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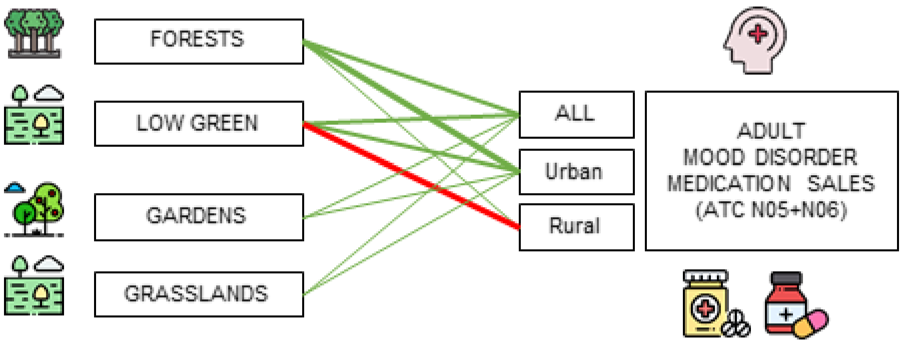

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Residential green space and mental health-related prescription medication sales: an ecological study in Belgium

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ABSTRACT

Background: Residential green space has been associated with mental health benefits, but how such associations vary with green space types is insufficiently known.

Objective: We aimed to investigate associations between types and quantities of green space and sales of mood disorder medication in Belgium.

Methods: We used aggregated sales data of psycholeptics and psychoanaleptics prescribed to adults from 2006 to 2014. Generalized mixed effects models were used to investigate associations between relative covers of woodland, low-green, grassland, and garden, and average annual medication sales. Models were adjusted for socio-economic background variables, urban-rural differences, and administrative region, and included random effects of latitude and longitude.

Results: Urban census tracts were associated with 9–10% higher medication sales. In nationwide models, a 10% increase in relative cover of woodland, garden, and grass was associated with a 1–2% decrease in medication sales. The same association was found for low green but only for men. In stratified models, a 10% increase in relative cover of any green space type in urban census tracts was associated with a decrease of medication sales by 1–3%. In rural census tracts, no protective associations between green space and mood disorder medication sales were observed, with the exception of relative woodland cover for women (-1%), and low green was associated with higher medication sales (+6–7%).

Conclusions: Taken together, these results suggest that living in green environments may be beneficial for adult mental health. Woodland exposure seemed the most beneficial, but the amount of green space was more important than the type. Results underline the importance of conserving green space in our living environment, for the conservation of biodiversity and for human health.

Keywords: Mental health; Environmental epidemiology; Medication sales; Mood disorders; Residential green space

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Human subjects

All health data were anonymized by aggregation to census tract level and were used under license of IMA-AIM. The protocol for this study did not require ethics approval.

1. Introduction

Depression, anxiety, and stress-related mood disorders are psychological conditions with a high prevalence and an important health burden globally (van den Bosch and Meyer-Lindenberg 2019). The Global Burden of Disease Study 2016 reported that major depressive disorders are the fifth most important cause of years lived with disability (GBD 2017) and there is ample evidence that depression is the leading cause of preventable distress worldwide (Herrman et al. 2022). The incidence of depression and other psychiatric disorders including mood disorders and schizophrenia, is particularly high in urban populations (van den Bosch and Meyer-Lindenberg 2019) and this may be related to environmental stress (Honold et al. 2012; Lecic-Tosevski 2019). Events that may trigger episodes of depression often interact with genetic, social, or environmental vulnerabilities (Herrman et al. 2022). Such environmental vulnerabilities include chronic and acute exposures to heat, noise, light at night, and air pollution, which are all common in urban environments (Hoare et al. 2019; van den Bosch and Meyer-Lindenberg 2019; Newbury et al. 2021). There may be several causal pathways underlying associations between environmental exposures and adverse mental health, but recent research suggests that urban environmental stressors may affect the central nervous system through inflammation and oxidative stress, and hereby contribute to increased risk of depression and other mood disorders (Hahad et al. 2020).

Conversely, there is increasing evidence that vegetation may mitigate these detrimental exposures and improve or protect mental health. Vegetation may reduce harm and negative emotions, build and restore capacities, and increase positive emotions (McMahan and Estes 2015; Tester-Jones et al. 2020; Callaghan et al. 2021; Marselle et al. 2021). According to the stress reduction and attention restoration theories, natural environments facilitate the recovery from physiological stress and mental fatigue, and assist psychological restoration and restoration of directed attention (Ulrich 1983, Kaplan 1995); these theories are now supported by biological evidence (e.g. Woo et al. 2009; Egorov et al. 2017). From an ecosystem service perspective, vegetation may provide shade, reduce heat, and contribute to an inviting setting for physical activity and social interaction. As such urban green space could have long-term human health benefits (Salmond et al. 2016; Aerts et al. 2018; Bratman et al. 2019; Engeman et al. 2019; Zhang et al. 2021), including lower probabilities for mood disorders (Barwise and Kumar 2020; De Petris et al. 2021) and lower counts of mood disorder treatments (Nutsford et al. 2013). For instance, Taylor et al. (2015) found an inverse association between street tree density and prescriptions for antidepressants in London. In Germany, Marselle et al. (2020) found a similar inverse association between street tree density within 100 m of the residence and the probability of being prescribed antidepressant medication, especially in participants with lower socio-economic status.

A recent systematic review and meta-analysis investigated whether the *type* of natural environment may have an influence on the association between depressive mood and exposure to green space. Most of the 33 studies included in the meta-analysis had used forests as the natural environment (n = 16), followed by urban parks (n = 11). No effect of green space type could be found in the meta-regression, but the quality of the evidence was considered to be very low (Roberts et al. 2019). In general, the differential health effects of different green spaces types remain underexplored (Engemann et al. 2020; Jarvis et al. 2020), as many studies on green space and mental health have commonly used exposure metrics that cannot adequately differentiate vegetation types such as the normalized difference vegetation index (NDVI).

An improved understanding of the interaction between mood disorders and exposure to different types of green space may inform urban planning, and reduce the burden and the costs to individuals affected by mental health disorders, to their families, and to society (Bratman et al. 2019; van den Bosch and Meyer-Lindenberg 2019; Pfeiffer et al. 2021). This is why we examined, by means of a nationwide ecological study, whether medication sales for mood disorders in Belgium were associated with relative covers of four different green space types, i.e. woodland, low-green, residential gardens, and grassland. We hypothesized that lower covers of different green space types would be associated with higher medications sales for mood disorders, but that the magnitude of this association might differ among green space types and that the associations might also vary between urban and rural areas.

2. Methods

2.1. Study design

This study is part of the GRESP-HEALTH project (Casas et al. 2015), a nationwide ecological study on the association between residential exposure to green space and specific health outcomes in Belgium. Belgium is a densely populated country, characterized by high degree of urbanization. There were 11.43 million inhabitants in 2019, residing in three administrative regions: the Walloon Region, the Flemish Region, and the Brussels-Capital Region. Data in this study were analyzed at the census tract level. Census tracts ("statistical sectors") are the official and the smallest administrative spatial units for statistical purposes at higher resolution than the municipality, defined by Statbel, the Belgian Statistical Office. In Belgium census tracts are subdivisions of municipalities (which differ in size) and the subdivision is based on socio-economic factors, urban planning, and morphological characteristics of the area. This results in census tracts that are internally relatively homogeneous but that differ widely in terms of population, population density, size, and shape. The total number of census tracts in Belgium is 19782, with an average census tract surface area of 1.54 km^2 (median 0.46 km^2; range 0.01–63 km^2) and an average of 539 inhabitants (median 1475; range 0–7029) (Statbel 2019).

2.2. *Medication sales data*

This study used health care data from the Belgian social security agency InterMutualistisch Agentschap-Agence InterMutualiste (IMA-AIM). The IMA-AIM manages health care data collected by the seven Belgian health insurance funds. In Belgium, health insurance is mandatory and the population in the IMA-AIM database corresponds to about 98% of the Belgian population (as registered in the national register). The IMA-AIM provided yearly data from 2006 to 2014 on sales of reimbursed psychotropic medication prescribed to adults, more specifically all drugs included in the ATC (Anatomical Therapeutic Chemical) codes N05 (psycholeptics) and N06 (psychoanaleptics). Psycholeptics are central nervous system depressants and comprise drugs that *tranquillize* (antipsychotics, anxiolytics, and hypnotics and sedatives). Psycholeptics are used to treat symptoms of psychosis, anxiety, and severe insomnia. Psychoanaleptics are central nervous system stimulants and comprise drugs that *stimulate* the mood (antidepressants, psychostimulants, agents used for attention-deficit hyperactivity disorder [ADHD], and nootropics). Psychoanaleptics are used to treat symptoms of clinical depression, to manage ADHD, and to improve cognitive abilities. Examples of mood disorder medication commonly used in Belgium include diazepam (trade name Valium®), used, among others, for the treatment of anxiety; fluoxetine (trade name Prozac®), an antidepressant used, among others, as an effective treatment for seasonal affective disorder or “winter blues”; and escitalopram (trade name Cipralexa®), a selective serotonin reuptake inhibitor used for the management of mood and anxiety disorders, including major depressive disorder, obsessive-compulsive disorder, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder.

The IMA-AIM provided the number of men and women (19–64 years old) per census tract and per year for whom at least one refundable medication was prescribed at least once during the study period (‘prescription-patients’). Higher age classes were excluded because competing risks for disease are often present in the elderly. The aggregated data did not contain information on the frequency or duration of use. Census tracts with no more than 5 reimbursed persons or registered inhabitants in at least one year during the study period were excluded by IMA-AIM due to privacy reasons. All health data were used under license of IMA-AIM. The protocol for this study did not require ethics approval or consent to participate.

Medication sales data were first age-standardized to produce comparable measures of prescription behavior, because the number of prescriptions in a given area depends on the age structure of the area. The methodological details on the standardization can be consulted in the report by Costa et al. (2019). First the standard medication sales ratio was calculated as the ratio between the number of observed prescription-patients in an area and the expected number of prescription-patients in that area if the prescription behavior were the same as that of the overall Belgian population, taking into account the age- and sex-specific structure of the area. This ratio was then adjusted with the crude rate of prescriptions. We expressed the medication sales ratio as the number of prescription-patients per 1000 inhabitants (expressed as a non-zero positive integer). We used the average annual rate of medication sales for the period 2006 to 2014 as the outcome variable (for women and men separately).

2.3. Exposure to residential green space

Land cover data were provided by the Belgian National Geographic Institute (NGI-IGN). Green space types and their relative cover were extracted from the Top10Vector database ("Soil cover and vegetation" dataset, version 1.1 2011). Top10Vector is the NGI's database of topographic vector data layers and geometrically the most accurate data available for the entire Belgian territory (photo-interpretation of land covers was made on the basis of aerial photographs at the scale of 1:10 000 and additional information was collected during systematic field campaigns of the topographic inventory of Belgium). First, vector data (polygons) were extracted from the land cover data set of Top10Vector for 15 land cover types associated with vegetation: 1. coniferous woodland, 2. predominantly coniferous mixed woodland, 3. mixed woodland, 4. predominantly broad-leaved mixed woodland, 5. broadleaved woodland, 6. permanent grassland or hay meadow (permanent grassy land, grazed or intended for hay production), 7. lawn (periodically mown grassy land, found for example on sports fields, on hard shoulders and road embankments and in parks), 8. garden (ornamental gardens or vegetable gardens near residences), 9-12. four types of heath, 13-14. two types of herbaceous vegetation, and 15. bushland. Using a spatial overlay procedure between the land cover data and census tract boundaries, the cumulative cover (m^2) of each of these 15 land cover types within every census tract in Belgium was determined. Woodland cover (m^2) was calculated as the sum of the covers of the five woodland types (land cover types 1–5), grassland cover (m^2) as the sum of grasslands, meadows and lawns (land cover types 6 and 7), and low-green as the sum of herbaceous vegetation, heath, and bushland (cover types 9–15). Woodland cover in this study includes forests, but also woodlands that are too small to possess a distinct forest microclimate. Such woodlands technically do not qualify as 'forest'. For the sake of conciseness, forests and smaller woodlands are further referred to as 'woodlands'.

Spatial overlays were performed using the package *sf* (Simple Features for R, version 0.8-0) implemented in the R system for statistical computing (R Core Team 2020). The main geometric operations were performed using the functions *st_intersection* for identifying features polygons overlaying with census tracts and *st_area* for measuring the surface area (in m^2) of each land use category per census tract. The total surface area per census tract was then calculated using the function *summarize* from the package *dplyr* (version 0.8.3). Absolute cover at the census tract level of the different land cover types was then expressed as relative cover (%).

2.4. Socio-economic background variables

Earlier studies in Belgium have demonstrated that associations between green space and health outcomes are influenced by socio-economic (SE) background variables, and notably by socio-economic deprivation (e.g. Aerts et al. 2020b). Education and profession are dimensions of socio-economic deprivation that strongly correlate to socio-economic status in Belgium (Bossuyt et al. 2004). Therefore, we used the percentage of primary educated or lower among the 25–64 year old as an indicator of education skills and training deprivation and the percentage of unemployed inhabitants as an indicator of employment deprivation. In addition, we used the percentage of foreign-born inhabitants from lower- and mid-income countries (LMIC, countries which did not belong to the World Bank classification of 'high-income economies' in 2000) as a third indicator of socio-economic deprivation, as communities with a migrant background are subject to important health inequalities in Belgium (Vantomme et al. 2021). Sociodemographic data were provided by Statbel. Data were derived from the 2001 census. These data were not provided by sex.

2.5. Statistical analyses

Generalized linear mixed effect models based on a zero-truncated negative-binomial distribution with log-link function were used to investigate associations between exposure to residential green space types and medication sales. We used a zero-truncated model because there are no negative values for medication sales and zeros have been privacy restricted (see also McDougall et al. 2021). Because medication sales for men and women at the level of the census tract were separate response variables, models were fit for men and women independently. Relative covers of woodland, grassland, low-green, and garden were all entered in the same model in units representing 10% relative cover. Only SE-adjusted models were evaluated. Socio-economic variables were added as continuous covariates.

Because cultural differences such as prescription behaviour may exist among regions and could therefore be a source of spatial dependencies (see e.g. Trabelsi et al. 2019), administrative region (Flanders, Wallonia, and Brussels) was entered as a fixed effect in all models. In addition we adjusted the models for urban-rural differences by adding a fixed factor 'urban' which was based on population density (urban was defined as having a population density ≥ 600 inhabitants/km²). Furthermore, we added random effects of latitude and longitude on a 5×5 km² grid to account for fine-scale spatial patterns.

In addition to the main multiple regression models (one response, multiple predictors), we evaluated i) models stratified by population density (urban vs. rural), ii) a multivariate model with men and women pooled (two responses and multiple predictor variables), iii) a multivariate model with total green space cover as the main predictor variable (defined as the sum of woodland, low green, garden and grass covers), and iv) a multivariate model with a Matérn correlation function replacing the random effects for latitude and longitude to more directly account for spatial correlation.

All models were evaluated with *spaMM*, a package for inference-based mixed-effects models with or without spatially-correlated random effects (Rousset et al. 2022) implemented in the R system for statistical computing (R Development Core Team 2012). We used the *fitme* function to fit multiple regressions for medication sales for men and women separately and the *fitmv* function to fit joint models for both responses, sharing random effects. In total, 9579 census tracts were included, 9574 census tracts for women and 9517 for men.

3. Results

3.1. Census tract characteristics

The characteristics of the census tracts included in the study are presented in Table 1. The average proportions of woodland, low-green, gardens, and grassland were 5.3%, 2.3%, 36.4% and 15.2%, respectively. Green space cover was higher in urban than in rural areas (Kruskal-Wallis non-parametric χ^2 test, all cover types $p < 0.001$).

3.2. Mood disorder medication sales

The average 12-month prevalence of mood disorder medication sales between 2006 and 2014 in Belgium was 147 (SD 38) prescription-patients per 1000 inhabitants for women and 148 (SD 42) for men. The average 12-month prevalence of mood disorder medication sales was higher in urban than in rural areas, both for women and men (Kruskal-Wallis non-parametric χ^2 test, for woman and men $p < 0.001$) (Table 1).

3.3. Associations with green space

Urban census tracts were associated with respectively 8.5 and 9.9% higher medication sales for mood disorders for men and women compared to rural census tracts (95% CI, men: 6.8%–10.2%; women: 8.4%–11.3%). Higher relative cover of green space was associated with lower mood disorder medication sales in seven out of eight investigated associations in the main models. Increases in relative covers of woodland, garden, and grass by 10% each were associated with decreases in mood disorder medication sales by 1.3, 1.3, and 2.1% for men, and by 1.8, 0.7 and 1.6% for women. For men, also a 10% increase in low green was associated with a decrease in mood disorder medication sales (-1.3%). In the models stratified by population density, the protective associations between relative green space cover and medication sales became consistently stronger in the urban census tracts. A 10%

increase in relative cover of any green space type in urban census tracts was associated with a decrease of mood disorder medication sales between 1.1 and 2.8% for women and between 1.7 and 2.7% for men (eight out of eight associations). In rural census tracts, there were no protective associations between green space and mood disorder medication sales, with the exception of relative woodland cover for women (-0.9%). On the contrary, low green was associated with higher mood disorder medication sales (6.2–7.4% higher medication sales per 10% increase in low green cover) (Fig. 1; Table 2). The multivariate model (fitted for men and women simultaneously) produced similar parameter estimates; estimates were slightly attenuated for women, and protective associations were a fraction stronger for men (Table S1). In the multivariate model with total green space as the main predictor variable, an increase of total green space cover by 10% was associated with a decrease in mood disorder medication sales by 1.0% for women (B = -0.010, 95% CI –0.013; -0.008) and by 1.6% for men (B = -0.016, 95% CI -0.019; -0.014); the multivariate model with spatial correlation function resulted in almost identical parameter estimates for the associations between total green and medication sales (women: B = -0.007, 95% CI -0.009; -0.005; men B = -0.013, 95% CI -0.016; -0.011).

4. Discussion

4.1. Main findings

We investigated the association between residential green space type and quantity and mood disorder medication sales in Belgium. We found that reimbursed sales of psycholeptics and psychoanaleptics at census tract level were lower in rural areas than in urban areas, and that sales in urban areas (and not so much in rural areas) decreased with increasing relative covers of green space, in particular woodland, but also grass, low green, and gardens.

4.2. Comparison with other studies

First, our results are in agreement with several earlier studies that have reported that living in greener areas is associated with several mental health benefits [e.g. in children (Engemann et al. 2020; Davis et al. 2021; Fyfe-Johnson et al. 2021); adolescents (Hartley et al. 2021); adults (Gascon et al. 2015; 2018); older adults (Pun et al. 2018)]. For instance, in a cross-sectional study that analyzed data from 94879 adult participants in the UK, an inverse association between residential "greenness" (measured as IQR increment of NDVI) and depression was observed (OR 0.96, 95%CI 0.93-0.99) (Sarkar et al. 2018). In a similar study in Canada, odds of poor self-rated mental health decreased by 6% per increase in IQR of NDVI (Crouse et al. 2021). In a smaller study in Louisville (USA), having views of green space at home was associated with satisfaction and with a lower Patient Health Questionnaire-9 (PHQ-9) score, indicating reduced depression severity (Pfeiffer et al. 2021). In two nation-wide studies including data of ~1 million people in Denmark, higher levels of residential green space during childhood (measured as NDVI in a 4.4 ha square around the residence, from birth to the age of 10 years, and percentage cover of urban, agriculture, near-natural green space and blue space in 0.5, 1 and 3 km wide squares) were associated with lower risks of psychiatric disorders in later life and these associations remained significant after adjustment for SE status and degree of urbanization (Engemann et al. 2018; 2020). A cross-sectional, ecological study in the Netherlands found reduced suicide risks in municipalities with a large or moderate proportion of green space compared to municipalities with less green space (Helbich et al. 2018a).

Second, our observation that the association between green space exposure and improved mental health is more prominent in urban than in rural areas, is supported by a recent review on the effect of urbanicity on green space-health relationships. In the set of analyses that demonstrated a difference between urban and rural areas (49.1% of the 57 analyses across 37 articles included in the review), associations were more often stronger in urban areas (38.6%) than in rural areas (10.5%). In addition there was an urban 'advantage' for residential green space, i.e. stronger associations between health and green space measured close to the home (Browning et al. 2022).

Third, our results provide some degree of support to previous findings that different types of green space may have distinct impacts on mental health outcomes. In the present study, higher relative covers of all green space types in urban areas were associated with reduced mood disorder medication sales. However, in rural areas (where exposure to green space is generally higher) there was some differentiation: woodland was inversely associated with medication sales for women, whereas low green was associated with higher medication sales for both sexes, and for the other types of green space we did not find evidence for associations in either direction (Table 2). In a panel study of 88 tree pollen allergy patients in Flanders (Belgium), residential green space, defined as the amount of low (< 3 m tall) and high green near the house, was inversely associated with the development of short-term emotional distress (OR=0.94 for high green, 0.85 for low-green, per 10 ha of green space), but the presence of specific allergenic vegetation (birch, alder, and hazel trees) emerged as a risk factor (OR=2.04 present vs. absent) (Aerts et al. 2020c). Underlying conditions such as pollen allergies may trigger depression and anxiety and are therefore able to affect relationships between different types of green space and mental health (Trikojat et al. 2017). A cross-sectional observational study analyzing data from the 2013-2014 Canadian Community Health Survey investigated the association between exposure to different types of urban natural environments and self-reported mental health outcomes in Metro Vancouver, Canada. Also here distinct effects of green space types emerged. In this study, exposure to shrub vegetation types was associated with reduced odds for reporting poor mental health (OR range 0.73-0.74 for shrubs within 250-1000m distance) and exposure to grass-herb vegetation types led to reduced odds for reporting common mental disorders (OR=0.98 for grass-herbs within 250 m); in contrast to our study results, no significant associations were found for exposure to woodlands (Jarvis et al. 2020). A study in older adults in Japan found results which are very similar to our own: areas with more green space had lower odds for depression, and in urban areas, more trees were associated with lower odds of depression; in rural areas not trees but grassland cover was associated with lower odds of depression (Nishigaki et al. 2020).

Finally, our results do concur well with previous studies that have used medication sales data as the outcome variable. Our finding that medication sales were lower in rural areas was corroborated by an earlier study among older people in Stockholm and in nine Finnish cities. In this study antidepressant use was associated with the density of the physical urban environment, with less antidepressant use in more open (less urban) neighbourhoods (Tarkiainen et al. 2021). A study across 18 countries including 16307 patients found that nature connectedness and green space visits were associated with a lower probability of using medication for depression (medication prescribed for 'depression' and 'tension and anxiety', but no ATC codes were specified) (White et al. 2021). Interestingly, the same study found that inland blue-space visits were associated with a higher likelihood of using anxiety medication, illustrating the complexity of nature-mental health associations. An ecological study in Auckland City, New Zealand, reported that anxiety/mood disorder treatments (secondary mental health treatment, medication for anxiety/mood disorder treatment, or specific laboratory tests) were inversely associated with total and usable green space within 3 km (Nutsford et al. 2013). However, this study found no such association within the more typical 'residential' green space range of 300 m. Conversely, a study including 958 adults in Barcelona, Spain, reported that increasing surrounding greenness within this short range (IQR increment of NDVI within 300 m) was associated with reduced odds of (self-reported) history of using benzodiazepines (ATC code N05BA - a subgroup of psycholeptics that was also included in our medication sales data) (Gascon et al. 2018). A cross-sectional, ecological study in 403 municipalities in the Netherlands reported an inverse (non-linear) association between green space and antidepressant prescription rates (Helbich et al. 2018b). In contrast, one study conducted in three Australian cities reported higher levels of antidepressant prescribing with increasing relative cover of green space, in particular grass. Tree canopy was not associated with antidepressant prescription rates in this study (Astell-Burt et al. 2022). Within Belgium, we previously found similar protective associations between green space and sales of cardiovascular medication, both in models where green space was defined by the number of forest patches and relative forest cover and in models where total green and blue space were considered (Aerts et al. 2020b). However, for medication sales for childhood asthma, we obtained contrasting results: there was no association with relative forest cover, and the relative covers of grasslands and gardens were associated with higher medication sales (Aerts et al. 2020a).

Compared to other green space types, woodlands had the strongest association with reduced mood disorder medication sales in our study. This suggests that maintaining and increasing relative cover of woodland where people live, through the conservation of existing forest and woodland patches in parks and private gardens, and the creation of new urban woodlands (e.g. "tiny forests" embedded in the urban matrix), could be complementary strategies to improve the ecological value of urban green space and to reduce the burden of mood disorders at the scale of the neighbourhood. Our results also lend support to recently recommended "health promoting actions at the population level" to reduce the prevalence of depression (Herrman et al. 2022), such as 'green prescriptions' and other 'nature-based interventions' which aim to improve health outcomes by increasing exposure to green space, connection with nature, physical activity, and social interaction (Ulmer et al. 2016; Van den Berg 2017; Coventry et al. 2021).

4.3. Strengths and limitations

In this study, residential exposure to green space was derived from very accurate (survey-based) land cover data. Our exposure metrics were much more precise than exposures based on NDVI or coarse land cover data, which have been frequently used in previous research. The detailed analyses allowed us to demonstrate that associations – in contrast to our initial hypothesis – varied little among different land cover types, at least in urban areas.

We are aware that our research may have a number of limitations. Ecological bias, associated with the ecological design of the study, may have concealed health effects of green space at the individual level, as in our earlier studies on medication sales (Aerts et al. 2020a,b). In addition, individual socio-economic status differences, including lifestyle, wealth, or general practitioner's prescription patterns, may influence associations between green space and medication sales. Even if we partially account for such differences by adjusting for regions, such individual effects cannot be observed in aggregated datasets. These are universal drawbacks of aggregated data. The ecological design is, despite these limitations, very useful as it is very effective in protecting personal data.

Exposure misclassification may have caused additional bias in a number of ways. First, residential exposure to green space may differ from real exposure as it ignores dynamic exposures that may vary during the day (e.g. home time, school or work hours, recreation, and time in traffic) and throughout life (Helbich 2018; Loder et al. 2020). Second, the mood disorder medication sales data is from the period 2006–2014, whereas the exposure data is from different years (SE background variables: 2001; land cover: 2013). The timing mismatch for land cover is minimal, but we acknowledge that the timing mismatch in SE variables could have caused some additional bias. However, these variables were only used to adjust our models, and we are confident that the parameter estimates for the exposures of interest are not gravely affected.

Finally, associations with green space were determined for pooled sales data of psycholeptics and psychoanaleptics. However, people who use such prescription medication for the management of mood disorders don't necessarily interact with green spaces in the same way, for instance because they may have different motivations to visit nature (Tester-Jones et al. 2020). Also, some medications commonly prescribed for mood disorders, for example diazepam, may have been prescribed for the management of other medical conditions, such as muscle spasms, back pain, or alcohol withdrawal. Therefore, additional studies based on individual data of exposure to green space in combination with more detailed mood disorder medication data may further elucidate the associations between green space and mental health. Despite these limitations, our findings provided satisfactory confirmation of the hypothesized positive associations between exposure to green space and mental health.

5. Conclusions

Based on aggregated data, the evidence from this study suggests that living in green neighborhoods may be associated with improved adult mental health, indicated by prescribed mood disorder medication sales. Exposure to green space may complement prescription medications, psychological counselling, and other interventions for the management of mood disorders, but longitudinal individual studies are needed to determine causal relationships. Meanwhile, it is important to conserve green space in our living environment, not only for the conservation of biodiversity but also for human health.

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.

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Data Statement

The research data is confidential. The land cover data that were used to quantify residential green space (Top10Vector, identifier BE.NGI-IGN/5F4130E6-DF5C-41E6-A956-BB9F04088D11) are copyrighted (©Institut Géographique National) and were used under federal use license 2016_F014 granted by the Institut Géographique National (NGI-IGN) to the Belgian Science Policy Office (BELSPO).

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Table 1. Characteristics of the study population at the level of the census tract: residential green space, socio-economic variables, and medication sales for mood disorders prescribed to adults in Belgium (2006-2014)

	All tracts (N=9579)		Urban (N=8109)		Rural (N=1470)	
	Mean	SD	Mean	SD	Mean	SD
Green space, relative cover (%)						
Woodland	5.3	9.0	4.0	6.6	12.2	15.1
Low-green	2.3	3.9	2.3	4.0	2.1	3.3
Garden	36.5	16.7	41.0	13.6	11.6	8.4
Grassland	15.1	12.9	12.7	11.0	28.6	14.3
Socio-economic variables (%)						
Immigrants (LMIC)	3.6	5.4	4.0	5.7	1.3	1.9
Unemployed	12.4	8.4	13.2	8.6	8.3	5.3
Low education	14.9	6.8	15.0	7.0	13.8	5.5
Medication sales (per 1000 inhabitants) (2006-2014)						
Women	147	38	151	37	127	32
Men	148	42	151	40	129	45

LMIC: low- and mid-income countries

Table 2. Adjusted associations between residential green space and mood disorder medication sales in women and men aged 19–64 years in Belgium

	All census tracts		Urban areas		Rural areas	
Women	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Urban vs. rural (ref)	0.099	0.084; 0.113				
Woodland (10%)	-0.018	-0.022; -0.013	-0.028	-0.034; -0.022	-0.009	-0.017; -0.001
Low green (10%)	-0.006	-0.015; 0.004	-0.015	-0.025; -0.006	0.062	0.028; 0.095
Gardens (10%)	-0.007	-0.010; -0.003	-0.011	-0.014; -0.007	0.007	-0.006; 0.019
Grass (10%)	-0.016	-0.020; -0.013	-0.019	-0.023; -0.015	-0.008	-0.017; 0.001
Men	**B**	**95% CI**	**B**	**95% CI**	**B**	**95% CI**
Urban vs. rural (ref)	0.085	0.068; 0.102				
Woodland (10%)	-0.013	-0.018; -0.008	-0.027	-0.034; -0.020	-0.002	-0.013; 0.009
Low green (10%)	-0.013	-0.024; -0.002	-0.027	-0.038; -0.016	0.074	0.029; 0.120
Gardens (10%)	-0.010	-0.014; -0.006	-0.017	-0.020; -0.013	0.015	-0.001; 0.032
Grass (10%)	-0.021	-0.026; -0.017	-0.026	-0.031; -0.022	-0.007	-0.019; 0.005

Parameter estimates β and 95 % confidence intervals are from generalized mixed models with a zero-truncated negative-binomial distribution, with the average annual rate of medication sales for the period 2006 to 2014 as the outcome variable. Models were adjusted for administrative region, the percentage of foreign-born inhabitants from LMIC, the percentage of unemployed inhabitants, and the percentage of primary educated or lower among the 25–64 year old, and included random effects for latitude and longitude in a 5×5km² grid.

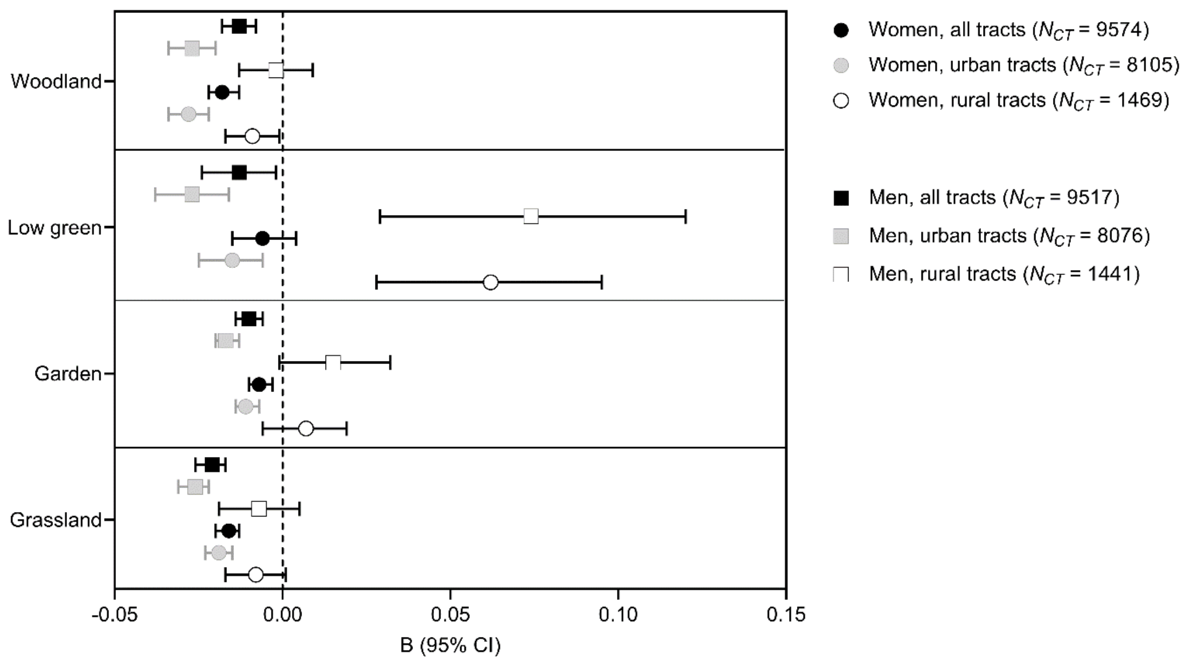

Figure 1. Adjusted associations between residential green space and mood disorder medication sales in women and men aged 19–64 years in Belgium [12-month prevalence of sales of psycholeptics (ATC code N05) and psychoanaleptics (N06) at the level of census tracts (*CT*)] for all census tracts and for census tracts stratified by population density (urban vs. rural). Parameter estimates β and 95 % confidence intervals for green space types (in units representing 10% relative cover) are from generalized linear mixed models with a zero-truncated negative-binomial distribution, with the average annual rate of medication sales for the period 2006 to 2014 as the outcome variable. Models were adjusted for administrative region, the percentage of foreign-born inhabitants from LMIC, the percentage of unemployed inhabitants, and the percentage of primary educated or lower among the 25–64 year old, and included random effects for latitude and longitude in a 5×5km² grid. Grassland cover includes permanent grassland, hay meadows and lawns; garden cover includes ornamental gardens and vegetable gardens near residences; low-green cover includes herbaceous vegetation, heath, and bushland; woodland cover includes coniferous, mixed and broadleaved woodlands.