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Two- and three-dimensional indicators of green and grey space exposure and psychiatric conditions and medicine use: A longitudinal study in a large population-based Italian cohort

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ABSTRACT

Background: Evidence available on the associations between urban greenness and mental health is mainly based on cross-sectional studies and has relied on 2D indicators of greenness. This longitudinal study aimed at investigating the association between 2D and 3D indicators of green and grey spaces and incident mental health-related outcomes in a large population-based cohort.

Methods: Our study used data from 593,894 Italian adults (≥30 years) from the Rome Longitudinal Study. Mental health outcomes were defined using either drug prescriptions (antidepressants, antipsychotics, lithium and other mood stabilisers, and anxiolytics, hypnotics and sedatives), or hospitalisation records (for schizophrenia spectrum disorder, depression, anxiety, stress-related and somatoform, or substance use disorders). We obtained 2D and 3D indicators of green and grey exposures including Normalized Difference Vegetation Index (NDVI), green volume, grey volume, number of trees, and Normalized Difference Green-Grey Volume Index around participants' homes. Cox proportional hazards regression models were developed to estimate the association of green and grey space exposure and psychiatric conditions and medicine use, adjusted for relevant covariates.

Results: We found beneficial associations of NDVI and the number of trees with antipsychotic and lithium and other mood stabiliser drugs. We also observed detrimental associations between grey volume and lithium and other mood stabilisers and anxiolytic, hypnotic and sedative drugs. Finally, we found a protective association of the NDGG with lithium and other mood stabilisers (HR: 0.977; 95% CI: 0.965–0.990) and anxiolytic, hypnotic and sedative drugs (HR: 0.851; 95% CI: 0.762–0.950). The associations for hospitalisation for psychiatric conditions were less consistent and generally not statistically significant.

Conclusions: Findings suggested that higher greenness areas around residential addresses are associated with reduced use of drugs for psychiatric conditions, while the opposite is true for higher grey space exposure. The study highlights the importance of accurately characterising green and grey spaces, using novel exposure indicators.

1. Introduction

In recent years, there has been an increasing interest in the association between urban environments and mental health. An accumulating body of evidence has associated urban-related environmental exposures, such as greenness availability or proximity, with mental

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health, in terms of self-reported symptoms, specialist visits, and registered prescriptions of psychotropic drugs (Klompmaker et al., 2019; Spano et al., 2020; Wolf et al., 2020; Nieuwenhuijsen et al., 2022; Sui et al., 2022). One of the first systematic reviews of the association between greenness and mental health (Gascon et al., 2015) reported promising albeit limited evidence supporting a relationship between residential surrounding greenness and mental health. Since then, existing evidence on long-term exposure to greenness and self-reported anxiety, depression, and stress, both in adults (Gascon et al., 2018; Pun et al., 2018) and in adolescents (Hartley et al., 2021) has provided an inconsistent picture, mainly grounded in cross-sectional studies. Moreover, most of the available evidence is based on symptomatology and/or subjective measures of mental health and only a few studies have considered objective measures (i.e., prescriptions and medications) as mental health indicators. Mixed results have also been found in the few available longitudinal studies exploring the association between greenness exposure and mental health outcomes (Geneshka et al., 2021). A study on 908,553 adults in Denmark (Engemann et al., 2020) demonstrated that growing up surrounded by a natural outdoor environment is associated with lower rates in 12 out of 18 diagnosed psychiatric disorders classified by the International Classification of Diseases (ICD) codes. Similarly, an inverse association between cumulative exposure to residential greenness and doctor-diagnosed depression was observed in a Finnish population-based cohort (Gonzales-Inca et al., 2022). Nevertheless, findings on the longitudinal association between residential exposure and mental health-related prescriptions and medications are scarce and conflicting, reporting beneficial, harmful, or no associations (Aerts et al., 2022; Astell-Burt et al., 2022; Chi et al., 2022).

To date, most of the available studies on the health effects of greenness in general, and on its effects on mental health in particular, have used 2-dimensional (2D) indicators of greenness, mainly the Normalized Difference Vegetation Index (NDVI). Moreover, these studies have mainly focused on vegetation, effectively excluding the share of the "grey" (built) environment that characterises an urban context. Additionally, 2D indicators may provide an inaccurate characterization of the diverse sets of vegetation types in combination with different types of grey spaces, as it is often the case in urban contexts. The expanded availability of Light Detection and Ranging (LiDAR) data has opened up the possibility of incorporating 3D indicators alongside traditional 2D indicators. LiDAR data is acquired through laser scanner sensors mounted on terrestrial, airborne, and mobile supports. The acquired data consists of a point cloud representing the three-dimensional shape of intercepted objects (vegetation or artificial) (Fig. 1). The point cloud can be processed to obtain a wide range of 3D indicators. For example, it is possible to rasterize the points and obtain volume of the scanned surfaces (e.g., vegetation elements, such as trees, and artificial surfaces, such as buildings), enabling immediate distinction between areas covered by grass and areas covered by trees, or segment the points to obtain the three-dimensional structure of individual trees (Giannico et al., 2016; Giannico et al., 2022).

Furthermore, 2D indicators of greenness often are not tangible for policymaking, 3D indicators could be easily translated into policy. For example, 3D indicators can indicate the amount of vegetation, namely urban forest, needed to achieve the desired health benefits, in terms of number or volume of trees (Mattijssen et al., 2017; Sanesi et al., 2007). Additionally, understanding the relationship between grey and green volumes can yield invaluable insights for implementing interventions and structuring the urban landscape (Badiu et al., 2019). To this aim, in addition to the green and grey volume, we adopted the Normalized Difference Green-Gray Volume index (NDGG) (Giannico et al., 2022). The NDGG represents the volume of green relative to the amount of building volumes in a determined area. Taking into account two areas with an equal amount of green volume, the NDGG would penalize (lower

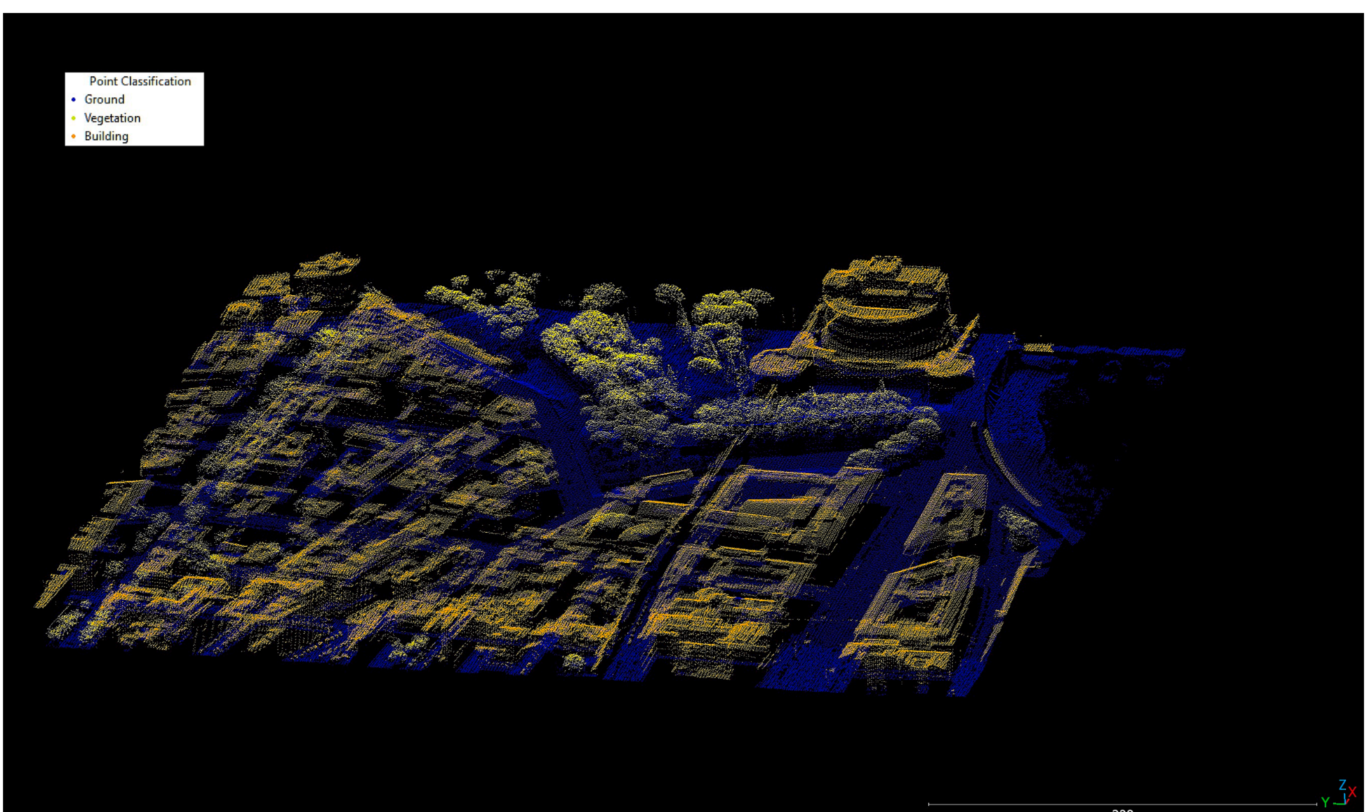

Fig. 1. Classified LiDAR point cloud covering an area of the Rome municipality (Piazza Adriana, 41° 54′ 12″ 12° 27′ 59″). Points are classified as ground (blue) vegetation/urban forest (green) and building (orange).

index value) areas with a higher number of buildings or larger buildings.

In summary, previous studies suggested a potential relationship between the availability of green spaces in urban areas and mental health, but the current picture remains uncertain and characterized by mixed results. This study aims at contributing to filling this gap, by providing a more in-depth insight on the effect that exposure to residential green and grey spaces has on mental health, using innovative 3D indicators such as the Normalized Difference Green-Gray Volume (NDGG) and tree count. To this end, we investigated the association between residential exposure to green and grey spaces and the incidence of mental health-related drug prescriptions and hospitalizations in a large population-based cohort in Rome, Italy. We focused on most psychotropic medicines prescribed for mental health-related symptoms and diseases, such as antidepressants, antipsychotics, lithium and other mood stabilisers, and anxiolytics, hypnotics, and sedatives. As secondary outcomes, we analysed four categories of mental disorders, i.e., schizophrenia spectrum disorder, depression, anxiety, stress-related and somatoform, and substance use disorders, based on data retrieved by the Hospital Discharge System and Co-payment Registry.

We utilised high-resolution NDVI as the benchmark for estimating the greenness of residential surroundings and compared it to new 3D indicators such as green volume, grey volume, a novel index called Normalized Difference Green-Gray Volume or NDGG (Giannico et al., 2022), and tree count, which captures various aspects of vegetation quality and quantity. The use of 3D indicators is a distinctive feature of this research. These indicators, obtained from LiDAR data, allow for a more precise and detailed assessment of the environment, enabling a more comprehensive and transparent analysis of the relationship between the presence of green spaces and mental health. Moreover, a crucial aspect of this research is its applicability to public policies. The findings of this analysis could provide urban administrators with a solid basis to make targeted and practical decisions regarding the urban environment, such as planting a specific number of trees to improve the mental health of the community.

2. Materials and methods

2.1. Study area

The study focused on the Rome municipality. The city is the capital of Italy and is located in the central part of the country (41°53′36″N 12°28′58″E) and extends for about 1290 km^2. The climate is mediterranean with an average temperature of 16 °C and 750 mm of annual rainfall. The city landscape is highly heterogeneous with a core city centre characterized by continuous urban fabric and agricultural, forest and discontinuous areas moving away from the centre. Having a public green space covering > 20 % of the municipality area, Rome is one of the greenest Italian cities, with nine natural reserves for a total cover of ~16,000 ha (Manes et al., 2012). Due to the limited availability of the remote sensing data, the study area covered less than half of the municipality area (i.e., 550 km^2) (Fig. 2, Giannico et al., 2022).

2.2. Study population

The study was nested in the Rome Longitudinal Study (RoLS) including the residents of Rome, Italy, on October 9, 2011 (n = 1,739,277). As described in more detail elsewhere (Cesaroni et al., 2010; Badaloni et al., 2017), the RoLS cohort was the result of the linkage

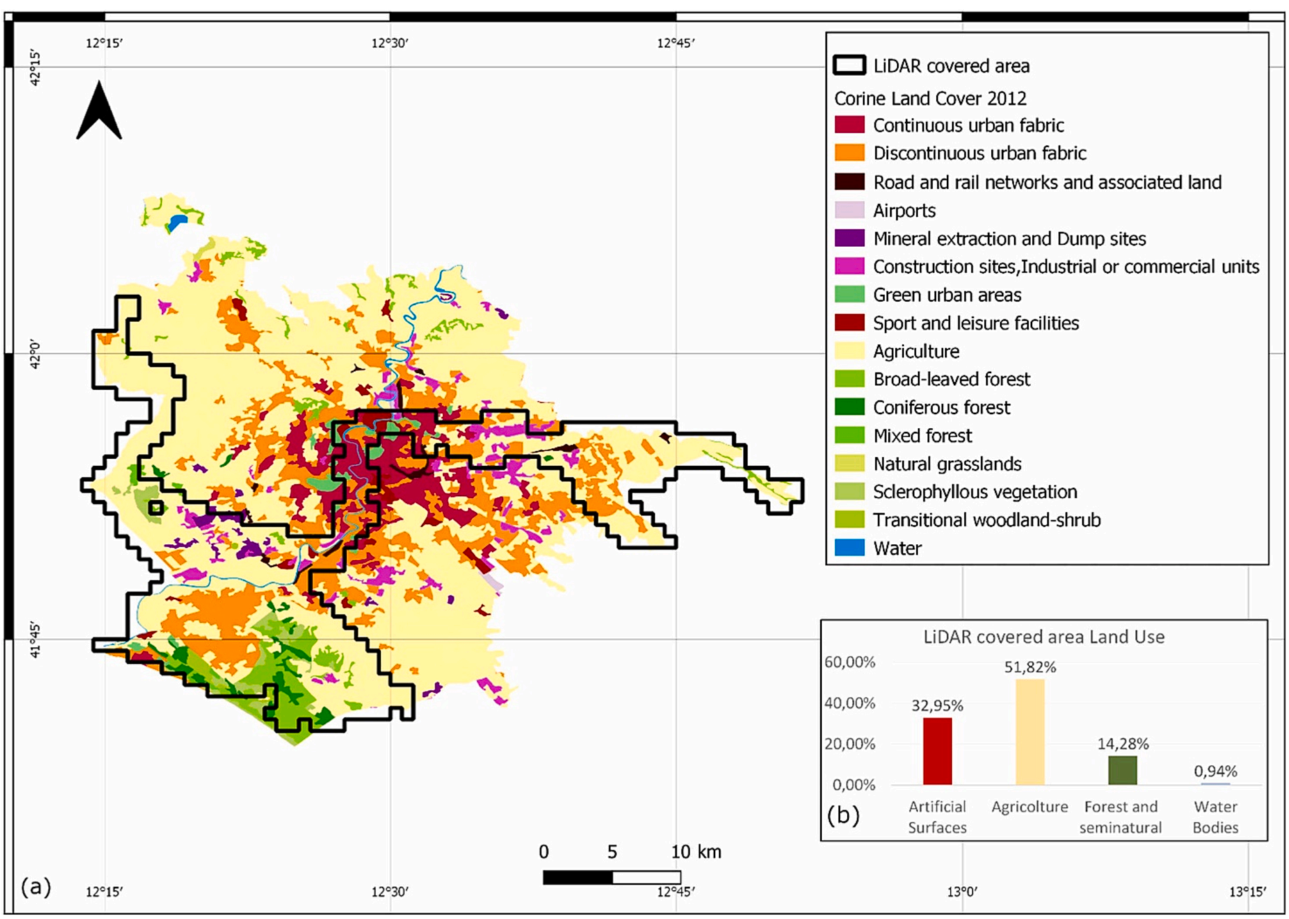

Fig. 2. Corine Land cover 2012 selected classes an LiDAR coverage area of the municipality of Rome (a). Frequency distribution of LiDAR coverage over Artificial Surfaces, Agriculture, Forest and seminatural and Water bodies classes (b) (Giannico et al., 2022).

between the Rome Municipal Register's data and the data from the 2011 Population Census, managed by Istat (Italian National Institute of Statistics). For the specific purposes of this study, we included individuals residing in areas of Rome covered by the 3D green and grey space maps, mentioned above, and aged more than 30 years old. We focused on the adults to analyze a population that could be more homogeneous in terms of the mechanisms of the onset and the development of mental diseases. Furthermore, we implemented additional exclusion criteria: residence at the baseline address for less than one year or in unconventional places (i.e., retirement homes or convents), homeless people, missing data for any socio-demographic characteristics, absence of the unique identification code and having mental health conditions at baseline. The final population consisted of 595,475 subjects, who were followed up from baseline until emigration from the study area, death, event of interest or end of follow-up on 31 December 2019, whichever came first.

Data analysis and linkage was performed using anonymous identification codes and under strict controls to protect personal data, according to the National Statistical Program, approved annually by the Italian Data Protection Authority (SiStaN, Sistema Statistico Nazionale).

2.3. Grey and green space exposure

We assessed green and grey spaces surrounding the residential address of each participant based on the average of 2D and 3D indicators of green and grey spaces across buffers of 50 m, 100 m, 300 m, and 500 m around each individual's geocoded residential address (Mataloni et al., 2022).

2.3.1. 2D indicators

The calculation of the NDVI was done using high-resolution RapidEye data that encompasses a 5-satellites constellation each one carrying a multispectral sensor acquiring data in five spectral bands (blue: 440–510 nm; green: 520–590 nm; red: 630–685 nm; red edge: 690–730 nm; and near infrared: 760–850 nm) at approximately 5 m x 5 m resolution (Planet Labs, 2016). The specific image selected was a RapidEye Analytic Ortho Tile acquired on July 8, 2012, around 11:00 UTC. The image covered 100 % of the study area with a cloud cover of 0 %. The RapidEye Analytic Ortho Tile product is an orthorectified, radiometrically, and atmospherically corrected surface reflectance product processed by the Planet team (Planet. Planet application program interface, 2023).

2.3.2. 3D indicators

Detailed information about the development of our 3D indicators and their assignment to the Rome Longitudinal Study Participants have been published elsewhere (Giannico et al., 2022). Briefly, we used light detection and ranging (LiDAR) data to develop our 3D indicators of green and grey spaces, including green volume, grey volume, Normalized Difference of Green-Grey Volume (NDGG). We also derived tree count from LiDAR data analysis. LiDAR data was provided by the "Ministero dell'Ambiente e della Tutela del Territorio e del Mare". Data were acquired in 2008 and 2010 with a resolution of about 3 points per m^2. The green and grey volumes were then used to calculate NDGG, a dimensionless indicator intended to summarise the relationship between the volume of vegetation and buildings at each point in space (Giannico et al., 2022), as following:

$$\text{NDGGpx} = (\text{green volume-grey volume}) / (\text{green volume} + \text{grey volume})$$

where green volume [m^3/ha] is the volume of green elements (e.g., shrubs, trees) for a given buffer and grey volume [m^3/ha] is the volume of buildings for a given buffer (e.g., 50 m or 300 m).

The NDGG ranges from −1 to 1 where a value of 1 indicates that the entirety of the volume is characterized by green features, a value of 0 suggests a balanced mix, where both green and grey features coexist in equal measure. Conversely, a value of −1 signifies that the entire volume is predominantly made up of grey features. Compared to absolute volumes indicators (i.e. green volume and grey volume), the NDGG values serve as a crucial indicator for evaluating the composition of features volume within a given city area and how those are perceived by citizens.

2.4. Outcomes

2.4.1. Psychiatric medicine prescription

We linked the cohort to the medicine prescriptions registry, maintained by the Regional Health Service of Lazio Region, which includes both territorial and direct pharmaceutical databases concerning the region. The former database encompasses prescriptions issued by general practitioners or by specialists and the latter refers to medications dispensed directly by the prescribers, as it occurs within hospitals, for example. This registry collects data from both the private and the public sector. According to the Anatomical Therapeutic Chemical (ATC) Classification System (WHO Collaborative Centre for Drug Statistics Methodology, 2020) we considered the incidence of (i) antidepressant drugs (ATC code: N06A), (ii) antipsychotic drugs (N05A), (iii) lithium and other mood stabilisers (N03A) and (iv) anxiolytic, hypnotic and sedative drugs (N05B and N05C) prescriptions as separate outcomes.

First, we identified prevalent cases for each medicine category: all participants with at least two prescriptions within a six-month period in the five years before the enrolment were flagged as prevalent cases and therefore excluded from the analyses. In addition, we linked the cohort to the Co-payment registry, which is a database managed by the Lazio Region Health Authority. It contains information on patients, residing in the Lazio Region, who are exempt from paying for medications and healthcare services due to health reasons. Thus, through this linkage, for the analysis of the incidence of lithium and other mood stabiliser drugs prescriptions, we also excluded all participants with an exemption of epilepsy in the five years before enrolment (code: 017). It was essential to be confident to consider prescriptions of these drugs due to mental illness, as required by the study, and not for epilepsy.

Then, we identified incident cases during the follow-up period, observing the same rule of at least two prescriptions within a six-month period.

2.4.2. Hospitalizations and exemptions for psychiatric conditions

We linked the cohort to the Hospital discharge System, maintained by the Regional Health Service of Lazio Region, which collects patient health information across all public and private hospitals in the region, including data about admissions, discharges, transfers, and diagnoses. In detail, the hospital discharge certificate includes a primary diagnosis, and there may also be secondary diagnoses, which should complete the clinical status of the patient. Based on this database, we developed four incident outcomes for hospitalisation for psychiatric conditions according to the International Classification of Diseases, 9th Revision (ICD-9) (World Health Organization, 1977): (i) schizophrenia spectrum disorder [ICD-9 codes: 295, 297, 298 (298.0 excluded)], (ii) depression (296.2–3, 298.0, 300.4, 309.0, 309.1, 311), (iii) anxiety, stress-related and somatoform disorders [300 (300.3, 300.4 and 300.7 excluded), 306, 307.4, 307.8–307.9, 308, 316] and (iv) substance use disorders (291, 292, 303, 304, 305).

First, we evaluated the reported primary and the secondary diagnoses to define prevalent cases in the 10 years before the enrolment. To this end, through the linkage to the Co-payment registry, we also considered the co-payment information system for schizophrenia spectrum disorder and depression, based on the available ICD-9 codes listed above. Following the same approach used for outcomes from drug prescriptions, we excluded these prevalent cases from the analyses.

Successively, for the identification of the incident cases during the follow-up period, we considered the primary diagnosis from the Hospital Discharge System and the Co-payment Registry, which added a few more cases where available.

2.5. Covariates

We collected multiple individual-level covariates at baseline: age, sex, marital status (single, married, separated/divorced, widowed/widow), place of birth (Rome, elsewhere), citizenship (Italian, foreign), level of education (primary or less, secondary, high school, university or more) and employment status (employed, seeking first employment, unemployed, retired, student, housewife, other). Moreover, based on the geocoded residence addresses, we assigned each participant several area-level socioeconomic indicators including quintiles of socioeconomic deprivation index (at census-block level, n = 13,656 areas) (Cesaroni, et al., 2013), unemployment rate, percentage of university graduates, and quintiles of house prices at district level (n = 155 areas) (Cesaroni et al., 2020).

2.6. Statistical analysis

As described above, through the linkage between the cohort and the available Health Information Systems, we defined several incident outcomes, grouped according to the severity. Our primary outcomes were derived from the medicine prescriptions registry, which enabled us to include psychiatric conditions that are prevalent in the population but do not necessitate access to health services, such as hospitals, for instance. Our secondary outcomes, representing the most severe aspects of the diseases, were from the Hospital Discharge System and the Co-payment registry.

About the exposure variables, furthermore, we evaluated those related to 100 m buffer as main and the others from different buffers were investigated in sensitivity analyses.

We applied single-exposure Cox proportional hazards regression models, considering successively more detailed adjustment: age as time axis and sex as strata term (model 1); age, sex, and individual-level covariates (place of birth, marital status, educational level, employment status and citizenship) (model 2); age, sex, educational level, employment status, and deprivation index (model 3); age, sex, educational level, employment status, marital status, and deprivation index (model 4); age, sex, individual- and area-level covariates (deprivation index, unemployment rate, percentage of university graduates, house prices) (model 5). The latter was considered as the “main” model.

Finally, we examined potential effect modification of the associations by sex, age (30–49, 50–64, 65 +) at baseline and deprivation index (low, medium level, high level) for the main exposure variables (100 m buffer). Potential interaction and effect modification was assessed by introducing an interaction term into the main model (model 5) and using the Wald test, which evaluates whether the coefficient for the interaction term differs significantly from zero, indicating whether the inclusion of the interaction term is necessary for the model or not.

The estimates were shown as Hazard Ratios (HR) and 95 % confidence intervals (95 %CI) and expressed by interquartile (IQR) increment of the exposure variables. The analyses were performed using software R version 4.0.0.

3. Results

The study population consisted of 595,475 participants, who represented the 34 % of the 2011 Rome administrative cohort. Due to missing values in the area-level covariates, a population of 593,894 participants was finally included in the analyses. Table 1 describes the individual- and area-level characteristics of the study participants at the baseline. The mean age was 56.2 years (SD = 15.8), 55.0 % were women, 55.0 % were born in Rome, 64 % were married, 37.8 % had a high school degree, 50.8 % were employed and 94.1 % were Italian citizens. Concerning the area level indicators, almost half of the participants (52.2 %) lived in areas with low or medium–low levels of deprivation index, 28.1 % in areas with low house prices, the mean unemployment rate was 6.4 (1.5) and the mean percentage of university graduates was 42.3 (21.8).

Table 1
Descriptive statistics of individual- and area-level covariates on the study population.

Covariate	N	%
<u>*Individual level*</u>		
Age at baseline *	56.21	15.83
Gender		
male	268,218	45.04 %
female	327,257	54.96 %
Place of birth		
elsewhere	268,823	45.14 %
Rome	326,652	54.86 %
Marital status		
unmarried	136,950	23.00 %
married	381,846	64.12 %
separated / divorced	25,174	4.23 %
widower / widow	51,505	8.65 %
Educational level		
primary school	91,174	15.31 %
middle school	132,935	22.32 %
high school	225,135	37.81 %
university or more	146,231	24.56 %
Employment status		
employed	302,343	50.77 %
seeking first employment	3695	0.62 %
unemplyed	17,988	3.02 %
retired	163,339	27.43 %
student	2572	0.43 %
housewife	71,554	12.02 %
other	33,984	5.71 %
Citizenship		
foreign	35,167	5.91 %
italian	560,308	94.09 %
<u>*Area level*</u>		
Deprivation index		
low level	138,903	23.33 %
medium–low level	171,835	28.86 %
medium level	105,226	17.67 %
medium–high level	77,194	12.96 %
high level	102,317	17.18 %
Unemployment rate *	6.41	1.52
Percentage of university graduates *	42.31	21.82
Houses price		
low level	166,882	28.10 %
medium–low level	96,805	16.30 %
medium level	75,198	12.66 %
medium–high level	123,916	20.87 %
high level	131,093	22.07 %

* The descriptive statistics reported for the continuous variables are mean and standard deviation (SD).

Table 2 presents the descriptive statistics of the exposure variables. The NDVI had a median between 0.23 and 0.28 across different buffers with the IQR of the main buffer (100 m) being 0.1. The median of the green volume ranged between 411.0 m^3/ha and 683.3 m^3/ha and the 100 m buffer IQR was 592.6 m^3/ha. The median number of trees across 100 m buffer was 53.1 n/ha and the IQR was 44.2 n/ha. The median Grey Volume ranged from 254.2 m^3/ha to 354.3 m^3/ha and the 100 m buffer IQR was 410.7 m^3/ha. Lastly, the minimum NDGG median was found for the 50 m buffer (0.2) and the maximum for the 500 m buffer (0.5). For the 100 m buffer, the median of NDGG was 0.3 and the IQR was equal to 0.8.

Pearson correlation coefficients between exposure variables are shown in Fig. 3 and their spatial distributions in the Rome territory are displayed in Figures S1-S5 (Supplementary material).

The population size changed for each outcome because of the elimination of different numbers of prevalent cases. During the follow-up period, there were more incident cases for antidepressant drugs prescriptions (N = 67,684), lithium and other mood stabilisers prescriptions (66,625) and antipsychotic drugs prescriptions (26,586), followed by anxiolytic, hypnotic and sedative drugs prescriptions (842). We observed 1234 incident cases of depression, 932 of schizophrenia

Table 2
Descriptive statistics of exposure variables on the study population.

Exposure	N	Mean	SD	Percentiles					IQR
				5th	25th	50th	75th	95th	
NDVI high resolution									
50 m	595,475	0.24	0.08	0.13	0.18	0.23	0.29	0.39	0.11
100 m	595,475	0.25	0.07	0.14	0.19	0.24	0.29	0.38	0.10
300 m	595,475	0.27	0.07	0.17	0.23	0.27	0.31	0.39	0.08
500 m	595,475	0.28	0.06	0.18	0.24	0.28	0.31	0.38	0.07
Green volume (m^3/ha)									
50 m	595,475	590.24	578.22	18.93	183.97	411.02	814.28	1748.90	630.32
100 m	595,475	626.04	497.23	82.47	265.98	491.70	858.55	1577.65	592.57
300 m	595,475	699.97	439.08	186.27	373.07	629.51	901.14	1519.61	528.07
500 m	595,475	742.37	419.80	214.08	442.71	683.00	938.36	1537.43	495.65
Number of trees (n/ha)									
50 m	595,475	54.94	37.02	3.79	25.24	50.47	78.23	123.66	53.00
100 m	595,475	56.57	31.51	11.77	32.78	53.14	77.01	113.29	44.23
300 m	595,475	57.76	24.29	19.41	40.82	57.19	73.24	98.01	32.42
500 m	595,475	58.20	20.73	22.63	45.49	58.77	71.71	90.93	26.22
Grey volume (m^3/ha)									
50 m	595,475	424.76	321.48	43.21	159.26	354.32	617.28	1050.62	458.03
100 m	595,475	396.50	280.18	54.89	164.35	336.91	575.08	945.43	410.73
300 m	595,475	312.05	215.95	53.21	132.19	276.36	433.90	751.40	301.71
500 m	595,475	275.67	188.59	47.53	117.79	254.19	377.56	659.45	259.77
NDGG									
50 m	595,266	0.08	0.58	−0.94	−0.40	0.18	0.58	0.89	0.98
100 m	595,446	0.18	0.50	−0.74	−0.19	0.28	0.58	0.85	0.76
300 m	595,475	0.36	0.37	−0.39	0.18	0.44	0.64	0.85	0.46
500 m	595,475	0.45	0.30	−0.15	0.30	0.51	0.66	0.85	0.36

spectrum disorders, 670 of anxiety, stress-related and somatoform disorders and 429 of substance use disorders, identified mainly through hospital admissions.

Table 3 presents the associations between main exposure variables (100 m buffer) and psychiatric drug prescriptions and hospital admissions based on model 5. We observed protective associations between NDVI and medicine prescriptions, which were statistically significant for antipsychotic (HR: 0.976; 95 % CI: 0.958–0.993) and for lithium and other mood stabilizers drugs (HR: 0.979; 95 % CI: 0.968–0.990) but not for antidepressant (HR: 0.999; 95 % CI: 0.988–1.010) and anxiolytic, hypnotic and sedative drugs prescriptions (HR: 0.912; 95 % CI: 0.822–1.012). The green volume was also beneficially associated with the first two categories of drugs mentioned above [HRs of 0.988 (95 % CI: 0.973–1.004) and 0.983 (95 % CI: 0.973–0.993) per IQR increments for antipsychotic and for lithium and other mood stabilizers drugs, respectively]. We also found a protective association between the number of trees and the medicine prescription, which was statistically significant for antipsychotic drugs (HR: 0.975; 95 % CI: 0.956–0.993), lithium and other mood stabilizers (HR: 0.970; 95 % CI 0.959–0.982) and anxiolytic, hypnotic, and sedative drugs (HR: 0.867; 95 % CI: 0.777–0.967), but not for antidepressants (HR: 0.994; 95 % CI: 0.983–1.006). On the other hand, we observed statistically significant harmful associations between grey volume and lithium and other mood stabilizers (HR: 1.022; 95 % CI: 1.008–1.036) and anxiolytic, hypnotic and sedative drugs (HR: 1.295; 95 % CI: 1.161–1.445) and statistically non-significant detrimental association between this exposure and antipsychotics (HR: 1.006; 95 % CI: 0.985–1.028). Finally, we observed a beneficial association of the NDGG, which was statistically significant for lithium and other mood stabilisers (HR: 0.977; 95 % CI: 0.965–0.990) and for anxiolytic, hypnotic and sedative drugs (HR: 0.851; 95 % CI: 0.762–0.950) and non-statistically significant for antidepressants (HR: 0.998; 95 % CI: 0.986–1.011) and antipsychotic drugs (HR: 0.984; 95 % CI: 0.965–1.005).

The associations for hospitalisation and exemptions for psychiatric conditions were less conclusive and generally non-statistically significant. For example, the number of trees indicator showed protective associations, with HRs of 0.987 (95 % CI: 0.893–1.092) for schizophrenia spectrum disorder, 0.974 (95 % CI: 0.893–1.062) for depression, 0.946 (95 % CI: 0.840–1.065) for anxiety, stress-related and somatoform disorders and 0.934 (95 % CI: 0.804–1.085) for substance use disorders, per IQR increments, but none attained statistical significance.

Table S1 (Supplementary material) shows the associations between covariates and the outcomes related to the main model (model 5) and the main exposure buffer (100 m). The results about the other adjustment models and all the exposure variables are shown in Table S2 and Table S3 (Supplementary material). In general, they were consistent with the main associations in Table 3. Furthermore, as a sensitivity analysis, we included a cluster term (Fox et al., 2011) related to the neighbourhood in the Cox models to better account for the possible spatial dependence among subjects, even though we have already adjusted the estimates for several area-level covariates at the same spatial resolution. Table S4 presents the results for the main exposure variables (100 m buffer), outcomes (medicine prescriptions), and adjustment model (model 5): the estimates generally remained stable.

In Table S5, the results of the modification effect analysis for medicine prescriptions by sex, age, and deprivation index and the p-values of the related Wald tests are presented. In general, there were not statistically significant differences by sex, age, and deprivation index. There were some exceptions such as potentially adverse effects for males for green and grey volume and antidepressant drugs prescriptions and for green volume and anxiolytic, hypnotic and sedative drugs prescriptions. There were also some suggestions that the associations between NDVI, number of trees, and NDGG and antipsychotic drugs prescriptions could be more protective for the younger age categories (30–49 and 50-64) compared to older one (65+); contrariwise, the associations between grey volume and this outcome were adverse for 30–49 and 50–64 years old subjects and flat for the older one (65+), (Fig. 4).

The effect modification results for the hospitalizations and exemptions for psychiatric conditions are shown in Table S6 (Supplementary

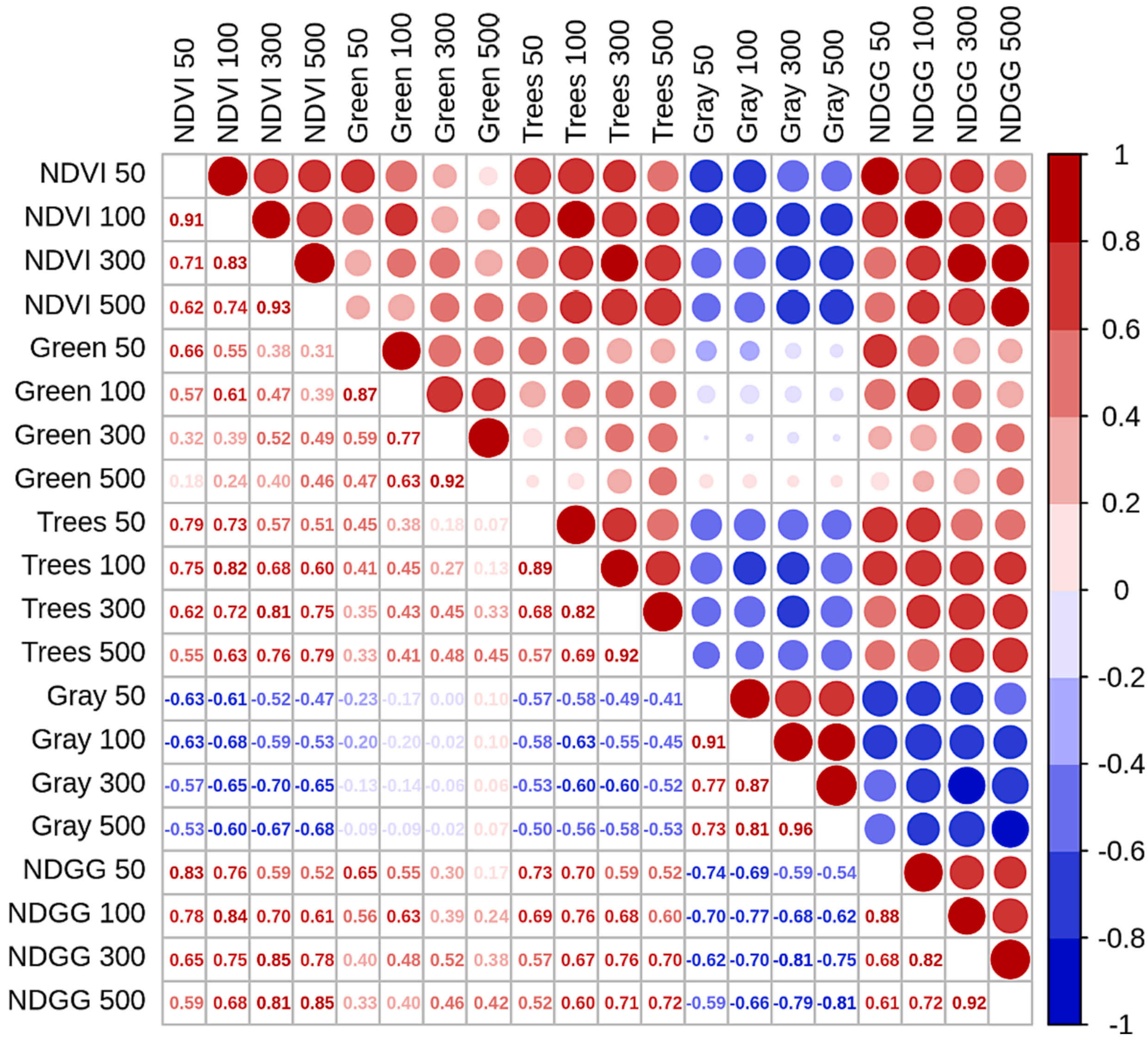

Fig. 3. Pearson correlation coefficients between exposure variables.

material). Also in this case, we did not observe statistically significant differences by sex, age, and deprivation index, except for potentially stronger associations for females between NDVI, number of trees, NDGG, and also grey volume and substance use disorders.

4. Discussion

To the best of our knowledge, this is the first epidemiological study to investigate the risk of intake of psychotropic drugs associated with grey and green spaces, and it is one of the first researches aimed at evaluating and comparing the association of both 2D and 3D indicators of green and grey spaces with mental health outcomes. Moreover, it is one of the largest longitudinal studies that has been carried out on this topic so far, as it benefits from data retrieved from a large population-based cohort of around 600,000 participants. We investigated the association of five different exposure indexes with both psychiatric medicine prescriptions as well as hospitalisations. We found that higher greenness, green volume, and tree counts surrounding the residential address of each participant were associated with a lower risk of prescriptions of antipsychotic and mood stabiliser medicines. Likewise, a higher number of trees were also related to lower prescriptions of anxiolytic drugs, and hypnotic and sedative drugs, while higher grey volume and lower levels of NDGG were associated with a higher risk of prescriptions of mood stabilisers, anxiolytic, and hypnotic and sedative medicines. The same investigation has been replicated for the incidence of hospital admissions due to psychiatric conditions including schizophrenia spectrum disorder, depression, anxiety, stress-related and somatoform, and substance use disorders. Although these findings mainly suggested that living in areas with higher green space and lower grey space were associated with lower risk of these psychiatric conditions, none of the associations attained statistical significance.

All the models were adjusted for key confounders, both at individual-level (e.g., age, sex, marital status, education level) and at area-level (e.g., deprivation index and unemployment rate). Overall, statistically significant estimates on the association of individual-level covariates met the expectations. For example, medium–high or high levels of education were protective factors for the use of all considered prescriptions as well as for substance abuse diagnoses. It is worth noting that in almost all cases, different employment statuses compared to employed category were an important risk factor, except for antidepressant prescriptions, for which being a student was also observed as a protective factor. Similarly, we observe that, compared to the presence of low levels of housing, even just medium–low levels could be a protective factor for the prescriptions of anxiolytic, hypnotic, and sedative drugs.

Previous studies using satellite-derived 2D measures of greenness have found associations between NDVI across different buffers and

Table 3
Associations between exposure variables (buffer 100 m) and psychiatric medicine prescriptions (primary outcomes) and hospitalizations and exemptions for psychiatric conditions (secondary outcomes) in model 5 (main model). The estimates are expressed as Hazard Ratio (HR), with 95 % confidence intervals (95 % CI), per interquartile range (IQR) increases and are adjusted for age (time axis), sex (strata), individual covariates (place of birth, marital status, educational level, employment status, citizenship) and area-level covariates (deprivation index, unemployment rate, houses price, percentage of university graduates).

Outcome	Exposure	N	Cases	HR (95 % CI)
Antidepressant drugs prescriptions				
	NDVI high resolution	505,087	67,684	0.999 (0.988–1.010)
	Green volume	505,087	67,684	1.002 (0.992–1.012)
	Number of trees	505,087	67,684	0.994 (0.983–1.006)
	Grey volume	505,087	67,684	0.988 (0.975–1.002)
	NDGG	505,062	67,678	0.998 (0.986–1.011)
Antipsychotic drugs prescriptions				
	NDVI high resolution	577,569	26,586	0.976 (0.958–0.993)
	Green volume	577,569	26,586	0.988 (0.973–1.004)
	Number of trees	577,569	26,586	0.975 (0.956–0.993)
	Grey volume	577,569	26,586	1.006 (0.985–1.028)
	NDGG	577,540	26,585	0.984 (0.965–1.005)
Lithium and other mood stabilizers prescriptions				
	NDVI high resolution	542,894	66,625	0.979 (0.968–0.990)
	Green volume	542,894	66,625	0.983 (0.973–0.993)
	Number of trees	542,894	66,625	0.970 (0.959–0.982)
	Grey volume	542,894	66,625	1.022 (1.008–1.036)
	NDGG	542,869	66,620	0.977 (0.965–0.990)
Anxiolytic, hypnotic and sedative drugs prescriptions				
	NDVI high resolution	592,525	842	0.912 (0.822–1.012)
	Green volume	592,525	842	1.036 (0.946–1.134)
	Number of trees	592,525	842	0.867 (0.777–0.967)
	Grey volume	592,525	842	1.295 (1.161–1.445)
	NDGG	592,496	842	0.851 (0.762–0.950)
Schizophrenia spectrum disorders				
	NDVI high resolution	591,476	923	0.998 (0.907–1.099)
	Green volume	591,476	923	1.032 (0.949–1.123)
	Number of trees	591,476	923	0.987 (0.893–1.092)
	Grey volume	591,476	923	1.098 (0.976–1.236)
	NDGG	591,447	923	1.000 (0.895–1.118)
Depression				
	NDVI high resolution	587,296	1234	1.041 (0.958–1.131)
	Green volume	587,296	1234	1.048 (0.973–1.129)
	Number of trees	587,296	1234	0.974 (0.893–1.062)
	Grey volume	587,296	1234	0.931 (0.839–1.034)
	NDGG	587,268	1234	1.141 (1.035–1.258)
Anxiety, stress-related and somatiform disorders				
	NDVI high resolution	586,400	670	1.032 (0.924–1.153)
	Green volume	586,400	670	1.026 (0.932–1.130)
	Number of trees	586,400	670	0.946 (0.840–1.065)
	Grey volume	586,400	670	0.991 (0.862–1.140)
	NDGG	586,373	670	1.035 (0.910–1.178)
Substance use disorders				
	NDVI high resolution	591,466	429	1.033 (0.898–1.189)
	Green volume	591,466	429	1.022 (0.907–1.152)
	Number of trees	591,466	429	0.934 (0.804–1.085)
	Grey volume	591,466	429	0.969 (0.812–1.155)
	NDGG	591,438	429	1.004 (0.856–1.177)

psychiatric medicine prescriptions. For example, a cross-sectional study (Gascon et al., 2018) reported an association between access to green spaces and self-reported history of diagnosed depression. Conversely, Pun et al. (2018) found a significant association between increasing residential greenness (NDVI at 250 m and 1000 m) and perceived stress but no existing relations between greenness and self-reported depression and anxiety symptoms. This was in line with the findings of another cross-sectional study (Hartley et al., 2021) which reported no associations between residential greenness (NDVI at 200 m, 400 m, and 800 m) and self-reported anxiety and depression symptoms in a sample of 12 years old adolescents.

Few studies have investigated whether satellite-derived indicators of green and grey space exposure are associated with mental health outcomes that rely objectively assessed mental health conditions (i.e., through prescriptions and medications). Besides, we reported a wide difference in findings among those studies, likely due to a variety of different indicators used. For example, Gascon et al. (2018) reported the association between increasing surrounding greenness (NDVI at 300 m) and self-reported history of benzodiazepines in a sample of 958 adults. Another cross-sectional study (Triguero-Mas et al., 2015) on 8793 Spanish adults reported associations of surrounding greenness (NDVI at 300 mt) and visits to mental health specialists and sedatives and antidepressants consumption (excluding sleeping medication) in non-densely populated areas. A study in Belgium (Aerts et al., 2022) reported that an increase in green covers was associated with a decrease in mood medication sales, in line with our findings. However, another analysis in Belgium (Astell-Burt et al., 2022) described an unexpected association between increase in green spaces and higher rates of antidepressant prescriptions while tree canopy was not associated with the same prescription types (Astell-Burt et al., 2022). In line with the abovementioned results, we did not find associations between any of the

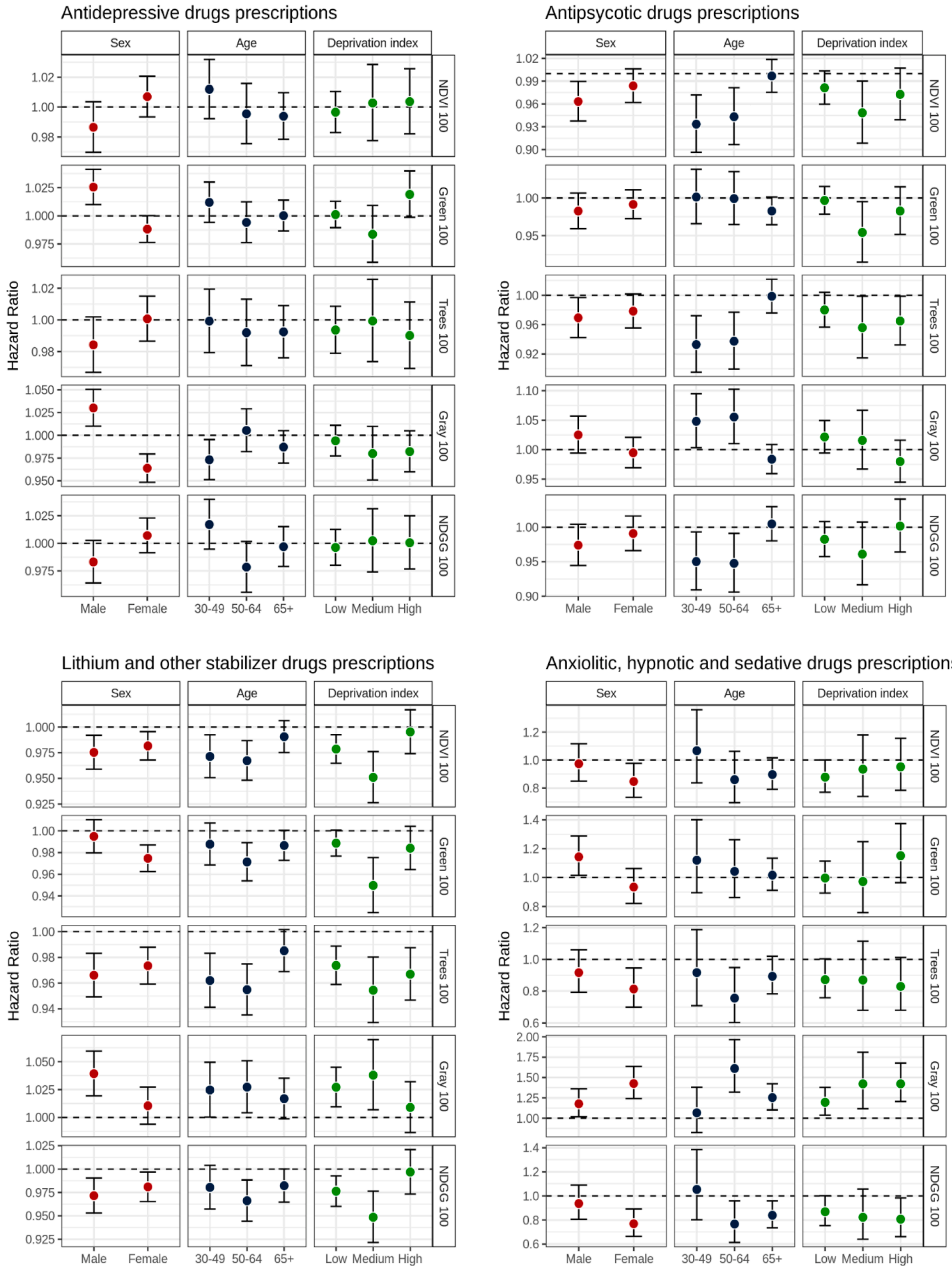

Fig. 4. Effect modification of the associations between the main exposure variables (buffer 100 m) and psychiatric medicine prescriptions (model 5) by sex (male, female), age (30–49, 50–64, 65 +) and deprivation index (low, medium, and high level).

considered exposure measures and antidepressant prescriptions, as reported by Marselle et al. (2020) on urban street trees and the probability of being prescribed antidepressants.

In another recent study carried out in Belgium (Chi et al., 2022), two different trends in the association between greenness exposure and mood medication sales were found. Higher crown volume, a 3D exposure indicator, was associated with a lower rate of mood medication sales, while a higher number of trees (i.e., stem density) was associated with higher sales. Regarding grey volume, we found beneficial associations with lithium and other mood stabilisers and antipsychotics, while no association was found with antidepressants and anxiolytics, hypnotics, and sedatives. NDGG, our novel 3D indicator, was found to be associated with a lower rate of lithium and other mood stabilisers and anxiolytics, hypnotics, and sedatives prescriptions; no associations were found with antidepressants and antipsychotics. Previous evidence suggested the existence of modest association between "urbanicity", i.e., the proportion of continuous urban fabric and the proportion of green space in the neighbourhood area, and lower odds in antidepressant use in Finnish but not in Italian older adults (Tarkiainen et al., 2021).

Our results on the association between exposure indicators and psychiatric diagnosis (derived using two databases, the Hospital Discharge System and the Co-payment Registry) were mixed yet suggestive of an overall protective association. It is worth pointing out that NDGG was found to be inversely associated with depression disorder. Although it may seem surprising, this result supports recent evidence reporting an opposite association between increase in the percentage of total green space (including tree canopy, open grass, and shrub) and open grass (that was not under tree canopy) with higher expenditure on antidepressant prescriptions or psychotherapy referrals (Astell-Burt et al., 2022). As also stated by the authors, it is recommended to take into account other variables related to the urban lifestyle, for example, the presence and functionality of public transports, and walkability levels, but also the accessibility to urban green areas. This could be also valid for our results. Also considering that the NDGG volume showed no associations with other diagnoses, future research on a wider number of incident cases is warranted.

The major strength of the present study is the use of a large population-based cohort in a large city (Rome), linked to multiple health information systems such as hospital discharge files and drug prescriptions. This allowed us to investigate the association between a broad range of mental health-related outcomes and a wide range of exposure variables related to both the natural and the built environment. Furthermore, we assessed the role of the combined proportion of green and grey spaces on mental health outcomes using a novel metric (i.e., NDGG). Another strength of this study was that the associations were controlled for several key covariates, both at individual-level (e.g., age, sex, education level) and at area-level (e.g., deprivation index and unemployment rate), that could reduce the potential for residual confounding from omitted confounders. Moreover, our study relied on clinical diagnosis of psychiatric conditions and their medicine prescriptions, which could be more robust compared to questionnaire-based and screening tools for characterising mental health conditions.

On the other side, a major limitation of this study was the relatively small number of incident cases regarding psychiatric diagnosis recorded in the Hospital Discharge System and the Co-payment registry, which could have possibly limited the statistical power of our analyses. Added to this, we acknowledge the fact that only hospitalised cases are included in our study, likely representing the most severe cases, while less severe cases (which represent the majority of psychiatric patients) were not included. Also, although we controlled our analyses for some important covariates, some potentially relevant other variables, not available in the administrative data that we used, may affect the explored associations.

Another limitation was the use of cross-sectional environmental data. This could represent a limitation, considering the growing evidence that greenness exposure in early life could be a strong protective factor against the onset of several psychiatric pathologies later in life ((Engemann et al., 2020). Moreover, assessment of exposure to greenness did not include some relevant related aspects, such as the use, the quality, and and visual access to green spaces.

In conclusion, our study complements previous research on the association between environmental exposures and mental health, applying traditional and novel remotely sensed 2D and 3D indicators of green and grey spaces to a wide array of objectively characterised psychiatric outcomes. Overall, we observed beneficial associations between greenness surrounding residential addresses and psychiatric medicine prescriptions. In contrast, we found a higher risk of psychiatric medicine prescriptions in association with higher grey space surrounding the residential address. Nevertherless, in terms of psychiatric hospitalizations, our findings were less conclusive. An added value of the present study lies in the opportunity to test the reliability of further techniques for characterization of grey and green spaces. Overall, the presented novel metrics can be further investigated, especially for NDGG. Despite different patterns of results have been found, we are far from completely replacing the use of NDVI with the novel index. However, we believe it is worth further exploring this research topic as greater accuracy in the characterization of green, namely urban forest, and grey spaces is expected to produce more detailed information on effects, mechanisms, and pathways between urban environment and different mental health outcomes.

Our results could have important policy implications: cities are increasingly implementing green infrastructure, also in term of Nature-based solution, for ecological, social, and health benefits, supported by scientific evidence that highlights the added value of urban greenness as ecosystem service for human health. However, even though providing indications on how to increase urban greenness remains a significant practical problem, it is also true that, many other environmental indicators, such as green volume, instructions on the number of trees to be planted can be clearly shared with urban planners.

Data sharing

Data from the Rome Longitudinal Study cannot be shared for confidentiality reasons. Requests for access to environmental data reported in this article will be considered by the corresponding author (VG).

CRediT authorship contribution statement

Giuseppina Spano: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Federica Nobile:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Vincenzo Giannico:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Mario Elia:** Conceptualization, Writing – review & editing. **Paola Michelozzi:** Conceptualization, Writing – review & editing. **Andrea Bosco:** Conceptualization, Writing – review & editing. **Payam Dadvand:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Giovanni Sanesi:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Massimo Stafoggia:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108320.

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