Joint associations between neighborhood walkability, greenness, and particulate air pollution on cardiovascular mortality among adults with a history of stroke or acute myocardial infarction

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Background: Fine particulate matter (PM₂.₅) is a known risk factor for cardiovascular disease (CVD). Neighborhood walkability and greenness may also be associated with CVD, but there is limited evidence on their joint or interacting effects with PM₂.₅. Methods: Cox proportional hazard models were used to estimate the risk of CVD mortality among adults with a history of acute myocardial infarction and/or stroke living in Northern California. We assessed the independent and joint effects of walkability, greenness (Normalized Differentiated Vegetation Index [NDVI]), and PM₂.₅ at residential addresses, controlling for age, sex, race/ethnicity, comorbidities, BMI, smoking, revascularization, medications, and socioeconomic status. Results: Greenness had a nonlinear association with CVD mortality (P = 0.038), with notably protective effects (HR = 0.87 [95% confidence interval {CI} = 0.78, 0.97]) at higher greenness levels (NDVI ≥ 0.3) and moderate attenuation after adjusting for PM₂.₅ (HR = 0.92 [95% CI = 0.82, 1.03]) per 0.1 increase in NDVI. Walkability had no independent effect on CVD mortality. PM₂.₅ had a strong independent effect in models adjusted for greenness and walkability (HR = 1.20 [95% CI = 1.08, 1.33]) per 10 μg/m³ increase in PM₂.₅. There was an interaction between walkability and PM₂.₅ (P = 0.037), where PM₂.₅ had slightly stronger associations in more walkable than less walkable neighborhoods (HR = 1.23 [95% CI = 1.06, 1.42] vs. 1.17 [95% CI = 1.04, 1.32]) per 10 μg/m³ increase in PM₂.₅. Greenness had no interaction with PM₂.₅ (P = 0.768) nor walkability (P = 0.385). Conclusions: High greenness may be protective of CVD mortality among adults with CVD history. PM₂.₅ associated CVD mortality risk varies slightly by level of neighborhood walkability, though these small differences may not be clinically meaningful. Keywords: National Walkability Index; Green space; Air pollutants; Effect modification; Susceptibility

Introduction

There is strong evidence of a causal relation between fine particulate matter less than 2.5 μm in diameter (PM₂.₅) exposure and cardiovascular (CVD) morbidity and mortality, with long-term (1 year or more) exposures inducing more risk than short-term exposures. Elevations of long-term PM₂.₅ exposure can reduce life expectancy by as much as a few years, and this reduction is most likely attributed to excess CVD mortality. Individuals with a history of CVD events may have a greater risk of CVD mortality and may be more susceptible to the harmful effects of air pollution. Air pollution is interrelated with these environmental factors. Although highly walkable neighborhoods are associated with increased walking and physical activity, they are also associated with greater exposure to air pollution. High levels of residential greenness have been associated with decreased exposure to air pollution and also with lower neighborhood walkability.

Evidence on the joint or interacting effects of these three environmental factors on cardiovascular outcomes is limited and mixed. Several studies have reported no or only moderate interactions between these factors, suggesting that the cardiovascular health benefits of more walkable environments may be counteracted by the deleterious effects of air pollution.

What this study adds

There is insufficient evidence on the joint effects of PM₂.₅, greenness, and neighborhood walkability on cardiovascular (CVD) events, despite these factors being interrelated and associated with CVD health. No studies have been among a vulnerable population with CVD history. We found that higher neighborhood greenness levels may protect against CVD mortality risk, although that effect was attenuated when accounting for PM₂.₅ exposure. We also discovered that the PM₂.₅ effect was slightly stronger in more walkable than less walkable neighborhoods, suggesting that the cardiovascular health benefits of more walkable environments may be counteracted by the deleterious effects of air pollution.
Individuals with a history of acute myocardial infarction (AMI) or stroke are one of the highest risk groups for further coronary and cerebral events and may greatly benefit from community-level interventions that promote healthier living environments. To our knowledge, no studies have looked at the effect modification by neighborhood walkability or greenness on the association between long-term PM$_{2.5}$ and CVD mortality in this vulnerable population. Among a population of adults with AMI and/or stroke history, we aim to determine the (1) independent effects of walkability and greenness on CVD mortality risk and (2) joint effects of walkability, greenness, and PM$_{2.5}$. Our goal is to understand how these interrelated environmental factors jointly affect CVD mortality risk among adults with a history of CVD events.

Methods

Study subjects

This retrospective cohort study includes adults with a documented medical history of AMI and/or stroke in the Kaiser Permanente Northern California (KPNC) electronic health record (EHR). KPNC is a large, integrated healthcare system that provides comprehensive medical services to over four million members who are broadly representative of Northern California’s diverse population. The study cohort has been described in detail previously. Briefly, subjects had to be KPNC members for at least one year following index date, and were followed to the first of the following dates: death, end of KPNC membership, moving away from study start address, or 31 December 2016. Each subject was followed to the end of the follow-up period: death, end of KPNC membership, moving away from study start address, or 31 December 2016. The institutional review board of the Kaiser Foundation Research Institute approved this study and no informed consent was required.

National Walkability Index

We assessed walkability by the National Walkability Index, which was developed by the US Environmental Protection Agency, and has been validated with self-reported walking data from the 2015 National Health Interview Survey. The Walkability Index is based on a weighted score of four urban planning indicators: intersection density, proximity to transit stops, employment types, and household types. Census 2010 block groups were ranked by each of these factors to determine the overall Walkability Index, which ranges from 0 (least walkable) to 20 (most walkable). We linked geocoded residential addresses of cohort members to the Walkability Index at the Census block-group level.

Greenness

Greenness is the land that is partly or completely covered with grass, trees, shrubs, or other vegetation and is commonly measured within a defined area around a residential address. We measured greenness using the Normalized Difference Vegetation Index (NDVI) data (see eFigure 1; http://links.lww.com/EE/A179 for study region). Study follow-up began on 1 January 2007 and ended on 31 December 2016. Each subject was followed to the first of the following dates: death, end of KPNC membership, moving away from study start address, or 31 December 2016. The institutional review board of the Kaiser Foundation Research Institute approved this study and no informed consent was required.

Long-term PM$_{2.5}$ exposure

PM$_{2.5}$ exposure was estimated from a validated ensemble model that combined satellite data, land-use data, meteorological data, chemical transport model predictions data, and ground monitor data using machine learning algorithms. The model estimated daily average PM$_{2.5}$ exposures at a resolution of 1 km × 1 km across the contiguous US from 2000 to 2016, with an R$^2$ of 0.89 for 1-year PM$_{2.5}$ predictions using 10-fold cross-validation. Using the daily PM$_{2.5}$ exposures and the geocoded residential addresses of all cohort members at baseline, we constructed individual-level 1-year average PM$_{2.5}$ exposures for each subject at baseline, defined as the year before study start date of each subject.

Cardiovascular mortality

Our primary outcome of interest was CVD mortality, defined by International Classification of Diseases codes for the underlying cause of death (ICD-10: I10.x-I70.x), based on previous studies of PM$_{2.5}$ and CVD mortality. Cause of death data was obtained from the official state of California death certificate data, health plan inpatient mortality, and the National Death Index state death certificate data.

Covariates

Individual-level baseline covariates were extracted from EHRs and included age, sex, self-reported race/ethnicity (Non-Hispanic White, Hispanic White, Hispanic [any race], Black, American Indian/Alaska Native, Asian/Pacific Islander, Multiple Races), hypertension (HTN), hyperlipidemia, diabetes, CVD history (AMI only, stroke only, both AMI and stroke), body mass index (BMI), smoking status (never, former, current), revascularization procedures (percutaneous coronary intervention and coronary artery bypass graft), statin medication use, HTN medication use (only among those with a HTN diagnosis), and Medicaid insurance (indicator of socioeconomic status [SES]). Another indicator of SES measured at the block-group level from Census data included high school education attainment (percent with less than high school diploma). CVD history was defined as prior stroke or AMI compiled from inpatient and outpatient data recorded in the EHR. For the small percentage of subjects with missing data on sex (0.0024%), race/ethnicity (0.64%), smoking status (3.01%), and BMI (1.99%), we used single data imputation using the fully conditional method.
**Statistical analyses**

Cox proportional hazards regression was used to model the associations between each exposure variable (greenness, walkability, PM$_{2.5}$) and CVD mortality. We assessed departures from the proportional hazards assumption by interaction terms with the natural logarithm of the time variable. For all models, we used time on study as the time scale and stratified the baseline hazards by 5-year age groups, allowing each age category to have its own baseline hazard (Liao et al., 2021).$^{26}$ Covariates were selected a priori based on previous epidemiologic studies of air pollution and CVD events.$^{36,47-49}$ Correlations of continuous variables were computed using the Pearson correlation coefficient. We fit five different models to assess the influence of sequentially adding covariates and related environmental factors. Model 1 minimally adjusted for age, sex, and study start year. Model 2 adjusted for additional individual-level factors: race/ethnicity, BMI, smoking, relevant comorbidities (HTN, hyperlipidemia, diabetes), CVD history, revascularization (percutaneous coronary intervention and coronary artery bypass graft), and medications (statins and hypertensive medication). Model 3 (main model) added neighborhood-level and individual-level SES measures (neighborhood education and Medicaid insurance). Model 4 added PM$_{2.5}$, and Model 5 included all individual-level, SES, and environmental factors (greenness, walkability, and PM$_{2.5}$) simultaneously. Independent effects of greenness and PM$_{2.5}$ are reported per 0.1 increase in NDVI and per 10 μg/m$^3$ increase in PM$_{2.5}$, respectively, consistent with other literature, and independent effects of walkability are reported per 5-unit increase in the National Walkability Index, approximate with its interquartile range (6.5). We assessed potential nonlinearity in the shape of each association using restricted cubic splines.

For our effect modification analyses, we assessed interactions between PM$_{2.5}$ greenness, and walkability using two-way interaction terms. We first assessed these interactions using continuous variables, and then in categories since interactions between continuous variables can be difficult to interpret. Categories were as follows: PM$_{2.5}$ (μg/m$^3$) (low: ≤9, moderate: 9–12, high: >12) as previously defined,$^{16}$ with concentrations above the state/federal regulation limit defined as high; walkability index (low: ≤6.67, moderate: 6.67–13.33, high: >13.33) using equal intervals$^{26}$; and NDVI (low: ≤0.2, moderate: 0.2–0.3, high: >0.3) based on its distribution. We then estimated interactions for walkability/PM$_{2.5}$, greenness/PM$_{2.5}$, and greenness/walkability pairs. We also categorized walkability into quartiles to present the linear PM$_{2.5}$ association by these quartiles. In sensitivity analyses, we looked at the pairwise combinations in a subset restricted to Census tracts with population densities ≥1,000 persons per square mile since more rural areas may have exceedingly higher greenness and lower walkability levels. In supplementary analyses, we analyzed three-way interactions between PM$_{2.5}$, walkability, and neighborhood education. Analyses were conducted using SAS software, version 9.4 (SAS Institute) and RStudio, version 2021.09.0.

**Results**

**Cohort characteristics**

The study cohort included adults with a history of AMI and/or stroke. Cohort characteristics are displayed in Table 1. Most subjects (56%) had a history of stroke only, 33% had a history of AMI only, and 10% had a history of both AMI and stroke. There were more males (56%) and individuals over 65 years of age (67%). The cohort was very diverse, with 64% non-Hispanic White, 11% Hispanic (any race), 10% Asian/Pacific Islander, 8% Black, and 8% multiple races. In addition, 43% of subjects were former smokers, 16% were current smokers, 37% were overweight, and 33% were obese. Subjects had high rates of comorbidities: 82% had HTN, 81% had hyperlipidemia, and 31% had diabetes. The maximum follow-up time was 10 years (average follow-up time 5.1 years), with a total of 424,719 person–years and 8,820 CVD mortality events in the analyses.

**Table 1. Characteristics of the walkability cohort at baseline.**

| Characteristic | N = 83,560 |
|----------------|------------|
| Sex$^a$        |            |
| Female         | 36,808     | 44.2 |
| Male           | 46,662     | 55.8 |
| Age (years)    |            |
| 18 to 39       | 2,134      | 2.6  |
| 40 to 64       | 25,348     | 30.3 |
| >65            | 56,078     | 67.1 |
| Race/ethnicity$^a$ |         |
| White, non-Hispanic | 53,400   | 63.9 |
| Hispanic white | 7,417      | 8.9  |
| Black          | 6,783      | 8.1  |
| American Indian/Alaska Native | 422 | 0.5 |
| Asian/Pacific Islander | 8,517 | 10.2 |
| Multiple races | 7,021      | 8.4  |
| Hispanic (any race) | 9,405   | 11.3 |
| Neighborhood education | Mean | SD |
| Yes            | 66,717     | 79.8 |
| No             | 16,843     | 20.2 |
| Smoking$^a$    |            |
| Never          | 34,952     | 41.8 |
| Former         | 35,614     | 42.6 |
| Current        | 12,994     | 15.6 |
| BMI$^a$        |            |
| Underweight (<18.5) | 1,709  | 2.1  |
| Normal (18.5–24.9) | 23,412   | 28.0 |
| Overweight (25.0–29.9) | 30,018   | 36.6 |
| Obese (>30.0)  | 27,821     | 33.3 |
| Comorbidities  |            |
| HTN            | 68,140     | 81.6 |
| Hyperlipidemia | 67,628     | 80.9 |
| Diabetes       | 25,597     | 30.6 |
| Revascularization |        |
| PCI            | 17,725     | 21.2 |
| CABG           | 11,883     | 14.2 |
| Statin medication use |        |
| Yes            | 66,232     | 79.3 |
| No             | 17,328     | 20.7 |
| HTN medication use |       |
| Yes            | 66,717     | 79.8 |
| No             | 16,943     | 20.2 |
| History of CVD |            |
| AMI only       | 27,872     | 33.4 |
| Stroke only    | 46,972     | 56.2 |
| Both AMI and stroke | 8,716 | 10.4 |
| PM$_{2.5}$ exposure (μg/m$^3$) |        |
| Mean           | SD         |
| 1-year at baseline | 10.43  | 2.13 |
| Walkability    | Mean       | SD   |
| National Walkability Index | 11.05 | 3.92 |
| Greenness      | Mean       | SD   |
| NDVI 1 km      | 0.32       | 0.08 |

$^a$Missing data were imputed for unknown values of sex (N = 2, 0.0024%), race/ethnicity (N = 532, 0.64%), smoking status (N = 2,513, 3.01%), and BMI (N = 1,664, 1.99%).

**Descriptions and correlations of environmental variables**

Distributions of NDVI, walkability, and PM$_{2.5}$ are displayed in eFigure 2; http://links.lww.com/EE/A179. NDVI within a 1km radius ranged from 0.03 to 0.53, with a median of 0.23. National Walkability Index values ranged from 1 to 20, with median of 11.00. PM$_{2.5}$ exposures among study subjects at
found no violations of the proportional hazards for walkability, CVD mortality appeared to be linear (Figure 1C, \( P = 0.950 \)). We no longer statistically significant when PM 2.5 was added to the protective effect at higher greenness levels was attenuated and \( 0.3 (HR = 1.00 [95\% CI = 0.95, 1.04] \) per 0.1 increase). The per 0.1 increase) and no apparent effect at NDVI levels below \( 0.3 (HR = 0.87 [95\% CI = 0.78, 0.97] \) per 0.1 increase). In sensitivity analyses modeling NDVI within 250 m and 500 m buffers, associations were very similar (eTable 1; http://links.lww.com/EE/A179).

**Main effects**

The main effects of greenness, walkability, and PM 2.5 on CVD mortality are given in Table 2 and Figure 1. Greenness had a non-linear association with CVD mortality (P = 0.038). Estimated risks seem null for NDVI < 0.3, and then decrease sharply thereafter. Based on the shape of association, we then estimated the linear effects above and below NDVI of 0.3 (Table 2, eFigure 3; http://links.lww.com/EE/A179). In model 3 (main model), greenness had a marked protective effect on CVD mortality risk at NDVI levels above 0.3 (HR = 0.87 [95\% CI = 0.78, 0.97] per 0.1 increase) and no apparent effect at NDVI levels below 0.3 (HR = 1.00 [95\% CI = 0.95, 1.04] per 0.1 increase). The protective effect at higher greenness levels was attenuated and no longer statistically significant when PM 2.5 was added to the model (HR = 0.92 [95\% CI = 0.82, 1.03] per 0.1 increase). In sensitivity analyses modeling NDVI within 250 m and 500 m buffers, associations were very similar (eTable 1; http://links.lww.com/EE/A179).

Walkability was associated with a suggestive, slightly increased risk of CVD mortality in the minimally adjusted model (model 1) (HR = 1.04 [95\% CI = 1.01, 1.07] per 5-unit increase). In the main model (model 3), this effect was attenuated and no longer statistically significant (HR = 1.03 [95\% CI = 1.00, 1.05] per 5-unit increase, \( P = 0.072 \)), with further attenuation once PM 2.5 was added to the model (HR = 1.02 [95\% CI = 0.99, 1.05] per 5-unit increase, model 4). We found no evidence of non-linearity for the association between walkability and CVD mortality (Figure 1B, \( P = 0.790 \) for test of nonlinearity).

There was substantial increased risk of CVD mortality associated with PM 2.5 exposure (HR = 1.20 [95\% CI = 1.08, 1.33] per 10 μg/m³ increase in 1-year average PM 2.5) (model 3), as we have reported previously. Furthermore, we found no change in these harmful effects after adjusting for greenness and walkability (models 4–5). The shape of association between PM 2.5 and CVD mortality appeared to be linear (Figure 1C, \( P = 0.950 \)). We found no violations of the proportional hazards for walkability, greenness, or PM 2.5.

**Joint effects**

Joint effects of environmental variables are given in Figure 2 and eTable 2; http://links.lww.com/EE/A179. For the combined effects of PM 2.5 and greenness, we found that living in an area of low greenness and high PM 2.5 was associated with an increased risk of CVD mortality (HR = 1.30 [95\% CI = 1.11, 1.52]) compared to living in an area of high greenness and low PM 2.5 (Figure 2A and eTable 2; http://links.lww.com/EE/A179). We found no interaction between greenness and PM 2.5 (\( P = 0.768 \)), indicating that the combined effect of PM 2.5 and greenness was driven by the strong independent effects of each environmental factor.

We found a statistically significant interaction between walkability and PM 2.5 (\( P = 0.037 \)). We highlight the very large difference in risk between living in a neighborhood with high walkability and high PM 2.5 (HR = 1.22 [95\% CI = 1.04, 1.43]) versus living in a neighborhood with high walkability and low PM 2.5 (Figure 2B). To further illustrate this, we present the linear association between PM 2.5 and CVD mortality by quartiles of walkability in Figure 3, since PM 2.5 had a linear association with CVD mortality in the analyses of main effects. The deleterious effect of PM 2.5 on CVD mortality was stronger in more walkable neighborhoods (HR = 1.23 [95\% CI = 1.06, 1.42] for Q4) compared to less walkable neighborhoods (HR = 1.17 [95\% CI = 1.04, 1.32] for Q1) per 10 μg/m³ increase in PM 2.5. Results were very similar when additionally adjusting for greenness (eTable 3; http://links.lww.com/EE/A179). We found no interaction between greenness and walkability (\( P = 0.385 \)). The number of subjects per category for joint effects is shown in eTable 4; http://links.lww.com/EE/A179. Sensitivity analyses restricted to people living in Census tracts with ≥1,000 persons per square mile showed little difference in effects, where the joint effect HRs of PM 2.5/greenness and PM 2.5/walkability were only slightly lower in areas with high greenness and high walkability (eTable 5; http://links.lww.com/EE/A179).

Although we found no evidence of a three-way interaction (\( P = 0.846 \)) between walkability, PM 2.5, and SES, the effect modification between walkability and PM 2.5 appeared to be more pronounced in the lowest SES quartile. See the Supplement for further details (eTable 6; http://links.lww.com/EE/A179; eAppendix 1; http://links.lww.com/EE/A179).

**Discussion**

Among a susceptible population of adults with a history of prior stroke and/or AMI, we looked at the risk of CVD mortality and found strong protective effects of higher levels of greenness, with

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**Table 2.** Independent associations of greenness, walkability, and PM 2.5 with CVD mortality.

| Model | Covariates | Greenness, NDVI < 0.3, HR (95% CI) | Greenness, NDVI ≥ 0.3, HR (95% CI) | Walkability HR (95% CI) | PM 2.5 HR (95% CI) |
|-------|------------|---------------------------------|---------------------------------|----------------|----------------|
| 1     | Age, sex, study start year | 0.94 (0.91, 0.98) | 0.83 (0.75, 0.92) | 1.04 (1.01, 1.07) | 1.34 (1.21, 1.48) |
| 2     | Model 1 + race, comorbidities, BMI, smoking, CVD history, revascularization, medication use | 0.96 (0.92, 1.00) | 0.85 (0.76, 0.94) | 1.04 (1.01, 1.07) | 1.30 (1.18, 1.44) |
| 3     | Model 2 + SES | 1.00 (0.95, 1.04) | 0.87 (0.78, 0.97) | 1.03 (1.00, 1.05) | 1.20 (1.08, 1.33) |
| 4     | Model 3 + PM 2.5 | 0.99 (0.95, 1.03) | 0.92 (0.82, 1.03) | 1.02 (0.99, 1.05) | 1.20 (1.08, 1.33) |
| 5     | Model 4 + (greenness or walkability) | 1.00 (0.95, 1.05) | 0.93 (0.83, 1.04) | 1.02 (0.98, 1.05) | 1.20 (1.08, 1.33) |

N = 83,560 and 8,820 CVD mortality events for all models without NDVI. N = 83,408 and 8,799 CVD mortality events for all models with NDVI.

*Hazard ratios per 0.1 increase in NDVI 1 km.

*Hazard ratios per 5-unit increase in the Walkability Index.

*Hazard ratios per 10 μg/m³ increase in PM 2.5.

*Adjusted for age using Cox models with age as strata.

*Model 4 includes 2 environmental factors simultaneously.

*For PM 2.5, independent effects, model 4 = model 3 + greenness.

*Model 5 includes 3 environmental factors simultaneously.

*For PM 2.5, independent effects, model 5 = model 4 + walkability.
moderate attenuation of effects after adjusting for PM$_{2.5}$ in models. We found no independent effect of walkability. We found a strong independent effect of PM$_{2.5}$ that remained robust when controlling for greenness and walkability in models. In effect modification analyses, we found that increased risk of CVD mortality associated with PM$_{2.5}$ varied by neighborhood walkability, where the harmful effects of long-term PM$_{2.5}$ exposure were greater in more walkable settings. This suggests that highly walkable neighborhoods may not be as health fostering as we might expect after considering PM$_{2.5}$ exposure in these settings.

**Main effects**

Previous research on the relation between greenness and CVD mortality is mixed. Some individual studies report no effect while other studies report a decrease in risk per 0.1 increase in NDVI. Meta-analyses of the greenness-CVD mortality association have reported small pooled effect sizes or little to no effect. A recent review emphasizes that majority of the literature only looks at linear relationships between greenness and mortality and there is lack of data on the shape of the greenness-mortality relation. Our study discovered a nonlinear relation between greenness and CVD mortality, with prominent protective effects at higher levels of NDVI, and these associations could be overlooked in studies that only examine linear effects. Moreover, multiple studies have reported little change in effects on the greenness-CVD mortality association after adjusting for air pollution. The moderate attenuation in our study implies that PM$_{2.5}$ may be a confounder of the greenness-CVD mortality association at higher greenness levels.

We found weak evidence of any association between walkability and CVD mortality. Similarly, two studies reported null associations between walkability indicators and CVD health measures, with small effect estimates in opposite directions. Other studies did find associations with other CVD outcomes, but in opposite directions as well. In more walkable neighborhoods, Hu et al. reported higher coronary artery calcium scores (a measure of atherosclerosis) and Yang et al reported lower risk of ischemic stroke. More research is needed to determine if there is an independent association between neighborhood walkability and CVD mortality.

The strong effects of PM$_{2.5}$ on CVD mortality were unchanged after adjustment for walkability and greenness in models. Showing the cardiovascular health effects of PM$_{2.5}$ with and without adjustment of these related environmental factors is an important contribution since review papers have found that there is a lack of air pollution studies that control for these variables in models. Our findings are consistent with four studies that found the independent effects of PM$_{2.5}$ on CVD mortality remained robust or changed little after controlling for greenness and/or walkability.

**Joint effects**

We found no evidence of effect modification by greenness on PM$_{2.5}$ associated CVD mortality risk. Our finding is similar to a study in Korea that found no statistically significant interaction between long-term PM$_{10}$ exposure and greenness on CVD mortality risk. However, two studies reported that in areas with more greenness, they found lower risk of cardiovascular hospitalization and all-cause mortality in association with short-term PM$_{10}$ and long-term PM$_{2.5}$, respectively, although PM particle size, time of exposure, and/or outcomes in these studies are different from ours. Additionally, another study found stronger associations between long-term PM$_{2.5}$ and CVD hospitalization in areas with higher greenness, although they looked at hospitalizations and not deaths. We found a statistically significant interaction between neighborhood walkability and long-term PM$_{2.5}$ exposure on CVD mortality risk, where the harmful effects of PM$_{2.5}$ exposure were stronger in more walkable neighborhoods. Three other studies also found that more walkable neighborhoods were associated with higher CVD health risks as air pollution levels increased, though Hankey et al did not report a formal interaction and Howell et al. reported an interaction between NO$_2$ and HTN and diabetes. On the contrary, one study analyzing short-term (2-day average) PM$_{2.5}$ exposure and CVD mortality risk did not find evidence of effect modification by walkability. In comparison, our study looked at long-term (1-year average) PM$_{2.5}$ exposure, which is identified as having stronger effects on CVD compared to short-term exposures, and this may be one factor influencing the difference in findings.
Mechanisms

Four proposed principal pathways by which greenness affects human health include: (1) improving air quality, (2) enhancing opportunities for physical activity, (3) reducing physiological stress, and (4) fostering greater social cohesion. Among individuals with existing CVD, residential greenness is associated with lower levels of sympathetic activation, reduced oxidative stress, and higher angiogenic capacity.

We hypothesize that the higher PM$_{2.5}$-associated CVD mortality risk observed in more walkable neighborhoods in our study may be due in part to increased exposure to PM$_{2.5}$ during outdoor physical activity. Furthermore, the National Walkability Index is based partly on intersection density and proximity to transit stops where automobiles may be idling; thus, individuals walking in these areas may be exposed to higher air pollution.

Mechanisms of the benefit–risk tradeoffs between increased outdoor exercise and increased exposure to air pollution have been researched among individuals with CVD. Physical activity in a less polluted area (park vs. street) can reduce arterial stiffness and have positive effects on stress levels and hemodynamic parameters. Thus, there are plausible mechanisms to support the effect modification by neighborhood walkability.

Strengths and limitations

We acknowledge several strengths of our study. To begin with, we have access to the large, highly detailed KPNC electronic health record which allows us to create a sizable cohort of individuals with previous CVD events and to control for numerous demographic, clinical, and lifestyle covariates in our analyses.
Our large cohort size also enables us to achieve enough study power to conduct a variety of effect modification analyses. Another strength is our study design, a longitudinal retrospective cohort that follows subjects to time of CVD death or censored event, increasing the scientific rigor of our study. Furthermore, the availability of residential address data rather than only zip code-level data allowed individual-level linkage to high-resolution exposure data. Finally, our exposure data came from a sophisticated model for PM$_{2.5}$ exposures with outstanding validation performance and a walkability index that has been previously validated with walking data.

We also acknowledge some limitations. First, although our study included residential location data on all participants, we did not have data on time spent at home, which could lead to exposure misclassification. However, adults in California have been shown to spend on average >65% of daily time at their home residence, and we would expect any exposure misclassification to be nondifferential. Second, although the National Walkability Index has been validated by walking data, it is based partly on intersection density and proximity to transit stops and may not be capturing some walking paths through greener, less dense areas. Third, our study did not include any individual-level data on physical activity or walking; therefore, we cannot rule out an ecologic association with neighborhood walkability. Fourth, we do not account for access to healthy food, neighborhood crime, sidewalk safety, physical activity facilities, or shade from street trees, all of which can influence the health effects of neighborhood walkability. Lastly, there are many causes of CVD and treatments for this disease, consequently our study population may not be representative of all different subjects with a prior AMI and/or stroke.

Conclusions
Air pollution, neighborhood walkability, and greenness are related to CVD, and their joint effects provide further insight into how interconnected environmental factors as a whole influence population health. In a population of adults with CVD history, we observed that high levels of greenness are associated with decreased CVD mortality risk, with some attenuation after controlling for PM$_{2.5}$ exposure. PM$_{2.5}$ had a strong association with increased risk of CVD mortality, and we found evidence of effect modification by neighborhood walkability but not greenness. Since the strength of the PM$_{2.5}$ and CVD mortality association only varied slightly by level of neighborhood walkability, we note that although these small differences were statistically significant, they may not be clinically meaningful. Additional studies with individual-level physical activity data should be conducted to better understand this effect, since our study is based on neighborhood-level walkability only and does not include individual-level walking data. Urban planning decisions that increase the amount of greenness and decrease exposure to air pollution should be high public health priorities.

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Conflicts of interest statement
The authors declare that they have no conflicts of interest with regard to the content of this report.

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