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Residential Greenness and Cardiovascular Disease Incidence, Readmission, and Mortality

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BACKGROUND: Living in greener areas of cities was linked to increased physical activity levels, improved mental well-being, and lowered harmful environmental exposures, all of which may affect human health. However, whether living in greener areas may be associated with lower risk of cardiovascular disease incidence, progression, and premature mortality is unclear.

OBJECTIVES: We conducted a cohort study to examine the associations between residential green spaces and the incidence of acute myocardial infarction (AMI) and heart failure (HF), post-AMI and HF hospital readmissions, and mortality.

METHODS: We simultaneously followed four large population-based cohorts in Ontario, Canada, including the entire adult population, adults free of AMI and HF, and survivors of AMI or HF from 2000 to 2014. We estimated residential exposure to green spaces using satellite-derived observations and ascertained health outcomes using validated disease registries. We estimated the associations using spatial random-effects Cox proportional hazards models. We conducted various sensitivity analyses, including further adjusting for property values and performing exploratory mediation analysis.

RESULTS: Each interquartile range increase in residential greenness was associated with a 7% [95% confidence interval (CI): 4%, 9%] decrease in incident AMI and a 6% (95% CI: 4%, 7%) decrease in incident HF. Residential greenness was linked to a ∼10% decrease in cardiovascular mortality in both adults free of AMI and HF and the entire adult population. These associations remained consistent in sensitivity analyses and were accentuated among younger adults. Additionally, we estimated that the decreases in AMI and HF incidence associated with residential greenness explained ∼53% of the protective association between residential greenness and cardiovascular mortality. Conversely, residential greenness was not associated with any delay in readmission or mortality among AMI and HF patients.

CONCLUSIONS: Living in urban areas with more green spaces was associated with improved cardiovascular health in people free of AMI and HF but not among individuals who have already developed these conditions. https://doi.org/10.1289/EHP6161

Introduction

Globally, cardiovascular disease (CVD) is a major public health concern, affecting ∼423 million people and resulting in 18 million deaths each year (WHO 2013a). Although CVD mortality has declined in many high-income countries during the past 20 years owing to advances in public health and medical care, the decreases have plateaued in recent years (Roth et al. 2017). Meanwhile, only small improvements in cardiovascular mortality have occurred in low-income regions (Roth et al. 2017). Thus, addressing the continuing threat of CVD to public health has been a global priority (WHO 2013b).

Over the last few decades, a growing body of literature has suggested that living in greener areas of cities may increase opportunities for improving physical activity levels (Fong et al. 2018; Markevych et al. 2017), a key target for individuals to prevent the onset and complications of CVD (Myers 2003). More recent studies further suggested that living in greener, natural environments may contribute to increased social interactions, improved mental well-being, and reduced exposure to harmful environmental stressors such as noise, heat, and air pollution (Fong et al. 2018; Markevych et al. 2017), all of which are likely to be conducive to human health. Indeed, a number of panel studies have found positive physiological responses, such as improved heart rate (Lanki et al. 2017; Ottooson and Grahn 2005), reduced stress (Aspinall et al. 2015; Gidlow et al. 2016; Honold et al. 2016), and enhanced parasympathetic nerve activity and restoration (Lee et al. 2011; Park et al. 2007) in participants after visiting parks and other green spaces.

To date, however, whether increasing urban greenness may be associated with reduced risk of cardiovascular morbidity and...
mortality is not well understood. A small number of population-based studies have been conducted to examine the relationship between residential exposure to urban greenness and cardiovascular mortality (Crouse et al. 2017; James et al. 2016; Vienneneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017); some reported a protective relationship (Crouse et al. 2017; Vienneneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017), but others did not find an association (James et al. 2016). Evidence is sparser about the associations between greenness and cardiovascular incidence and progression. The few existing studies were limited by a lack of comprehensive CVD outcome data and the spatially resolved estimates of exposure to greenness, small sample size, and cross-sectional study design (Donovan et al. 2015; Pereira et al. 2012; Seo et al. 2019; Tamoussian et al. 2014). With continuing urbanization globally and the ever-growing burden of CVD, understanding of the influence of urban greenness on cardiovascular morbidity and mortality, especially how it may unfold along different stages of cardiovascular health, can have a broad public health implication. We thus conducted a population-based cohort study to examine the relationships between residential greenness and the incidence of two leading CVDs [acute myocardial infarction (AMI) and heart failure (HF)], their progression, and ultimately death in Ontario, the most populous province in Canada.

Methods

Study Design and Population

We constructed four population-based cohorts in Ontario, including: a) the entire adult population of Ontario (referred to full cohort); b) the entire adult population of Ontario who had no history of physician-diagnosed AMI and HF before cohort inception (referred to as incidence cohort); and c) survivors of AMI (AMI cohort) or HF (HF cohort) (Figure S1). The full cohort was used to facilitate comparison of this study with previous population-based studies that investigated urban greenness and mortality (Crouse et al. 2017; James et al. 2015; Vienneneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). We restricted the four cohorts to urban residents who were 35–100 years of age at baseline, lived in common postal-code areas shared by cohorts, and were followed up simultaneously over time. The four cohorts consisted of participants at different stages of cardiovascular health, but they were exposed to similar green environments. This design allowed us to better disentangle the potentially different impacts of greenness on various cardiovascular outcomes.

To establish the full cohort comprising all Ontario adults, we used data from the Ontario Population Health and Environment Cohort (OPHPEC), a large population-based comprising all Ontario residents who, on 1 April 1996 and onward, were registered with provincial health insurance and lived in Ontario for >5 y (Chen et al. 2016a). ONPHPEC was constructed through record linkage of population-based health administrative databases (e.g., hospitalizations, emergency department visits, physician office visits) (Chen et al. 2016a). From the full cohort, we further restricted to those who were free of physician-diagnosed AMI and HF at baseline, yielding the incidence cohort. The follow-up of both cohorts extended from 1 January 2000 through 31 December 2014.

To establish the AMI and HF cohorts, we used data from the Enhanced Feedback For Effective Cardiac Treatment (EFFECT) study, a large randomized trial in Ontario (Tu et al. 2009). This EFFECT study comprised all patients admitted to 86 Ontario hospitals with AMI or HF during two periods (April 1999 to March 2001 and April 2004 to March 2005) (see Supplemental Material for more detail). An important feature of the EFFECT study is that trained nurses extracted detailed clinical information (e.g., laboratory tests, treatment, and medical history) from medical charts of all study participants. Because long-term outcomes after AMI or HF were strongly influenced by clinical severity and quality of care, using data from the EFFECT study allowed for better controlling for these potential confounders, which were otherwise unavailable from using routine health administrative databases. Like previous studies (Berglind et al. 2009; Chen et al. 2016b; Tonne and Wilkinson 2013), we restricted AMI and HF patients to those who had survived for at least 28 d after index hospital discharge (baseline). Thus, for the AMI and HF cohorts, the follow-up extended from the 29th day after the index hospital discharge until 31 December 2014.

All four cohorts were linked using unique encoded personal identifiers and analyzed at ICES. Participants living in residential postal-code areas not shared by all four cohorts were excluded. The use of data in this analysis was authorized under section 45 of Ontario’s Personal Health Information Protection Act, which does not require review by a research ethics board.

Outcomes

The study outcomes of interest were the incidence of AMI and HF [AMI: International Classification of Diseases, Ninth Revision (ICD-9) code 410 and ICD-10 code I21-22; HF: ICD-9 code 428 and ICD-10 code I50], first readmission after the index hospital discharge from any cardiovascular cause (ICD-9: 401-459 and ICD-10: 110-I99), and death from any cardiovascular cause (ICD-9: 401-459 and ICD-10: I10-I99). To assess potential bias because of unmeasured confounding and other errors that may lead to spurious inference, we also ascertained nonaccidental mortality (ICD-9: <800 and ICD-10: A00-R99) as a positive control outcome in this study (Bowe et al. 2018) because nonaccidental mortality has been regularly investigated by previous studies of urban greenness (Crouse et al. 2017; James et al. 2015; Vienneneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017).

To ascertain incident AMI and HF, we used record linkage to disease registries of these two conditions in Ontario. The two disease databases have been previously validated using chart reviews and shown to have high sensitivity (85%–89%) and specificity (93%–97%) (Austin et al. 2002; Yeung et al. 2012). We also used record linkage to the Ontario Registrar General’s Death database to ascertain deaths and the Canadian Institute for Health Information’s hospital discharge abstracts for hospital readmissions. Prevalent cases of AMI and HF diagnosed before the baseline in 2000 were excluded from the incidence cohort, but for other three cohorts, they were retained as comorbidities.

Green Spaces

Exposure to urban green spaces was estimated using the satellite-derived Normalized Difference Vegetation Index (NDVI). Calculated as a function of vegetative absorption of infrared light and reflection of near-infrared light, NDVI is an objective measure of vegetative greenness that has been widely used in epidemiological studies of urban green spaces (Crouse et al. 2017; James et al. 2016; Vienneneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). NDVI values range from −1 to 1, with negative values corresponding to bodies of water and positive values corresponding to green vegetation.

We obtained 30-m NDVI measures using all cloud-free images from the Landsat 5 Thematic Mapper for 1996–2012 (available until 2012). We removed values for water because they would artificially lower NDVI levels (Crouse et al. 2017; Hystad et al. 2014; Markevych et al. 2017). Following the methods shown in previous studies (Crouse et al. 2017; Hystad et al. 2014; James et al. 2016), we calculated NDVI annual measures...
for a 250-m buffer area around each residential postal code across Ontario over the periods of 1996–2000, 2001–2005, 2006–2010, and 2011–2012. This overcame the limitation of relatively low temporal resolution of the Landsat images, especially under cloud-free conditions in Ontario. As a sensitivity analysis, we also estimated annual averages of NDVI for 100-m, 500-m, and 1,000-m buffer areas (Crouse et al. 2017). We noted that annual averages of NDVI and maximum green season NDVI in Ontario were highly correlated (Pearson’s correlation coefficient \( r > 0.95 \), depending on buffer size).

To account for residential mobility and long-term changes in urban greenness, we assigned the closest annual average measures of NDVI according to participants’ yearly postal-code residences during the follow-up. For example, a participant’s exposure for 2000 would be estimated using annual average measures of NDVI for the period 1996–2000. Participants’ annual postal codes were obtained from the Ontario Registered Persons database, a registry of all Ontario residents.

**Covariates**

For all cohorts, we considered *a priori* age at baseline, sex, and seven time-varying variables for neighborhood-level sociodemographic status (SES): (a) percentage of population age >15 y with less than high school education; (b) percentage of recent immigrants; (c) unemployment rate; (d) income quintile, a measure of relative household income accounting for household size; (e) deprivation based on the Ontario Marginalization Index that quantifies the degree of marginalization in health and social well-being (Matheson et al. 2012); (f) population density (individuals per square kilometer); and (g) average property values, using Canadian census dissemination area data from the closest census year (Table S1). A dissemination area (with 400–700 people) is the smallest census geographic area for which census data are disseminated. In addition, we derived area-level active commuting and transit use using census tract data, because active commuting is known to improve fitness and cardiovascular health (Celis-Morales et al. 2017). Additionally, we created variables for residential proximity to the nearest acute-care hospital (in meters) and access to primary care based on density of family physicians (per 10,000 individuals, at the census subdivision level) (see Supplemental Material for descriptions about census geographic areas). Furthermore, to control for regional differences in mortality and hospitalization, we created a dichotomous variable classifying Ontario into the Greater Toronto Area, a densely populated urban mega-region, and all other areas. Toronto tends to differ from other areas in Ontario with respect to socioeconomic and demographic characteristics, health care, and mortality rate (Chen et al. 2016b).

In addition, we obtained the annual mean concentrations of fine particulate matter (PM\(_{2.5}\)) and nitrogen dioxide (NO\(_2\)) at participants’ residential postal codes in each year during the follow-up using the satellite-based estimates of PM\(_{2.5}\) (van Donkelaar et al. 2015) and a national land-use regression (LUR) model for NO\(_2\) (Hystad et al. 2011). Briefly, estimates of ground-level concentrations of PM\(_{2.5}\) were derived from satellite retrievals of aerosol optical depth, in conjunction with outputs from a global atmospheric chemistry transport model (GEOS-Chem CTM) (van Donkelaar et al. 2015). The PM\(_{2.5}\) estimates were further calibrated using the information on urban land cover, elevation, and aerosol composition using a geographically weighted regression, thus producing annual mean concentration of ground-level PM\(_{2.5}\) at a spatial resolution of 1 x 1 km for each year between 1998 and 2012. These annual estimates of PM\(_{2.5}\) have been shown to closely agree with ground measurements at fixed-site monitoring stations across North America (\( R^2 = 0.82, n = 1,440 \) (van Donkelaar et al. 2015). Similarly, to derive exposure to NO\(_2\), we made use of a national LUR model developed using measurements of NO\(_2\) at the fixed-site stations of Environment Canada’s National Air Pollution Surveillance Network (Hystad et al. 2011). This model was constructed by regressing measured annual mean concentrations of NO\(_2\) in Canada against an array of predictors (e.g., satellite estimates of NO\(_2\), area of industrial land use, road length) to capture background and regional variations of NO\(_2\) (Hystad et al. 2011).

The estimates were then augmented by incorporating local-scale variations of NO\(_2\) caused by vehicle emissions by applying spatially varying multipliers that represented distance-decay gradient in NO\(_2\). The LUR model explained 73% of the variability in annual 2006 measurements of NO\(_2\), with a root mean square error of 2.9 ppb (Hystad et al. 2011). The resulting LUR NO\(_2\) estimates were available for each year between 1996 (5 y before baseline) and 2014, after applying temporal adjustment, as done previously (Chen et al. 2017). Similarly, we applied the temporal calibration to produce annual PM\(_{2.5}\) exposure surfaces between 1995 and 1997 and between 2013 and 2014, respectively.

Furthermore, we ascertained the presence of comorbidities at baseline, including hypertension, diabetes, stroke, asthma, chronic obstructive pulmonary disease (COPD), and dementia, using validated chronic disease databases in Ontario (see Table S2 for ICD-9 and ICD-10 codes). These databases were created using hospital discharge abstracts from the Canadian Institute for Health Information, physician service claims from the Ontario Health Insurance Plan database, and emergency department records from the National Ambulatory Care Reporting System (NACRS), and they were validated using chart reviews, which showed sensitivity of 72%–89% and specificity of 76%–100%, depending on the disease (Austin et al. 2002; Gershon et al. 2009a, 2009b; Hux et al. 2002; Jaakkimainen et al. 2016; Tu et al. 2008, 2013; Yeung et al. 2012). In addition, we ascertained prior history of cancer using the Ontario Cancer Registry, which captures diagnostic and demographic information on all Ontario residents who were diagnosed with cancer.

For the AMI and HF cohorts, we further retrieved information from medical charts about in-hospital care, clinical severity, cardiovascular medications (e.g., statins) at discharge, family history of coronary artery disease (for AMI patients only), and history of atrial fibrillation (for HF only). To characterize the clinical severity of AMI patients, we assessed the type of AMI [ST-elevated MI (STEMI) vs. non-STEMI] and derived the Global Registry of Acute Cardiac Events (GRACE) risk score based on age, heart rate, systolic blood pressure, and several other prognostic variables (Bradshaw et al. 2006). Similarly, for HF patients, we assessed the type of HF (ischemic etiology or not) (Chun et al. 2012) and derived the EFFECT-HF mortality risk score based on age, respiratory rate, sodium serum level, and other prognostic variables (Lee et al. 2003). To characterize in-hospital care for both patient cohorts, we obtained data on the length of hospital stay (days), attending physician specialty (general/cardiologist/internist), and hospital type (teaching/community/small). Additionally, we extracted information from medical charts on smoking status (current smoker or not), employment (employed or not), marital status, hyperlipidemia, pulmonary edema, and any history of percutaneous coronary intervention. Last, we obtained information about coronary revascularization during follow-up through data linkage to hospital discharge abstracts and physician service claims.

**Statistical Analysis**

We used two-level spatial random-effects Cox proportional hazards models to estimate the association between residential green space and each outcome separately. Briefly, a multilevel random-effects Cox model can be expressed as: \( h(t) = h_0(t) \exp \{X_b + Z_j \} \)

where \( Z_j \) represents a random effect associated with the \( j \)th \( Z_j \).
cluster (Austin 2017). It entails that all individuals within the same cluster share the same random effect, and it has been extended to allow for a nested set of clusters (Therneau 2020). Like previous studies (Chen et al. 2016b; Crouse et al. 2012), we defined a first cluster level by census divisions (equivalent to counties) and a second level defined by census tracts within census divisions. We assumed that any two census divisions were independent, as were census tracts within each census division. This approach accounted for spatial clustering in the health status of participants from the same communities.

We developed separate models for each cohort and outcome. In all models, time variable was survival time from the baseline. Study participants who did not have the outcome of interest were censored at the time of death, ineligible for provincial health insurance (i.e., migration out of Ontario) (Table S3), or end of study (31 December 2014). We also allowed the baseline hazard function to differ by region and by the period of EFFECT enrollment (for the AMI and HF cohorts only). To assess chronic greenness exposure, we estimated 5-y running average exposure for the full and incidence cohorts. Conversely, for the AMI and HF cohorts, we modeled time-weighted exposure from baseline (i.e., hospital discharge) until outcome to assess postdischarge exposure, with weights for each patient defined by the time spent at each residence. We included participants with nonmissing information on exposure and covariates, except for marital status and employment status, for which we created a separate category of missing values to avoid losing substantial statistical power.

We grouped similar covariates together and added them incrementally to obtain fully adjusted Cox models. Our final models included age, sex, and time-varying area-level SES variables (i.e., education, income, unemployment, percent of immigrants, and population density). For the AMI and HF cohorts, we further adjusted the final models for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables (marital and employment status). For all models, we tested the proportional hazards assumption by adding the cross-product of each variable with the natural logarithm of the time variable, but we did not find any violation of this assumption ($p > 0.05$). Hazards ratios (HRs) were scaled to an interquartile increase (IQR) in NDVI for all models.

Sensitivity Analyses

To evaluate the robustness of our effect estimates, we performed sensitivity analyses by further adjusting for exposure to PM$_{2.5}$ and NO$_2$, comorbidities, and access to primary care; adjusting for proximity to acute-care hospitals using a natural spline with three degrees of freedom; and additionally adjusting for neighborhood deprivation. We estimated exposure to each air pollutant using the degrees of freedom; and additionally adjusting for neighborhood deprivation. We estimated exposure to each air pollutant using the cumulative distribution of the size of their postcodes (Table S5). Most study participants lived within 10,676) (Figure S1 and Table S5). Most study participants lived in a narrow band above the Canada–U.S. border, at approximately the 49th parallel, following the pattern of the majority of Canadians (see a map of study area in Figure S2). In addition, of all four cohorts, the distribution of the size of their postcodes ranged from 0.0019 to 0.0514 km$^2$ (25th percentile: 0.0059 km$^2$; 75th percentile: 0.0162 km$^2$; and median: 0.0125 km$^2$).

Further Analyses

In addition, we conducted a post hoc mediation analysis to examine the proportion of the association between residential green space and cardiovascular mortality that was mediated through the development of AMI and HF using the incidence cohort, following VanderWeele (2011). The mediator was defined as the occurrence of either AMI or HF during the follow-up. The outcome and mediator models were fitted using the random-effect Cox models adjusting for all available covariates, as in the primary analysis. We assumed no unmeasured exposure–outcome, mediator–outcome, and exposure–mediator confounding, as well as no exposure–mediator interaction (VanderWeele 2011). We computed proportion mediated and their 95% CIs using bootstrapping procedures, as done previously (VanderWeele 2016).

Furthermore, we examined whether age, sex, income quintile, disease severity (for the AMI and HF cohorts only), and smoking (for the AMI cohort only) may modify the HRs, by assessing whether the interaction term that was the cross-product of each variable with NDVI value was statistically significant ($p < 0.05$). We used R statistical package (version 3.3.1) with the Coxe library for conducting statistical analysis and ArcGIS (version 10.4) (ESRI) for mapping.

Results

Study Participants

Among the entire population of ~4 million long-term adult residents of Ontario, we made the following restrictions: a) those living in postal-code areas common to all four study cohorts with NDVI > 0 and nonmissing data on area-level SES variables and PM$_{2.5}$ and NO$_2$, yielding the full cohort (~1.4 million adults); b) further restricting to those free of both AMI and HF (incidence cohort, ~1.3 million); and c) those discharged alive with AMI or HF in the EFFECT study (AMI cohort: 10,790 and HF cohort: 10,676) (Figure S1 and Table S5). Most study participants lived in a narrow band above the Canada–U.S. border, at approximately the 49th parallel, following the pattern of the majority of Canadians (see a map of study area in Figure S2). In addition, of all four cohorts, the distribution of the size of their postcodes ranged from 0.0019 to 0.0514 km$^2$ (25th percentile: 0.0059 km$^2$; 75th percentile: 0.0162 km$^2$; and median: 0.0125 km$^2$).
Table 1. Baseline characteristics of two population-based cohorts of urban residents in Ontario, Canada in 2000 (percent or count, otherwise specified).

| Baseline characteristics | Full cohort (n = 1,362,723) | Incidence cohort (n = 1,290,288) |
|--------------------------|-----------------------------|--------------------------------|
| Age at entry [y (mean ± SD)] | 56.3 ± 14.8 | 55.3 ± 14.3 |
| Sex | Male 637,754 (47) | 602,564 (47) |
| | Female 724,969 (53) | 687,724 (53) |
| Preexisting comorbidity | Diabetes 124,008 (9) | 103,223 (8) |
| | Hypertension 402,004 (30) | 350,959 (27) |
| | Acute myocardial infarction 27,255 (2) | — |
| | Heart failure 54,509 (4) | — |
| | Stroke 38,156 (3) | 28,386 (2) |
| | Asthma 29,980 (2) | 27,096 (2) |
| Chronic obstructive pulmonary disease 138,998 (10) | 114,836 (9) |
| Dementia | 25,892 (2) | 19,354 (2) |
| Cancer | 83,127 (6) | 73,547 (6) |
| Area-level risk factors | Income quintile | |
| | Lowest 246,244 (18) | 229,155 (18) |
| | Lower middle 273,907 (20) | 257,671 (20) |
| | Middle 283,447 (21) | 268,896 (21) |
| | Upper middle 276,360 (20) | 263,864 (20) |
| | Upper 281,947 (21) | 270,057 (21) |
| | % of recent immigrants | 4 | 4 |
| | % population age >15 y with | 35 | 34 |
| | under high school education | % population age >15 y without | 9 | 9 |
| | employment | |

Note: —, no data; AMI, acute myocardial infarction; HF, heart failure; SD, standard deviation.

1. Full cohort comprised all urban residents ages 35–100 y in Ontario who lived in the same postal-code areas as in two patient cohorts with AMI or HF (see Table 2). Incidence cohort comprised all individuals in the full cohort who were free of any AMI and HF.

2. During the past 10 y before cohort inception.

3. From the 2001 Canadian Census, at the dissemination area level.

Of the incidence and full cohorts, the mean age was ~56 y at baseline, 47% were male, 30% had hypertension, and 10% had COPD (Table 1, Table S6, and as a comparison, baseline description of residents excluded from the full cohort is presented in Table S7). In comparison, the AMI and HF patients were considerably older and had more chronic conditions at baseline (Table 2). Of the AMI cohort, 4,419 patients were readmitted to hospitals for any cardiovascular cause and nearly half of the cohort died during the follow-up (mean follow-up: 9.4 y). Of the HF cohort, 5,482 were readmitted, and most of the cohort died during the study (mean follow-up: 5.4 y).

Associations of Urban Greenness with Cardiovascular Incidence and Mortality

From 2000 to 2014, we identified 58,553 and 134,655 incident cases of AMI and HF, respectively (Figure 1). In addition, a total of 277,174 nonaccidental deaths occurred in the incidence cohort and 330,560 in the full cohort, of which ~32% were attributed to CVD.

In the fully adjusted models, we observed a HRQR of 0.93 [95% confidence interval (CI): 0.91, 0.96] and 0.94 [95% CI: 0.93, 0.96] for the associations between residential greenness and incident AMI and HF, respectively (Figure 1). Increased amounts of greenness were also associated with a HRQR of 0.90 [95% CI: 0.88, 0.92] for cardiovascular mortality in the incidence cohort. A similar protective association was observed for the full cohort. In addition, higher levels of greenness were linked to lower

Table 2. Baseline characteristics of two cohorts of patients diagnosed with acute myocardial infarction or heart failure, respectively, enrolled in the EFFECT study, and lived in an urban area across Ontario, Canada (percent or mean ± standard deviation).

| Baseline characteristics | AMI cohort | HF cohort |
|--------------------------|------------|----------|
| Age at entry [y (mean ± SD)] | 67.3 ± 13.3 | 75.9 ± 11.2 |
| Marital status | Married 65 | 50 |
| Employment status | Employed 27 | 6 |
| Clinical severity | Acute pulmonary edema 5 | 20 |
| | Patients with acute myocardial infarction | | |
| | GRACE risk score 142 ± 36 | — |
| | In-hospital care | Length of stay (d) 7.6 ± 6.9 | 8.1 ± 7.9 |
| | Speciality of attending physician | Internal medicine 28 | 32 |
| | Cardiovascular medication at discharge | ACE inhibitor 62 | 64 |
| | | Beta-blockers 74 | 28 |
| | | Cardiology 49 | 27 |
| | | Ischemic etiology | — |
| | | Patients with heart failure | — |
| | | EFFECT-heart failure mortality risk score | 87 ± 25 |
| | | — | Ischemic etiology | — |
| | | — | Teaching 23 | 24 |
| | | — | Community 76 | 75 |
| | | — | Small 1 | 1 |
| | | — | Community 76 | 75 |
| | | — | Small 1 | 1 |
| | — | Cardiovascular medication at discharge | ACE inhibitor 62 | 64 |
| | — | Beta-blockers 74 | 28 |
| | — | Cardiology 49 | 27 |
| | — | Ischemic etiology | — |
| | — | Patients with heart failure | — |
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| | — | — | Teaching 23 | 24 |
| | — | — | Community 76 | 75 |
| | — | — | Small 1 | 1 |
| | — | — | Community 76 | 75 |
| | — | — | Small 1 | 1 |

Note: EFFECT cohorts comprised all patients who were discharged alive with AMI or HF from one of 86 hospitals across Ontario in two periods, 1999–2000 and 2004–2005, respectively. In the present study, we restricted EFFECT cohorts to urban residents ages 35–100 y. AMI, acute myocardial infarction; EFFECT, Enhanced Feedback For Effective Cardiac Treatment study; GRACE, Global Registry of Acute Coronary Syndromes; HF, heart failure; SD, standard deviation.

1. For HF cohort, only data from the first phase of EFFECT study (1999–2000) were collected.

2. From the 2001 Canadian Census, at the census dissemination area level.

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nonaccidental mortality in both cohorts (incidence cohort: HR_{IQR} = 0.89, 95% CI: 0.88, 0.91; full cohort: HR_{IQR} = 0.89, 95% CI: 0.88, 0.90).

Conversely, there was no association between residential greenness and hospital readmissions in AMI and HF patients (HR_{IQR} = 1.00 to 1.02, depending on the cohort) (Figure 1). We did not find any strong evidence associating urban greenness with mortality in these two patient cohorts (e.g., cardiovascular death: HR_{IQR} = 0.99; 95% CI: 0.93, 1.05 for AMI cohort and HR_{IQR} = 0.99; 95% CI: 0.94, 1.04 for HF cohort).

### Sensitivity Analyses

The associations between greenness exposure and cardiovascular incidence, readmissions, and mortality were insensitive to further adjustments for air pollution, comorbidities (e.g., diabetes, hyperlipidemia, COPD, and cancer), deprivation, and proximity to hospitals (Table 3). Using the NDVI with alternative radiiuses of 100 meters, 500 meters, and 1000 meters yielded similar results as those using a 250-m radius (Table 3 and Table S8). As well, the magnitude of the associations was not materially altered after further restricting to participants who were followed up for ≥ 5 y and adjusting for neighborhood-level estimates of property values and active commuting (Table 3). Furthermore, the estimated associations without restricting to common postal code areas shared by cohorts were broadly consistent with the main analysis, although the association with AMI incidence was somewhat attenuated (Table S9).

For the full and incidence cohorts, further adjustment for smoking, education, and access to primary care did not appreciably alter the associations with incident AMI and HF and mortality (Table 4). For the AMI and HF cohorts, the null associations remained similarly unchanged with additional control for access to primary care and coronary revascularization and exclusion of patients who were discharged and subsequently died within the same winter (Table S10).

### Discussion

In this large cohort study in Ontario, living in urban areas with more green spaces was associated with lower risks of developing AMI and HF and dying from any cardiovascular cause. Each IQR increase in NDVI was associated with a 6% reduction in HF incidence, a 7% reduction in AMI incidence, and an 11% reduction in cardiovascular mortality among individuals free of AMI and HF. The protective associations were robust with various sensitivity analyses and were further accentuated among younger adults. In addition, ∼ 53% of the protective association between greenness and cardiovascular mortality was found to be mediated through the decreases in AMI and HF incidence associated with greenness. On the other hand, living in these same areas was not associated with the risk of hospital readmission or mortality in AMI and HF patients.

We conducted, for the first time, a study to simultaneously examine the influence of urban greenness on a wide array of cardiovascular outcomes, from the development of two major CVDs, to hospital readmission, and ultimately to premature death. Our

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**Study populations**

|                  | Events | Protective | Harmful | Hazard ratio (95% CI) |
|------------------|--------|------------|---------|----------------------|
| **Full cohort**  |        |            |         |                      |
| Mortality: CVD   | 114,208|            |         | 0.89 (0.87 - 0.91)   |
| Mortality: nonaccidental | 330,560|            |         | 0.88 (0.88 - 0.90)   |
| **Incidence cohort** |       |            |         |                      |
| Mortality: CVD   | 88,263 |            |         | 0.90 (0.88 - 0.92)   |
| Mortality: nonaccidental | 277,174|            |         | 0.89 (0.88 - 0.91)   |
| Incidence: AMI   | 58,553 |            |         | 0.93 (0.91 - 0.96)   |
| Incidence: HF    | 134,655|            |         | 0.94 (0.93 - 0.96)   |
| **AMI cohort**   |        |            |         |                      |
| Readmission: CVD | 4,419  |            |         | 1.02 (0.98 - 1.07)   |
| Mortality: CVD   | 2,788  |            |         | 0.99 (0.93 - 1.05)   |
| Mortality: nonaccidental | 5,463 |            |         | 0.99 (0.95 - 1.04)   |
| **HF cohort**    |        |            |         |                      |
| Readmission: CVD | 5,482  |            |         | 1.00 (0.95 - 1.05)   |
| Mortality: CVD   | 4,981  |            |         | 0.99 (0.94 - 1.04)   |
| Mortality: nonaccidental | 9,151 |            |         | 0.99 (0.95 - 1.03)   |

**Figure 1.** Associations between green spaces within 250 m of study participants’ residences and cardiovascular mortality, nonaccidental mortality, and cardiovascular-related incident and hospital readmission in four population-based cohorts of urban residents in Ontario, Canada. Note that hazard ratios were scaled to an interquartile increase in NDVI (full and incidence cohorts: IQR = 0.17; AMI cohort: IQR = 0.12; HF cohort: IQR = 0.13). For the full and incidence cohorts, the models adjusted for age, sex, region (lived or not in the Greater Toronto Area), area-level unemployment, percent less than high school education, percent recent immigrants, and household income (quintiles), and population density. For the AMI and HF cohorts, the models further adjusted for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables. Note: AMI, acute myocardial infarction; CVD, cardiovascular disease; HF, heart failure.

**Further Analyses**

Using mediation analysis, we estimated that the decreases in AMI and HF incidence associated with urban greenness explained 52.7% (95% CI: 37.6%–67.3%) of the protective association between urban greenness and cardiovascular mortality. In the subgroup analyses, we observed stronger, more protective associations between NDVI and incident AMI and HF and mortality in younger adults (e.g., AMI incidence: HR_{IQR} = 0.90; 95% CI: 0.86, 0.93 in younger adults vs. HR_{IQR} = 0.99; 95% CI: 0.94, 1.03 in older adults) (Figure 2 and Tables S11). The protective association of NDVI with cardiovascular mortality was also more pronounced in those with higher income (e.g., HR_{IQR} = 0.86; 95% CI: 0.80, 0.94 vs. HR_{IQR} = 1.00; 95% CI: 0.95, 1.04 between highest and lowest income). For AMI and HF patients, there was no strong evidence for effect modification of greenness with factors examined (Figures 2 and Tables S12–S14).
Table 3. Sensitivity analysis for associations between green spaces and cardiovascular incidence, readmission, and mortality in four population-based cohorts of urban residents in Ontario, Canada, 2000–2014.

| Outcome | +NO₂ and PM₂ | +Comorbidities | +Proximity to hospitals | +Deprivation | +Active commuting | +Average property value | Restricted to those surviving >5y | Within a 500-m buffer |
|---------|---------------|----------------|-------------------------|-------------|------------------|------------------------|-------------------------------|---------------------|
|         | HR (95% CI)   | HR (95% CI)    | HR (95% CI)             | HR (95% CI) | HR (95% CI)      | HR (95% CI)            | HR (95% CI)                  | HR (95% CI)           |
| Full cohort	 |               |               |                         |             |                  |                        |                              |                     |
| Mortality |               |               |                         |             |                  |                        |                              |                     |
| CVD     | 0.89 (0.87, 0.91) | 0.91 (0.89, 0.92) | 0.90 (0.89, 0.92) | 0.91 (0.89, 0.92) | 0.89 (0.87, 0.91) | 0.91 (0.89, 0.92) | 0.91 (0.89, 0.93) | 0.89 (0.87, 0.90) |
| NAC     | 0.90 (0.88, 0.91) | 0.91 (0.90, 0.92) | 0.90 (0.89, 0.91) | 0.90 (0.89, 0.91) | 0.90 (0.88, 0.91) | 0.90 (0.89, 0.91) | 0.91 (0.90, 0.92) | 0.89 (0.88, 0.90) |
| Incidence cohort |               |               |                         |             |                  |                        |                              |                     |
| Mortality |               |               |                         |             |                  |                        |                              |                     |
| CVD     | 0.89 (0.87, 0.91) | 0.91 (0.90, 0.93) | 0.90 (0.88, 0.92) | 0.91 (0.89, 0.92) | 0.89 (0.87, 0.91) | 0.91 (0.89, 0.92) | 0.91 (0.89, 0.93) | 0.89 (0.88, 0.91) |
| NAC     | 0.90 (0.88, 0.91) | 0.91 (0.90, 0.92) | 0.90 (0.89, 0.91) | 0.90 (0.89, 0.91) | 0.90 (0.88, 0.91) | 0.90 (0.89, 0.91) | 0.91 (0.90, 0.92) | 0.89 (0.88, 0.90) |
| AMI     | 0.95 (0.92, 0.97) | 0.94 (0.92, 0.96) | 0.96 (0.94, 0.98) | 0.93 (0.91, 0.95) | 0.93 (0.91, 0.95) | 0.93 (0.91, 0.96) | 0.93 (0.91, 0.95) | 0.91 (0.89, 0.93) |
| HF      | 0.95 (0.94, 0.97) | 0.95 (0.93, 0.96) | 0.95 (0.93, 0.96) | 0.92 (0.91, 0.94) | 0.94 (0.92, 0.95) | 0.94 (0.93, 0.96) | 0.94 (0.92, 0.95) | 0.93 (0.92, 0.95) |
| AMI cohort	 |               |               |                         |             |                  |                        |                              |                     |
| Mortality |               |               |                         |             |                  |                        |                              |                     |
| CVD     | 1.03 (0.98, 1.07) | 1.02 (0.98, 1.06) | 1.02 (0.98, 1.06) | 0.99 (0.94, 1.05) | 1.03 (0.98, 1.07) | 1.02 (0.98, 1.06) | 1.03 (0.98, 1.08) | 1.01 (0.96, 1.05) |
| NAC     | 0.99 (0.92, 1.05) | 0.99 (0.93, 1.05) | 0.99 (0.93, 1.05) | 0.98 (0.91, 1.05) | 0.99 (0.93, 1.05) | 0.99 (0.94, 1.05) | 0.96 (0.97, 1.04) | 0.96 (0.90, 1.02) |
| HF cohort |               |               |                         |             |                  |                        |                              |                     |
| Mortality |               |               |                         |             |                  |                        |                              |                     |
| CVD     | 1.00 (0.95, 1.06) | 0.99 (0.94, 1.04) | 0.99 (0.95, 1.04) | 0.99 (0.94, 1.04) | 1.00 (0.95, 1.04) | 0.99 (0.95, 1.04) | 0.99 (0.92, 1.06) | 0.99 (0.95, 1.04) |
| NAC     | 0.99 (0.94, 1.05) | 0.98 (0.93, 1.03) | 0.98 (0.93, 1.04) | 1.01 (0.96, 1.06) | 0.99 (0.94, 1.03) | 0.99 (0.94, 1.03) | 0.99 (0.90, 1.08) | 0.98 (0.93, 1.03) |

Note: Each covariate was added individually to the main analysis presented in Figure 1. AMI, acute myocardial infarction; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; IQR, interquartile range; NAC, nonaccidental.

*Two-level nested, spatial random-effects Cox proportional hazards model (level one: census division, level two: census tract). Hazard ratios were scaled to an interquartile increase in NDVI (full and incidence cohorts: IQR = 0.17). The fully-adjusted model included age, sex, region (lived or not in the Greater Toronto Area), area-level unemployment, percent less than high school education, percent recent immigrants, and household income (quintiles), and population density. The number of events are: n = 114,208 (CVD death) and n = 330,560 (nonaccidental death) for full cohort; n = 88,263 (CVD death), n = 277,174 (nonaccidental death), n = 58,553 (AMI incidence), and n = 134,655 (HF incidence) for incidence cohort.

*For the AMI and HF cohorts, the models further adjusted for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables (AMI cohort: IQR = 0.12; HF cohort: IQR = 0.13). The number of events are: n = 2,788 (CVD death), n = 5,463 (nonaccidental death), n = 4,419 (CVD readmission) for AMI cohort; n = 4,981 (CVD death), n = 9,151 (nonaccidental death), n = 5,482 (CVD readmission) for HF cohort.

*Within 250 m of study participants’ postal-code residences.
findings of an inverse relationship between green spaces and cardiovascular mortality are consistent with several population-based cohort studies (Crouse et al. 2017; Vienneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). For the AMI and HF cohorts, the models further adjusted for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables (AMI cohort: IQR = 0.12, HF cohort: IQR = 0.13). The fully adjusted model included age, sex, region (lived or not in the Greater Toronto Area), area-level unemployment, percent less than high school education, percent recent immigrants, and household income (quantiles), and population density.

The associations between urban green spaces and cardiovascu lar mortality are consistent with several population-based cohort studies (Crouse et al. 2017; Vienneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). For the AMI and HF cohorts, the models further adjusted for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables (AMI cohort: IQR = 0.12, HF cohort: IQR = 0.13). The fully adjusted model included age, sex, region (lived or not in the Greater Toronto Area), area-level unemployment, percent less than high school education, percent recent immigrants, and household income (quantiles), and population density.

The associations between urban green spaces and cardiovascular mortality are consistent with several population-based cohort studies (Crouse et al. 2017; Vienneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). For the AMI and HF cohorts, the models further adjusted for clinical severity, in-hospital care, medications at discharge, smoking, and individual-level SES variables (AMI cohort: IQR = 0.12, HF cohort: IQR = 0.13). The fully adjusted model included age, sex, region (lived or not in the Greater Toronto Area), area-level unemployment, percent less than high school education, percent recent immigrants, and household income (quantiles), and population density. The results of this study should be interpreted in light of some limitations. First, we were unable to identify undiagnosed incident cases of AMI and HF. However, the HRs remained unchanged when we adjusted for access to health care and deprivation. Given universal health care in Ontario, incomplete diagnosis may lead to an underestimation of the true effect because this measurement error was likely independent of greenness exposure. Second, we lacked information on individual-level socioeconomic and behavioral variables (e.g., smoking, education, and employment status).
for the full and incidence cohorts. Similarly, although we directly adjusted for smoking (current smoker or not) with the AMI and HF cohorts, we were unable to fully account for the other important aspects of smoking (e.g., intensity) because of data availability. To further account for potential confounding by these factors, we adjusted for various indicators for neighborhood SES and comorbidities. Because neighborhood SES is strongly associated with individual socioeconomic and behavioral variables (Gan et al. 2012; Janssen et al. 2006), and comorbidities and cardiovascular health share some common behavioral factors, adjusting for these variables would reduce the influence of these unmeasured variables on the HRs. Additionally, we adjusted indirectly for smoking and education for the full and incidence cohorts and found similar results. Furthermore, our observed greenness–mortality association in the full cohort closely agrees with that of previous studies using similar general populations (Crouse et al. 2017; Vienneau et al. 2017; Villeneuve et al. 2012; Wang et al. 2017). Despite these efforts, we acknowledge that our inability to fully account for the potential impact of individual-level covariates such as smoking on the HRs is a limitation of this study. Third, although the NDVI is an objective measure of greenness, it does not describe how people use green spaces around their homes, nor does it separate parks from green-belt areas, which can be assumed to have different impacts on cardiovascular health. Due to the inherent imprecision of NDVI as urban greenness variable, we were unable to further elucidate which types of natural environments (e.g., forests, public parks, or private yards) may be more beneficial to cardiovascular health. Additionally, we used annual NDVI levels to represent long-term exposure to average NDVI levels. Some previous studies used summer or maximum NDVI levels (Vienneau et al. 2017). We found a high correlation between maximum NDVI and annual NDVI levels ($r > 0.95$), but our mean and IQR NDVI levels may be lower because we used NDVI measures throughout the year. However, this approach likely better reflects actual long-term NDVI exposure. Furthermore, we excluded negative values of NDVI in our analysis and thus did not take into account of the full range of NDVI. Future research to evaluate the negative values of NDVI (often related to water bodies) in association with cardiovascular effects is needed. Last, we were able to ascertain exposure to greenness at participants’ residential postal codes (rather than street addresses), which inevitably led to spatial misalignment that could further result in exposure misclassification and for only a limited time period (as opposed to over an individual’s lifetime among people free of AMI and HF) because of data availability. These limitations further lead to an underestimation of associations between greenness and cardiovascular risks in this study.

Our study has several strengths that merit highlighting, including its large size and population-based representation of individuals who were either at risk or lived with AMI and HF. By simultaneously examining the impact of urban greenness on subpopulations at different stages of cardiovascular health but with similar exposures to green environments, this study provided a refined understanding of green space and cardiovascular health. In addition, we obtained extensive individual-level information including clinical data and
in-hospital care for the AMI and HF patients, which allowed for better control for clinical severity and quality of care that are known to strongly influence post-AMI and HF survival. Aspects of our analytic approach further reduced concerns about confounding, such as the use of spatial random-effect Cox models, which accounted for the possibility that spatial dependencies in cardiovascular risk may not be completely explained by included variables. Furthermore, our study benefited from having detailed information on medical and residential history, allowing us to adjust for important cardiovascular risk factors (e.g., diabetes and hypertension) and account for the influence of residential mobility on exposure.

Conclusions

In this large population-based study, we found that living in urban areas with more green space was associated with lower risks of developing AMI or HF, however, increased exposure to green spaces was not associated with any delay in disease progression or mortality. With growing urban populations worldwide, this study adds weight to previous studies that suggested that increasing urban greenness could have a broad public health implication, especially for improving cardiovascular health, and that future research is necessary to understand why certain subpopulations (e.g., AMI and HF patients) did not benefit from urban greenness and identify opportunities to improve the benefits of greenness for these subpopulations.

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