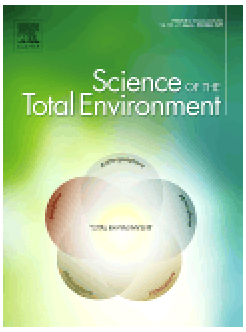

Residential green space, air pollution, socio-economic deprivation and cardiovascular medication sales in Belgium: a nationwide ecological study

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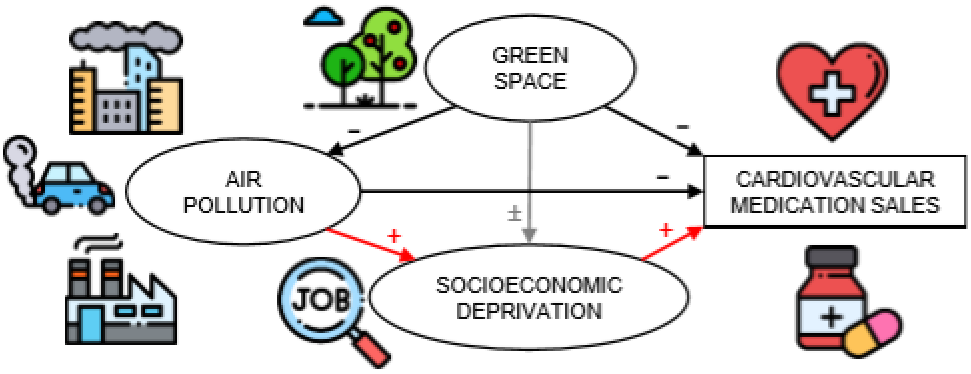

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Residential Green Space, Air Pollution, Socioeconomic Deprivation and Cardiovascular Medication Sales in Belgium: a Nationwide Ecological Study

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ABSTRACT

Green space may improve cardiovascular (CV) health, for example by promoting physical activity and by reducing air pollution, noise and heat. Socioeconomic and environmental factors may modify the health effects of green space. We examined the association between residential green space and reimbursed CV medication sales in Belgium between 2006 and 2014, adjusting for socioeconomic deprivation and air pollution. We analyzed data for 11,575 census tracts using structural equation models for the entire country and for the administrative regions. Latent variables for green space, air pollution and socioeconomic deprivation were used as predictors of CV medication sales and were estimated from the number of patches of forest, census tract relative forest cover and relative forest cover within a 600 m buffer around the census tract; annual mean concentrations of $PM_{2.5}$, BC and NO_2; and percentages of inhabitants that were foreign-born from lower- and mid-income countries, unemployed or had no higher education. A direct association between socioeconomic deprivation and CV medication sales [parameter estimate (95% CI): 0.26 (0.25; 0.28)] and inverse associations between CV medication sales and green space [–0.71 (–0.80; –0.61)] and air pollution [–1.62 (–1.69; –0.61)] were observed. In the regional models, the association between green space and CV medication sales was stronger in the region with relatively low green space cover (Flemish Region, standardized estimate –0.16) than in the region with high green space cover (Walloon Region, –0.10). In the highly urbanized Brussels Capital Region the association tended towards the null. In all regions, the associations between CV medication sales and socioeconomic deprivation were direct and more prominent. Our results suggest that there may be an inverse association between green space and CV medication sales, but socioeconomic deprivation was always the strongest predictor of CV medication sales.

Keywords: Cardiovascular disease, Epidemiology, Environment, Exposure, Medication sales, Public health

Highlights

- Ecological study of cardiovascular medication sales in Belgium.
- Structural equation models used to analyze census tract data.
- Inverse association between green space and cardiovascular medication sales.
- Socioeconomic deprivation strongest predictor of medication sales.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. The 2017 Global Burden of Disease study estimated that coronary or ischaemic heart disease and cerebrovascular disease (stroke) accounted for more than 1 million deaths each worldwide in 2017 (IHME 2018). In Europe, CVD mortality rates have decreased substantially in most countries over the past 10 years. However, CVD remains accountable for more than 4 million deaths or 45% of all deaths across Europe annually and contributes considerably to rising health care costs (Townsend et al. 2016).

In many urbanized regions lifestyle choices and environmental exposures can pose substantial risks to develop CVDs (Nayyar and Hwang 2015). There is robust evidence that indoor and outdoor air pollution, noise, urban heat, psychological stress, physical inactivity, obesity, high salt and fat intake, alcohol use, smoking, food pollutants and the lack of social contact contribute to CVD morbidity and premature mortality (Nawrot et al. 2011; Wirtz and von Känel 2017; Nieuwenhuijsen 2018; Argacha et al. 2018; Argacha et al. 2019; Wu et al. 2019). In contrast, there is increasing scientific evidence for the benefits of exposure to residential green space for the prevention and reduction of risk of CVD (Crouse et al. 2017; Vienneau et al. 2017; Vivanco-Hidalgo et al. 2019; Wang et al. 2019; Orioli et al. 2019; Yeager et al. 2018; 2019). In systematic reviews of studies investigating the association between green space and mortality, Gascon et al. (2016) and Rojas-Rueda et al. (2019) reported, respectively, that five out of eight and seven out of nine included studies found evidence for an inverse relationship between increases in residential greenness and CVD and all-cause mortality risk. In a systematic review and meta-analysis of green space and health outcomes, Twohig-Bennett and Jones (2018) showed that increased green space exposure was associated with reductions in diastolic blood pressure, heart rate and cardiovascular mortality. Similarly, a reduction of exposure to green space, for instance through the loss of trees induced by drought, climate change or (invasive) pest outbreaks, has been associated to increased incidence of CVD (Donovan et al. 2013; 2015).

Residential green space can be defined as open pieces of land near the house, partially or completely covered by vegetation and typically includes forests, public parks, private gardens, remnant patches of vegetation and urban green infrastructure such as street trees (Vienneau et al. 2017; Lai et al. 2019). Mechanisms through which residential green space may improve cardiovascular health include the reduction of psychological stress, the promotion of physical activity and social interactions, and the attenuation of environmental risk factors including air pollution, heat and noise (Dadvand et al. 2016; Shen and Lung 2016; Markevych et al. 2017; Nieuwenhuijsen et al. 2017; Fiuza-Luces et al. 2018; Franchini and Mannucci 2018; Nieuwenhuijsen 2018; Wu et al. 2018). However, green space and therefore the health benefits of green space may be inequitably distributed or differently used among groups or neighborhoods with different socioeconomic status (Richardson and Mitchell 2010; Jennings and Gaither 2015; Chaparro et al. 2018; Kabisch 2019; Schüle et al. 2019). Such demographic inequities have also been observed for environmental burdens such as air pollution and urban heat (Arbuthnott and Hajat 2017; Fairburn et al. 2019; Servadio et al. 2019). Some authors have suggested that health benefits of residential green space are more pronounced in neighborhoods with lower socioeconomic status (Maas et al. 2006; van den Berg et al. 2015; Yitshak-Sade et al. 2019) while others have found the opposite (Crouse et al. 2017). Studies of the association between green space and health should therefore always consider the potential complex interactions between green space, correlated environmental exposures and socioeconomic background variables (Hu et al. 2008; Crouse et al. 2019; Klompmaker et al. 2019).

A better understanding of the relationships between CVD prevalence and socioeconomic status, air pollution and green space may be used to inform CVD prevention policies and thus help to reduce the burden of CVD on society. Therefore, the aim of this study was to assess the multiple associations between exposure to residential green space, air pollution, socioeconomic status and cardiovascular medication sales in Belgium. We hypothesized that air pollution and socioeconomic deprivation would be associated with higher cardiovascular medication sales whereas exposure to green space would be associated with lower cardiovascular medication sales.

2. Methods

2.1. Study Design

This observational study was designed as a nationwide ecological study in Belgium, with data from the years 2006 to 2014 [a brief description of the GRESP-HEALTH project protocol is presented in Casas et al. (2015)]. The levels at which the data are analyzed are the administrative region and the census tract. Belgium (11.43 million inhabitants in 2019; 30,528 km²) has three administrative regions: the Flemish Region (Flanders, 13,522 km²), the Walloon Region (Wallonia, 16,844 km²) and the Brussels Capital Region (161 km²). The Flemish Region in the north is generally characterized by a dense network of cities and roads, high densities of population, industrial activities and traffic, and, consequently, high levels of air pollution and highly fragmented green spaces (Supplementary material Maps S1-S4) (Trabelsi et al. 2019). The landscape in the Walloon Region in the south is less densely populated and more green, except along the former industrial backbone in the Sambre and Meuse valley. In this area unemployment rates and air pollution are relatively high (Maps S1-S4, S6). The census tracts are a nationwide geographic subdivision of municipalities based on urban development, socioeconomic characteristics and morphological properties. The census tracts are the official administrative spatial units for statistical analyses at finer scale than the municipality. The total number of census tracts in Belgium is 19,782, with an average census tract surface area of 1.54 km² (range 0.01–63 km²) and an average of 539 inhabitants (range 0–7029) (Statbel 2019).

2.2. Cardiovascular Medication Sales

This study used health care data from the Belgian social security agency Intermutualistisch Agentschap-L'Agence Intermutualiste (IMA-AIM). The IMA-AIM manages an extensive collection of healthcare 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 ~98% of the Belgian population (as registered in the national register). The IMA-AIM provided data on general cardiovascular medication sales. The data included the number of individuals aged 19 to 64 years old for whom at least one refundable medication was prescribed at least once in a given year (2006 to 2014) per census tract, the costs per census tract and the number of registered individuals per census tract. Higher age classes were excluded to avoid competing risks for disease that are often present in the elderly. General cardiovascular (CV) medication was defined as all reimbursed drugs included in the ATC (Anatomical Therapeutic Chemical) codes B01A (antithrombotic agents), C01 (cardiac therapy, including cardiac glycosides, antiarrhythmics, cardiac stimulants and vasodilators), C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin-angiotensin system). Other substances that are classified in main groups B (Blood and blood forming organs) and C (Cardiovascular system) are not specifically associated to treatment of CVD (i.e. therapeutic groups B02 Antihemorrhagics, B03 Antianemic preparations, B05 Blood substitutes and perfusion solutions, B06 Other hematological agents, C04 Peripheral vasodilators, C05 Vasoprotectives and C10 Lipid modifying agents) and were therefore not included. A number of hypolipidemic drugs that belong to group C10 such as statins and fibrates may be used for the primary prevention of CVD or for the treatment of hypercholesterolemia after myocardial infarction. In such cases these drugs are usually not used in isolation but in combination with other CVD medication that is included in our dataset such as beta blocking agents (C07) or ACE inhibitors (C09A). The medication sales data that support the findings of this study did not contain the distribution of costs among ATC codes, nor did it contain information on the frequency of use. All health data were used under license of IMA-AIM and the protocol for this study did not require ethics approval or consent to participate.

We used the mean indirect Adjusted Standardized Morbidity Ratio (ASMR) for reimbursed cardiovascular (general) medication as the outcome variable. The methodological details on the calculation of the ASMR can be consulted in the report by Costa et al. (2019). In brief, age-standardization was essential to produce comparable measures of prescription behavior because the number of prescriptions in a given area depends on the age structure of the area. To that end, first a Standard Morbidity Ratio (SMR) was calculated as the ratio between the observed number of prescription-patients and the expected number of prescription-patients in a given 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. Then the ASMR was calculated as the SMR adjusted by the crude rate of prescriptions, expressed as prescription-patients per 100 individuals (%). The ASMR was calculated for males and females separately and for three year groups (2006–2008, 2009–2011, 2012–2014). Because all ASMR variables were significantly correlated to each other (Pearson r 0.60–0.86, all $p < 0.001$), we calculated one overall mean ASMR value for males and females for all years per census tract (age standardized prescribed medication sales per 100 inhabitants aged 19-64 year old, males and females) and used this as the dependent variable for our models.

2.3. Definition of Potential Predictors

2.3.1. Residential green space

To objectively quantify tree/forest cover, the number of forest patches, the surface area of forest within the census tract (Supplementary material Map S1), and the surface area of forest within the census tract and in a 600 m buffer around the census tract were derived from the CORINE Land Cover (CLC) dataset of 2006 (minimal mapping unit: 25 ha). We used CORINE Land Cover classes 311 (broadleaved forest), 312 (coniferous forest) and 313 (mixed forest) to define tree/forest cover. For the sensitivity analysis, we also quantified the number of patches, the surface area within the census tract and the surface area within the census tract and in a 600 m buffer around the census tract for agricultural land, natural green other than forest and urban green. Agricultural land comprised the CLC classes 211 (non-irrigated arable land), 222 (fruit trees and berry plantations), 231 (pastures), 242 (heterogeneous agricultural areas with complex cultivation patterns) and 243 (agriculture with significant areas of natural vegetation). Natural green (other than forest) comprised the CLC classes 321 (scrub with grass, including scattered woody vegetation with < 50% cover, trees occupying < 30% of area), 322 (moors and heathland), 324 (transitional woodland/shrub), 331 (beaches, dunes and sands), 411 (inland marshes), 412 (peat bogs), 421 (salt marshes) and 423 (intertidal flats). Urban green comprised the CLC classes 141 (green urban areas) and 142 (sport and leisure facilities) (more details on CLC nomenclature can be downloaded online at https://land.copernicus.eu/user-corner/technical-library/corine-land-cover-nomenclature-guidelines/html). These data were then combined into variables for total green and blue space (number of patches, the total surface area within the census tract and the total surface area within the census tract and in a 600 m buffer around the census tract).

2.3.2. Air pollution

Air pollution data were provided by the Belgian Interregional Environment Agency (IRCEL-CELINE). The data at census tract level were generalized from high resolution models (25 m × 25 m) of the annual mean concentrations (in µg/m³) particulate matter < 2.5 µm ($PM_{2.5}$; Map S2), black carbon (BC; Map S3) and nitrogen dioxide (NO_2; Map S4) for the year 2015. The statistical air pollution models are based on a spatial interpolation of air pollution measurements using data from 54 monitoring stations and CORINE Land Cover information (Janssen et al. 2008; Lefebvre and Vranckx 2013).

2.3.3. Sociodemographic characteristics

Sociodemographic data were provided by the Belgian Statistical Office (Statbel). Data were derived from the 2001 census. We included indicators of socioeconomic status (SES) that are related to socioeconomic deprivation. In Belgium, the dimensions that most strongly define SES are education, profession and income (Bossuyt et al. 2004). Using the aggregated SES data at hand, we included the following three dimensions of deprivation in the present study: the percentage of foreign-born inhabitants from lower- and mid-income countries (LMIC; Map S5), the percentage of unemployed inhabitants (employment deprivation) (Map S6) and the percentage of primary educated or lower among the 25–64 year old (education skills and training deprivation) (Map S7).

2.4. Study Population

A total of 19,782 census tracts (11,150,902 inhabitants) was assessed for eligibility. From these, 7,554 census tracts (630,743 inhabitants) were excluded due to privacy reasons (census tracts with a population of 200 inhabitants or less and census tracts with 5 reimbursements or less were excluded by IMA-AIM). From the 12,228 census tracts with health outcome data (10,520,159 inhabitants), 640 were excluded because of missing socioeconomic data (171,720 inhabitants) and 13 were excluded because of missing environmental data (4,959 inhabitants). A total of 11,575 census tracts were included in the analysis (10,343,480 inhabitants): 6,588 census tracts in the Flemish Region (72%; 6,133,092 inhabitants); 4,386 census tracts in the Walloon Region (44%; 3,056,490 inhabitants) and 601 census tracts in Brussels Capital Region (83%; 1,153,898 inhabitants) (Fig. 1).

2.5. Statistical Analyses

The Wilcoxon test was used to compare predictor variables among regions. For the main analysis, we used structural equation models (SEM). Structural equation models enable users to estimate relationships between unobserved variables (latent variables) via observed variables (manifest variables) and to test models with predefined (hypothesized) structure. We constructed an a-priori model of associations between the latent variables "residential green space", "air pollution" and "socioeconomic deprivation". These latent variables were estimated, respectively, from the number of patches of forest, census tract relative forest cover and relative forest cover within a 600 m buffer; annual mean concentrations of $PM_{2.5}$, BC and NO_2; and percentages of inhabitants that were foreign-born from lower- and mid-income countries (LMIC), unemployed or had no higher education. We limited the number of manifest variables per latent variable to three (the minimum amount of observed variables for a latent variable) to avoid overfitting as a preliminary screening of our initial larger dataset demonstrated strong correlations between several potential indicator variables of interest (e.g. PM_{10} and $PM_{2.5}$; Pearson $r = 0.90$, $p < 0.001$).

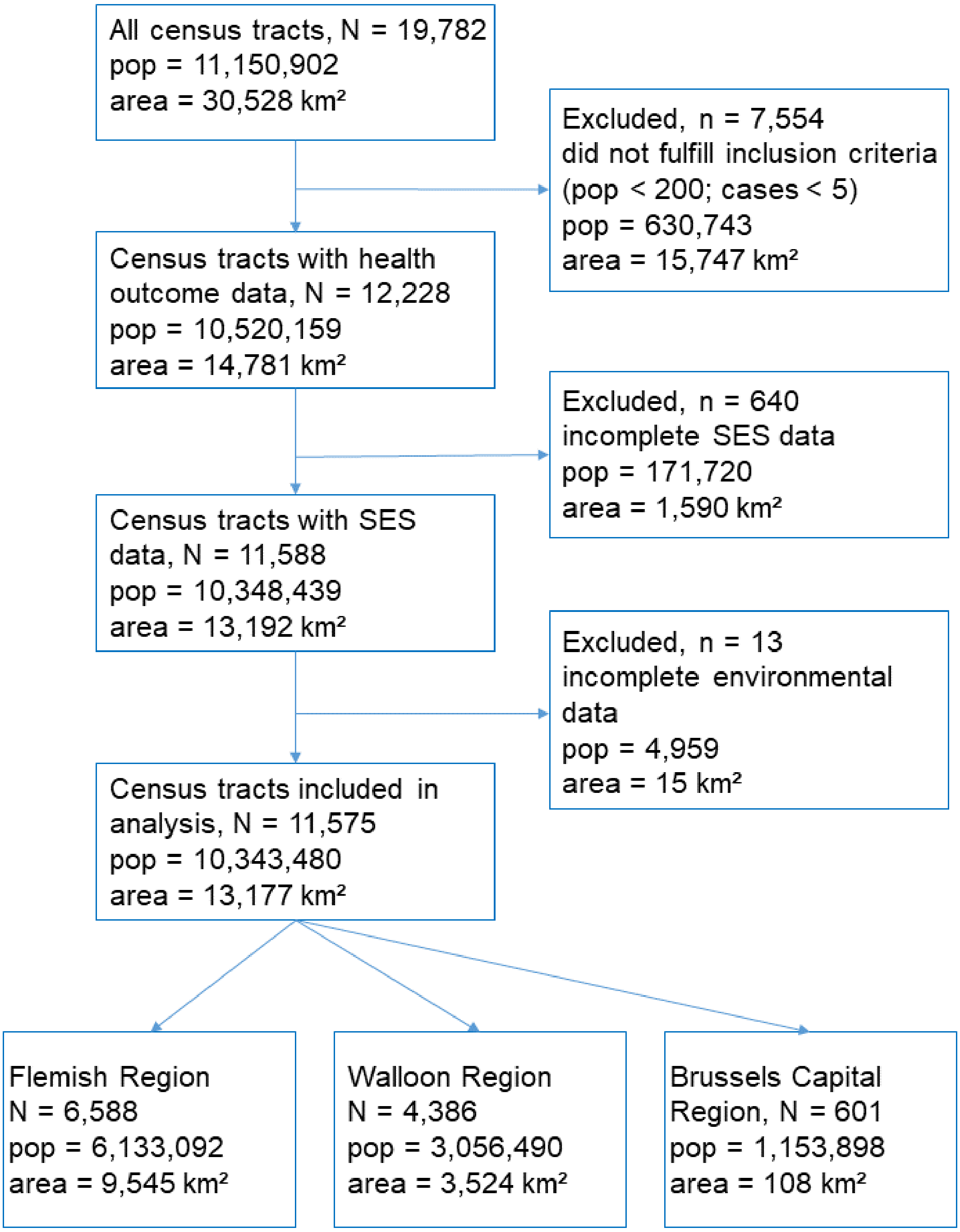

Figure 1. Flow diagram of the census tracts included and excluded in the study. Population data represents the average population in 2013–2015.

We hypothesized that there would be inverse associations between green space and both air pollution and socioeconomic deprivation; and that there would be a direct association between air pollution and socioeconomic deprivation. Green space was thus defined as exogenous (independent) latent variable and both air pollution and socioeconomic deprivation as endogenous (dependent) latent variables. We then expanded this model to a second-order factor analysis model by adding the outcome variable for general cardiovascular medication sales (ASMR) as endogenous observed variable, via regressions on the latent variables (Eq. 1).

Latent variable definitions

green space =~ forest patches + forest cover + forest cover with 600m buffer

air pollution =~ $PM_{2.5}$ (2015) + BC (2015) + NO_2 (2015)

socioeconomic deprivation =~ % unemployed + % low education + % LMIC origin

Regressions between latent variables

air pollution ~ green space

socioeconomic deprivation ~ green space

socioeconomic deprivation ~ air pollution

Regression between latent variables and dependent variable

ASMR ~ green space + air pollution + socioeconomic deprivation

(Eq. 1)

We hypothesized that there would be an inverse association between green space and cardiovascular medication sales, and that there would be direct associations between cardiovascular medication sales and both air pollution and socioeconomic deprivation (Fig. 2). We fitted a single group model for the entire dataset and performed a multiple group analysis to fit the same structural equation model on data stratified by administrative region.

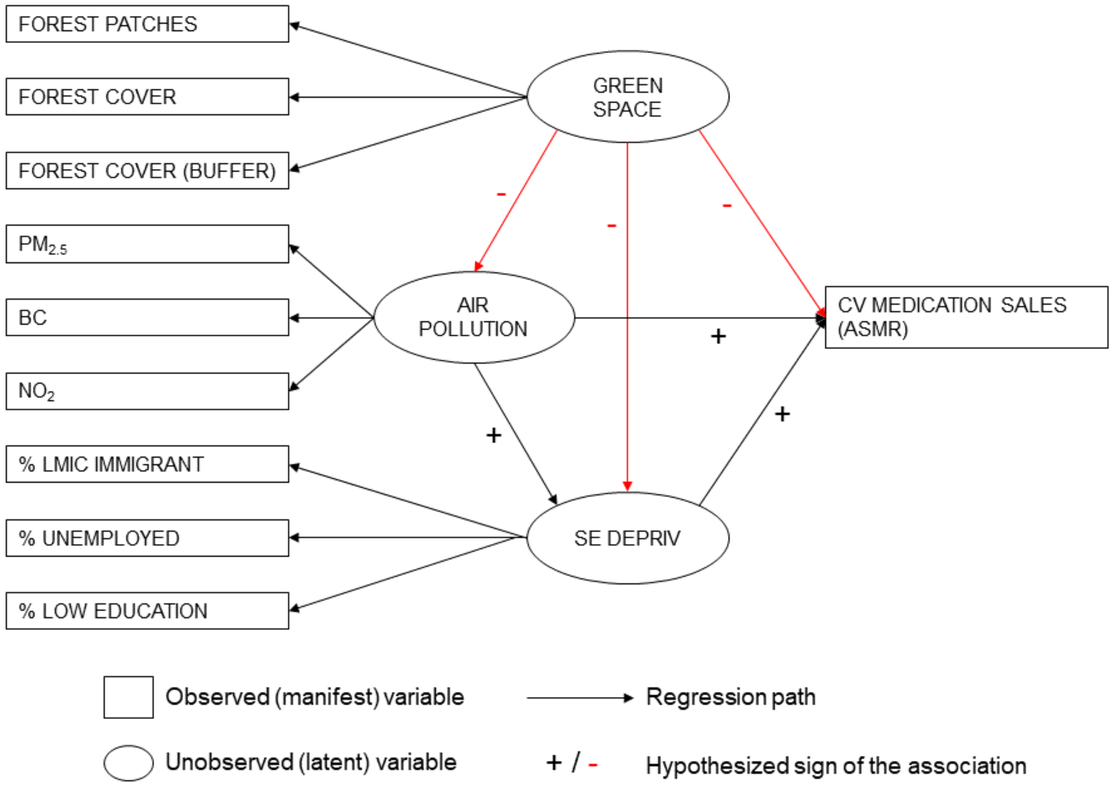

Figure 2. A-priori structural equation model with hypothesized direct and indirect effects of residential exposure to green space, air pollution and socioeconomic deprivation (SE DEPRIV) on cardiovascular (CV) medication sales (mean indirect adjusted standardized morbidity ratio for reimbursed general CV medication; ASMR). Expected positive associations are given in black and inverse associations in red. Observed variables are represented by boxes, latent variables by ovals. PM: particulate matter; BC: black carbon; LMIC: low- and mid-income countries.

The chi-square statistic (χ^2), its degrees of freedom and p value, the root mean square error of approximation (RMSEA) and its associated confidence interval, the standardized root mean square residual (SRMR) and the comparative fit index (CFI) were reported as model fit indices (Hooper et al. 2008). We calculated the difference in Akaike information criteria (ΔAIC) to compare the fit of single group and multiple group models. We report parameter estimates β, standard error (SE) and standardized estimates β'. For sensitivity analysis, we ran additional multiple group analyses: (i) using a latent variable estimated from the number of patches of total green and blue space, census tract total green and blue space cover and relative total green and blue space cover within a 600 m buffer around the census tract; (ii) using data stratified by unemployment rate (above vs. below the national median of 9.6%) and (iii) using data stratified by population density (above vs. below the national median of 1,476 inhabitants/km²). All models were fit and evaluated using the package lavaan (Rosseel 2012), implemented in the R system for statistical computing (R Development Core Team 2012).

3. Results

3.1. Population Characteristics

The characteristics of the census tracts that were included in the study are presented in Table 1. Average exposure to residential tree/forest cover was the highest in the Walloon Region and the lowest in the highly urbanized Brussels Capital Region. The average annual mean concentrations of air pollutants were the highest in the Brussels Capital Region, followed by the Flemish Region, and were the lowest in the Walloon Region. The average unemployment rate and the proportion of LMIC immigrants were the highest in the Brussels Capital Region and the lowest in the Flemish Region. With the exception of the proportion of inhabitants with primary education or lower, all included census tract characteristics differed significantly between regions (all $p < 0.001$).

3.2. Cardiovascular Medication Sales

The overall mean ASMR in Belgium was 21.0% (SE 0.04). The mean ASMR was the lowest in the Brussels Capital Region (16.2%; SE 0.16). In the Flemish Region, the mean ASMR was 19.6 %(SE 0.04); the highest mean ASMR was recorded in the Walloon Region (23.6% SE

0.06) (Fig. 3, Fig. S1). CV medication sales were statistically significantly different between the regions (all pairwise $p < 0.001$).

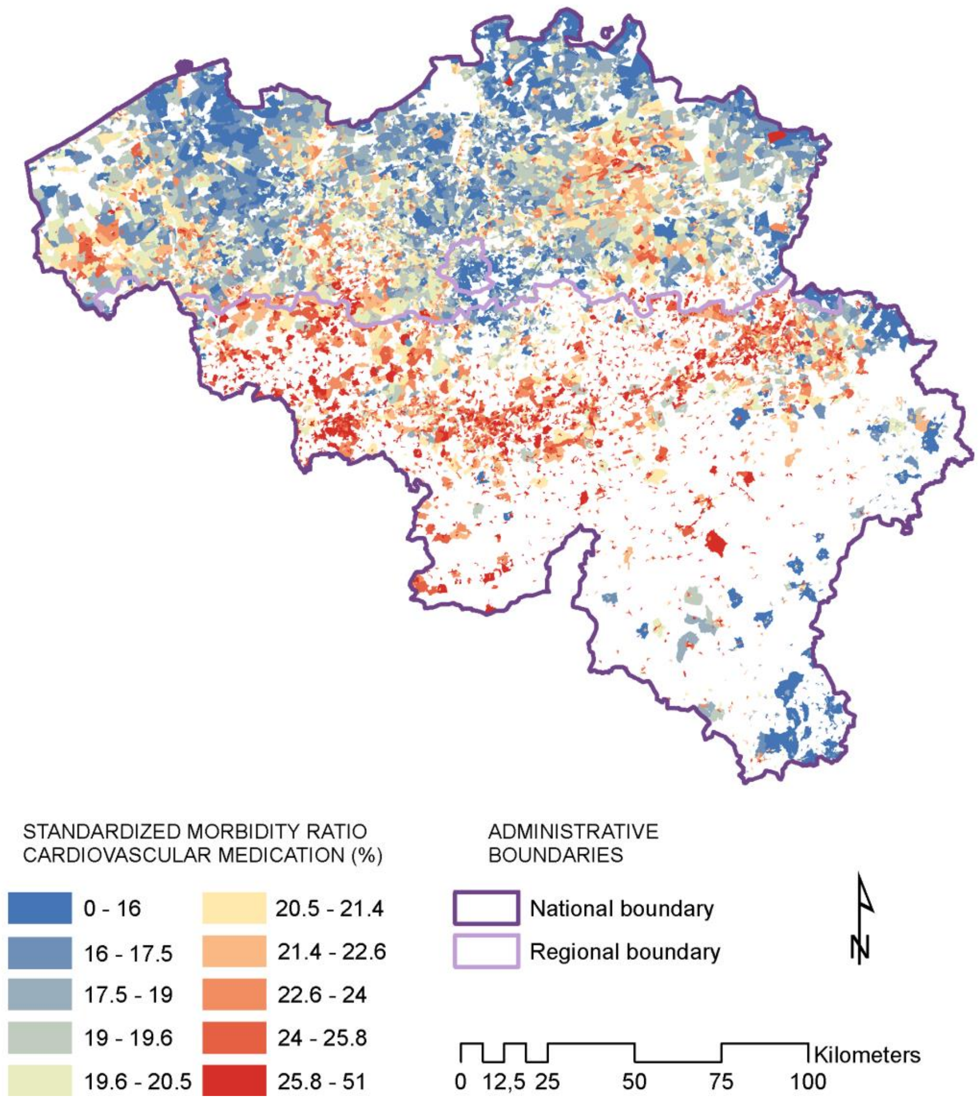

Figure 3. Mean indirect adjusted standardized morbidity ratio (ASMR) for reimbursed general cardiovascular medication in Belgium, by census tract (deciles, %). White areas are missing data (privacy restricted).

3.3. Predictors of Cardiovascular Medication Sales

3.3.1. Single group model

The single group model (Table S1, Fig. 4) provided support for the predictions of an inverse association between residential green space and CV medication sales [regression coefficient β (SE): –0.71 (0.05)] and of a direct association between socioeconomic deprivation and CV medication sales [0.27 (0.01)]. In contrast to the hypothesis, the model showed an inverse association between air pollution and CV medication sales [–1.62 (0.04)]. However, the fit indices for the single group model pointed to a poor-fitting model (Table 2), limiting the potential for a reliable interpretation of the regression coefficients of the single group model.

3.3.2. Multiple group models

The multiple group analysis improved model fit compared to the single group model (ΔAIC = –44,437) and the two-index combination of CFI (0.88; threshold > 0.95) and SRMR (0.08; threshold < 0.08) pointed to moderate model fit (Table 2). The unstandardized coefficients for the associations between latent variables (green space, air pollution and socioeconomic deprivation) and for the associations between latent variables and CV medication sales showed little variation and were similar to the coefficients of the single group model (Fig. 5A). Only the unstandardized coefficients for the association between socioeconomic deprivation and air pollution showed considerable variation among regions, with higher values for the Brussels Capital Region and the Walloon Region compared to the Flemish Region and the single group model (Fig. 5A).

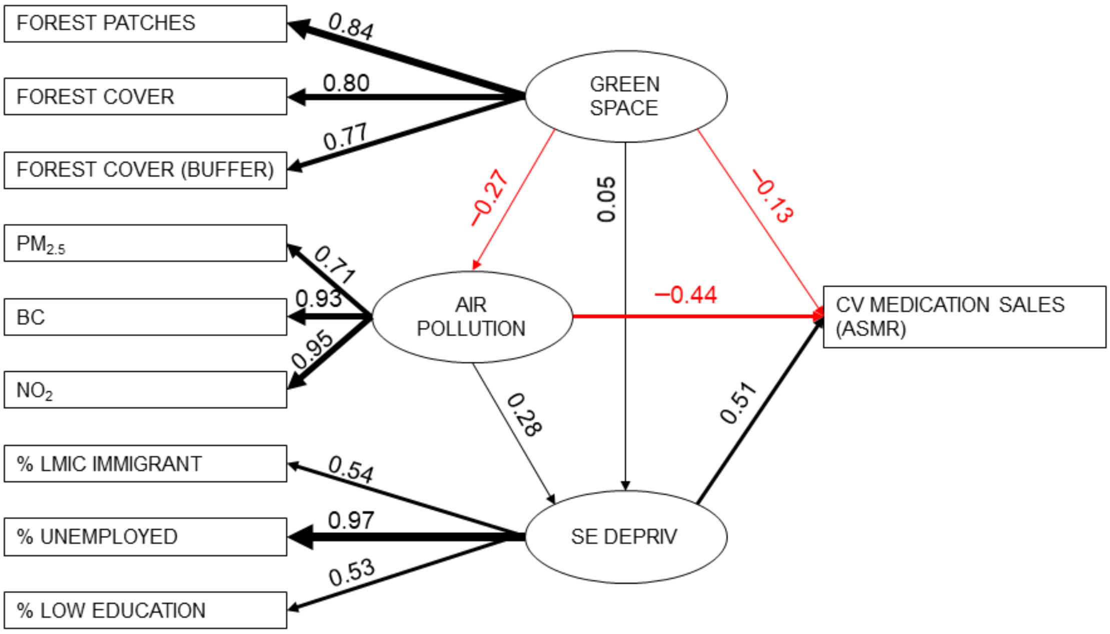

Figure 4. Structural equation model (N = 11,575 census tracts) of the associations between residential green space, air pollution, socioeconomic deprivation (SE DEPRIV) and cardiovascular (CV) medication sales in adults in Belgium between 2006 and 2014 (mean indirect adjusted standardized morbidity ratio for reimbursed general CV medication; ASMR). Black arrows represent significantly ($p < 0.001$) positive and red arrows significantly inverse associations. Paths labels and thickness of paths represent standardized regression coefficients. PM: particulate matter; BC: black carbon; LMIC: low- and mid-income countries.

The models for the Flemish Region (Fig. S2; Table S2) and the Walloon Region (Fig. S2; Table S3) provided additional support for the prediction of an inverse association between residential green space exposure and CV medication sales [Flemish Region, regression coefficient β (SE): –0.62 (0.05); Walloon Region: –0.49 (0.08)] and of a direct association between socioeconomic deprivation and CV medication sales [Flemish Region: 0.22 (0.01); Walloon Region: 0.12 (0.01)] (Fig. 5A). In the model for the Brussels Capital Region (Fig. S2; Table S4), there was a direct association between socioeconomic deprivation and CV medication sales [0.18 (0.02)] but no association between green space and CV medication sales (Fig. 5A). All three models showed an inverse association between air pollution and CV medication sales [Flemish Region: –0.88 (0.06); Walloon Region: –0.28 (0.05); Brussels Capital Region: –1.24 (0.26)] (Fig. 5A). For all but one association between latent variables and CV medication sales, the standardized regression coefficient β' was smaller in the multiple group models (for the administrative regions) than in the single group model (for Belgium) (Fig. 5B). Compared to the single group model, only the standardized coefficient of the association between green space and CV medication sales in the Flemish Region was higher (Fig. 5B).

3.3.3. Sensitivity analyses

When using a broader definition of green space [sensitivity analysis (i)], there was more evidence for an inverse association between green space and CV medication sales in the Flemish Region (β' –0.22 compared to –0.16), whereas in the Walloon and Brussels Capital Regions this association became weakly positive (Walloon Region β' 0.05 vs. –0.10; Brussels Capital Region β' 0.12 vs. –0.03).

In a subset of census tracts with a high proportion of unemployed inhabitants [sensitivity analysis (ii)], the direct association of socioeconomic deprivation on CV medication sales disappeared in the model for the Flemish Region (β' –0.011, P = 0.705), but the inverse association between green space and CV medication sales remained (Fig. S3). The regression coefficients of the models for the Walloon Region and Brussels Capital Region remained comparable (data not shown).

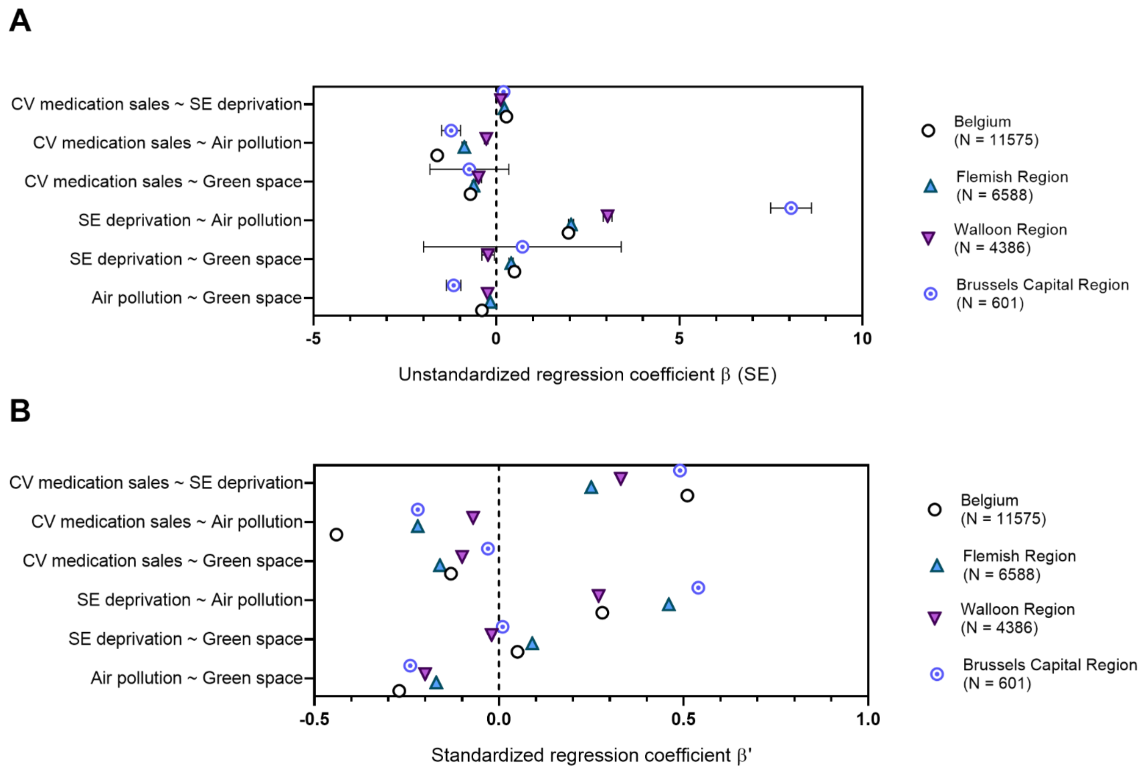

Figure 5. Associations between residential green space, air pollution, socioeconomic deprivation and cardiovascular (CV) medication sales in adults in Belgium between 2006 and 2014 (mean indirect adjusted standardized morbidity ratio for reimbursed general CV medication; ASMR) from a structural equation model for Belgium and from a multiple group structural equation model for the administrative regions: A. unstandardized regression coefficient estimates β (with standard error SE), B. standardized regression coefficient estimates β'.

In subsets of census tracts with high population density [sensitivity analysis (iii)] the inverse association between air pollution and CV medication sales became stronger in the Flemish Region (β' –0.32 vs. –0.22) indicating that observed associations with air pollution might be attributed primarily to urbanization. The inverse association between green space and CV medication sales disappeared in the Walloon Region (β' 0.010, P = 0.658). The sensitivity analysis models did not converge for the subsets of tracts with low unemployment and with low population density.

4. Discussion

4.1. Main Findings

This study investigated cardiovascular medication sales in Belgium by assessing associations between aggregated data of reimbursed cardiovascular medication sales and data on green space, air pollution and socioeconomic deprivation. This study found support for an inverse association between green space and CV medication sales, but socioeconomic deprivation was always the strongest predictor of CV medication sales. Inverse associations between air pollution and medication sales that remained after stratification by administrative region suggest that certain unmeasured differences between urban areas (with high air pollution) and rural areas (with lower air pollution) such as lifestyle, affluence or prescription patterns may influence health and medication sales.

4.2. Comparison with Other Studies

4.2.1. Green space

The evidence provided by this ecological study is consistent with the evidence for the beneficial effects of living in or near green environments on cardiovascular health presented in earlier ecological studies (e.g. Hu et al. 2008; Richardson and Mitchell 2010; Kardan et al. 2015; Jennings et al. 2019) and systematic reviews (e.g. Gascon et al. 2016; Nieuwenhuijsen 2018). Forests and trees in urban environments may have impacts on cardiovascular health through their impacts on air pollution, noise and heat, on physical activity, on immune system regulation and on stress and mental health (Shen and Lung 2016; de Keijzer et al. 2019; Rojas-Rueda et al. 2019; Turner-Skoff and Cavender 2019). The inverse (protective) association between green space and CV medication sales was stronger in the highly urbanized Flemish Region than in the much greener Walloon Region. Although counterintuitive, these results suggest that effects of green space on CV health may be stronger when green space is limited. In an ecological study of the association between green space and cause-specific mortality (mortality from CVD and lung cancer) in New Zealand, green space did not influence CVD mortality, potentially because green space is very abundant and evenly distributed in this country (Richardson et al. 2010). Saturation effects and even declines in health effects with increasing exposure to green space have been proposed in hypothetical nature dose-health response relationships (Shanahan et al. 2015). Shanahan et al. (2015) note that saturation effects may be particularly the case when considering the quantity of green and that increasing green space "may have no additional effect once a particular threshold point is reached". Bergmann and Sypniewska (2011) even suggest that increasing tree cover may eventually increase mortality from cardiovascular disease if critical thresholds of allergenic pollen loads are exceeded. Other studies suggest that not the overall amount of greenness (indicated by NDVI) but the variability of the land use mix (indicated by SD of NDVI) may better explain the health impact of neighborhood green space by affecting, for instance, neighborhood attractiveness and walkability (Pereira et al. 2012; Nieuwenhuijsen 2018). Thus, dose-response relationships and differences in attractiveness and green space use may partially explain why the inverse association between green space and CV medication sales is stronger in the Flemish Region, where inhabitants generally experience a lower nature dose than those living in the Walloon Region. The absence of a significant association between green space and CV medication sales in the Brussels Capital Region suggests that there is also a minimum threshold – if exposure to green space is very low, no effects of green space on health may be observed. However, the absence of a statistical effect in the Brussels Capital Region could also be the result of a lack of power (smaller sample size) or because the green space indicator used in this study may have inadequately captured the numerous but small green spaces that are present in this region.

4.2.2. Air pollution

The present study showed consistent inverse associations between residential green space and air pollution. This is in line with the regional differences in population, air pollution and green space in Belgium. The population density and the annual mean concentrations of air pollutants, in particular PM, generally decrease in Belgium from north(west) to south(east) whereas forest cover and thus green space exposure increase along the same gradient (IRCEL-CELINE 2015) (Maps S1-S4). At a smaller scale, it has been shown that greenness is often associated with lower levels of traffic-related air pollutants (Dadvand et al. 2015). Our results therefore support the notion that areas with numerous trees generally have superior air quality (Franchini and Mannucci 2018; Nowak and Van den Bosch 2019). However, our study also showed unexpected inverse associations between air pollution and the prevalence of cardiovascular medicine sales. There is overwhelming evidence of the detrimental effects of air pollution on human health. In their landmark "652 Cities" paper, Liu et al. (2019) used daily data on mortality and air pollution from 652 cities in 24 countries and demonstrated that an increase of 10 $\mu g/m^3$ in 2-day average PM_{10} concentration was associated with 0.36–0.47% increases in daily all-cause, cardiovascular and respiratory mortality. For $PM_{2.5}$ a similar increase was associated with 0.55–0.74% increases in mortality. Long-term exposure to ultra-fine particles (particles <100 nm) has also been linked to CVD (Downward et al. 2018). The observed inverse association between air pollution and CV medication sales may therefore be the result of ecological bias or residual confounding by an unmeasured variable, resulting in lower CVD medication sales in areas with a higher burden of air pollution, i.e. the Brussels Capital Region and the Flemish Region.

4.2.3. Socioeconomic deprivation

In all models, socioeconomic deprivation was the strongest predictor for CV medication sales (Fig. 5). There was an inverse association between green space and the prevalence of CV medication sales in the Flemish Region in the group of census tracts characterized by above-average unemployment rates (Fig. S3), but no such association and even no useful model solution was found in the group of census tracts characterized by low unemployment rates. These results are consistent with earlier studies that have shown that socioeconomic confounders such as socioeconomic deprivation may have a higher impact on (cardiovascular) health than exposure to urban green space (Kabisch 2019). Investing in green spaces, e.g. the greening of vacant lots and the improvement of urban green infrastructure (van den Bosch and Sang 2017; Hunter et al. 2019), may generate important environmental, public health and wellbeing benefits. It is important to realize that such potential health benefits are not necessarily uniform for all population subgroups. An ecological study in the UK found a protective association between the proportion of green space in urban wards and CVD and respiratory disease mortality in males but not in females (Richardson and Mitchell 2010). Our results suggest that green space interventions could be most effective in areas with lower socioeconomic status and where green space is lacking, but it is likely that all population groups are expected to benefit from more green (Vienneau et al. 2017; Kabisch 2019).

4.3. Strengths and Limitations

This study examined the effect of residential green space on general cardiovascular health (by means of CV medication sales as a proxy) while specifically accounting for potential interaction with socioeconomic background variables and simultaneous exposure to air pollution. However, this study has a number of limitations.

The ecological study design is prone to bias and ecological data is prone to ecological fallacy. Health effects of green space observed at individual or small area level may not be observed at aggregated levels (Richardson et al. 2012; Bixby et al. 2015). Also, different groups may have different background risks or different groups may have unequal risk differences (Webster 2007). Older adults, socioeconomically deprived persons and people with chronic conditions belong to vulnerable subpopulations in which such background risks, risk differences or both are usually higher than in the general population. To minimize magnification of bias in ecological studies, within-group exposure should be as homogeneous as possible. We believe that we have achieved this by using census tracts as the level of aggregation.

Medication sales differ from the real prevalence of CVD. Some diagnosed CVD patients may choose not to buy the prescribed medication and are therefore not recorded in the IMA-AIM database. Other CVD patients may not seek or have access to cardiovascular care. Also there is no indication of other medication that may have been used at the same time and no conclusions on multimorbidity can be made [e.g. comorbidity of CVD and diabetes (Kovacic et al. 2014)].

Residential green space was quantified by means of land cover data derived from the CORINE Land Cover database. CORINE source images acquired by the SPOT satellite have a 10 m resolution and those acquired by the (older) LANDSAT satellites have a 80 m resolution. However, the minimal mapping unit in the CORINE Land Cover dataset is 25 ha (~500 m × 500 m). Smaller patches of green, such as small isolated forests, urban parks or generally urban green are generalized in a mixed CORINE Land Cover class. Therefore, exposure to green, and its association with CV health, is most likely underestimated in the built environment in the present study. While high-resolution (1 m × 1 m) green space data is available for the Flemish Region, no such data was available for the entire territory of Belgium during the course of this study.

Residential exposure may differ from true exposure because it ignores time-activity patterns (work, school hours, transport, leisure time…) which have an impact on daily exposure (Dons et al. 2011; Setton et al. 2011; Lane et al. 2015). Also, physical activity may attenuate the negative effects of environmental exposures (e.g. to PM and NO_2) on CV health (Vivanco-

Hidalgo et al. 2019). Individual exposures and individual protective or risk factors, however, cannot be taken into account in an ecological study.

The CV medication sales data is from the period 2006–2014, whereas the exposure data is from different years (SE deprivation: 2001; land cover: 2006; air pollution: 2015). Air quality in Belgium has improved between 2006 and 2015 and the exposure to air pollution in 2006–2014 may thus be underestimated by using air pollution data from 2015. However, the spatial patterns of air pollution have not changed and areas with poor air quality in 2006–2014 still exhibited poor air quality in 2015 compared to other areas. the bias in exposure to forest cover caused by timing mismatch is expected to be minimal: between 2005 and 2015 the country lost 1266 ha forest, which corresponds to only 0.04% of the land surface. We acknowledge the fact that timing mismatch could have caused additional bias, but at the time of analysis, this was the best possible match based on the availability of nationwide datasets.

The fit indices (χ^2, RMSEA, SRMR and CFI) pointed to weak-fitting models, in particular in the single group model. However, the model χ^2 statistic is sensitive to sample size and almost always rejects models with large sample sizes (Hooper et al. 2008), as is the case in the present study. Also, the thresholds for the other fit indices are only ‘rules of thumb’ and the strict rejection of models based on these thresholds increases the probability for incorrect rejection of acceptable models (Hooper et al. 2008).

4.4. Key Findings and Implications

Living in or near green areas was associated with lower cardiovascular medication sales, also when taking into account differences in air quality and socioeconomic status. Green space interventions should consider socioeconomic background variables.

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Competing Financial Interests

The authors declare they have no actual or potential competing financial interests.

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Data statement

The research data is confidential.

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Table 1. Characteristics of the census tracts included in the study.

	Belgium	Flemish Region	Walloon Region	Brussels Capital Region
N (tracts)	11,575	6,588	4,386	601
N (10^6 inhabitants)	10.34	6.13	3.06	1.15
Area (km²)	13,177	9,545	3,524	108
Green space (2006 mean and standard error)				
Forest patches	0.3 (0.01)	0.4 (0.01) [b]	0.4 (0.01) [c]	0.02 (0.01) [a]
Forest cover (%)	2.1 (0.07)	2.3 (0.09) [b]	2.7 (0.13) [c]	0.3 (0.11) [a]
Forest cover including 600m buffer (%)	5.4 (0.09)	4.1 (0.10) [b]	7.8 (0.18) [c]	1.3 (0.23) [a]
Air pollution (2015 annual mean and standard error)				
$PM_{2.5}$ (µg/m³)	11.3 (0.01)	12.0 (0.01) [b]	10.1 (0.02) [a]	13.4 (0.03) [c]
BC (µg/m³)	1.0 (0.01)	1.0 (0.01) [b]	0.9 (0.01) [a]	1.6 (0.02) [c]
NO_2 (µg/m³)	17.0 (0.06)	17.0 (0.07) [b]	15.3 (0.08) [a]	29.5 (0.18) [c]
Socioeconomic deprivation (2001)				
% LMIC	3.3 (0.05)	2.1 (0.04) [a]	3.3 (0.05) [b]	16.3 (0.40) [c]
% Low education	14.7 (0.06)	14.5 (0.08)	14.8 (0.11)	16.5 (0.46)
% Unemployed	12.2 (0.08)	8.0 (0.05) [a]	17.4 (0.13) [b]	19.7 (0.42) [c]
General cardiovascular medication sales (reimbursed medication sales, 2006–2014)				
ASMR (%)	21.0 (0.04)	19.6 (0.04) [b]	23.8 (0.06) [c]	16.2 (0.16) [a]

[a,b,c] Different superscript letters indicate significant pairwise differences between regions (Wilcoxon test, $p < 0.001$)

Table 2. Fit indices and acceptable thresholds for the single group and multiple group structural equation models with direct and indirect effects of residential exposure to green space, air pollution and socioeconomic deprivation on cardiovascular medication sales in Belgium.

			Multiple group model	
Fit Index	Threshold	Single group model	Green space = tree/forest	Green space = all green/blue
Absolute fit				
χ^2		13310	7559	11370
df		30	90	90
p	$p > 0.05$	< 0.001	< 0.001	< 0.001
RMSEA	< 0.08	0.20	0.15	0.18
(95% CI)		(0.193–0.198)	(0.144–0.149)	(0.177-0.183)
SRMR	< 0.08	0.12	0.08	0.09
CFI	> 0.90	0.80	0.88	0.84

RMSEA: root mean square error of approximation; SRMR: standardized root mean square residual; CFI: comparative fit index

Table S1. Single-group structural equation model (N = 11,575 census tracts) of the associations between residential green space, air pollution, socioeconomic deprivation and cardiovascular (CV) medication sales in adults in Belgium between 2006 and 2014.

Latent variables	Estimate β	SE	p	Std. Est. β’
Green space =~				
Forest patches	1			0.84
Forest cover	8.16	0.10	< 0.001	0.80
Forest cover (600m buffer)	10.32	0.12	< 0.001	0.77
Air pollution =~				
$PM_{2.5}$	1			0.71
BC	0.25	0.003	< 0.001	0.93
NO_2	5.13	0.05	< 0.001	0.95
Socioeconomic deprivation (SES) =~				
% unemployed	1			0.97
% lower education	0.46	0.009	< 0.001	0.53
% LMIC immigrant	0.34	0.007	< 0.001	0.54
Regressions among latent variables				
Air pollution ~ green space	–0.40	0.02	< 0.001	–0.27
SES ~green space	0.49	0.11	< 0.001	0.05
SES ~ air pollution	1.97	0.07	< 0.001	0.28
Regressions with outcome variable				
CV medication sales ~				
Green space	–0.71	0.05	< 0.001	–0.13
Air pollution	–1.62	0.04	< 0.001	–0.44
Socioeconomic deprivation	0.27	0.006	< 0.001	0.51

Table S2. Multiple group structural equation model of the associations between residential green space, air pollution, socioeconomic deprivation and cardiovascular (CV) medication sales in adults between 2006 and 2014: Flemish Region (N = 6,588).

Latent variables	Estimate β	SE	p	Std. Est. β’
Green space =~				
Forest patches	1			0.83
Forest cover	8.09	0.12	< 0.001	0.83
Forest cover (600m buffer)	8.75	0.13	< 0.001	0.81
Air pollution =~				
$PM_{2.5}$	1			0.70
BC	0.31	0.004	< 0.001	0.95
NO_2	6.62	0.09	< 0.001	0.93
Socioeconomic deprivation (SES) =~				
% unemployed	1			0.86
% lower education	0.78	0.03	< 0.001	0.43
% LMIC immigrant	0.74	0.02	< 0.001	0.76
Regressions among latent variables				
Air pollution ~ green space	–0.17	0.01	< 0.001	–0.17
SES ~green space	0.40	0.06	< 0.001	0.09
SES ~ air pollution	2.04	0.07	< 0.001	0.46
Regressions with outcome variable				
CV medication sales ~				
Green space	–0.62	0.05	< 0.001	–0.16
Air pollution	–0.88	0.06	< 0.001	–0.22
Socioeconomic deprivation	0.22	0.01	< 0.001	0.25

Table S3. Multiple group structural equation model of the associations between residential green space, air pollution, socioeconomic deprivation and cardiovascular (CV) medication sales in adults between 2006 and 2014: Walloon Region (N = 4,386).

Latent variables	Estimate β	SE	p	Std. Est. β'
Green space =~				
Forest patches	1			0.87
Forest cover	8.24	0.16	< 0.001	0.77
Forest cover (600m buffer)	12.05	0.24	< 0.001	0.77
Air pollution =~				
$PM_{2.5}$	1			0.70
BC	0.18	0.003	< 0.001	0.78
NO_2	5.76	0.005	< 0.001	1.09
Socioeconomic deprivation (SES) =~				
% unemployed	1			1.20
% lower education	0.37	0.01	< 0.001	0.57
% LMIC immigrant	0.11	0.005	< 0.001	0.34
Regressions among latent variables				
Air pollution ~ green space	–0.24	0.02	< 0.001	–0.20
SES ~green space	–0.23	0.17	0.175	–0.02
SES ~ air pollution	3.04	0.12	< 0.001	0.27
Regressions with outcome variable				
CV medication sales ~				
Green space	–0.49	0.08	< 0.001	–0.10
Air pollution	–0.28	0.05	< 0.001	–0.07
Socioeconomic deprivation	0.12	0.006	< 0.001	0.33

Table S4. Multiple group structural equation model of the associations between residential green space, air pollution, socioeconomic deprivation and cardiovascular (CV) medication sales in adults between 2006 and 2014: Brussels Capital Region (N = 601).

Latent variables	Estimate β	SE	p	Std. Est. β’
Green space =~				
Forest patches	1			0.99
Forest cover	15.8	0.80	< 0.001	0.82
Forest cover (600m buffer)	22.72	1.68	< 0.001	0.56
Air pollution =~				
$PM_{2.5}$	1			0.94
BC	0.57	0.01	< 0.001	0.98
NO_2	6.39	0.12	< 0.001	0.97
Socioeconomic deprivation (SES) =~				
% unemployed	1			0.98
% lower education	1.04	0.02	< 0.001	0.93
% LMIC immigrant	0.81	0.02	< 0.001	0.83
Regressions among latent variables				
Air pollution ~ green space	–1.17	0.20	< 0.001	–0.24
SES ~green space	0.71	2.70	0.793	0.01
SES ~ air pollution	8.05	0.56	< 0.001	0.54
Regression with outcome variable				
CV medication sales ~				
Green space	–0.74	1.08	0.496	–0.03
Air pollution	–1.24	0.26	< 0.001	–0.22
Socioeconomic deprivation	0.19	0.02	< 0.001	0.49

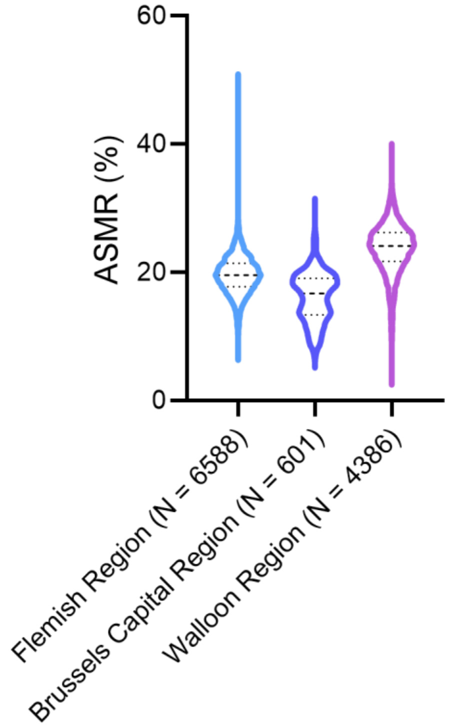
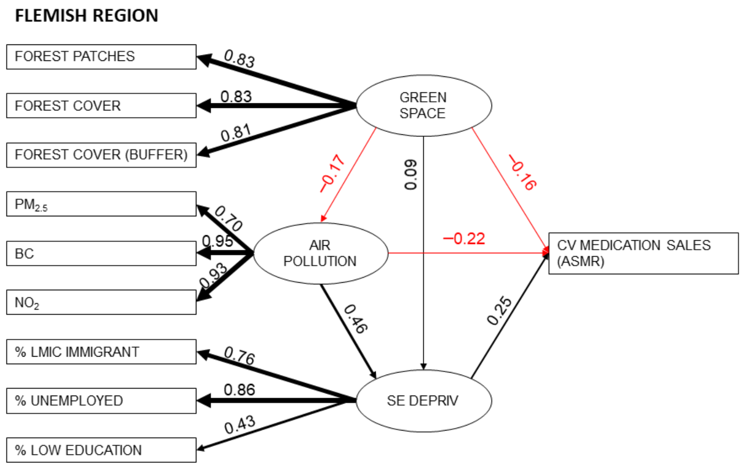
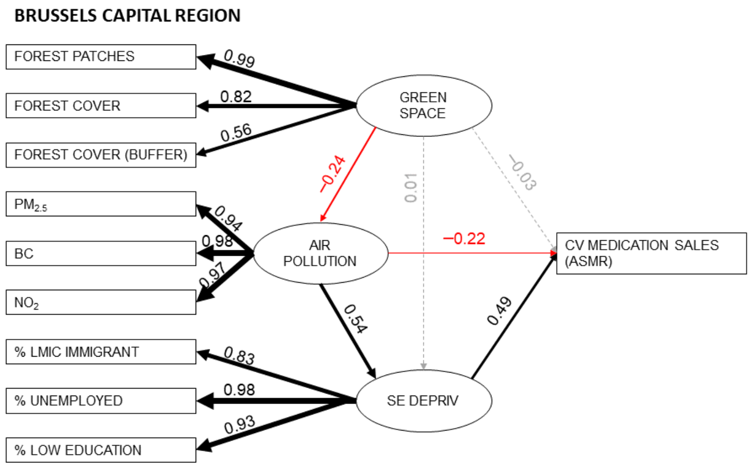


Figure S1. Mean indirect adjusted standardized morbidity ratio for reimbursed general cardiovascular medication (ASMR, % of the registered patients per census tract that received reimbursed general cardiovascular medication) observed in the three administrative regions of Belgium (2006-2014).





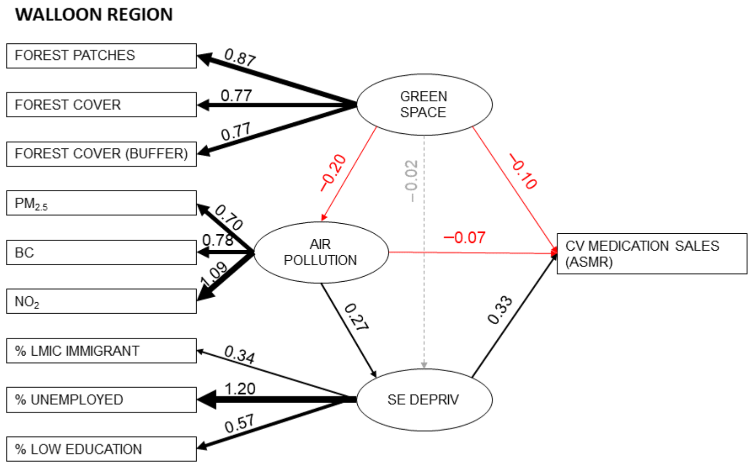
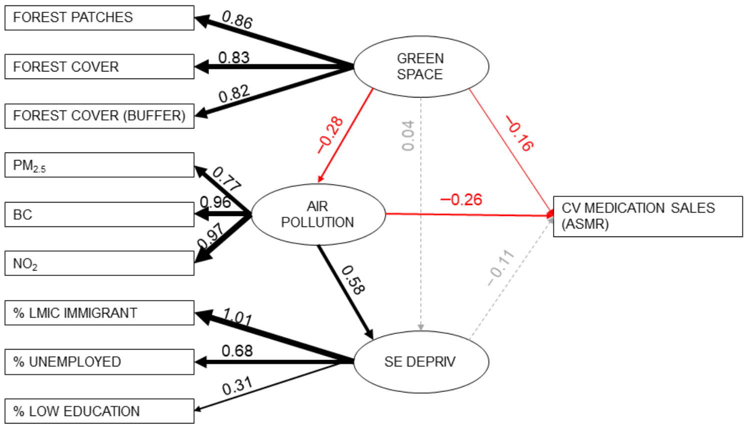
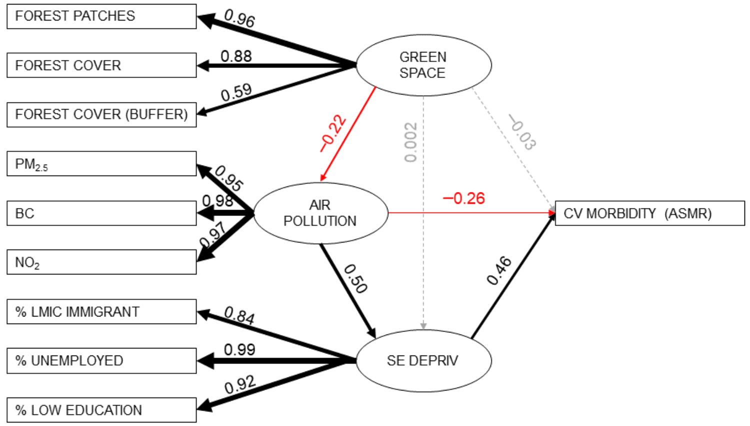


Figure S2. Multiple group structural equation model of the associations within administrative regions between residential green space, air pollution, socioeconomic deprivation (SE DEPRIV) and cardiovascular (CV) medication sales in adults in Belgium between 2006 and 2014 (mean indirect adjusted standardized morbidity ratio for reimbursed general CV medication; ASMR). Black arrows represent significantly ($p < 0.001$) positive, red arrows significantly inverse, and grey arrows not significant ($p > 0.05$) associations. Paths labels and thickness of paths represent standardized regression coefficients. PM: particulate matter; BC: black carbon; LMIC: low- and mid-income countries.

FLEMISH REGION (UNEMPLOYMENT > 9.6% [BE P50])



BRUSSELS CAPITAL REGION (UNEMPLOYMENT > 9.6% [BE P50])



WALLOON REGION (UNEMPLOYMENT > 9.6% [BE P50])

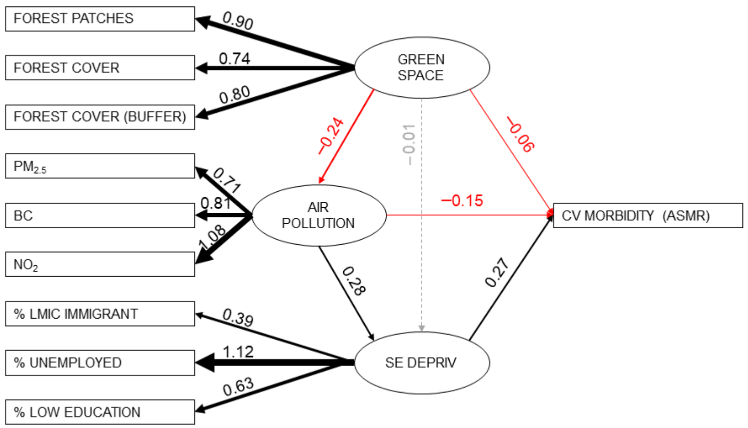
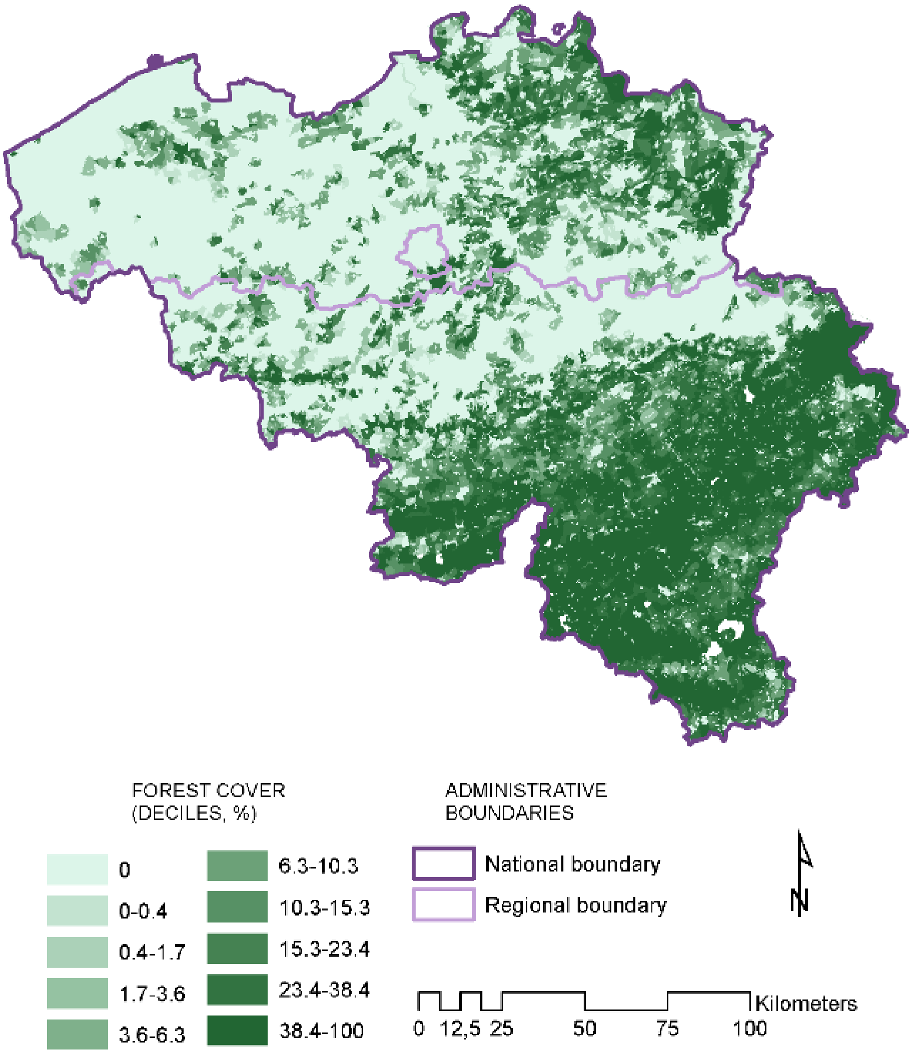
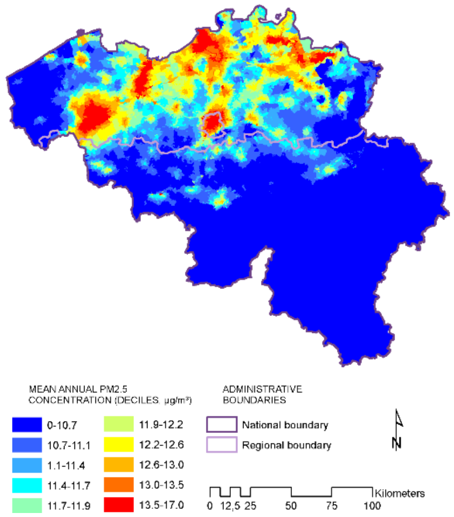


Figure S3. Multiple group structural equation model of the associations within administrative regions between residential green space, air pollution, socioeconomic deprivation (SE DEPRIV) and cardiovascular (CV) medication sales in adults in Belgium between 2006 and 2014 (mean indirect adjusted standardized morbidity ratio for reimbursed general CV medication; ASMR) in census tracts with high unemployment rates (above the national median rate of 9.6%). Black arrows represent significantly ($p < 0.001$) positive, red arrows significantly inverse, and grey arrows not significant ($p > 0.05$) associations. Paths labels and thickness of paths represent standardized regression coefficients. PM: particulate matter; BC: black carbon; LMIC: low- and mid-income countries.

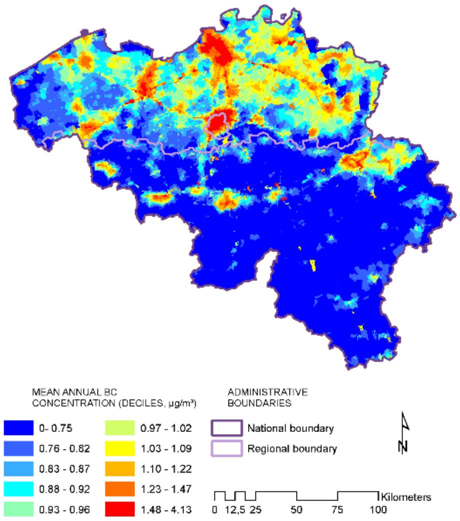


Map S1. Forest cover in Belgium, by census tract (deciles, %).

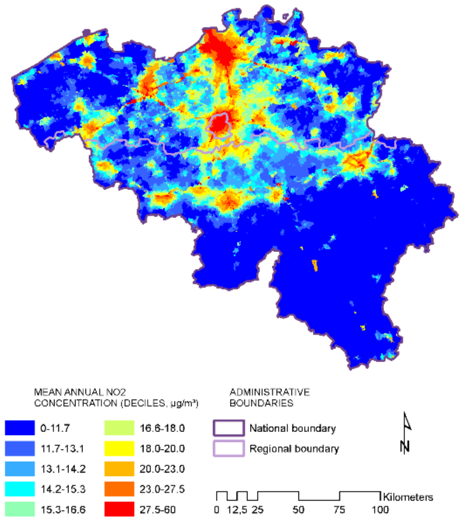
S2



S3

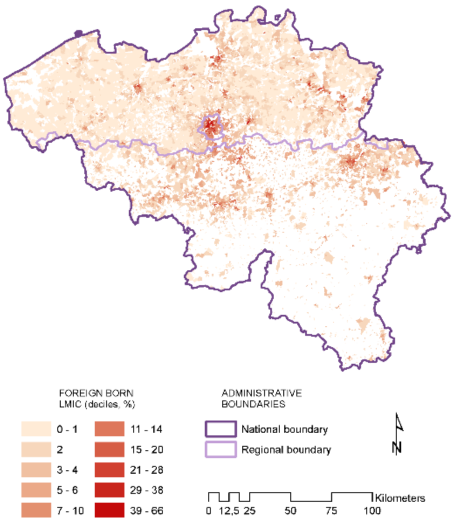


S4

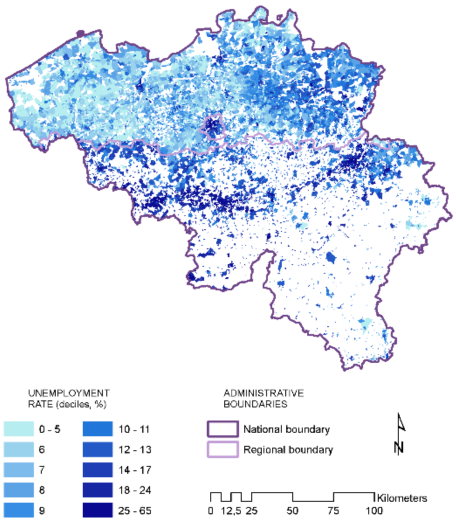


Maps S2-S4. Air pollution indicators in Belgium, by census tract: mean annual concentrations of $PM_{2.5}$, black carbon (BC) and NO_2 (deciles, µg/m³).

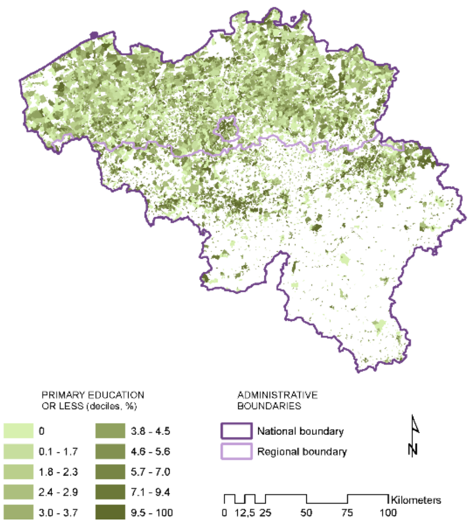
S5



S6



S7



Maps S5-S7. Social deprivation indicators in Belgium, by census tract: proportion of inhabitants foreign born from low- and mid-income countries (LMIC) (%), unemployment rate (%) and proportion of inhabitants primary educated or less (%). White areas are missing data (privacy restricted).

CRediT author statement

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