala et al., 1998 [23]	Sept. – Nov. 1992	Daily asthma attacks and asthma-like symptoms	Daily av. conc.: SO <sub>2</sub> , suspended black particulates BS, suspended particulates with an aerodynamic diameter close to 10 μm (PM <sub>1.3</sub> ), NO <sub>2</sub>	0, 1, 2, 3, 4, 5, 6	T, RH (daily av.)	Generalized estimating equations
Atkinson et al., 1999 [11]	Jan. 1992 – Dec. 1994	Daily emergency department visits for asthma and all other respiratory complaints	Daily av. conc.: NO <sub>2</sub> , O <sub>3</sub> , SO <sub>2</sub> , CO, particles (as BS), PM <sub>10</sub>	0, 1, 2, 3	T (daily max., min.); RH (06:00 h, 15:00 h)	Poisson regression analysis
Norris et al., 1999 [24]	Sept. 1995 – Dec. 1996	Daily emergency department visits for asthma	PM <sub>10</sub> (daily av.), CO (daily av.); SO <sub>2</sub> (1-hr av.); NO <sub>2</sub> (daily max. 1 hr and daily av. conc.); O <sub>3</sub> (daily max. 8-hr)	0, 1, 2, 3, 4	T (daily av.), dew point T (daily av.)	Poisson regression analysis
Bobak and Leon, 1999 [25]	1986 – 1988	Low birth weight, stillbirth	Daily av. conc.: TSP, SO <sub>2</sub> , NO <sub>x</sub> (daily av.)	/	/	Logistic regression analysis
Gouveia and Fletcher, 2000 [26]	1991 – 1993	Mortality due to all causes, respiratory and pneumonia	PM <sub>10</sub> , SO <sub>2</sub> (daily av. conc.); CO (max. 8-hr moving av.); O <sub>3</sub> , NO <sub>2</sub> (max. hourly mean during the daily period)	0, 1, 2	T, RH, atmospheric pressure, rainfall, wind speed, wind direction (daily – av., max., min. level)	Poisson regression analysis
Gouveia and Fletcher, 2000 [12]	Nov. 1992 – Sept. 1994	Daily hospital admissions due to respiratory diseases	Daily av. conc.: PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> , O <sub>3</sub> , CO	0, 1, 2	T, RH (daily level – av., max., min.)	Poisson regression analysis
Fusco et al., 2001 [13]	Jan. 1995 – Oct. 1997	Daily hospital admissions due to respiratory conditions, acute respiratory infections, asthma	Daily av. conc.: particles, SO <sub>2</sub> , NO <sub>2</sub> , CO (daily integrated measure); O <sub>3</sub> (mean 08:00 h – 16:00 h)	0, 1, 2, 3, 4	T, RH (daily av.)	Poisson regression analysis
Thompson and Shields, 2001 [27]	Jan. 1993 – Dec. 1995	Treatment of acute asthma exacerbations in the emergency department	Daily av. conc.: PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>x</sub> , NO, NO <sub>2</sub> , O <sub>3</sub> , CO, benzene	0, av. 0-1, 0-2, 0-3	T, rainfall (daily av.)	Poisson regression analysis
Hajat et al., 2002 [28]	Jan. 1992 – Dec. 1994	Number of consultations made at family practices due to upper respiratory disease	Daily av. conc.: SO <sub>2</sub> , BS, NO <sub>2</sub> , CO, O <sub>3</sub> , PM <sub>10</sub>	0, 1, 2, 3	T, RH (daily – max., min.)	Generalized additive model
Galan et al., 2003 [29]	1995 – 1998	Daily emergency department admissions due to asthma	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> (daily av.); O <sub>3</sub> (av. of max. 8-hr)	0, 1, 2, 3, 4	T, RH (daily av.)	Poisson regression analysis
Zhang et al., 2006 [30]	Jan. 2001 – Dec. 2004	Daily mortality (all causes excluding accidents and injuries), cardiovascular and respiratory diseases	Daily av. conc.: O <sub>3</sub> , NO <sub>2</sub> , SO <sub>2</sub> , PM <sub>10</sub>	0, 1, 2, 3, 4, av. 0-1, 0-4	T, RH (daily – min., max., av.)	Generalized additive model
Conceição et al., 2009 [31]	Jan. 1994 – Dec. 1997	Daily records of mortality due to respiratory diseases	SO <sub>2</sub> , PM <sub>10</sub> (daily av. conc.); CO (greatest 8-hr moving av.); O <sub>3</sub> (24-hr peak)	1, 2, 3, av. 1-5	T (min.), RH (daily av.)	Poisson regression analysis
Nastos et al., 2010 [32]	2001 – 2004	Daily counts of childhood asthma hospital admissions	Daily av. conc.: PM <sub>10</sub>	0, 1, 4	/	Poisson regression analysis and logistic regression analysis
Mansourian et al., 2010 [33]	Mar. 2005 – Mar. 2006	Hospital admission due to respiratory diseases	Daily av. conc.: SO <sub>2</sub> , NO <sub>2</sub> , PM <sub>10</sub> ; CO (8-hr av.)	/	/	Poisson regression analysis
Hua et al., 2014 [14]	Jan. 2007 – Jul. 2012	Daily asthma hospital admission	Daily av. conc.: PM <sub>2.5</sub> , BC, NO <sub>2</sub> , SO <sub>2</sub>	1, 3, 5	T, RH (daily av.)	Distributed lag model

**Legend:**

hr – hour; av. – average; conc. – concentration; max – maximum; min – minimum; NO<sub>2</sub> – nitrogen dioxide [μg/m<sup>3</sup>]; SO<sub>2</sub> – sulphur dioxide [μg/m<sup>3</sup>]; CO – carbon monoxide [μg/m<sup>3</sup>]; PM<sub>10</sub> – particulate matter of 10 micrometres in diameter [μg/m<sup>3</sup>]; O<sub>3</sub> – ozone [μg/m<sup>3</sup>]; BS – black smoke [μg/m<sup>3</sup>]; BC – black carbon [μg/m<sup>3</sup>]; TSP – total suspended particulates [μg/m<sup>3</sup>]; T – temperature [°C]; RH – relative humidity [%].

**Table 2:** Overview of ecological spatial studies at the population level included in systematical analysis

Research	Observed health outcome	Exposure to outdoor air pollution – pollutants and spatial units of observation	Methods
Pikhard et al., 2001 [34]	Prevalence of respiratory outcomes (wheezing, asthma, dry cough)	SO <sub>2</sub> concentration measurement by passive samplers (2 week campaigns in October 1993 and February 1994). Kriging interpolation technique had been used/used for spatial distribution of SO <sub>2</sub> conc. (Results: map of log-term estimation of winter levels of SO <sub>2</sub> for each point = 10×10 m). The arithmetic mean of SO <sub>2</sub> concentration at the location of home and school.	Logistic regression analysis
Hwang and Chan, 2002 [35]	Daily clinic visits for lower respiratory tract illness	Daily av.: NO <sub>2</sub> , SO <sub>2</sub> , PM <sub>10</sub> ; hr max.: O <sub>3</sub> ; max. 8-hr running av.: CO. Spatial units of observation: 50 individual small communities in Taiwan (50 townships and city districts in Taiwan where ambient air monitoring stations of the Taiwan Air Quality Monitoring Network are situated).	Poisson regression analysis (1 <sup>st</sup> step), Bayesian hierarchical modelling (2 <sup>nd</sup> step)
Wolf, 2002 [36]	Hospitalization chronic rhinosinusitis	SO <sub>2</sub> , NO <sub>x</sub> , dust fall (TSP). Spatial units of observation: 85 administrative districts in Cologne, Germany all measurements are aggregated to these units. Preparing map for spatial variation of health and air pollution data on the level of administrative units by using GIS.	Ordinary least-squares (OLS) regression
Scoggins et al., 2004 [37]	Mortality circulatory and respiratory causes	Annual av. NO <sub>2</sub> . Spatial units of observation: 1296 grid cells (3×3 km), Auckland region, New Zealand. Spatial units of observation: Annual av. NO <sub>2</sub> modelling conc. was converted from point-based grid coverage into 3 km by 3 km polygon grid coverage in ARC INFO and ArcView GIS. Polygon grid coverage conc. were converted to census area unit (CAU) conc. by calculating an area weighted av. conc. for all individual CAUs that overlapped more than one grid cell.	Separate logistic regression Models and Poisson regression analysis
Oyana and Rivers, 2005 [38]	Hospitalization and outpatient visits for asthma and gastroenteritis	PM <sub>2.5</sub> and other pollutants in vehicle emissions (e.g. NO <sub>2</sub> ) Spatial units of observation: Buffalo's west side, east side, parts of the downtown areas, and 4 geographic regions) which is second-largest city in New York State. Data processing, GIS mapping, and analysis were conducted in ArcGIS and Microsoft Excel. ClusterSeer 2.03 was used to implement cluster analysis and Diggle's model. Final map production was completed using Corel Draw 11.	Multiple-comparison test
Wilson, 2006 [39]	Hospital admissions due to respiratory diseases	PM <sub>10</sub> Spatial units of observation: TAPM (The Air Pollution Model) annual concentration outputs are produced on a grid with 1,500 m resolution in Christchurch, New Zealand. This gridded annual data was input into a GIS and then interpolated using a regular spline with five points of interpolation and a 100 m grid resolution. The zonal statistics tool in spatial analyst was then used to calculate the mean concentration for each CAU (Census Area Unit).	Poisson distribution model
Albuquerque et al., 2007 [40]	Daily records on asthma in the primary health system	CO, SO <sub>2</sub> , PM <sub>10</sub> , O <sub>3</sub> , NO <sub>2</sub> . The daily records from the air quality monitoring program were provided by the State Environmental Secretariat (SEAMA) and State Environmental Institute (IEMA). The air quality program is managed by the IEMA, which is responsible for five automatic monitoring stations. Spatial units of observation: 27 primary health units in the municipality of Greater Vitória, Brasil. (The municipality was divided by district and the outpatient treatment rates were calculated using the DATASUS database 8 per age bracket and home address.) An asthma distribution map was developed for using ArcGis.	Pearson correlation coefficient

Research	Observed health outcome	Exposure to outdoor air pollution – pollutants and spatial units of observation	Methods
Wang, 2008 [41]	Cardio-respiratory mortality	<p>O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>. The daily gaseous air pollutants conc. were aggregated to annual means. Data were obtained from 13 monitoring stations by the Queensland Environmental Protection Agency (QEPA), including 8 stations within Brisbane city and 5 around the city.</p> <p>Spatial units of observation: 162 statistical local areas (SLA) cover the whole of Brisbane, Australia. The average size of a SLA was approximately 8 km<sup>2</sup> (ranged from 0.4 to 184.8 m<sup>2</sup>).</p> <p>GIS techniques were used in mapping the spatial patterns of annual average O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub> conc. at a SLA level.</p>	Spatial distribution analysis, multivariable logistic regression model
Choi et al., 2009 [42]	Daily mortality due to natural and cardiovascular causes	<p>Annual av. of total PM<sub>2.5</sub> mass. The data were provided by the U.S. Environmental Protection Agency. 1<sup>st</sup> source of data: Federal Reference Method (FRM) monitoring network; 2<sup>nd</sup>: Interagency Monitoring of Protected Visual Environments (IMPROVE) network; 3<sup>rd</sup>: three-dimensional regional scale air quality models such as the U.S. EPA Community Multiscale Air Quality (CMAQ) modelling system.</p> <p>Spatial units of observation: CMAQ (36 × 36 km), FRM (38 monitoring sites), IMPROVE 83 monitoring sites).</p>	Map outdoor PM <sub>2.5</sub> air conc. (1 <sup>st</sup> step), Poisson regression analysis (2 <sup>nd</sup> step)
Orru et al., 2009 [43]	Mortality and hospitalization due to cardiovascular and respiratory diseases	<p>PM<sub>10</sub>, PM<sub>2.5</sub> (annual levels) (3 monitoring states)</p> <p>Spatial units of observation: Tallinn was divided into 84 sections according to neighbourhoods. Grid resolution: 200 × 200 meters.</p> <p>The annual levels of PM<sub>2.5</sub> were calculated for all 84 Tallinn sections using the average concentration of modelled grid cells in a section. The average concentration for each section was then assigned to all residents of that neighbourhood.</p>	Exposure-response functions
Maheswaran et al., 2012 [44]	Incidence of ischemic and hemorrhagic stroke	<p>NO<sub>2</sub> and PM<sub>10</sub>. The modelled data had been produced for Greater London and were available at a 20×20 m grid point resolution.</p> <p>Spatial units of observation: 948 census output areas in south London. The distribution of pollutants across output areas in the study area is shown in maps (PM<sub>10</sub> and NO<sub>2</sub>).</p>	Poisson regression analysis
Leem et al., 2015 [45]	Asthma attack, acute bronchitis	<p>PM<sub>2.5</sub>, PM<sub>10</sub> (a one-month period of each season in 2010 and 2024; January, April, July, and October).</p> <p>CMAQ (Comprehensive Multiscale Air Quality) was used to simulate air quality over the Seoul Metropolitan Area for a one month period of each season in 2010 and 2024; January, April, July, and October.</p> <p>Spatial units of observation: 3538 cells (3×3 km), Seoul Metropolitan Area.</p>	Epidemiology based exposure response functions
Wang et al., 2015 [46]	Lung function parameters: forced expiratory volume in 1 sec (FEV <sub>1</sub> ), forced vital capacity (FVC), peak expiratory flow (PEF)	<p>NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>, PM<sub>2.5</sub> soot (annual av.). Three 2-week measurements within 1 year were conducted at 40 (PM) and 80 (NO<sub>2</sub>) locations in Netherlands.</p> <p>Spatial units of observation: spatial resolution of 1 × 1 km.</p> <p>LUR: estimate annual average air pollution concentrations at the participants' home addresses at birth and at the time of the lung function tests.</p> <p>They used linear regression analyses with natural log (ln)-transformed lung function parameters as the dependent variables to estimate associations between continuous lung function parameters and air pollution levels at the birth address and at the home address at the time of the lung function measurement.</p>	Dispersion and land use regression (LUR) models (1 <sup>st</sup> step), The Dutch dispersion model (2 <sup>nd</sup> step), linear regression analyses with natural log (3 <sup>th</sup> step)

**Legend:**

hr – hour; av. – average; conc. – concentration; max – maximum; min – minimum; NO<sub>2</sub> – nitrogen dioxide; SO<sub>2</sub> – sulphur dioxide; CO – carbon monoxide; PM<sub>10</sub> – particulate matter of 10 micrometres in diameter; PM<sub>2.5</sub> – particulate matter of 2.5 micrometres in diameter; O<sub>3</sub> – ozone; GIS – geographical information system.

The meteorological parameters used in ecological spatial studies were temperature [35, 40, 42], relative humidity [40], wind speed and pressure [42].

Previous research of the outdoor air pollution's effect on children's health at the population level in Slovenia area

In Slovenia epidemiological ecological research has not yet been extensively implemented. First studies of this type are displayed in Table 3.

**Table 3:** Overview of epidemiological ecological studies of the outdoor air pollution's effect on children's health at the population level in Slovenia area

Research	Type of study	Observed health outcome	Exposure to outdoor air pollution		Meteorological parameters	Methods
			Pollutants and spatial units	Lag [day]		
Šimac, 2008 [47]	TSS	Daily admissions due to respiratory diseases on the primary level of health system	O <sub>3</sub> (1-hr av.)	/	T	non parametric t-test
Kucec, 2013 [48], Kucec et al, 2014 [49]	TSS	Daily number of first consultations on the primary level of health system for any respiratory disease	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> (24-hr av. conc); O <sub>3</sub> (8-hr max. av. conc.)	0, 1, 2, 3, 4, 5	air T, RH	Poisson regression analysis
Kucec, 2013 [48]; Kucec et al., 2014 [50]; Kucec et al., 2014 [51]	SS	Daily number of first consultations on the primary level of health system for any respiratory disease	Winter and summer av.: PM <sub>10</sub> , SO <sub>2</sub> ; annual av.: NO <sub>2</sub> . Spatial units of observation: small units of observation for each observed pollutant. Small spatial units of study were defined using the evaluated level of outdoor air pollution (dispersion model for each point = 200X200m) and digital maps of local communities and settlements in the municipalities of the Zasavje Region.	/	wind direction and speed, air T, turbulence	Bayesian hierarchical models
Rems-Novak et al., 2014 [52]	TSS	Daily number of first consultations on the primary level of health system due to asthma	O <sub>3</sub> (daily max. av.) PM <sub>10</sub> , NO <sub>2</sub> (daily av.);	0, 1, 2, 3, 4, 5	T, RH (daily av.)	Logistic regression model

**Legend:**

TSS – time-series study; SS – spatial study; hr – hour; av. – average; conc. – concentration; max – maximum; NO<sub>2</sub> – nitrogen dioxide; SO<sub>2</sub> – sulphur dioxide; PM<sub>10</sub> – particulate matter of 10 micrometres in diameter; O<sub>3</sub> – ozone; T – temperature; RH – relative humidity.



### Possible limitations in connection to defined associations between outdoor air pollution and its effects on children's health at the population level

In Table 4 possible limitations of scientific articles with ecological study design (both time-series and spatial studies) are presented.

**Table 4:** Possible limitations of analysed ecological studies researching the effect of outdoor air pollution on children's health

Limitation	Research
<b>Time-series studies</b>	
Usefulness and unavailability of environmental data as the input data for linkage with health data	Kukec et al., 2014 [49]
Usefulness of health data as the input data for linkage with environmental data	Nastos et al., 2010 [32]; Rems-Novak et al., 2014 [52], Kukec et al., 2014 [49]
Exposure misclassification	Nastos et al., 2010 [32]; Thompson et al., 2001 [27]; Zhang et al. 2006 [30]; Mansourian et al., 2010 [33]; Galan et al., 2003 [29]
To low station of outdoor air pollution monitoring and varying distances from monitoring sites	Atkinson et al., 1999 [11]; Bobak and Leon, 1999 [25]; Thompson et al., 2001 [27]; Rems-Novak et al., 2014 [52]; Hua et al., 2014 [14]
Lack of accuracy in the measurements of exposure	Galan et al., 2003 [29]
Short period of observation	Rems-Novak et al., 2014 [52]
Small sample of observed population	Rems-Novak et al., 2014 [52]
Observed population does is not representative for the whole population	Mansourian et al., 2010 [33]; Rems-Novak et al., 2014 [52]
Difficult to separate the independent effect for individual pollutant in outdoor air pollution and there health effect	Hua et al., 2014 [14]
<b>Spatial studies</b>	
Usefulness and unavailability of environmental data as the input data for linkage with health data	Kukec, 2013 [48]; Kukec et al., 2014 [50]; Beale et al., 2008 [53]; Stroh et al., 2007 [54]
Unavailability of input air pollution data (emission) for air quality modelling Questionable validity of available data	Oyana and Rivers, 2005 [38]; Kukec, 2013 [48]; Kukec et al., 2014 [50]
Adequatbility of air quality modelling technique for dispersion of outdoor air pollution	Kukec, 2013 [48]; Kukec et al., 2014 [50]
Exposure misclassification	Porta et al., 2008 [55]; Maheswaran et al., 2012 [44]; Kukec, 2013 [48]; Kukec et al., 2014 [50]
Missing data on any individual-level risk factors, missing data of exposure	Eitan et al., 2010 [56]; Wolf, 2002 [36]
Difficulty to separate the independent effects for individual pollutant in outdoor air pollution and their health effect	Oyana and Rivers, 2005 [38]; Kukec, 2013 [48]
No control over the effects of all confounders	Oyana and Rivers, 2005 [38]; Kukec, 2013 [48]; Leem et al., 2015 [45]

## DISCUSSION

### **The progress of research in the field of outdoor air pollution's effect on children's health at the population level**

The research of outdoor air pollution's effect on children's health started in 1977. At that time all research was made at individual level and only in 1996 [22] and later in 1998 [10, 23] the first articles that were made at population level were published. These three studies were of ecological time-series design, where the association between outdoor air pollution and asthma and other respiratory symptoms are investigated. Previous research was made on the whole population [57, 58]. First ecological spatial studies were published after 2000 [34-36], where the association between outdoor air pollution and respiratory diseases was studied as time-series studies for the first time.

### **Methods of defining the association between outdoor air pollution and children's health at the population level**

The effect of outdoor air pollution on children's health has been frequently studied in epidemiological studies; at the individual level (cross-sectional studies, case control studies and follow-up studies) and at population level (ecological studies). Overview of our review article shows that observed health outcomes in epidemiological ecological studies were frequent hospital admissions and visits to prime care due to respiratory diseases [10-14, 24, 27-29, 32, 33, 35, 38-40, 43, 47-52] and rarely cardiovascular diseases [43]. Up to 1990 in the epidemiological researches only outdoor air pollution's effect on respiratory diseases was observed [5].

In ecological studies  $PM_{10}$ ,  $SO_2$ ,  $NO_2$ ,  $O_3$  and CO were commonly observed pollutants for estimation of exposure to outdoor air pollution. The first reason (for inclusion in monitoring) is their effect on health [9, 59] and secondly, they are the most common outdoor air pollutants [8]. For measurements of  $PM_{10}$ ,  $NO_2$  and  $SO_2$  in outdoor air daily average concentrations were used. For measurements of  $O_3$  and CO daily maximum 8-hour or 24-hour concentrations were used. The most frequently used lags for health effects in time-series studies were from zero up to three or five days from the exposure. Daily data collecting of meteorological factors (air temperature and relative humidity) have been frequently used in time-series studies. Rarely measured meteorological parameters were dew point temperature, atmospheric pressure, rainfall, wind speed and direction of wind.

Poisson regression analysis was frequently used statistical method of defining the association between outdoor air pollution and children's health effects in time-series and spatial studies. Generalized additive model, logistic regression model, distributed lag model and generalized estimating equations were also used in singles time-series studies. Logistic regression analysis, Bayesian hierarchical model, multivariable logistic regression model and epidemiology based exposure response functions were also used in singles spatial studies.

Spatial units of observation in spatial studies were administrative units [35, 36, 38, 40, 41, 44] or small area units [34, 37, 39, 45, 46, 48].

Previous researches of the outdoor air pollution's effect on children's health at the population level in Slovenia area

In Slovenia methods of time-series and spatial studies have not yet been very extensively used. In time-series studies different methods of defining the association between outdoor air pollution and health effects have been used such as non-parametric [47], logistic regression model [52] and Poisson regression analysis [48, 49]. In Slovenia three spatial studies were made on the case of Zasavje region [48, 50, 51], two of them used Bayesian hierarchical models [48, 50]. In previous study [60] in Koper municipality maps with spatial distributions of observed health outcomes were prepared. The most important reasons for the rare use of ecological studies in Slovenia is uselessness and unavailability of environmental and health data for linkage analysis [48, 49, 52].

### **Limitations and strengths of our review**

In our study only free full text available studies were overviewed. Due to this limitation not all studies in this research field had been overviewed.

On the other hand, this study has its strengths. Firstly, our overview of methods of association between outdoor air pollution and health effects on children focused on the methods used at population level. Several previous reviews included researches both at individual and population level and their results, not methods. Secondly, the overview of all ecological studies in Slovenia with used methods was included. The last strength of our research, a list of limitations of time-series and spatial researches was prepared.

### **Future researches**

For future research ecological studies with pollutants that have already known effects on the whole population should be investigated on children. One of the investigated pollutants should be ultrafine particles; the effect of this air pollutant has already been investigated with ecological time trend studies for the whole population but not for children [61-63]. In future, special care should be given to data-collecting so that the data will be useful for linkage environmental and health data on population level [64]. Special challenge presents the preparation of hazard analysis at individual level. For hazard analysis of outdoor air pollution exposure fixed monitoring sites have been used. However, for improve exposure assessment in the future spatial investigation with exposure assessment in the small spatial units is necessary. Hazard analysis on pollutant's health effects should be made because of simultaneous exposure to mixture of different pollutants. An individual is exposed to different harmful factors from the environment with different effects. Because of lag time, slow and lasting effect they are usually hard to determine, because of their dispersion in the environment are also hard to control and are unpredictable. That is why in the future multiple effects [65], synergistic effect [66] and antagonistic effects [66] should be taken into account.

## CONCLUSION

In conclusion, the most frequently used method of defining the association between outdoor air pollution and children's health effects in time-series and spatial studies was Poisson regression analysis. The respiratory diseases were frequently observed health outcomes, gaseous pollutants and particulate matter were frequently monitored pollutants in ecological studies. Exposure misclassification was the most frequent and repeated limitation in ecological studies.

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