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Urban grey spaces are associated with increased allergy in the general population

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ABSTRACT

Background: the built environment in urban areas may have side effects on children's respiratory health, whilst less is known for adulthood.
Aim: to assess the association between increasing exposure to grey spaces and allergic status in an adult general population sample.
Methods: 2070 subjects (age range 15–84 yrs), living in Pisa/Cascina, Italy, were investigated in 1991–93 through a questionnaire on health status and risk factors, skin prick test (SPT), serum Immunoglobulins E (IgE), and serum antibodies to benzo(a)pyrene diol epoxide (BPDE)-DNA adducts.
Land-cover exposure within a 1000 m buffer from each subject's home address was assessed through the CORINE Land Cover program (CLC 1990) within the FP7/HEALS project (2013–2018). Participants' residential addresses were geocoded and the proportion of surrounding grey spaces was calculated.
Through logistic regression models, adjusting for potential confounding factors, the effect of a 10% increase in grey spaces exposure on allergic biomarkers/conditions was assessed; the relationship with serum antibodies to BPDE-DNA adducts positivity was also analyzed.
Results: A 10% increase in grey spaces coverage was associated with a higher probability of having SPT positivity (OR 1.07, 95% CI 1.02-1.13), seasonal SPT positivity (OR 1.12, 1.05-1.19), polysensitization (OR 1.11, 1.04-1.19), allergic rhinitis (OR 1.10, 1.04-1.17), co-presence of SPT positivity and asthma/allergic rhinitis (OR 1.16, 1.08-1.25), asthma/allergic rhinitis (OR 1.06, 1.00-1.12), presence of serum antibodies to BPDE-DNA adducts positivity (OR 1.07, 1.01-1.14).
Conclusions: grey spaces have adverse effects on allergic status and are related to a biomarker of polycyclic aromatic hydrocarbons exposure in adulthood. Thus, they may be used as a proxy of urban environmental exposure.

1. Introduction

Adverse effects of air pollution span the human life cycle and affect a wide range of communicable (i.e. respiratory tract infections) and non-communicable diseases (i.e. allergic diseases, chronic obstructive pulmonary disease, cardiovascular diseases, lung cancer, diabetes), from mild symptoms to premature mortality (Thurston et al., 2017; Shamsipour et al., 2019; Barzeghar et al., 2020).

Recent reviews of scientific evidence have clearly shown that urban outdoor pollution affects respiratory health worldwide, causing an increase in the prevalence of respiratory symptoms/diseases in both children and adults (Thurston et al., 2017; Landrigan et al., 2018; Eguiluz-Gracia et al., 2020). Detrimental effects due to urban air pollution have also been confirmed by assessing disease biomarkers such as skin prick test (SPT), spirometry, and bronchial hyper-responsiveness (Maio et al., 2009; Nuvolone et al., 2011; Ruokolainen et al., 2015; Bowatte et al., 2017; Thurston et al., 2017).

Rapid urbanization and industrialization have increased air

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pollution and population exposures (D'Amato et al., 2018; Eguiluz--Gracia et al., 2020). People living in urban areas more frequently experience allergic rhinitis and bronchial asthma than those living in rural areas: one of the main determinants is the increased presence of outdoor air pollutants, from energy consumption and vehicle exhaust emissions, which promote airway sensitization (Baldacci et al., 2015; D'Amato et al., 2018; Eguiluz-Gracia et al., 2020).

A common method of assessing air pollution exposure in urban areas is to measure/estimate air pollutants concentration and their spatial variation through outdoor air monitoring data (Ebisu et al., 2011; Faridi et al., 2019) or exposure models that combine data from air quality monitoring stations and satellite data, along with land use and meteorological parameters (Kloog et al., 2014; Stafoggia et al., 2019).

For places and periods with lack of data from outdoor air monitors, land use information can be used to obtain exposure estimates. Given the strong contribution of traffic to air pollution in urban centers, the fraction of urban land use in a subject's neighborhood may be linked to air pollution levels, but may also encompass other factors (e.g., industrial emissions, urban heat island effect, and noise) (Ebisu et al., 2011).

Indeed, the built environment in urban areas appears to have side effects on children's health (Cilluffo et al., 2018; Dzhambov et al., 2020; Tischer et al., 2017), mainly due to increasing exposure to air pollution, noise, urban heat island effect, lower access to natural environments, and accentuated sedentary life (Cilluffo et al., 2018; Ebisu et al., 2011). However, few investigations on the association between "urbanicity" (i.e. the impact of living in urban area) and allergic symptoms are available for childhood (Cilluffo et al., 2018; Dzhambov et al., 2020; Tischer et al., 2017) and even fewer for adulthood.

Recent epidemiological studies have used the Coordination of Information on the Environment (CORINE) Land Cover (CLC) data to evaluate the health impacts of specific land cover types, including urban/grey spaces, green spaces, and proximity to agricultural areas or water bodies (blue space) (Parmes et al., 2020). CLC is a European-wide standardized land cover map, managed by the European Environmental Agency (EEA), combining geospatial environmental information from national databases and satellite images (Kosztra et al., 2017). The grey spaces, identified using CLC, comprise multiple aspects related to urban areas like industrial, transport infrastructures, and urban-fabric characteristics.

In this framework, our study aimed at assessing the association of increasing exposure to grey spaces with allergic biomarkers, symptoms/diseases, and a biomarker of benzo(a)pyrene exposure, in an adult general population sample.

2. Methods

2.1. Setting and study population

Pisa (Tuscany, Italy) is a small urban area (185 km^2) located in a flat region 4 m above sea level and few kilometers from the mouth of the Arno River, which passes through the city; it is characterized by residential areas and urban/inter-urban roads (Fig. 1).

Cascina is a suburban area (79 km^2) located on the left bank of the Arno river, in its alluvial plain, 6 m above sea level, and 16 km South-East of Pisa. The municipality is characterized by agricultural and handcraft activities, as well as by sparse buildings and intersections with small streets. The main source of vehicular traffic pollution is a highway connecting Pisa to Florence, crossing Cascina and entering the easternmost part of Pisa (Fig. 1).

Since 1980, the Pulmonary Environmental Epidemiology Unit of the Institute of Clinical Physiology of the Italian National Research Council (IFC-CNR) has performed epidemiological surveys to assess the effects of outdoor air pollution on human health. A sample of subjects living in the urban area of Pisa and the suburban area of Cascina was selected using a multistage stratified family-cluster design. Detailed information on population characteristics and methods have been reported in previous publications of our research Group (Baldacci et al., 1997; Viegi et al., 1999, 2004; Maio et al., 2016, 2019).

A cross-sectional survey was conducted in the area of Pisa/Cascina on 2841 subjects investigated from 1991 to 1993 through the CNR questionnaire on respiratory symptoms/diseases and risk factors derived from the National Heart Lung and Blood Institute questionnaire (Viegi et al., 1999). Part of the sample performed objective tests: skin prick test (SPT) to common airborne allergens (Baldacci et al., 1996) and total serum Immunoglobulin E (IgE), as markers of atopy (Baldacci et al., 1997; Sapigni et al., 1998); serum antibodies to benzo(a)pyrene diol epoxide (BPDE)-DNA adducts, as a marker of environmental carcinogens exposure and DNA damage (Petruzzelli et al., 1998).

At the time of the survey, Italian law did not require Ethical Committee approval. The protocol was approved by an Internal Review Board. The study was carried out in accordance with the fundamental principles of the Helsinki Declaration.

2.2. Exposure assessment

2.2.1. Grey spaces

At the time of the survey, only total suspended particulates (TSP) and sulphur dioxide (SO_2) were routinely monitored at the city level in Pisa and Cascina: mean values of 94 and 99 μg/m^3, respectively, for TSP and of 15 and 24 μg/m^3, respectively, for SO_2, in 1992 (Baldacci et al., 1997) were measured. Within the FP7 HEALS ("Health and Environment-wide

Fig. 1. Map of the study area
Timelapse in Google Earth (year 1990).

Associations based on Large population Surveys") project (carried out in 2013–2018), CLC data referring to land cover/land use status of the year 1990 (CLC, 1990) were obtained (Parmes et al., 2020) and used in the analyses of the current manuscript as an indicator of individual exposure to urban-related air pollution.

The CORINE framework is a Europe-wide satellite-based inventory of land-cover developed in 1985 by the EEA, in order to gather information relating to the environment. It combines geospatial information from national databases and satellite images into 44 land cover classes (Level 3) describing various types of artificial surfaces, agricultural land, forests, wetlands, and water bodies (Kosztra et al., 2017).

For each participant, the percentage of different land cover classes within a 1000 m buffer around the geocoded home address was calculated. Residential surrounding grey spaces were estimated by summing up the percentages of the associated land-use types (industrial, commercial and transport units, port sites, airports, or urban fabric-related features) (Parmes et al., 2020). Residential grey spaces ranged from 0% (no grey space) to 100% (complete grey spaces).

2.2.2. Exposure biomarker

1688 subjects, out of the 2841 participating in the Pisa survey, accepted to undergo a blood sample for the determination of serum antibodies to BPDE-DNA adducts, using a modified version of the enzyme-linked immunosorbent assay (ELISA). Details on the method are described in previous publications (Newman et al., 1988; Petruzzelli et al., 1998). The results were expressed as being positive or negative to the presence of anti-BPDE-DNA adducts.

Our Research Group had already shown that serum antibodies to BPDE-DNA adducts may be used as a putative marker of polycyclic aromatic hydrocarbon (PAH) exposure (Petruzzelli et al., 1998). Indeed, an independent effect of urban living (vs suburban one) on the positivity to serum antibodies to BPDE-DNA adducts (odds ratio - OR - 1.49, 95% confidence interval - CI - 1.16-1.92) was found through a multivariate analysis adjusted for other independent factors such as smoking habit, family history of lung cancer and presence of family members positive to serum antibodies to BPDE-DNA adducts (Petruzzelli et al., 1998).

2.3. Health status assessment

2.3.1. Allergic symptoms/diseases

The following outcomes, collected on all participants (n = 2841) through the CNR questionnaire, were considered:

- current asthma symptoms/diagnosis, if the subject reported current asthma diagnosis or current attacks of shortness of breath with wheezing, apart from common colds, or persistent (months in which they occurred for most days) wheeze, apart from common colds.
- current allergic rhinitis symptoms/diagnosis, if the subject reported current hay fever or any other condition making the nose runny or stuffy, apart from common colds.

In particular, with regard to allergic conditions, the following mutually exclusive variable was computed and used in the analyses: 1. asthma & allergic rhinitis (subjects reporting current asthma symptoms/diagnosis & current allergic rhinitis symptoms/diagnosis); 2. only allergic rhinitis (subjects reporting current allergic rhinitis symptoms/diagnosis and not reporting current asthma symptoms/diagnosis); 3. only asthma (subjects reporting current asthma symptoms/diagnosis and not reporting current allergic rhinitis symptoms/diagnosis); 4. neither asthma nor allergic rhinitis (subjects not reporting current asthma symptoms/diagnosis and not reporting current allergic rhinitis symptoms/diagnosis).

2.3.2. Atopy

IgE values were measured in 1915 subjects using a direct paper radio-immunosorbent test and were transformed in logarithm10 values (log IgE) to obtain a normal distribution (Sapigni et al., 1998). Dichotomized values through the 75th percentile (1.81 kU/L) were analyzed.

SPT reactivity was measured in 2184 subjects, using a standardized protocol, with 12 local allergens (pollens, house dust mites, animal dander, and molds). An SPT result was considered positive if it yielded a maximal wheal diameter of at least 5 mm, after subtracting the maximal diameter of the negative control reaction (Baldacci et al., 1996).

In particular, the following atopic conditions were considered: positivity to SPT - positivity to at least one of the 12 local allergens; perennial positivity - positivity to at least one perennial allergen like house dust mites or pets (cat, dog, cow or horse) or aspergillus; seasonal positivity - positivity to at least one seasonal allergen like pollens (olive tree, grasses, Parietaria officinalis and Compositae) or spores (Alternaria); monosensitization - positivity to only one allergen; polysensitization - positivity to two or more allergens.

Moreover, a mutually exclusive variable was computed and used in the analyses to assess the compresence of SPT positivity and asthma/allergic rhinitis: 1. SPT positivity & asthma/allergic rhinitis (subjects having SPT positivity and reporting current asthma symptoms/diagnosis or allergic rhinitis symptoms/diagnosis); 2. only SPT positivity (subjects having SPT positivity and not reporting current asthma symptoms/diagnosis or allergic rhinitis symptoms/diagnosis); 3. only asthma/allergic rhinitis (subjects having no positive SPT and reporting current asthma symptoms/diagnosis or allergic rhinitis symptoms/diagnosis); 4. neither SPT nor asthma/allergic rhinitis (subjects having no positive SPT and reporting no current asthma symptoms/diagnosis nor allergic rhinitis symptoms/diagnosis).

2.4. Potential confounders

The following potential confounders, collected through the questionnaire, were considered: age; sex; body mass index (BMI) (Kg/m^2); smoking habits - non-smoker (subjects who had never smoked any kind of tobacco), smoker (subjects who currently smoked), ex-smoker (subjects who had smoked in the past but did not smoke at the moment of the survey); educational level - literate/elementary/middle high school ($\leq$8 years), college/high school (9–13 years), graduate (>13 years); occupational exposure, if subjects reported regular exposure to fumes, gases, dusts or chemicals in working environments; family history of respiratory diseases, if subjects reported that some relatives suffered from asthma or chronic bronchitis or emphysema; family history of allergic diseases, if subjects reported that some relatives suffered from hay fever or eczema or allergic eye problems or milk crust; family members positive for serum antibodies to BPDE-DNA adducts, if other members of the family, beside the subject, were assessed for the presence of serum antibodies to BPDE-DNA adducts and resulted positive.

2.5. Statistical analyses

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS version 26.0). The characteristics of the study sample were summarized as mean and standard deviation (SD) for normally distributed quantitative variables, as median and interquartile range (IQR) for non-normally distributed quantitative variables and as percentage (%) for categorical variables.

Median percentages of residential surrounding grey spaces in relation to different allergic biomarkers/conditions and to serum antibodies to BPDE-DNA adducts positivity were analyzed through Kruskal-Wallis and Mann-Whitney U tests for independent samples.

The effect of 10% increase in grey spaces coverage near home (within a 1000 m buffer) on the presence of allergic biomarkers/conditions was assessed using multivariable logistic regression models, adjusted for sex, age, BMI, educational level, smoking habits, occupational exposure, family history of respiratory diseases and family history of allergic diseases. The relationship between a 10% increase in grey spaces coverage around home and serum antibodies to BPDE-DNA

adducts positivity was also assessed using a multivariable logistic regression model, adjusted for sex, age, BMI, educational level, smoking habits, occupational exposure and, presence of family members positive to serum antibodies to BPDE-DNA adducts.

Multinomial logistic regression models were run in the presence of dependent variables with more than two categories. Results were expressed as OR and 95% CI. The significance level was set at 0.05.

Statistical analyses were run in the subsample of ≥15 yr subjects with complete information from the questionnaire and SPT (n=2070). Out of them, 1745 and 1538 had information about IgE and serum antibodies to BPDE-DNA adducts, respectively (Fig. 2).

Sensitivity analyses were run selecting the subsample of long-term residents (over five years) (n = 1817) and the subsample of subjects with complete information on SPT, IgE and, serum antibodies to BPDE-DNA adducts (n = 1459).

3. Results

The mean age of the 2070 participants was 45.11 years (range 15–84). 53% of the subjects were females; 70.6% had a low educational level (≤8 years); 43.7% had an occupational exposure; 27.4% were smokers and 29.4% were ex-smokers. Over 45% reported a family history of respiratory or allergic diseases (45.4% and 48.1%, respectively) (Table 1).

The prevalence of allergic status varied according to the considered outcomes: 16.2% of the subjects had a SPT positivity to at least one local allergen, 9.6% to at least one perennial allergen and 9.9% to at least one

Table 1
Descriptive characteristics of the subjects (n = 2070).

Gender (%):	
males	47.0
females	53.0
Age (years) (mean ± SD)	45.11 ± 16.64
min-max	15–84
Body mass index (kg/m^2) (mean ± SD)	25.61 ± 4.25
Groups of body mass index (%):	
underweight	1.6
normal weight	46.9
overweight	38.1
obese	13.4
Educational level (%):	
literate/elementary/medium high school (≤8 years)	70.6
college/high school (9–13 years)	25.1
graduate (>13 years)	4.3
Smoking habits (%):	
smoker	27.4
ex-smoker	29.4
non-smoker	43.1
Occupational exposure to fumes/gases/dusts/chemicals (%)	43.7
Family history of respiratory diseases (%)	45.4
Family history of allergic diseases (%)	48.1
Family members positive for serum antibodies to BPDE-DNA adducts (%)	26.2

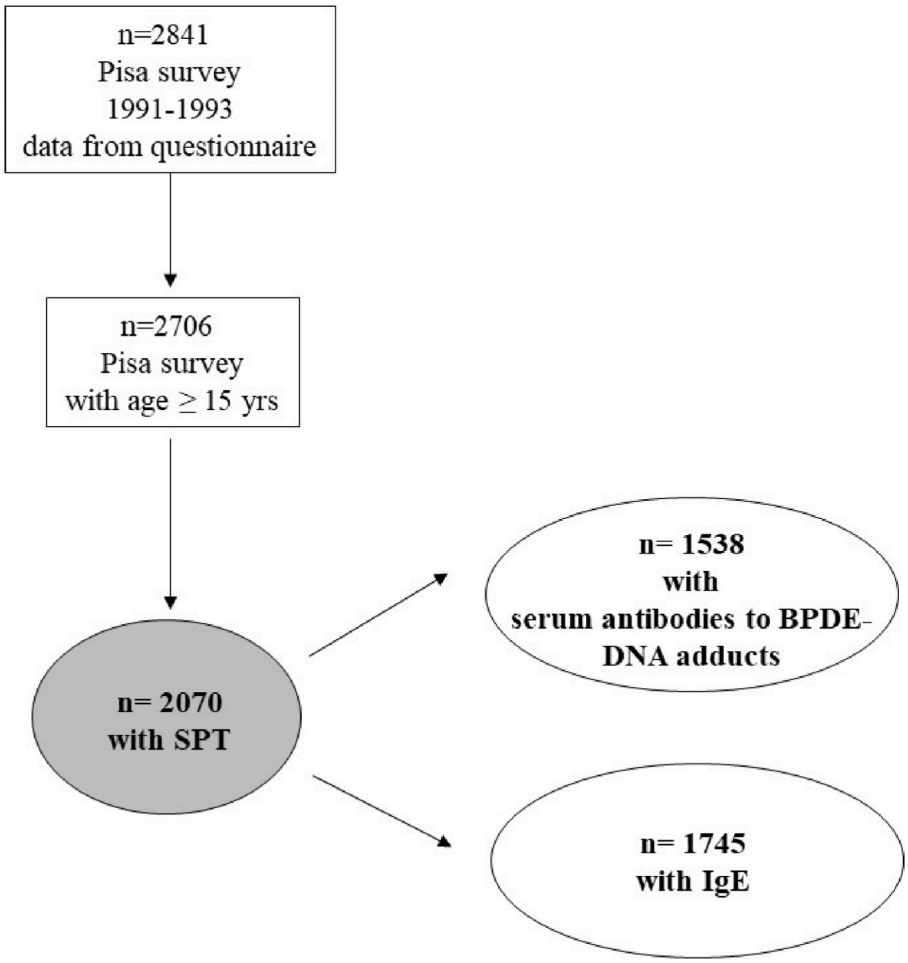

Fig. 2. Flow-chart of the study sample
SPT: skin prick test; IgE: immunoglobulins E; serum antibodies to BPDE-DNA adducts: serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts.

seasonal allergen. 8.6% of subjects had a polysensitization while 7.6% a monosensitization. 25.1% of subjects had an elevated value of IgE (Table 2).

The prevalence of subjects with a co-presence of current allergic rhinitis and asthma was 2.9%, with only allergic rhinitis 13.3% and with only asthma 8.7%. Further, 8.0% of subjects had copresence of SPT positivity and asthma/allergic rhinitis, 8.3% only SPT positivity and 16.9% only asthma/allergic rhinitis (Table 2). Of the 1538 subjects assayed for the presence of serum antibodies to BPDE-DNA adducts, 21.8% were positive (Table 2).

Median exposure to grey spaces within a 1000 m buffer from each subject's home address was 46.52% (range 0.0–98.04%; interquartile range 40.83%) (Table 2). 32.8% of the population lived in areas characterized by 31–40% of grey spaces and 17.1% lived in areas characterized by 81–90% of grey spaces (Fig. 3).

The highest values of grey space exposure were found in subjects with allergic biomarkers/conditions (except for IgE) and in those positive to serum antibodies to BPDE-DNA adducts (Table 3).

Table 4 shows associations of a 10% increase in residential exposure to urban grey spaces with probabilities of having allergic biomarkers/conditions and serum antibodies to BPDE-DNA adducts. A significantly higher probability was found for SPT positivity (OR 1.07, 95% CI 1.02-1.13), seasonal SPT positivity (OR 1.12, 1.05-1.19), polysensitization (OR 1.11, 1.04-1.19), only allergic rhinitis (OR 1.10, 1.04-1.17), only asthma/allergic rhinitis (without SPT positivity) (OR 1.06, 1.00-1.12); a borderline association emerged for only current asthma (OR 1.07, 0.99-1.15). In addition, a 10% increase in individual exposure to urban grey spaces was positively associated with the copresence of SPT positivity and asthma/allergic rhinitis (OR 1.16, 1.08-1.25). No significant association was found for IgE. There was also a significant relationship between exposure to grey spaces and positivity to serum antibodies to BPDE-DNA adducts (OR 1.07, 1.01-1.14) (Table 4).

4. Discussion

In our population, increased residential exposure to urban grey spaces was significantly associated with adverse effects on allergic status. Significant associations were shown for both allergic biomarkers and conditions.

Table 2
Allergic biomarkers/conditions and exposure (n = 2070).

Allergic biomarkers/conditions	
Positivity to SPT (%)	16.2
Perennial positivity (%)	9.6
Seasonal positivity (%)	9.9
Type of sensitization (%):	
polysensitization	8.6
monosensitization	7.6
Asthma/allergic rhinitis co-presence (%):	
asthma & allergic rhinitis	2.9
only allergic rhinitis	13.3
only asthma	8.7
SPT and asthma/allergic rhinitis co-presence (%):	
SPT positivity & asthma/allergic rhinitis	8.0
only SPT positivity	8.3
only asthma/allergic rhinitis	16.9
Log IgE value ≥ 1.81 kU/L (%) (n = 1745)	25.1
Exposure	
Positivity to serum antibodies to BPDE-DNA adducts (%) (n = 1538)	21.8
% of grey spaces coverage:	
median	46.52
min-max	0.0–98.04
IQR	40.83

SPT: skin prick test; IgE: immunoglobulins E; serum antibodies to BPDE-DNA adducts: serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts; IQR: interquartile range.

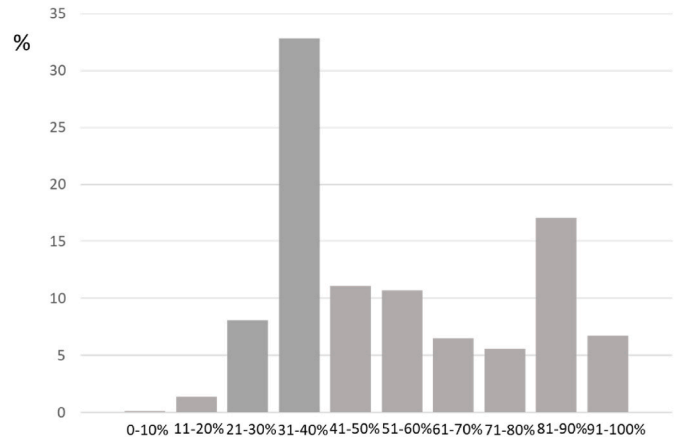

Fig. 3. Percentage of subjects exposed to different levels of grey spaces.

Table 3
Median exposure to grey spaces in relation to different allergic biomarkers/conditions and to serum antibodies to BPDE-DNA adducts positivity.

	Median, IQR of percentage of grey spaces coverage	p-value
Allergic biomarkers/conditions		
SPT positivity:		**0.030**
yes	50.06, 45.22	
no	46.01, 39.55	
Perennial positivity:		
yes	46.37, 45.28	0.195
no	46.65, 39.73	
Seasonal positivity:		
yes	53.96, 44.99	**0.004**
no	45.85, 39.54	
Type of sensitization:		
polysensitization	50.20, 45.76	**0.020**
monosensitization	49.91, 41.65	
no sensitization	46.01, 39.55	
Asthma/allergic rhinitis co-presence:		
asthma & allergic rhinitis	57.40, 44.07	**0.001**
only allergic rhinitis	57.26, 44.44	
only asthma	51.13, 43.08	
neither asthma nor allergic rhinitis	43.57, 39.72	
SPT and asthma/allergic rhinitis co-presence:		
SPT positivity & asthma/allergic rhinitis	57.47, 44.82	**0.000**
only SPT positivity	43.17, 42.52	
only asthma/allergic rhinitis	53.07, 41.03	
neither SPT nor asthma/allergic rhinitis	43.75, 39.66	
Log IgE value:		
≥1.81 kU/L	44.65, 39.38	0.722
<1.81 kU/L	47.90, 42.16	
Exposure biomarker		
Positivity to serum antibodies to BPDE-DNA adducts:		
yes	45.53, 40.22	**0.003**
no	40.95, 27.16	

IQR: interquartile range; SPT: skin prick test; IgE: immunoglobulins E; serum antibodies to BPDE-DNA adducts: serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts; SD: standard deviation.

Previous studies have reported that living in urban areas can affect allergic respiratory diseases, including asthma (Baldacci et al., 2015; Son et al., 2015; Maio et al., 2016; Thurston et al., 2017; Landrigan et al., 2018; D'Amato et al., 2018; Eguiluz-Gracia et al., 2020). The loss of natural environments and biodiversity, corresponding to a

Table 4
Effects of 10% increase in residential exposure to urban greyness on allergic biomarkers/conditions and serum antibodies to BPDE-DNA adducts (n = 2070).

	OR (95% CI)
Allergic biomarkers/conditions	
SPT positivity	**1.07 (1.02–1.13)**
Reference category: negativity	1.00
Perennial SPT positivity	1.05 (0.98-1.12)
Reference category: negativity	1.00
Seasonal SPT positivity	**1.12 (1.05–1.19)**
Reference category: negativity	1.00
Type of sensitization:	
polysensitization	**1.11 (1.04–1.19)**
monosensitization	1.03 (0.96-1.11)
Reference category: negativity	1.00
Asthma/allergic rhinitis co-presence:	
asthma & allergic rhinitis	1.10 (0.98-1.23)
only allergic rhinitis	**1.10 (1.04–1.17)**
only asthma	***1.07(0.99-1.15)***
Reference category: neither asthma nor allergic rhinitis	1.00
SPT and asthma/allergic rhinitis co-presence:	
SPT positivity & asthma/allergic rhinitis	**1.16 (1.08–1.25)**
only SPT positivity	1.02 (0.95-1.09)
only asthma/allergic rhinitis	**1.06 (1.00–1.12)**
Reference category: neither SPT nor asthma/allergic rhinitis	1.00
Log IgE value:	
≥1.81 kU/L	1.00 (0.95-1.05)
Reference category: < 1.81 kU/L	1.00
Exposure biomarker	
Positivity to serum antibodies to BPDE-DNA adducts	**1.07 (1.01–1.14)**
Reference category: negativity	1.00

Adjusted for sex, age, BMI, educational level, smoking habits, occupational exposure, family history of allergic/respiratory diseases (or other family members positive for anti-BPDE-DNA antibodies).
SPT: skin prick test; IgE: immunoglobulins E; serum antibodies to BPDE-DNA adducts: serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts; OR: odds ratio; CI: confidence intervals.

complementary increase of artificial areas, might be related to the parallel increase in the global prevalence of inflammatory diseases, such as asthma and allergy, in the rapidly urbanizing world (Ruokolainen, 2017; Tischer et al., 2017; Paciência and Rufo, 2020; Ruokolainen et al., 2020). Furthermore, the reduced exposure to microbial diversity adversely affects the human microbiome and may lead to the development of allergic disorders (Tischer et al., 2017).

Recent epidemiological studies have used CLC data to evaluate the health impacts of specific land cover types, particularly focusing on green spaces; however, few studies have assessed the effects of grey spaces on allergic respiratory disorders. The grey spaces, identified using CLC, are indicators of multiple aspects related to an urban environment, like air pollution levels, noise, industrial emissions and, heat islands that may contribute to the overall health risk (Ebisu et al., 2011; Tischer et al., 2017; Cilluffo et al., 2018). Moreover, CLC data are easily available and exposure standardization allows pooled results and consistency across studies.

Considering a buffer of 300 m, Italian children living in highly urbanized areas (i.e. areas with continuous urban fabric) showed increased risks of having ocular (OR 1.49, 95% CI 1.10-2.03) and general symptoms (like dry/sore throat, cold feeling, headache, malaise, physical discomfort, excessive fatigue, flu or fever, chills) (OR 1.18, 95% CI 1.00-1.48), compared to those living in areas with less degree of urbanization (i.e. areas with discontinuous urban fabric) (Cilluffo et al., 2018). More recently, a 20% increase in imperviousness (% of sealed soil within a buffer of 500 m) was associated with a higher risk of allergic rhinitis (OR 1.35, 95% CI 1.05-1.73) in Austrian and Italian schoolchildren (Dzhambov et al., 2020). A 10% increase in urban land-use within 1540 m buffer from each infant's residence was associated with an increased risk of wheeze in the USA (OR 1.09, 95% CI 1.02-1.16) (Ebisu et al., 2011). A higher residential surrounding greyness (buffer of 300 m; 3rd tertile versus 1st tertile of residential surrounding greyness in m^2) was linked to an increased risk of bronchitis (OR 1.58, 95% CI 1.19-2.08) in children living in the Mediterranean biogeographic region of Spain (Tischer et al., 2017).

Differently from other studies, we assessed adverse effects of increased urban exposure on allergic disorders in an adult general population sample. Our results are in line with the findings of a Korean cross-sectional study in an adult population (≥19 years) showing that a 10% increase of urban land use (housing units, commercial/industrial areas, parking lots, schools and roads) was associated with an increased risk of self-reported diagnosed asthma (OR 1.02, 95% CI 1.01-1.04) and asthma symptoms while breathing in the last 12 months (OR 1.01, 95% CI 1.00-1.02) (Son et al., 2015). Furthermore, the role of urban living in contrast to suburban living as a risk factor for allergic rhinitis in the total Pisa/Cascina sample was previously reported (Maio et al., 2016).

In the current study, for each 10% increase in residential exposure to urban grey spaces a higher probability of having atopic sensitization was found (+7% for overall SPT positivity and +12% for seasonal SPT positivity). Few studies have examined the association between urban living and allergic sensitization in adults using different exposure indicators. In Finnish children, the amount of green environment (forest and agricultural land) around homes (within 2–5 km) was inversely associated with the risk of atopic sensitization (assessed through serum IgE) (Ruokolainen et al., 2015). In cross-sectional studies, the prevalence of allergic sensitization was higher in subjects living in urban areas with respect to rural areas, in both Mongolian general population (Viinanen et al., 2005) and in Polish children (Majkowska–Wojciechowska et al., 2007). In Swiss adults, living close to busy roads was associated with a higher risk for pollen sensitization, suggesting a possible interaction between pollens and air pollutants (Wyler et al., 2000). On the contrary, no association between busy roads exposure and increased risk of atopy emerged in German adults (Heinrich et al., 2005). Other studies have shown an increased risk of atopy in Australian and Italian general population samples living near main roads (within 200 m) (Bowatte et al., 2017; Nuvolone et al., 2011); this relationship was also confirmed considering an increased mean annual NO_2 exposure (Bowatte et al., 2017).

Noteworthy, our analyses brought out a strong relationship between grey spaces exposure and allergic conditions in subjects with a confirmed allergic full-blown disease (+16% of SPT positivity and current asthma/allergic rhinitis for each 10% increase in urban grey spaces exposure) and with polysensitization (+11%), conditions possibly linked to more severe disease. Indeed, polysensitization is an immunological phenomenon that may be associated with more impaired quality of life, severe symptoms and frequent asthma comorbidity than monosensitization (Ciprandi and Cirillo, 2011).

We also showed a significant relationship between positivity to serum antibodies to BPDE-DNA adducts and increased grey spaces exposure. These findings suggest that the degree of urbanicity, evaluated through grey spaces exposure, may be used as a proxy of outdoor air pollutants exposure in epidemiological studies performed in small urban and suburban areas in which individual exposure data are often not available. Indeed, in our previous publication, it was shown that serum antibodies to BPDE-DNA adducts may be a reliable biomarker of environmental carcinogens exposure through the evidence of an urban-suburban gradient in adducts positivity (Petruzzelli et al., 1998). Other Authors have found that a higher fraction of urban land use was correlated to higher estimated NO_2 levels, considered to be a marker of vehicular pollution (Ebisu et al., 2011). However, grey spaces may also include other urban factors like industrial emissions, the urban heat island effect, and noise, as well as social factors (Ebisu et al., 2011); thus, an in-depth study and effective validation of this hypothesis would be advisable.

One limitation of our study is that the general population data were

collected in the field approximately 25 years ago, which might represent an environment and health framework different from today. However, studies published in the last two decades showed elevated values of allergy incidence in adult subjects, particularly in westernized countries, highlighting the possible relationship with living in urban areas. A deeper understanding of the possible association between urbanicity and allergic status, therefore, becomes important for today's society, even utilizing dated but exhaustive information.

Moreover, as reported in other papers (Hoek, 2017; Fasola et al., 2020) and in other important European studies (Laden et al., 2006; Downs et al., 2007; Schikowski et al., 2014), the spatial stability for traffic-related pollutants can be expected and the within-city spatial patterns remain constant over the years, also when mean concentrations of air pollutants change over time. Thus, we can hypothesize that the relative differences (spatial contrasts) in the average levels of grey spaces exposure among the locations (residential addresses) remained approximately constant. In other words, the effect of a 10% increase of grey exposure in the past can be informative for today's society.

A further concern may be the cross-sectional nature of the study, making it difficult to establish a temporal relationship between exposure and allergic conditions. However, after performing the analyses on the subsample of long-term residents (subjects living for more than 5 years at the same residential address), we confirmed the same results (Table S1).

Moreover, after performing another sensitivity analysis on the subsample of subjects having complete information on SPT, IgE, and serum antibodies to BPDE-DNA adducts (n = 1459), we confirmed the results obtained on the larger sample (n = 2070) (Table S2).

The main strengths of this study were the large sample size spanning from adolescents to late adulthood (elderly people), the standard protocols which already had passed the scrutiny of independent reviewers, and the availability of individual risk factors collected through a standardized questionnaire.

The use of a questionnaire for collecting data on respiratory symptoms/diseases is potentially affected by a reporting bias, as it relies upon individual memory; nevertheless, the standardized questionnaire is one of the main investigation tools used in respiratory epidemiology (Bakke et al., 2011; Pistelli and Maio, 2014) and the use of objective measurements (i.e. skin-prick test, IgE and serum antibodies to BPDE-DNA adducts) allows overcoming this limit. Further, the use of CLC data as a standardized dataset ensures consistency across grey space measurement values for each subject of our sample.

At last, the current manuscript could be an example of the added value inherent the general population sample studies carried out through standardized tools, e.g. questionnaire, skin prick test, blood sample, biomarkers. Suck kind of data may be reanalyzed when the technological advancement, as in this case, permits to provide new environmental data which were not available at the survey period.

5. Conclusion

Grey spaces have adverse effects on allergic status and are related to a biomarker of polycyclic aromatic hydrocarbons exposure in a general population sample of adults. They may be used as a proxy of urban environment exposure, in particular in small urban and suburban areas.

Author contributions

Sara Maio: Conceptualization, Data curation, Formal analysis, Roles/Writing - original draft, Writing - review & editing **Sandra Baldacci:** Funding acquisition, Investigation, Methodology, Writing - review & editing **Sofia Tagliaferro:** Roles/Writing - original draft **Anna Angino:** Data curation, Formal analysis **Eja Parmes:** Methodology, Writing - review & editing **Juha Pärkkä:** Methodology, Writing - review & editing **Giancarlo Pesce:** Writing - review & editing **Cara Nichole Maesano:** Writing - review & editing **Isabella Annesi-Maesano:** Writing - review & editing **Giovanni Viegi:** Funding acquisition, Investigation, Methodology, Supervision, Writing - review & editing.

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At the time of the survey, Italian law did not require Ethical Committee approval. The protocol was approved by an Internal Review Board. The study was carried out in accordance with the fundamental principles of Helsinki Declaration.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112428.

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Table S1. Effects of 10% increase in residential exposure to urban greyness on allergic biomarkers/conditions and serum antibodies to BPDE-DNA adducts on the subsample of long-term resident (n=1817)

	OR (95% CI)
Allergic biomarkers/conditions	
Overall SPT positivity Reference category: negative	**1.07 (1.01-1.13)** 1.00
Perennial SPT positivity Reference category: negative	1.04 (0.97-1.12) 1.00
Seasonal SPT positivity Reference category: negative	**1.11 (1.04-1.19)** 1.00
Type of sensitization: polysensitization monosensitization Reference category: negative	 **1.09 (1.01-1.18)** 1.04 (0.96-1.13) 1.00
Asthma/allergic rhinitis co-presence: asthma & allergic rhinitis only allergic rhinitis only asthma Reference category: neither asthma nor allergic rhinitis	 1.07 0.95-1.21 **1.09 1.03-1.16** ***1.07 0.99-1.16*** 1.00
SPT and asthma/allergic rhinitis co-presence: SPT positivity & asthma/allergic rhinitis only SPT positivity only asthma/allergic rhinitis Reference category: neither SPT nor asthma/allergic rhinitis	 **1.14 (1.06-1.23)** 1.02 (0.94-1.10) **1.06 (1.00-1.12)** 1.00
Log IgE value: ≥ 1.81 Reference category: < 1.81	 1.00 (0.94-1.05) 1.00
Exposure biomarker	
Positivity to serum antibodies to BPDE-DNA adducts Reference category: negativity	**1.10 (1.02-1.17)** 1.00

Adjusted for sex, age, BMI, educational level, smoking habits, occupational exposure, family history of allergic/respiratory diseases (or other family members positive for serum antibodies to BPDE-DNA adducts).

Serum antibodies to BPDE-DNA adducts: serum antibodies anti-benzo(a)pyrene diol epoxide-DNA adducts; CI: confidence intervals; IgE: immunoglobulins E; OR: odds ratio; SD: standard deviation; SPT: skin prick test.

Table S2. Effects of 10% increase in residential exposure to urban greyness on allergic biomarkers/conditions on the subsample with complete information on SPT, IgE and serum antibodies to BPDE-DNA adducts (n=1459)

	OR (95% CI)
Allergic biomarkers/conditions	
Overall SPT positivity Reference category: negative	***1.06 (0.99-1.13)*** 1.00
Perennial SPT positivity Reference category: negative	1.00 (0.92-1.09) 1.00
Seasonal SPT positivity Reference category: negative	**1.11 (1.02-1.21)** 1.00
Type of sensitization: polysensitization monosensitization Reference category: negative	 ***1.09 (0.99-1.19)*** 1.03 (0.94-1.13) 1.00
Asthma/allergic rhinitis co-presence: Asthma & allergic rhinitis only allergic rhinitis only asthma Reference category: neither asthma nor allergic rhinitis	 1.11 0.95-1.29 **1.11 1.04-1.20** 1.08 0.98-1.17 1.00
SPT and asthma/allergic rhinitis co-presence: SPT positivity & asthma/allergic rhinitis only SPT positivity only asthma/allergic rhinitis Reference category: neither SPT nor asthma/allergic rhinitis	 **1.14 (1.05-1.25)** 1.01 (0.92-1.11) **1.07 (1.00-1.15)** 1.00
Log IgE value: ≥ 1.81 Reference category: < 1.81	 0.96 (0.90-1.02) 1.00
Exposure biomarker	
Positivity to serum antibodies to BPDE-DNA adducts Reference category: negativity	**1.08 (1.01-1.15)** 1.00

Adjusted for sex, age, BMI, educational level, smoking habits, occupational exposure, family history of allergic/respiratory diseases (or other family members positive for serum antibodies to BPDE-DNA adducts).

Serum antibodies to BPDE-DNA adducts: serum antibodies anti-benzo(a)pyrene diol epoxide-DNA adducts; CI: confidence intervals; IgE: immunoglobulins E; OR: odds ratio; SD: standard deviation; SPT: skin prick test.