**Long-term exposure to residential green spaces and site-specific cancer mortality in urban Belgium: a 13-year follow-up cohort study**

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**Abstract**

**Background:** Residing in greener areas may decrease the burden of chronic diseases, but the association with cancer is unclear. We studied the associations between residential green spaces and site-specific cancer mortality in urban Belgium.

**Methodology:** We linked the 2001 Belgian census, register mortality data for 2001-2014, and environmental information (green spaces and air pollution) at baseline residence (2001). We included residents from the largest Belgian urban areas aged ≥30 years at baseline. Exposure to residential green spaces was assessed using the Normalized Difference Vegetation Index (NDVI), Urban Atlas, and perceived neighbourhood greenness (from the census). We used Cox proportional hazards models to obtain hazard ratios (HR) and their 95% confidence intervals (95%CI) of the mortality risk from lung, colorectal, breast (in women) and prostate cancer (in men) per interquartile range increment in residential green spaces. We further analyzed the role of outdoor air pollution and effect modification by age and socioeconomic position (SEP) in main associations.

**Results:** 2,441,566 individuals were included at baseline. During follow-up, 1.2% died from lung cancer, 0.6% from colorectal cancer, 0.8% from breast cancer, and 0.6% from prostate cancer. After adjustment, higher exposure to green spaces was associated with a reduced mortality risk from lung cancer and breast cancer [e.g., for NDVI within 300 m, HR:0.946 (95%CI:0.924,0.970), and HR:0.927 (95%CI:0.892,0.963), respectively], but not with colorectal or prostate cancer mortality. For the latter, a suggestive hazardous effect of green spaces was found. Air pollution seemed to have only a marginal role. Beneficial effects of greenspace were generally stronger in <65-year-old, but no clear trend by SEP was found.

**Conclusions:** Our findings suggest that residing in green areas could decrease mortality risk from lung and breast cancer, potentially independent from air pollution. Future studies should consider different indicators of greenspace exposure and investigate potential pathways underlying the associations.

**Keywords:** Cancer mortality; Green spaces; Built environment; Perception; Air pollution; Social factors.

1. **Introduction**

Cancer is the second leading cause of death worldwide, only preceded by cardiovascular diseases (Ferlay et al., 2021). In Belgium, cancer burden accounted for almost one third (26.4%) of total mortality in 2016 (Statistics Belgium (Statbel), 2019). Within Europe, Belgium stands among the countries with the highest cancer risks, presenting the fourth highest all-cancer incidence in 2020 (European Cancer Information System (ECIS), 2020).

More than 98% Belgians resided in urban areas in 2020 (United Nations, 2018), where exposure to environmental hazards, reduced physical activity, and limited access to nature presumably increase the burden of non-communicable diseases, including cancer (World Health Organization, 2022). Exposure to certain environmental characteristics, such as green spaces, could help counterbalance some of the negative effects of urban living (van Den Bosch and Ode Sang, 2017). First, green spaces could mitigate urban environmental hazards, including air pollution (Markevych et al., 2017). Air pollution is a recognized carcinogen (International Agency for Research on Cancer (IARC), 2013) associated with several cancer outcomes, especially lung cancer (Turner et al., 2020). Second, green spaces could promote physical activity, associated with decreased cancer risk (Brenner et al., 2016; Schmid and Leitzmann, 2014). Third, green spaces could enhance social cohesion (Maas et al., 2009), which may influence cancer survival (Rosskamp et al., 2021). Finally, spending time in natural environments could reduce stress (Gascon et al., 2015), potentially improving cancer prognosis (Pinquart and Duberstein, 2010).

Studies focusing on the effect of green spaces on cancer mortality are scarce. Most studies were cross-sectional and focused on lung cancer mortality, for which a meta-analysis found no association (Gascon et al., 2016). Two recent individual longitudinal studies showed contradictory findings in the associations with lung cancer mortality (Klompmaker et al., 2021, 2020). In contrast, one longitudinal study observed a strong reduction in all-cancer mortality risk with increased exposure to green spaces in a cohort of female nurses (James et al., 2016).

The effect of green spaces on health could be influenced by sociodemographic and socioeconomic characteristics, since they likely determine the exposure and susceptibility of individuals to the environment (Science for Environment Policy, 2016). Moreover, cancer risk is known to follow a social gradient across the population (Hagedoorn et al., 2018; Rosskamp et al., 2021). Nevertheless, the evidence on effect modification by social factors in the association between green spaces and cancer mortality is limited (James et al., 2016).

Finally, despite air pollution being carcinogenic (IARC, 2013), only two case-control studies evaluated the role of air pollution mitigation in the associations between green spaces and cancer, and findings were inconclusive (Demoury et al., 2017; O’Callaghan-Gordo et al., 2018).

We previously reported beneficial associations between green spaces and all-cause, cardiometabolic, and respiratory mortality in the five largest Belgian urban areas (Bauwelinck et al., 2021; Rodriguez-Loureiro et al., 2022). In this study we aimed to examine the associations between exposure to green spaces and site-specific cancer mortality in adults residing in urban areas in Belgium. We also explored the role of air pollution and effect modification by sociodemographic and socioeconomic indicators in these associations.

1. **Methodology**
	1. **Data design and study population**

Our dataset consisted of an individual linkage between the 2001 Belgian census and register data on emigration and mortality during a follow-up period from the 1st of October 2001 until the 31st of December 2014. The 2001 Belgian census was administered to the total population officially residing in Belgium in 2001 and contains detailed information on sociodemographic and socioeconomic characteristics at baseline. This dataset was additionally linked to information on environmental indicators (i.e., green spaces and air pollution) using the residential address of every individual in the census. Our study population included the non-institutionalized population aged 30 years or older and residing in one of the five largest urban areas in Belgium (Antwerp, Ghent, Brussels, Charleroi, and Liège). These areas comprise more than 250,000 inhabitants each and include the city and its commuting zone (Luyten and Van Hecke, 2007).

* 1. **Site-specific cancer mortality**

Mortality data provided information on the original cause of death issued in the death certificates. The cause of death is coded using the 10th revision of the International Classification of Diseases (ICD-10) (World Health Organization (WHO), 2016). We considered deaths from lung cancer (ICD-10 code: C34) and colorectal cancer (ICD-10 codes: C18-C22) in the total study population; breast cancer (ICD-10 code: C50) in women; and prostate cancer (ICD-10 code: C61) in men. These are the most prevalent cancers in Belgium (Belgian Cancer Registry, 2020) and are potentially influenced by the built environment at different stages of the cancer continuum (e.g., prevention, incidence/risk, or survival) (Gomez et al., 2015).

* 1. **Residential green spaces**

To assess exposure to green spaces in the residence, we used two objective indicators and one subjective indicator. The objective indicators were surrounding greenness and surrounding green areas, both calculated within 300 m, 500 m, and 1,000 m Euclidean circular buffers around the geocoded residential address of each person in the census. A description of the obtention of both indicators has been detailed elsewhere (Bauwelinck et al., 2021). In brief, **surrounding greenness** was measured using the Normalized Difference Vegetation Index (NDVI), an indicator of vegetation density obtained through remote sensing, ranging from -1 to +1 (maximum green). Atmospherically corrected images from the Landsat 5 were retrieved for the summer period of 2006, with a 30x30m resolution. Surrounding greenness captured the mean NDVI value around the residential address. Negative NDVI values represent water surfaces and were set to zero (i.e., no green) (Bauwelinck et al., 2021). **Surrounding green areas** were assessed using the Urban Atlas 2006 (UA), a land-use classification map of European urban areas, with a minimum mapping unit of 25x25m (European Environmental Agency, 2011). Surrounding green areas was approximated as the percentage of surface around the residential address covered by green areas. Furthermore, we used **perceived neighbourhood greenness** as a subjective indicator of exposure to residential green spaces at the level of the census tract (i.e., the smallest geographical unit in Belgium, capturing neighbourhoods). This indicator was obtained by calculating the percentage of households in each census tract reporting a very good provision of green spaces in their neighbourhoods in the 2001 Belgian census. Contrary to the objective indicators, which were linked individually to the residential address, the subjective indicator was aggregated at the level of the census tract. Such approximation was made to avoid bias from reverse causation (i.e., healthier individuals reporting better greenspace provision).

* 1. **Ambient air pollution**

Data on outdoor air pollution concentrations at high spatial resolution (25x25m) were provided by the Belgian Interregional Environment Agency (IRCEL-CELINE) (<https://irceline.be/en>). Fixed monitoring stations constantly measure atmospheric concentrations of air pollutants in Belgium, which are then used in spatial-temporal (kriging) interpolation models combined with Gaussian dispersion models to calculate pollutant concentrations in the whole country, based on land-use data, traffic and industrial sources’ emissions and meteorological data (Hooyberghs et al., 2006; Lefebvre and Vranckx, 2013). We used 2010 annual mean concentrations [micrograms per cubic meter (μg/m3)] of fine and coarse particulate matter, with an aerodynamic diameter of ≤2.5 and 2.5-10 micrometres (μm), respectively (PM2.5 and PM10), and nitrogen dioxide (NO2) linked to the baseline residential address.

* 1. **Covariates**

Information on sociodemographic and socioeconomic characteristics at baseline were obtained from the 2001 Belgian census. We included age, gender, migrant background [capturing the family history of migration, classified according to the income of the country of origin (World Bank, 2020): originating from Belgium, other high-income country (HIC) or low and middle-income countries (LMIC)], educational level (tertiary education, higher secondary education, lower secondary education, and primary/no formal education), housing tenure (owner or tenant) and household living arrangement [cohabiting with the partner or spouse, single, and other (e.g., multigenerational households)].

We used several socioeconomic indicators at the level of the census tract to create an index of area-level socioeconomic position (SEP), since prior studies have observed that contextual sociodemographic variables may confound the associations between green spaces and health beyond the effect of individual SEP (Bauwelinck et al., 2021; Rodriguez-Loureiro et al., 2022). From the 2001 Belgian census we obtained the unemployment rate, the percentage of residents originating from low and middle-income countries and the percentage of houses with very low comfort (i.e., without a toilet inside the house or a bathroom). We also obtained the median net taxable income for 2005 from Statistics Belgium (<https://statbel.fgov.be/en>). These four indicators were combined using principal component analysis (PCA) applying varimax rotation to calculate an index of neighbourhood SEP, capturing 76.9% of the total variance of the indicators.

* 1. **Statistical analyses**

We calculated the Spearman correlations of the environmental indicators and the index of neighbourhood socioeconomic position. We fitted mixed-effects Cox proportional hazards models of the association between residential green spaces and site-specific cancer mortality, using age as the underlying time scale. Observations were censored when emigration, death from other causes or end of follow-up occurred, in chronological order. The proportional hazards’ assumptions of our Cox models were tested by plotting and examining Kaplan-Meier curves. Assumptions did not hold for gender, and we therefore specified a strata term for this variable.We considered a hierarchical structure of our data: individuals (level 1) being nested within census tracts (level 2), nested in turn in each one of the five Belgian urban areas (level 3). To account for the random effects on site-specific cancer mortality of residing in the different areas considered, we included frailty terms allowing for different distributions of the baseline hazard function(Austin, 2017)*.* We constructed our model stepwise, with increasing covariate adjustment. For each green spaces’ indicator and each site-specific cancer mortality outcome, we first fitted a Model 1 (M1) including the baseline hazard, two frailty terms (one for the urban areas and one for the census tract within the urban areas) and a strata term for gender. Model 2 further adjusted for individual sociodemographic and socioeconomic variables (migrant background, educational level, housing tenure, and household living arrangement). Model 3, our main model, added the index of socioeconomic position (SEP) in the neighbourhood. For surrounding greenness and green areas we selected *a priori* buffer sizes of 300 m, based on the WHO’s recommendation of accessibility to green spaces (reflecting a five-minute walk from residence) (WHO, 2016). This buffer size has been used in most prior studies on greenspace exposure and cancer risk (Demoury et al., 2017; Klompmaker et al., 2020; O’Callaghan-Gordo et al., 2018; Zare Sakhvidi et al., 2021). We evaluated the linearity of the exposure-response association of our main model for each one of the studied outcomes. We fitted models with natural cubic splines with three degrees of freedom for each indicator of residential green spaces, which we compared to our main model with the linear term using a likelihood ratio test (LRT). We only observed significant deviations from linearity for the associations of surrounding greenness and perceived neighbourhood greenness with lung cancer mortality (Figure S1). Hence, results are expressed as hazard ratios (HR) and their 95% confidence intervals (95%CI) of cancer mortality risk for one interquartile range (IQR) increment in each residential green space indicator. In addition, for lung cancer mortality we also conducted the models with the abovementioned green spaces’ indicators categorised into quintiles. For lung cancer and colorectal cancer mortality, we present the results for the total population and for women and men separately.

In additional analyses we examined the role of air pollution in the associations under study (Klompmaker et al., 2019). We first adjusted our main models for ambient air pollution concentrations, including each pollutant (PM2.5, PM10 and NO2) separately. We then evaluated the role of each air pollutantas a mediator in the associations between residential green spaces and cancer mortality using the package *mediation* (Tingley et al., 2014)in R statistical software. In brief, we fitted two fully adjusted models for each exposure, outcome, and mediator singly: one model for the associations between exposure and outcome, including the mediator, and one linear regression model for the associations between exposure and mediator. From these models weobtained the average causal mediation effects (ACME), also known as indirect effects, and the average direct effect (ADE). We then calculated the proportion of risk reduction in the outcome after exposure to green spaces that is mediated by a reduction in air pollution [i.e., ACME/(ACME+ADE)], and its 95% Quasi-Bayesian confidence intervals (95%CI) using 1,000 Monte Carlo simulations. The validity of the mediation analyses lies in four statistical assumptions: there must be no unmeasured confounding between exposure and outcome, between mediator and outcome, between exposure and mediator, and between mediator and outcome affected by exposure (VanderWeele, 2016). We only evaluated mediation if the association between exposure and outcome was statistically significant in the main model.

We furthermore considered effect modification by age group, educational level, and quartiles of the neighbourhood socioeconomic position (SEP) index. In age-stratified analyses we used 65 years old as cut-off point, except for breast cancer mortality, where we established 50 years old as a proxy to distinguish between pre- and postmenopausal women. Exposure to green spaces could influence physical activity and BMI, and BMI may have a different effect on breast cancer risk according to menopausal status at diagnosis (Renehan et al., 2008; van Gemert et al., 2015). We built a model that included an interaction term between the exposure and the effect modifier, and we evaluated the improvement in the goodness-of-fit of this model in predicting the outcomes compared to our main model with LRT. Furthermore, we stratified our analyses by each sociodemographic indicator.

In sensitivity analyses, we evaluated the robustness of our results by a) using different buffer sizes of surrounding greenness and green areas (500 m, 1,000 m); and limiting our analyses to b) individuals who did not move from their census tract during the 10 years prior to baseline (1991-2001) and therefore were exposed at least 10 years to the same residential green (referred to as non-movers); c) residents originating from Belgium; d) a healthy subpopulation, i.e., people who reported good and very good self-perceived health and not having functional limitations at baseline; and e) individuals residing in the city, i.e., excluding residents from the commuting zones.

All the statistical analyses were conducted using the packages *coxme* (Therneau, 2020), *splines* (R Core Team, 2020), *corrplot* (Wei and Simko, 2021), *ggplot2* (Wickham, 2016), *mediation* (Tingley et al., 2014), and dependencies from R/4.3 (R Core Team, 2020).

1. **Results**

*Our* study population consisted of 2,441,566 individuals aged 30 years or older and officially residing in one of the five largest Belgian urban areas in 2001 (Table 1). *We excluded observations* with incomplete information on geocoded address (5.3%) and with missing information on covariates (10.2%) (Figure S2)*.* During the follow-up (2001-2014), 29,584 (1.2%) individuals died from lung cancer and 13,618 (0.6%) individuals died from colorectal cancer. Men died more frequently from lung cancer than women (1.8% and 0.6%, respectively).Breast cancer was recorded as the cause of death in 10,880 (0.8%) women, whereas prostate cancer was registered in 6,915 (0.6%) men. The median exposure to surrounding greenness and surrounding green areas was *0.59 (IQR: 0.23)* *and* *0.15 (IQR: 0.32)*, respectively. The median percentage of individuals in the census tract reporting very good provision of green spaces in their neighbourhood was 23.3 (IQR: 22.8). A detailed description of environmental indicators can be found in Table S1.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total population (n=2,441,566)** | **Men (n=1,159,047)** | **Women (n=1,282,519)** |
| **Age at baseline, mean (SD)** | 52.5 (15.1) | 51.5 (14.5) | 53.5 (15.6) |
| **Site-specific cancer mortality (2001-2014), n (%)** |  |  |  |
| Lung cancer | 29,584 (1.2) | 21,404 (1.8) | 8,180 (0.6) |
| Colorectal cancer | 13,618 (0.6) | 7,082 (0.6) | 6,536 (0.5) |
| Breast cancer | - | - | 10,880 (0.8) |
| Prostate cancer | - | 6,915 (0.6) | - |
| **Migrant background, n (%)** |  |  |  |
| Belgian | 1,999,495 (81.9) | 939,409 (81.1) | 1,060,086 (82.7) |
| Other HIC | 270,715 (11.1) | 131,778 (11.4) | 138,937 (10.8) |
| LMIC | 171,356 (7.0) | 87,860 (7.6) | 83,496 (6.5) |
| **Educational level, n (%)** |  |  |  |
| Tertiary education | 641,973 (26.3) | 327,536 (28.3) | 314,437 (24.5) |
| Higher secondary | 621,544 (25.5) | 300,914 (26.0) | 320,630 (25.0) |
| Lower secondary | 610,397 (25.0) | 286,150 (24.7) | 324,247 (25.3) |
| Primary or lower | 567,652 (23.2) | 244,447 (21.1) | 323,205 (25.2) |
| **Housing tenure, n (%)** |  |  |  |
| Owner | 1,770,123 (72.5) | 845,877 (73.0) | 924,246 (72.1) |
| Tenant | 671,443 (27.5) | 313,170 (27.0) | 358,273 (27.9) |
| **Household living arrangement, n (%)** |  |  |  |
| Cohabiting | 1,664,358 (68.2) | 851,834 (73.5) | 812,524 (63.4) |
| Single | 635,477 (26.0) | 230,718 (19.9) | 404,759 (31.6) |
| Other | 141,731 (5.9) | 76,495 (6.6) | 65,236 (5.1) |
| **Residential green spaces, median (IQR)** |  |  |  |
| Surrounding greenness (300 m) | 0.59 (0.23) | 0.59 (0.24) | 0.59 (0.23) |
| Surrounding green areas (300 m) | 0.15 (0.32) | 0.15 (0.33) | 0.15 (0.32) |
| Perceived neighborhood greenness (%) | 23.3 (22.8) | 23.1 (35.8) | 23.4 (23.0) |
| **Ambient air pollution concentrations, median (IQR)** |  |  |  |
| PM2.5 (μg/m3) | 19.2 (2.2) | 19.2 (2.17) | 19.2 (2.2) |
| PM10 (μg/m3) | 27.5 (3.8) | 27.5 (3.8) | 27.5 (3.7) |
| NO2 (μg/m3) | 29.1 (12.4) | 29.0 (12.5) | 29.2 (12.3) |
| **Non-movers, n (%) a** | 1.714,017 (70.2) | 791,012 (68.2) | 923,005 (72.0) |
| **Healthy subpopulation, n (%) b** | 1,402,218 (57.8) | 695,552 (60.4) | 706,666 (55.6) |
| **City residents, n (%)** | 2,055,994 (84.2) | 972,903 (83.9) | 1,083,091 (84.5) |
| a Individuals who did not move from census tract during the 10 years prior to baseline (1991-2001).b Individuals who at baseline (2001 census) reported (very) good self-perceived health or not having any longstanding limiting illnesses. |

**Table 1.** Description of the study population at baseline *(total and by gender*). Five largest Belgian urban areas, 2001-2014.

Spearman correlations between environmental and area-level socioeconomic position (SEP) indicators are displayed in Figure S3. We observed strong positive correlations between surrounding greenness and surrounding green areas. Both were positively but moderately to weakly correlated with perceived neighbourhood greenness (for surrounding greenness, 300-m: r=0.42). Air pollution concentrations were strongly negatively correlated with surrounding greenness and green areas (e.g., for NO2 and surrounding greenness, 300-m: r=-0.76, but weakly correlated with perceived neighbourhood greenness. All green spaces’ indicators showed moderate to weak negative correlations with area-level SEP, being strongest for surrounding greenness (for 300-m buffer: r=-0.56) and weakest for surrounding green areas.

The associations (HR and 95%CI) between residential green spaces and site-specific cancer mortality are shown in Figure 1 and fully reported in Table S2. In the total population, we observed an inverse association between residing in greener areas and lung cancer mortality after full adjustment; the strongest association was observed for perceived neighbourhood greenness (HR 0.94, 95%CI: 0.92, 0.96). By gender, we observed that the associations with perceived neighbourhood greenness were inverse and significant for men only (M3: HR 0.90, 95%CI: 0.88, 0.92), whereas for women the associations were only beneficial with surrounding green spaces (e.g., for surrounding greenness: HR 0.91, 95%CI: 0.87, 0.96). The results for lung cancer mortality in the total population using the exposure indicators categorised into quintiles are shown in Table S3. We observed slight deviations from linearity, more evident for surrounding greenness in the two highest quintiles of exposure (Q4 and Q5), for which the observed effect magnitude was the same. Hence, we decided to continue performing the analyses with the linear exposure term. For colorectal cancer mortality, analyses in the total population and by gender showed inverse associations, but close to null and non-significant after full adjustment. The associations with breast cancer mortality were protective and significant for surrounding greenness and surrounding green spaces (e.g., for M3: HR 0.93, 95%CI: 0.89, 0.96; HR 0.95, 95%CI: 0.93, 0.99, respectively), but not significant for perceived neighbourhood greenness. Regarding prostate cancer mortality, we did not observe statistically significant associations with any of the indicators of green spaces.

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**Figure 1.** Stepwise adjustment of the associations (HR and 95%CI) between IQR increments in residential green spaces and site-specific cancer mortality. Model 1 (M1) included the baseline hazard and two frailty terms, for the urban areas and for the census tracts within the urban areas; Model 2 (M2) added migrant background, educational level, housing tenure, and household living arrangement; Model 3 (M3) added area-level socioeconomic position (SEP). Surrounding greenness *(*NDVI, 300 m), interquartile range (IQR): 0.23; surrounding green areas (UA, 300 m), IQR: 0.32; perceived neighbourhood greenness, IQR: 22.8. Five largest Belgian urban areas, 2001-2014.

We further adjusted our main models for ambient air pollution concentrations (PM2.5, PM10, NO2), including pollutants one by one (Table S4). Associations between green spaces’ indicators and lung, colorectal and prostate cancer mortality generally attenuated but remained significant after adjustment for air pollution. For breast cancer mortality, the associations with surrounding greenness became slightly stronger (e.g., for PM10: HR 0.91, 95%CI: 0.87, 0.96).

The results of the mediation analyses can be found in Table S5. We conducted mediation analyses for the associations with lung and breast cancer mortality, as they were significantly associated with the exposures in our main models. The results of the mediation analyses were only significant for PM10 and NO2 in the associations between perceived neighbourhood greenness and lung cancer mortality. Our results suggested that the proportion of lung cancer mortality reduction mediated by reductions in PM10 and NO2 concentrations after exposure to increased perceived neighbourhood greenness was very modest, e.g., 0.06 (95%CI: 0.01, 0.12) for PM10. Results with PM2.5 were similar but not significant. With surrounding greenness and green areas, mediation results were not significant. The mediation analyses for breast cancer mortality did not yield significant results.

Results of the effect modification analyses by age, educational level and area-level SEP can be found in Figure 2 and the exact estimates are shown in Table S6. Results for surrounding green areas were very similar to those of surrounding greenness and are shown in Table S5. When exploring interaction, age appeared as a significant effect modifier in all associations, including for breast cancer mortality when using 50 years as cut-off point. We observed that the effect of residential greenness on lung cancer and colorectal cancer mortality was stronger in younger individuals (<65 years) (e.g., for lung cancer and perceived neighbourhood greenness: HR 0.91, 95%CI: 0.88, 0.93). On the contrary, for breast cancer mortality, the association with surrounding greenness was stronger for women older than 50 years old. For prostate cancer mortality there was no clear difference between age groups. Education was a significant effect modifier in the association between surrounding greenness and green areas and lung and breast cancer mortality. No clear trend was found across educational levels for any outcome. For lung cancer mortality, individuals with higher secondary education seemed to have a greater beneficial effect of higher surrounding greenness, whereas for perceived neighbourhood greenness the effect was stronger in the tertiary educated (HR 0.89, 95%CI: 0.85, 0.93). For breast cancer mortality, we observed that residing in areas with higher surrounding green areas was most beneficial in tertiary educated women. Results by quartiles of area-level SEP did not show any clear trend either. Evidence of significant effect modification was only found for lung cancer mortality with both exposures. With surrounding greenness no considerable differences across groups were found, while with perceived neighbourhood greenness we observed inverse associations in all quartiles of area-level SEP, except in the second least deprived areas (Q2).

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**Figure 2.** Stratified analyses of the associations between residential green spaces and site-specific cancer mortality, by age groups, educational level and quartiles of area-level SEP. Cox proportional hazard models using age as the underlying time scale, a strata term for gender and two frailty terms (one for urban area and one for census tracts within the urban area), and adjusted for migrant background, educational level, housing tenure, household living arrangement and area-level SEP. Asterisks next to estimatesindicate a significant (p-value<0.05) likelihood ratio test comparing our main model to the model with the interaction term between exposure and effect modifier. Five largest Belgian urban areas, 2001-2014.

(\*) Age groups for breast cancer mortality: 30-49 years; 50 years +.

In sensitivity analyses we used different buffer sizes for surrounding green spaces, limited our analyses to non-movers, residents with Belgian origin, a healthy subpopulation and individuals residing in the city (Table S7). Sensitivity analyses were generally in line with the results of main analyses. Residential green spaces generally hada stronger beneficial effect for site-specific cancer mortality in the subgroups analysed*,* with some exceptions. The only exception was observed for the association between perceived neighbourhood greenness and breast cancer mortality in the healthy subpopulation, with a null and non-significant association. In addition, the associations between surrounding green areas and prostate cancer mortality, when limiting the analyses to residents originating from Belgium, the healthy subpopulation, and individuals residing in the city, strengthened and became significantly positive (e.g., for the healthy subpopulation: HR 1.12; 95%CI: 1.04, 1.21).

**4. Discussion**

**4.1. Summary of main findings**

In this census-based longitudinal study including the five largest urban areas in Belgium, we observed that exposure to residential green spaces was associated with decreased risk of dying from lung cancer mortality in the total population and from breast cancer mortality in women. For lung cancer mortality, the findings differed by gender and by exposure assessment method: men seemed to benefit more from residing in a neighbourhood with an overall positive perception of greenspace provision, while for women the protective association of residing near greener areas was stronger when using indicators based on remote sensing and land-use classification. We did not observe significant associations between exposure to green spaces and colorectal cancer mortality after full adjustment. We found a suggestive hazardous effect of greenspace exposure on prostate cancer mortality. The role of air pollution mitigation seemed to be only marginal in the associations between exposure to green spaces and lung cancer mortality. We also foundstronger beneficial associations for individuals younger than 65 years old, but no clear trends were found for educational level or area-level socioeconomic position.

**4.2. Comparison with previous studies**

Few studies have focussed on green spaces and cancer mortality. A longitudinal study with a similar study design as ours observed a 15% reduction in mortality rates from all cancer types when exposed to surrounding greenness in a cohort of female nurses (James et al., 2016). As far as we are aware, only lung cancer mortality has been studied separately. Our findings are in line with those of a recent registry-based study in the Netherlands, where they observed reduced lung cancer mortality risk with higher exposure to green spaces (Klompmaker et al., 2021). However, most previous studies reported null associations between greenspace exposure and lung cancer mortality. This includes a longitudinal study using a health survey of around 300,000 participants linked to mortality register data for a four-year period (2013-2017) (Klompmaker et al., 2020). Potentially this study lacked statistical power to detect associations due to a smaller sample size and shorter follow-up period. Remaining studies reporting null associations were cross-sectional and used area rather than individual-level measures to assess exposure to green spaces, which maylead to exposure misclassification (Bixby et al., 2015; Richardson et al., 2010, 2012; Richardson and Mitchell, 2010).

Other studies investigated associations between greenspace exposure and the same cancer sites as in our study, but using cancer incidence and survival (Coleman et al., 2021; Datzmann et al., 2018; Demoury et al., 2017; O’Callaghan-Gordo et al., 2018; Zare Sakhvidi et al., 2021). Therefore,comparisonwith our findings on cancer mortalityshould be done with caution.Furthermore, all these studies were highly heterogeneous regarding exposure assessment, geographical location, and study design. For breast cancer, most studies have reported beneficial effects of green spaces in studies on survival (Coleman et al., 2021) and incidence (Datzmann et al., 2018; O’Callaghan-Gordo et al., 2018; Zare Sakhvidi et al., 2021), although some of them found mixed results depending on the exposure assessment used, namely, satellite imagery or land-use classification maps (O’Callaghan-Gordo et al., 2018; Zare Sakhvidi et al., 2021).

As mentioned earlier in the Introduction, green spaces may reduce the risk of lung and breast cancer by promoting physical activity, providing opportunities for social cohesion, inducing stress and attention restoration, and mitigating exposure to environmental hazards (Nieuwenhuijsen et al., 2017). In our study,air pollution mitigation did not seem to play an important role in main associations. If causal assumptions to conduct mediation analyses were met,we only observed a marginal mediating role of outdoor air pollution in the associations between perceived neighbourhood greenness and lung cancer mortality. Our findings showing beneficial effects of exposure to green spaces on lung and breast cancer mortality may be thus operated through the other proposed pathways.

We *a priori* hypothesized an association with colorectal cancer mortality, since exposure to natural environments could increase exposure to microbes and cytokines, benefitting gut microbiome diversity (Tasnim et al., 2017), and minimise sedentary lifestyles, potentially reducing the risk of colorectal cancer (Drewes et al., 2016; Keum and Giovannucci, 2019). Studies on green spaces and colorectal cancer incidence have reported mixed findings so far (Datzmann et al., 2018; Zare Sakhvidi et al., 2021).

Prostate cancer typically has a good prognosis, being death from this cancer type rare. Our results are thus likely to reflect aggressive prostate cancer, rather than prostate cancer in general. Lethal prostate cancer has been more strongly associated with BMI, and therefore may be influenced by greenspace exposure (Perez-Cornago et al., 2017). Our findings do not corroborate the results from two previous studies, where a beneficial effect was found between exposure to green spaces and prostate cancer incidence in Canada and the United States, using general and lethal prostate cancer, respectively (Demoury et al., 2017; Iyer et al., 2020). Moreover, in the latter study, beneficial associations were only found in highly populated areas (Iyer et al., 2020). Our contradictory results in Belgium’s urban dwellers are therefore intriguing, although different study population characteristics, exposure and outcome assessment, and study design may be at play. Further investigation is hence needed.

Interestingly, we found that the effect on lung cancer mortality differed by gender and exposure assessment method. Contrary to our findings, prior results of a similar census-based cohort study in adults residing in urban Belgium found that for women the association between green spaces and non-accidental, cardiovascular, and diabetes mortality was only beneficial when using the perception indicator (Bauwelinck et al., 2021; Rodriguez-Loureiro et al., 2022).Potentially this indicator captured qualitative features of green spaces, such as walkability, levels of maintenance, or perceived safety, which may be important for cardiometabolic outcomes (Rodriguez-Loureiro et al., 2022). Some of these features may also be specific of green spaces located in dense areas of a city. One study in the Belgian context found that higher population density was a risk factor for lung cancer mortality in women, but not in men (Hagedoorn et al., 2018), and population density was strongly negatively correlated with surrounding greenness in a previous study in urban Belgium, but not with perceived neighbourhood greenness (Rodriguez-Loureiro et al., 2022). Hence, residing in greener and less densely populated areas may influence certain behaviours in women, but not in men, potentially affecting lung cancer mortality risk.

Exposure to green spaces seemed to be more beneficial in young adults, which is in line with findings from previous studies using mortality cohorts (Bauwelinck et al., 2021; Crouse et al., 2017; Orioli et al., 2019; Vienneau et al., 2017; Villeneuve et al., 2012). Regarding breast cancer mortality, a stronger beneficial effect was found for women older than 50 years old. A potential explanation is that BMI is a risk factor for breast cancer among postmenopausal women, but such effect is not clear for premenopausal women (van Gemert et al., 2015). In their case-control study, O’Callaghan-Gordo et al. (2018) did not find an interaction between green spaces and menopausal status in relation to breast cancer risk. Hence, further research is needed to confirm our results.Effect modification by individual and neighbourhood socioeconomic position (SEP) yielded no consistent patterns across the exposures and outcomes studied. Similarly, previous studies did not find significant effect modification by individual or socioeconomic characteristics (Demoury et al., 2017; James et al., 2016; O’Callaghan-Gordo et al., 2018). Social inequalities in cancer mortality are well reported in Belgium (Hagedoorn et al., 2018), but exposure to green spaces may not influence health inequalities in cancer, contrarily to what has been suggested for other health outcomes (Mitchell and Popham, 2008). Further research is thus needed to confirm our results.

**4.3. Strengths and limitations**

The findings in our study should be interpreted along with its several limitations. Although we were able to adjust for several key potential confounders, our estimates may still be affected by residual confounding. We lacked information related to lifestyle factors, such as alcohol consumption or tobacco use, which are well-known risk factors of the site-specific cancers under study (WHO, 2022). The study by Klompmaker et al. (2020) did adjust for these factors, and the association between exposure to surrounding greenness and lung cancer mortality was considerably attenuated. Information on other important covariates that could lie in the causal pathway between green spaces and site-specific cancer mortality, like stress or physical activity, was also unavailable in our study. These data could have helped explain the mechanisms involved in the observedassociations between green spaces’ indicators and site-specific cancer mortality, including differences by gender.Nevertheless, despite this limitation, we were able to evaluate the role of another suggested mechanism, mitigation of air pollution, using high-resolution individual data of exposure to different pollutants. Another important limitation is that exposure assessment of green spaces was only available for the year 2006. Although we acknowledge that the quantity of green spaces may have varied during the period under study, we assumed that their spatial distribution remained relatively stable. The year of measurement of exposure to green spaces was close to the middle of the follow-up period, which potentially captured the average exposure throughout follow-up. Air pollution data was only available for the years 2005 and 2010. We purposely used the 2010 measurement so that the time of measurement of the exposure preceded that of the mediator.Moreover, exposure assessment was based on the residential address of each individual at baseline (2001), and no information on residential changes during follow-up was available (2001-2014). However, we were able to select a subgroup of the population who resided in the same census tract 10 years prior to the start of the follow-up (1991-2001), which confirmed our main results. Another limitation of our exposure assessment is that we did not have information on episodes of nature interaction, for instance, on the time spent in green spaces, the frequency of visits, or type of use (e.g., picnicking, walking). In addition, assessing exposure exclusively at residence may lead to exposure misclassification, as exposure to green spaces may occur in other contexts, e.g., at the workplace or during holidays. Information on sociodemographic and socioeconomic characteristics was available at baseline (2001) only. Although there is still a probability of residual confounding, we believe it is minimal, as we *a priori* selected variables capturing long-term SEP, e.g., educational level or housing tenure, which are thus unlikely to change considerably over time in the adult population (Galobardes et al., 2006).Finally, our data did not allow us to distinguish between cancer survival and incidence*,* which would result in a better picture of cancer risk related to greenspace exposure in our study population. Data on site-specific cancer mortality was derived from death certificates. Although standardized coding rules are used in Belgium, misclassification of cause of death is possible. Individuals with more comorbidities are more likely to have cause of death misclassified. If these comorbidities were linked to green spaces, e.g., cardiovascular diseases, this could affect our estimates. However, a potential bias can reasonably be expected to be conservative and deviate estimates to the null. In a recent study evaluating concordance between death certificates and medical files to identify breast cancer-specific death in Belgium, a fair agreement between both data sources was reported (Izci et al., 2021). Similar estimates are to be expected for other cancer types. In this regard, we also ignored if people had cancer or related disorders at baseline. However, we could identify a subsample of individuals reporting (very) good self-perceived health and not having longstanding illnesses at baseline, and our results did not change substantially.

Our study also presents several strengths. We used a large and representative dataset including the total population officially residing in urban Belgium at baseline (2001) with a long follow-up period (2001-2014). We furthermore used a complex matrix of green spaces’ indicators, aiming to capture different quantitative and qualitative features of residential natural environments. We also conducted mediation analyses by air pollution, and we assessed effect modification by gender, age, and socioeconomic characteristics for representative subgroups.

**5. Conclusions**

In this large study including the whole Belgian population in 2001, we observed that residing near greener areas was associated with reduced mortality risk from lung cancer and breast cancer, but not with colorectal cancer mortality. A suggestive harmful effect of greenspace exposure on prostate cancer mortality was also found. Moreover, the beneficial effect of exposure to green spaces on lung and breast cancer mortality might be independent from lower outdoor air pollution concentrations. Finally, associations might be stronger among younger individuals. Cancer is a public health problem of utmost importance, being the second leading cause of death worldwide (Ferlay et al., 2021). Expanding strategies for prevention, and specially focusing on implementing those that may affect the greatest number of individuals, is key to reduce the burden of the disease. Our study lays the path to address the residential built environment and access to natural environments as an important measure to decrease mortality risk from lung and breast cancer.

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