Global greenness in relation to reducing the burden of cardiovascular diseases: ischemic heart disease and stroke

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Abstract

This ecological study aimed to identify the association between greenness and cardiovascular diseases in terms of ischemic heart disease (IHD) and stroke in 183 countries worldwide. The country-level disability-adjusted life year (DALY) database provided by the WHO was used to represent the health burden due to IHD and stroke for the study countries. Normalized Difference Vegetation Index (NDVI—MOD13A3) was assessed to estimate the greenness in each country. After considering potential covariates, the generalized linear mixed model penalized quasi-likelihood coupled with a sensitivity test was applied to identify the greenness in relation to DALY loss due to IHD and stroke. Stratified analysis was then conducted to determine the effects of greenness among the different levels of gender, age, and economic status. A consistently significant negative association was found between greenness and both IHD and stroke; the NDVI coefficients of the main model were $-11.245$ (95% CI: $-16.770, -5.720$) and $-4.387$ (95% CI: $-7.926, -0.085$), respectively, in the DALY changes based on the increase of NDVI from 0 to 1. The stratified analysis recognized these effects in both females and males. Negative associations between greenness and IHD as well as stroke were also found in various age groups and were confirmed as significant in low and middle-income countries.

1. Introduction

Cardiovascular disease is the most common health burden worldwide. The Global Burden of Disease (GBD) study from 2016 states that ischemic heart disease (IHD) and stroke are two types of cardiovascular diseases, and cardiovascular diseases overall is categorized as the leading cause of death in the human population (GBD 2017 Causes of Death Collaborators 2018, WHO 2019). Represented by disability-adjusted life years (DALY), the total global health burden due to IHD is around 2567 years and 2004 years for strokes per 100 000 people. IHD has an influential impact on the health of a population because of its acute manifestation and acute coronary syndrome (Dégano et al 2013), and how it is followed by health burden due to stroke, which is often associated with socio-economic conditions (GBD 2016 Neurology Collaborators 2019). National and international inequalities in income, education and wealth, socioeconomic status, and health behavior (alcohol consumption and smoking) have been
focused on as the important determinants of cardiovascular diseases (Schultz et al 2018).

Numerous studies exist related to researching cardiovascular diseases, including etiology and risk factors. One of those factors is how natural exposures such as greenness can reduce the risk of IHD and stroke (Maas et al 2009, Pereira et al 2012, Wilker et al 2014, Shen and Lung 2016, Wang et al 2019). Several potential mechanisms were proposed in the previous studies related to the beneficial effects of greenness exposure on cardiovascular diseases (Mitchell and Popham 2008, Brook et al 2010, Richardson et al 2013, Basner et al 2014, Dzhambov 2015, Kim et al 2019). These mechanisms described how exposure to greenness offers opportunities to reduce risk factors that can increase the burden of cardiovascular diseases. For example, the increase of green space could reduce air pollution concentrations in either short-term or long-term exposures by influencing dispersion and removal (Brook et al 2010). Greenness exposure was also negatively associated with noise pollutants and traffic that increase the risk of cardiovascular diseases, metabolic disorders, cognitive disorders, and mental health (Basner et al 2014, Dzhambov 2015). A study conducted in Korea also confirmed that greenness can reduce the impact of ambient air particles, which is important since ambient air particles can increase the risk of death due to cardiovascular diseases (Kim et al 2019). Considering lifestyle aspects, prior study reported that living in an area close to a green space allowed people to do physical activities, therefore improving physical health (Richardson et al 2013). In addition, knowing the potential for stress reduction, people who lived in areas with green exposure could be at lower risk for heart disease compared to those who resided in the area without green spaces (Mitchell and Popham 2008).

Previous studies have discussed the relationship between greenness exposure and cardiovascular diseases in terms of IHD as well as stroke. However, most of them focused on local-scale analysis and only a very limited number of studies have identified how greenness could affect health burdens globally. A global-scale study could provide stronger scientific evidence to explain the association, therefore, we conducted an ecological study that involved including 183 countries from six regions, including Africa, America, Eastern Mediterranean, Europe, Southeast Asia, and Western Pacific. Considering that exposure to greenness has advantages on human health, this study aimed to investigate the association between global greenness and cardiovascular diseases across countries. Specifically, we assumed greenness would be linked to a lower burden of cardiovascular diseases in terms of IHD and stroke. By applying the statistical approaches of generalized linear mixed model penalized quasi-likelihood (GLMMPLQ) and stratified analysis, we attempt to identify how greenness exposure could reduce health burdens due to IHD and stroke with DALY as a measurement for disease burden. Although this global analysis involved population-based proxies and had a lack of individual data, in concept, it could serve as a global research baseline for environmental development that supported human health and well-being.

2. Materials and methods

2.1. The burden of cardiovascular diseases

Health data were collected from the GBD study database provided by the World Health Organization (WHO-Disease burden and mortality estimates 2019). In this study, the raw estimations of DALY were used to represent the health burden due to cardiovascular diseases. Four periods of global health data were available for each country, including annual estimation data in 2000, 2010, 2015, and 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html). DALY is a summary metric of population health that includes two components: years of life lost due to premature mortality and years lived with disability. DALY contains an absolute measure of health loss; it counts how many years of healthy life are lost due to death and non-fatal illness or impairment (Murray et al 2012). DALY measures the entire population and is also provided by gender (male and female) and for seven age groups (age 0–4, age 5–14, age 15–29, age 30–49, age 50–59, age 60–69, and age > 70 years). The DALY estimations used in this study represent data for entire populations on a country-level and are provided for four years (2000, 2010, 2015, 2016). Therefore, in the statistical calculations, we used a ratio to represent DALY for each country. In this ecological study, we focused on the analysis of cardiovascular diseases including IHD (ICD-10, I20-I25), also referred to as IHD, and stroke (ICD-10, I60-I69) for non-communicable diseases. In a total, 183 WHO member countries with supportive health burden and demographic information were included as the study countries (table S1 and figure S1 (stacks.iop.org/ERL/15/124003/mmedia)). IHD and stroke were selected for our analysis because these two cardiovascular diseases are the two leading causes of death due to non-communicable diseases worldwide (GBD 2016 Neurology Collaborators 2019). Spatial distribution of DALY loss due to IHD and stroke for each country is shown in figures S2 and S3, respectively.

2.2. Greenness assessment

We used the Normalized Difference Vegetation Index (NDVI) data obtained from the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) sensor to assess greenness exposure globally (NASA, 2018). These data include a satellite-image-based
vegetation index provided by the National Aeronautics and Space Administration (NASA) for measuring and monitoring plant growth, vegetation, and biomass production, as well as representing components of greenness including leaf area, chlorophyll, and canopy structure (Gascon et al 2016b). The MODIS NDVI product used in this study was MOD13A3 version 6. This satellite-based greenness database provided monthly greenness measurement at a 1 \( \times \) 1 km spatial resolution (Chen et al 2006, Song et al 2019). The relative algorithm of NDVI produces a range of values from \(-1.0\) to \(+1.0\) for a given pixel. Positive values indicate more green vegetation and negative values indicate a lack of vegetation (Wu et al 2017). MODIS provided two NDVI measures for each cell in each month. In our study, images with the acquisition date closer to the mid-season were collected from January, April, July, and October; the selection of the months in data collection has taken into the consideration for countries with two seasons and/or four seasons. In addition, 292 MODIS NDVI images were used to assess the greenness in the global area (covering 183 countries). For images integration, we generated a monthly global greenness map by combining 292 images and estimating the greenness exposure for each country accordingly. We then conducted the same processes to estimate the greenness level in the four selected months. Finally, monthly NDVI values were then aggregated to obtain the annual average greenness values for each country. The process resulted a total of 4672 images (292 images \( \times \) 4 months \( \times \) 4 years = 4672) used for 2000, 2010, 2015, and 2016, the four follow-up years. Since recent studies have indicated that the proximity to water can improve physical and mental health (Wheeler et al 2012), grids with negative values of NDVI were excluded to avoid the misclassification bias due to the effects of water. Figure 1 shows the spatial distribution of global greenness based on the NDVI measurements.

2.3. Covariates
Several country-level covariates database associated with IHD or stroke were employed and controlled for model adjustment in this ecological study, including:

2.3.1. Fine particulate matter (PM\(_{2.5}\))
Previous studies stated that air pollutants such as PM\(_{2.5}\) was associated with cardiovascular diseases (Balluz et al 2007, Hayes et al 2019). Global PM\(_{2.5}\) concentration measurements at 1 km x 1 km resolution were obtained from the website of the Atmosphere Composition Analysis Group established by Prof. Randall Martin from Dalhousie University. A daily total column of aerosol optical depth retrievals from satellites was coupled with the GEOS-Chem transport model and geographically weighted regression model to estimate PM\(_{2.5}\) concentration variations globally (van Donkelaar et al 2016). Country-level PM\(_{2.5}\) concentration levels were calculated for the four study years and applied for model adjustment.

2.3.2. Demographic factors
Demographic factors have long been very important variables in studies related to the environment and health (Sitzia and Wood 1997, Degl’Innocenti et al 2005). In line with DALY data, we used country-level demographic data provided by the United Nations in 2000, 2010, 2015, and 2016 (United Nations 2019) for model adjustment. In addition to being served as covariates, this data was also applied to calculate the DALY due to IHD and stroke.

2.3.3. Economic level
Some studies have noted that economic status affected health burden worldwide, including the burden of cardiovascular diseases (GBD 2016 Neurology Collaborators 2019). In this study, we used the country-level economic database established in the GBD 2000–2016 study by World Bank Group. We used the economic levels of each country based on the 2016 Atlas gross national income per capita (World Bank Group 2019) for model adjustment. In our study, economic status was classified into three levels, including low-income, middle-income, and high-income levels.

2.3.4. Education
Krieger’s study pointed that education could impact how a person adapts to chronic diseases such as IHD and stroke (Krieger et al 1997). Country-level education data provided by the World Bank group was used to identify the prevalence rate of education (%) from 2000 to 2016.

2.3.5. Behavior
Behaviors such as alcohol consumption and smoking are important risk factors to cardiovascular diseases (Barry et al, 1989, Kawano 2010, Roerecke and Rehm 2014). In early 2020, the WHO reported that smoking was estimated to cause about 10% of cardiovascular diseases worldwide (WHO 2019). We used alcohol consumption and prevalence of smoking data obtained from the World Bank in 2000, 2010, 2015, and 2016 for model adjustment.

2.3.6. Healthcare expenditure
Prior study figured out that healthcare status has association with cardiovascular disease risk factors (Brooks et al 2010). Total health expenditure including the provision of health services (preventive and curative), family planning activities, nutrition activities, and emergency aid designated for health provided by World Bank Group were taken into account in our adjustment.
2.3.7. Risk factors
Risk factors affected the burden of cardiovascular diseases included obesity-related to BMI or body mass index (Khan et al 2018, Carbone et al 2019), cholesterol (Peters et al 2016), and higher blood pressure (Kokubo and Iwashima 2015, Satoh et al 2019). In this study, the prevalence rate of obesity attributed to high BMI (>30) were obtained from the World Bank for the four study periods. We also used the country-scale data of mean total cholesterol and mean systolic blood pressure (age-standardized estimate) provided by the WHO-Global Health Observatory to adjust the developed models.

2.4. Statistical analysis
Statistical summaries were performed to describe the data characteristics of all variables used including DALY (represent the health burden due to IHD and stroke), environmental exposures (greenness-NDVI and PM$_{2.5}$), demographic factors (population size, gender, and age), social-economic status (level of income and the prevalence rate of education), health behaviors (alcohol consumption and the prevalence rate of smoking), risk factors (obesity, cholesterol, and blood pressure), and healthcare expenditure.

Having considered all covariates, the main model was developed using the GLMMPQL to identify the association between greenness exposure and the burden of IHD and stroke. Considering fixed effects and random effects in the calculations, GLMMPQL provides a more flexible approach for analyzing health outcomes and has been used in many fields of studies (Leroux et al 2000, Casals et al 2014, Leung et al 2019). In conditions where spatial data are available from several distinct areas, GLMMPQL can adjust the overall fixed effects while the structure of correlation is nested within regions, allowing the accommodation of regional differences in e.g. autocorrelation distances, and assuming spatial autocorrelation (SAC) only between observations in the same region (Dormann et al 2007). Given a high number for DALY loss due to IHD and stroke in some countries (clustered spatial patterns), we added an additional term of 'continent' in the GLMMPQL calculation based on Leung et al (2019) to minimize the biases due to SAC effect. Then, a Spatial Autocorrelation Global Moran’s I was calculated to see whether a SAC could be found for the residual estimations (Leung et al 2019). Moreover, GVIFs (generalized variance-inflation factors) were applied to examine the multicollinearity across covariates. The obtained GVIFs values were <4 for all covariate variables, thus, all variables were remained for the model adjustment (table S2) (Fox 2015, Helbich et al 2018).

Several types of sensitive test were conducted to evaluate the robustness of the model estimates. The first type of sensitivity test was designed to gradually include one covariate at a time. This test aimed to determine whether the significant effect of greenness on IHD and stroke remained stable even some covariates were not considered. We used different combination of covariates in six separated models while population size, age, gender, and year were always remained for model adjustment. More specifically, Model 1 included only greenness exposure; Model 2 included greenness and PM$_{2.5}$; Model 3 added economic status in addition to greenness and PM$_{2.5}$, Model 4 additionally included alcohol consumption based on Model 3; Model 5 additionally included smoking prevalence and education based on Model 4; and in Model 6 we further considered the risk factors including obesity attributed to BMI,
cholesterol, and systolic blood pressure. In addition, taking into account some uncountable confounding factors (i.e. historical and current political regime), Model 7 excluded data of countries in Eastern Europe and Central Asia as the second type of sensitivity test. In the third approach, quartiles of greenness exposure were selected as a sensitivity test to evaluate potential nonlinearity and to minimize the influence of outliers in the NDVI.

Since the previous studies confirmed an association between obesity and cardiovascular diseases (Carbone et al. 2019) also an inverse association between obesity and greenness exposure (Huang et al. 2020), then we performed the additional causal mediation analysis using obesity. Furthermore, the selection of obesity for mediation analysis is based on the results of the bivariate test Spearman correlation which shows a significant negative association between greenness and obesity and significant positive between DALY (both IHD and stroke) with obesity (p-value < 0.01). In this study, the mediator models were adjusted for gender (% of females), age, economic status (level of income), the prevalence rate of smoking, alcohol consumption, the prevalence rate of education, and PM$_{2.5}$ exposures. Outcome models were adjusted for NDVI, gender, age, economic status, smoking, alcohol consumption, education, PM$_{2.5}$ exposures, cholesterol, and systolic blood pressure. The magnitude of natural indirect effect was estimated based on one-unit increments on NDVI, and a 1000-bootstrap resampling was applied to construct the 95% confidence intervals.

Finally, stratified analysis was conducted to assess the association between greenness in relation to reducing the burden of IHD and stroke among different genders, age groups, and economic statuses.

### 2.5. Positive-negative control tests

Positive-negative control variables were used to check the strength of a causal inference of an exposure-outcome association when unobserved variables were thought to be present. Two approaches were used in this study, including a positive-negative outcomes control and a positive-negative exposures control. Outcomes of positive-negative controls aimed to identify whether using the same exposure (greenness) and replacing risk variables (IHD and stroke) with other health outcomes could yield consistent results. By using the same database (DALY-WHO), we examined the association between greenness and the burden of disease due to falls (representing the positive outcome control) and road injuries (representing the negative outcome control). Falls were chosen as a positive outcome control because Lee’s study showed that greenness reduced the risk of fall-related injuries (Lee and Maheswaran 2011). Road injury was chosen as a negative outcome control since no studies focused on these two issues.

In contrast, in the positive-negative exposure control analysis, we identified whether using the same risk variable (e.g. IHD) and replacing exposure could yield a consistent finding. For the positive exposure control, we assessed the relationship between PM$_{2.5}$ exposure and risk of IHD. A previous study found that PM$_{2.5}$ was highly correlated with an increased risk of IHD (Hayes et al. 2019). Wind speed was used for the negative exposure control with the assumption that no association between wind speed and IHD.

All the spatial and statistical analyses were performed using ArcGIS 10.5 and R version 3.3.2 (The R packages Foundation for Statistical Computing, Vienna, Austria). Coefficient and risk estimate with 95% confidence intervals were reported and p-values < 0.05 were considered as statistical significance.

### 3. Results

#### 3.1. Summary statistics

By using the country-level DALY data obtained from 183 countries worldwide, table 1 shows the statistical summary of all variables used in this study. From the four periods analysis we could know, the average global health burden due to IHD and stroke for the study countries were 27.28 years (Std. Dev.: 19.88 years) and 16.20 years (Std. Dev.: 10.04 years), respectively. As displayed in figures S4(a) and (b), countries in Europe had the highest disease burden for IHD and stroke. As for the environmental exposures, the average values of NDVI and PM$_{2.5}$ was 0.49 (Std. Dev.: 0.21) and 19.45 µg m$^{-3}$ (Std. Dev.: 16.10 µg m$^{-3}$), respectively. The results of demographic statistics showed that the average population size of the selected countries was around 38 million people (Mean ± Std. Dev.: 37,992,370 ± 139,909,540 people); In terms of gender and age, 49.95% of the study population was female. The female population is almost equal in the number to the male population; Age from 15–29 and 30–49 had the highest proportion, with each group accounting for approximately 25% of the total population; In addition, analysis of socioeconomic status showed the prevalence rate of education reached 83.70% (Std. Dev.: 19.68%). For economic status, income levels are classified into level 1 (covers 80 countries), level 2 (covers 52 countries), and level 3 (covers 51 countries) for representing the low to high income levels; As for the behavior, the average alcohol consumption was 3.26 l per person (Std. Dev.: 3.61) and the prevalence rate of smoking was 18.6% (Std. Dev.: 13.79%). Furthermore, the average proportion for healthcare expenditure was 6.22% (Std. Dev.: 2.39%). Finally, the average numbers of risk factors were 9.64%, 4.71, and 125.53 mmHg for the prevalence of obesity attributed to BMI, total cholesterol, and systolic blood pressure, respectively.
Table 1. Statistical summary of the variables.

| Variable                                      | Mean   | Std. Dev. | Min  | 25th  | Median | 75th  | Max   |
|-----------------------------------------------|--------|-----------|------|-------|--------|-------|-------|
| Burden of cardiovascular diseases—DALY        |        |           |      |       |        |       |       |
| DALY loss due to Ischemic heart disease (years) | 27.28  | 19.88     | 3.92 | 14.84 | 21.44  | 31.01 | 128.69|
| DALY loss due to Stroke (years)               | 16.20  | 10.04     | 2.88 | 9.84  | 13.59  | 18.47 | 57.13 |
| Environmental exposures                       |        |           |      |       |        |       |       |
| Greenness (NDVI)                              | 0.49   | 0.21      | 0.08 | 0.34  | 0.54   | 0.65  | 0.87  |
| PM$_{2.5}$ ($\mu g/m^3$)                      | 19.45  | 16.10     | 0.46 | 7.34  | 15.02  | 27.45 | 87.53 |
| Demographic and socioeconomic factors         |        |           |      |       |        |       |       |
| Population ('000)                             | 37 992.37 | 13 9909.54 | 81.00 | 2 418.75 | 8 723.50 | 26 165.25 | 1 411 415.00 |
| Gender (female %)                             | 49.95  | 3.05      | 24.17 | 49.77 | 50.32  | 50.92 | 54.21 |
| Age 0–4 (%)                                   | 10.55  | 4.48      | 4.03 | 6.37  | 9.94   | 14.59 | 20.99 |
| Age 5–14 (%)                                  | 19.17  | 6.42      | 8.04 | 13.22 | 19.05  | 25.53 | 31.28 |
| Age 15–29 (%)                                 | 25.38  | 4.13      | 14.52 | 22.30 | 26.66  | 28.17 | 36.76 |
| Age 30–49 (%)                                 | 25.30  | 5.26      | 15.77 | 21.07 | 25.94  | 28.70 | 52.04 |
| Age 50–59 (%)                                 | 8.62   | 3.58      | 2.88 | 5.30  | 7.85   | 12.01 | 16.08 |
| Age 60–69 (%)                                 | 5.89   | 3.29      | 1.14 | 3.16  | 4.62   | 8.59  | 14.30 |
| Age > 70 (%)                                  | 5.10   | 3.97      | 0.39 | 1.95  | 3.28   | 7.75  | 19.08 |
| Alcohol consumption (liter/population)        | 3.26   | 3.61      | 0.00 | 0.21  | 2.00   | 4.82  | 16.64 |
| Smoking (%)                                   | 18.60  | 13.79     | 0.00 | 6.70  | 19.10  | 28.30 | 73.40 |
| Healthcare expenditure (%)                    | 6.22   | 2.39      | 0.00 | 4.62  | 6.01   | 7.84  | 15.88 |
| Education (%)                                 | 83.70  | 19.68     | 0.00 | 72.60 | 92.80  | 98.80 | 100.00|
| Income level                                  |        |           |      |       |        |       |       |
| Number (countries)                            | 80     | 43.71     | -    | -     | -      | -     | -     |
| Income level %                                | 52     | 28.42     | -    | -     | -      | -     | -     |
| High—income                                   | 51     | 27.87     | -    | -     | -      | -     | -     |
| Risk factors                                  |        |           |      |       |        |       |       |
| Prevalence of obesity attributed to BMI (Body Mass Index) | 9.64   | 5.38      | 1.15 | 4.91  | 9.92   | 13.88 | 28.19 |
| Mean total cholesterol                        | 4.71   | 0.41      | 3.90 | 4.40  | 4.70   | 5.05  | 5.60  |
| Mean systolic blood pressure (mmHg)           | 126.53 | 3.39      | 116.61 | 124.39 | 126.65 | 129.23 | 134.49 |
3.2. Association between greenness and cardiovascular diseases

The results of the statistical analysis related to the association between greenness and cardiovascular diseases in terms of IHD and stroke are shown in table 2. After adjusting the covariates (population, gender, age, economic status, the prevalence of education, alcohol consumption, smoking, PM$_{2.5}$, healthcare expenditure, and year), the main model in this study showed a significantly negative association between greenness and IHD and stroke, with coefficient estimates of $-11.245$ (95% CI: $-16.770$, $-5.720$; p-value: $<0.001$) and $-4.387$ (95% CI: $-7.926$, $-0.885$; p-value: $<0.05$), respectively. These findings indicate greenness exposure could significantly reduce health burden due to IHD and stroke. From the six sensitivity test models developed (Model 1 to 6), a consistently significant negative association between greenness and IHD and stroke was observed with different covariates settings for the model adjustments. Furthermore, by excluding several countries in Eastern Europe and Central Asia, Model 7 still found a significantly negative association between greenness and cardiovascular diseases for both IHD and stroke, with the coefficient estimates of $-6.102$ (95% CI: $-10.410$, $-1.798$; p-value: $<0.01$) and $-1.618$ (95% CI: $-5.523$, $-0.002$; p-value: $<0.05$), respectively. We also assessed the spatial-autocorrelation effects in the model. As shown in table S3, no statistically significant clustering effects (p-value > 0.05) was found in the residual estimations.

Considering that greenness exposure varies by country, we analysed the four regional groups. showed the coefficient estimations of greenness by quartile attributed to cardiovascular diseases in multivariable adjusted models. We coded the countries with the lowest greenness exposure (Q1) as the reference group in the analysis. In the models adjusted for all confounding variables, the coefficient estimates for countries with the highest quartile of green exposure compared to the lowest quartile was $-9.527$ (95% CI: $-16.770$, $-3.635$ for Q1. We also identified a negative relationship between greenness and stroke in all classes, although it was not significant.

Furthermore, as shown in table S4, our mediation analysis presented a moderate mediation effect of obesity on the NDVI-IHD association (coefficient $= -0.022$), compared with the total effect of NDVI on IHD. This finding indicates that with the increase of NDVI exposure, the prevalence of obesity would be decreased, and eventually, the IHD-related DALY will be reduced. However, this mediation effect did not reach the statistical significance (i.e. 95% CI accepted the null value), and it could be resulted from insufficient control for confounding on the obesity-IHD association. Since obesity is not the primary target at the stage of study design, therefore the risk factors contributing to obesity collected in this research were limited. It may partially explain the positive but insignificant mediation effect of obesity on the NDVI-stroke association.

3.3. Stratified analysis

The results of the stratified analysis (after adjusting for all covariates) among different levels of gender, age group, and economic status are shown as down bars in figure 2. By analyzing DALY based on gender with similar population ratios, we found that the effect of greenness on IHD and stroke for both females and males indicates a significant negative association with p-values of <0.001 and <0.05, respectively. This finding indicates there is no significant difference in the impact of exposure between genders in reducing the burden of IHD or stroke. We subsequently examined seven age groups and those results are shown in figure 2(a). We found the health burden due to IHD had a significant negative association with greenness in all age groups except for the population group aged 0–4 years. We found a negative correlation in all age groups for strokes and there is significance for ages 15–29, 50–59, and 60–69 years, all of which are displayed in figure 2(b). In addition, the stratified analysis by economic status shows greenness has a significant negative correlation with IHD in low and middle-income countries and is negatively correlated at all economic levels for stroke.

3.4. Positive-negative control variables

From table S5, the positive-negative control tests confirmed the robustness and reliability of NDVI estimates. First, the results of positive outcome control found a significantly negative association (p-value < 0.001) between greenness exposures and fall-related injuries; As a negative outcome control, the relationship between greenness and road injury did not achieve the statistically significant level (p-value 0.70 for Model 1 and 0.58 for Model 2), and this indicated no relationship between greenness and road injury; As for the positive exposure control, a significantly positive association (p-value < 0.01) was obtained from IHD versus PM$_{2.5}$. This finding was consistent with previous studies that PM$_{2.5}$ could increase the burden of IHD; The relationship between IHD and wind speed as a negative control had an insignificant association (p-value = 0.15), implied no association between IHD and wind speed.

4. Discussion

This study is the first global-scale ecological study to assess the association between greenness and cardiovascular diseases. By analyzing the global NDVI and DALY of cardiovascular diseases, our results showed
that greenness has a significantly negative relationship with these two disease burdens. Our results were strengthened by previous studies which focused on the local-level analysis (Maas et al 2009, Pereira et al 2012, Wilker et al 2014, Shen and Lung 2016, Wang et al 2019). Furthermore, the main findings of this study were in line with current research which confirmed that greenness was linked with lower levels of health burden in terms of physical and psychological conditions such as diabetes, stroke, cardiovascular diseases, and stress (James et al 2015, Dadvand et al 2016). A four-year longitudinal study conducted in Ontario–Canada showed that higher levels of greenness were associated with a lower risk of cardiovascular diseases and stroke mortality (Villeneuve et al 2012). In other health studies, the benefits of greenness were also found to improve the health statuses of people with obesity (Villeneuve et al 2018). Greenness as an environmental feature plays an important role in reducing sedentary behavior, which is a causative factor of obesity. Greenness has also been referred to as natural space, which contributes to obesity prevention by providing opportunities to regenerate physical activity (James et al 2015). In a study of 15 477 Chinese urban dwellers, Yang showed that greenness has beneficial associations with the body’s metabolic system including blood pressure and cholesterol (Yang et al 2020). They stated that higher greenness levels were associated with lower odds of metabolic syndrome and could have an effective impact on people younger than 65 years old and those with higher household income. It is known that health burdens such as obesity, cholesterol, and high blood pressure are risk factors which are closely related to cardiovascular diseases. We, thus, realized that exposure to greenness could not only reduce the health burden of cardiovascular diseases directly, but also provide benefits to its causal factors.

Our findings were supported by the comparison between the spatial distribution of greenness

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**Table 2.** Association models between greenness exposure and cardiovascular diseases (ischemic heart disease and stroke) in the DALY changes based on an increase in NDVI from 0 to 1, supported by stratified analysis.

| | Ischemic heart disease | Stroke |
|---|---|---|
| | Coefficient of NDVI (95% CI) | p-value | Coefficient of NDVI (95% CI) | p-value |
| **Main Model**<sup>b</sup> | −11.245 (−16.770, −5.720) | <0.001 | −4.387 (−7.926, −0.085) | <0.05 |
| **Model 1**<sup>c</sup> | −11.810 (−17.730, −5.884) | <0.001 | −5.270 (−9.061, −1.479) | <0.01 |
| **Model 2**<sup>d</sup> | −11.874 (−17.830, −5.922) | <0.001 | −5.451 (−9.266, −1.635) | <0.01 |
| **Model 3**<sup>e</sup> | −11.870 (−17.830, −5.922) | <0.001 | −5.728 (−9.565, −1.891) | <0.01 |
| **Model 4**<sup>f</sup> | −11.530 (−17.490, −5.576) | <0.001 | −4.960 (−8.810, −1.100) | <0.01 |
| **Model 5**<sup>g</sup> | −10.230 (−15.990, −4.462) | <0.001 | −4.102 (−7.714, −0.487) | <0.05 |
| **Model 6**<sup>h</sup> | −10.720 (−16.290, −5.139) | <0.001 | −4.097 (−7.675, −0.519) | <0.05 |
| **Model 7**<sup>i</sup> | −6.102 (−10.410, −1.798) | <0.01 | −1.618 (−5.523, −0.002) | <0.05 |

<sup>a</sup>Continuous variable

<sup>b</sup>Control variables included population size, gender (percentage of females), age, economic status (level of income), smoking, alcohol consumption, education, PM<sub>2.5</sub> exposure, obesity attributed to BMI (Body Mass Index), cholesterol, systolic blood pressure, healthcare expenditure, and year.

<sup>c</sup>Adjusted for population size, gender (percentage of females), age, and year.

<sup>d</sup>Adjusted for population size, gender (percentage of females), age, PM<sub>2.5</sub> exposures, and year.

<sup>e</sup>Adjusted for population size, gender (percentage of females), age, PM<sub>2.5</sub> exposures, economic status (level of income), and year.

<sup>f</sup>Adjusted for population size, gender (percentage of females), age, PM<sub>2.5</sub> exposures, economic status (level of income), alcohol consumption, and year.

<sup>g</sup>Adjusted for population size, gender (percentage of females), age, PM<sub>2.5</sub> exposures, economic status (level of income), alcohol consumption, smoking, education, and year.

<sup>h</sup>Adjusted for population size, gender (percentage of females), age, PM<sub>2.5</sub> exposures, economic status (level of income), alcohol consumption, smoking, education, obesity attributed to BMI, cholesterol, systolic blood pressure, and year.

<sup>i</sup>Considered all covariates and eliminated data from Eastern Europe and Central Asia/Russia countries data

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**Table 3.** Coefficient estimations of greenness by quartile attributed to cardiovascular diseases in multivariable adjusted models.

| Quartile of NDVI | Ischemic heart disease | Stroke |
|---|---|---|
| | Coefficient of NDVI (95% CI) | p-value | Coefficient of NDVI (95% CI) | p-value |
| **Q1** (NDVI: 0.085–0.389)<sup>b</sup> | Referent | | Referent | |
| **Q2** (NDVI: 0.390–0.524)<sup>b</sup> | −3.635 (−8.939, 1.669) | 0.19 | | |
| **Q3** (NDVI: 0.525–0.622)<sup>b</sup> | −7.804 (−13.170, −2.443) | <0.01 | −0.118 (−0.359, 0.012) | 0.34 |
| **Q4** (NDVI: 0.623–0.808)<sup>b</sup> | −9.527 (−15.210, −3.849) | <0.001 | −0.071 (−0.319, 0.176) | 0.57 |

<sup>a</sup>Continuous variable

<sup>b</sup>Control variables included population size, gender (percentage of females), age, economic status (level of income), smoking, alcohol consumption, education, PM<sub>2.5</sub> exposures, obesity attributed to BMI (Body Mass Index), cholesterol, systolic blood pressure, healthcare expenditure, and year.
Figure 2. Stratified analysis among different gender, age, and economic status for greenness in relation to (a) IHD and (b) stroke in the DALY changes based on an increase in NDVI from 0 to 1. Variable adjustments included population size, gender (percentage of females), age, economic status, smoking, alcohol consumption, education, PM$_{2.5}$, obesity attributed to BMI (Body Mass Index), cholesterol, systolic blood pressure, healthcare expenditure, and year.

(figure 1) and DALY loss due to IHD (figure S2) and stroke (figure S3). From the generated maps, we could know that several countries in Europe and Eastern Mediterranean were categorized as lower exposure to greenness countries, while some countries in Southern and Central Africa as well as Southeast Asia were categorized as higher exposure to greenness countries (figure 1). When took a look at the spatial distribution of cardiovascular diseases including IHD and stroke (figures S2 and S3), the spatial distribution of cardiovascular diseases had an inverse pattern with greenness in most of the countries. These patterns also supported our main findings that greenness had a negative association with cardiovascular diseases.

It is widely known that economic disparity not only affects the quality of the environment but also...
relates to the quality of health including medical services and coping strategies to adapt to the burden of disease. In this study, we recognized that there was a significantly negative correlation between greenness and IHD in low-income and middle-income countries, but insignificant for high-income countries. Our findings were consistent with a study in Florida–USA which showed the highest quartile of greenness was associated with a 20% lower likelihood of IHD compared with the lowest quartile of greenness (Wang et al 2019). In addition, Seo’s study showed those within the highest quartile of urban green space had a reduced risk of total cardiovascular diseases (HR 0.85, 95% confidence interval, CI 0.81–0.89) and coronary heart disease or IHD (HR 0.83, 95% CI 0.78–0.89) compared to those within the lowest quartile of green space coverage (Seo et al 2019). Knowing that developed regions are dominated by high-income countries basically with a proper medical service system, then we considered that the insignificant relationship related to the protective effects of greenness for high-income countries should be reasonable. To minimize the burden of health due to chronic diseases such as IHD, high-income countries have several strategies not only depend on how the nature exposure can help to reduce the health burdens, but also through various implementations of adequate medical services and preventive actions. This statement was supported by the prior studies which stated that high-income countries had experienced large reductions in the incidence and mortality of cardiovascular diseases due to the strategies to overcome risk factors including the adoption of a healthy diet, smoking reduction, and the application of secondary prevention related to the risk of disease (Vartiainen et al 1994, Ford et al 2007, Mirzaei et al 2009). As for stroke, we found a negative relationship, although it was not significant. The lack of significance is possibly due to fluctuations in increases and decreases in stroke burden in several countries. Compared to IHD, lower DALY estimations for stroke in almost all countries around the world could reduce the statistical power of the model estimates.

We further assessed the effects of exposure in all seven age groups. A significantly negative relationship for IHD in all age groups was found except for ages 0–4 years. The lack of significance of the relationship between greenness and IHD at the age of 0–4 years may be due to the low health burden and ineffectiveness of IHD symptom detection for this age. The symptoms of this disease arise as a result of lifestyle factors in adult years, so people in this youngest age group do not exhibit the noted symptoms (Pelanda et al 2002). Researchers have suggested symptoms of IHD, such as obesity, can begin to be detected at the age of 6 years. For adults, the odds of hospitalization for heart disease or stroke are 37% lower among adults in neighborhoods with highly variable greenness as compared to those in predominantly non-green neighborhoods (Pereira et al 2012).

Gender difference is another important social determinant of health that has not been widely considered in environmental health research to this point. Previous studies have argued gender inequality may affect health burden due to differences in perception (Hyun et al 2016). Their results showed that cardiovascular diseases which have been portrayed as a man’s disease may also be suffered by women, although at a lower number. From the results of stratified analysis, we recognized that exposure to greenness had a significantly negative relationship with IHD and stroke in both males and females. Despite having a different number of cases, these findings indicated that greenness could provide benefits to reduce the risk of disease burden regardless of gender inequalities. Our results were supported by Bolte’s study, which showed that greenness could provide benefit and no consistent gender differences regard to the effects of green space on health (Bolte et al 2019). In addition, a longitudinal study conducted in seven Korean metropolitan areas also showed the association between greenness and cardiovascular diseases was significantly negative regardless of the sex of participants (Seo et al 2019).

European countries had the highest health burden due to cardiovascular diseases for both IHD and stroke. The WHO Regional Office for Europe (2020) confirmed that cardiovascular diseases caused more than half of all deaths across the European Region. Over the past decade, the highest IHD mortality rates were found in European countries (Finegold et al 2013) and the monthly fatality rate for stroke was ranged from 13% to 35% (Béjot et al 2016). Furthermore, we also found that the health burden due to stroke increased in Southeast Asian countries. While the world’s largest population living in these developing countries, the burden of stroke is expected to be high in Asia. In addition, the economic transition in South Asian and Southeast Asian countries such as India, Pakistan, and Bangladesh towards achieving developed country status is ongoing. In these countries, risk factors such as hypertension, obesity, and smoking would become more common and increase the risk of stroke (Venketasubramanian et al 2017).

In this study, MODIS-NDVI images with $1 \times 1$ km² resolution were used for greenness exposure assessment. We realized that $1 \times 1$ km² is not the best spatial resolution of MODIS-NDVI to estimate greenness exposure. Given that the focus of our study covered a global area, we considered the use of $1 \times 1$ km² resolution satellite images as reliable images for estimating greenness in each country. In a different application, the literature by Chang and Hong (2012) stated that compared to the 250-m resolution MODIS, the 1-km resolution image offered almost the same accurate depiction of the shape, coverage, and location of
Knowing that the DALY data provided by WHO is a country as the basic unit in the statistical analysis. Finally, this study focused on a global analysis with recognized their association with cardiovascular diseases.

eological factors since several studies have recognized the association with cardiovascular diseases. We suggest future studies consider these meteorological factors such as temperature and precipitation. Related to exposures, we did not consider meteorological factors such as temperature and precipitation. We suggest future studies consider these meteorological factors since several studies have recognized their association with cardiovascular diseases.

Some limitations of the study should be noted. Knowing that this study was conducted with an ecological study design, the measure of exposure and outcome variables were only a proxy-based on the country-level average. Used country-level databases might not best proportion for variable assessment and could impact on the modifiable areal unit problem as a source of statistical bias. However, due to the lack of residential neighborhood greenness and tree species database for each country, the effects of neighborhood greenspace and biodiversity in the developed models cannot take into account. We also recognized the lack of individual health information might have some impacts on the strength of evidence provided by the results. The causality remains to be explored even though a negative statistical association was found between greenness exposure and the burden of cardiovascular diseases in terms of IHD and stroke. Nevertheless, given we have considered several potential risk factors to adjust the models and identified the robustness estimations, this study could serve an essential role in a better knowledge of how exposure to greenness can be linked to the burden of cardiovascular diseases in terms of IHD and stroke globally. Furthermore, the study findings also openly provide a substantial possibility for further study in the understanding of alleviating human health burdens. Furthermore, we found a negative mediation effect of obesity on the association between greenness and IHDs. However, the interpretation of this finding should be cautious since several factors contributing to obesity (e.g. dietary, physical activity) were not controlled that may lead to confounding bias on the obesity-IHD association. This limitation may also explain the unexpected positive mediation role of obesity on the relationship between greenness and stroke that can be discussed in subsequent studies. Otherwise, some covariates have not been adjusted in the model due to the lack of global datasets, such as genetic or hereditary disease, ethnic/race, and other covariates those may influence cardiovascular diseases. Related to exposures, we did not consider meteorological factors such as temperature and precipitation. We suggest future studies consider these meteorological factors since several studies have recognized their association with cardiovascular diseases.

5. Conclusion

This study is the first global-scale study with an ecological study design to assess the association between greenness and cardiovascular diseases based on the data from 183 countries worldwide. Our results showed a consistently significant negative relationship between greenness and the burden of cardiovascular diseases, including both IHD and stroke. The stratified analysis showed that greenness could provide health benefits regardless of gender differences and age groups. Greenness exposure was also confirmed to have a significant effect in low and middle-income countries and could impact on the modifiable areal unit problem. Despite the limitations noted, our study contributed to a global research baseline that could be used as a reference for environmental development and public health. We suggest policymakers and communities to green environment management in order to reduce the global health burden.

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years (DALY) database to estimate global health burden of IHD and stroke; the National Aeronautics and Space Administration (NASA), which provided global greenness—NDVI data (MOD13A3); the Atmospheric Composition Analysis Group, which provided global PM$_{2.5}$ data; the United Nations Agency, which served demographic data; and the World Bank Group, which provided the provisions of economic status, the prevalence rate of smoking, alcohol consumption and risk factor data at a country-level.

**Author contributions**

Conceptualization, C.D.W., J.D.S., A.KA., and H.J.S.; methodology, C.D.W., A.KA., and W.C.P.; formal analysis, A.KA., and W.C.P.; writing—original draft preparation, C.D.W, and A.K.A.; writing—review and editing, C.D.W., A.K.A., Y.L.G., S.C.C.L., C.P.Y., W.C.P., J.D.S., and H.J.S.; visualization, A.K.A.; supervision, C.D.W., S.C.C.L., and H.J.S.; funding acquisition, C.D.W., H.J.S., S.C.C.L., and J.D.S.

**Conflicts of interest**

The authors declare no conflict of interests. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

**Data availability statement**

The data that support the findings of this study are openly available at the following URL/DOI: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

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