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Potential causal links and mediation pathway between urban greenness and lung cancer mortality: Result from a large cohort (2009 to 2020)

Wenjing Wu [a,1], Gonghua Wu [a,1], Jing Wei [b,1], Wayne R Lawrence [c], Xinlei Deng [d], Yuqin Zhang [a], Shirui Chen [a], Ying Wang [a], Xiao Lin [a], Dan Chen [a], Xinling Ruan [a], Qiaoxuan Lin [e], Zhiqiang Li [a], Ziqiang Lin [f], Chun Hao [a], Zhicheng Du [a], Wangjian Zhang [a,*], Yuantao Hao [g,h,**]

[a] *Department of Medical Statistics, School of Public Health & Center for Health Information Research &Sun Yat-sen Global Health Institute, Sun Yat-sen University, Guangzhou, China*
[b] *Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, USA*
[c] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA*
[d] *Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Durham, USA*
[e] *Department of Statistics, Guangzhou Health Technology Identification & Human Resources Assessment Center, China*
[f] *Department of Preventive Medicine, School of Basic Medicine and Public Health, Jinan University, Guangzhou, China*
[g] *Peking University Center for Public Health and Epidemic Preparedness & Response, Peking, China*
[h] *Key Laboratory of Epidemiology of Major Diseases, Peking University, Ministry of Education, China*

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ABSTRACT

Urban greenness, as a vital component of the urban environment, plays a critical role in mitigating the adverse effects of rapid urbanization and supporting urban sustainability. However, the causal links between urban greenness and lung cancer mortality and its potential causal pathway remain poorly understood. Based on a prospective community-based cohort with 581,785 adult participants in southern China, we applied a doubly robust Cox proportional hazard model to estimate the causal associations between urban greenness exposure and lung cancer mortality. A general multiple mediation analysis method was utilized to further assess the potential mediating roles of various factors including particulate matter (PM_1, $PM_{2.5-1}$, and $PM_{10-2.5}$), temperature, physical activity, and body mass index (BMI). We observed that each interquartile range (IQR: 0.06) increment in greenness exposure was inversely associated with lung cancer mortality, with a hazard ratio (HR) of 0.89 (95 % CI: 0.83, 0.96). The relationship between greenness and lung cancer mortality might be partially mediated by particulate matter, temperature, and physical activity, yielding a total indirect effect of 0.826 (95 % CI: 0.769, 0.887) for each IQR increase in greenness exposure. Notably, the protective effect of greenness against lung cancer mortality could be achieved primarily by reducing the particulate matter concentration.

Abbreviations: AC, Absolute Correlation; ADE, Average Direct Effect; ATE, Average Indirect Effect; CCI-HBV, Community-based Collaborative Innovation Hepatitis B Virus; CHAP, China High Air Pollutants; CIs, Confidence Intervals; DAG, Directed Acyclic Graph; DR, Doubly Robust; EMM, Effect-Measure Modification; HRs, Hazard Ratios; IQR, Interquartile Range; LGHAP, Long-term Gap-free High-resolution Air Pollutants; MMA, Multiple Mediation Analysis; MOD13Q1, Terra Moderate Resolution Imaging Spectro-Radiometer Vegetation Indices; NDVI, Normalized Difference Vegetation Index; NIR, Near-infrared Radiation; NOAA-AVHRR, National Oceanic and Administration-Advanced Very High-Resolution Radiometer; NPP-VIIRS, National Polar-orbiting Partnership Visible Infrared Imaging Radiometer Suite; NTL, Nighttime Light; PH, Proportional Hazard; PM_{10}, Particulate Matter with Aerodynamic Diameter $\leq$ 10 μm; PM_1, Particulate Matter with Aerodynamic Diameter $\leq$ 1 μm; $PM_{2.5}$, Fine Particulate Matter; PRE, Precipitation; Red, Red Reflectance; RMSE, Root Mean Square Errors; STET, Space-time Extremely Randomized Trees; TMP, Temperature.

* Corresponding author at: Department of Medical Statistics, School of Public Health, Sun Yat-sen University, Guangzhou, China.
** Corresponding author at: Peking University Center for Public Health and Epidemic Preparedness & Response, Peking, China.
E-mail addresses: zhangwj227@mail.sysu.edu.cn (W. Zhang), haoyt@bjmu.edu.cn (Y. Hao).
[1] The authors contributed equally to this work.

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1. Introduction

Urban sustainable development stands as a critical global concern with far-reaching implications for the future of society and humanity (Vigier et al., 2023). While urbanization has experienced significant growth over the past decades, economic development has not always kept pace with the expanding urban population's needs, particularly in low- and middle-income countries (Sun et al., 2020). Consequently, this imbalance has led to various urban environmental problems (e.g. air pollution, urban heat island [UHI] effect), posing a significant threat to urban sustainability (Rajagopal et al., 2023; Son et al., 2023). Urban greenness (the total volume of vegetation in an urban area), as a vital component of the urban environment, has the potential to alleviate the adverse impacts of rapid urbanization and supports urban sustainability by contributing to the environmental and social well-being of urban communities (Ji et al., 2020; Twohig-Bennett & Jones, 2018). Moreover, there is a growing interest in investigating the potential health benefits of urban greenness, which could provide valuable insight into sustainable urban living (Liu et al., 2023).

Numerous epidemiological studies have assessed the association between urban greenness and various health outcomes, including cardiovascular diseases (Yuan et al., 2021), respiratory diseases (Mueller et al., 2022), and psychological well-being (White et al., 2021); however, lung cancer, being one of the leading chronic disease and a crucial concern in sustainable cities (Mishra et al., 2021), has received relatively limited attention (Mueller et al., 2022; Zare Sakhvidi et al., 2022; Coleman et al., 2022). Based on a literature review (Table S1), much effort on the topic has predominantly originated from developed countries and relied heavily on cross-sectional or ecological study designs, therefore the inconsistent findings from which could not be directly generalized to low- and middle-income countries. In the context of China, a rapidly urbanizing developing country with a substantial burden of lung cancer mortality (Sung et al., 2021), only two relevant cohort studies have been conducted, both of which observed a reduced risk of lung cancer incidence or mortality with increasing in greenness (Huang et al., 2022; Yang et al., 2021). Moreover, most of the existing evidence has been derived from traditional association models, with limited utilization of causal inference approaches. Thus, a particular lack of high-quality evidence provides causal insights into the link between urban greenness exposure and lung cancer mortality based on a large-scale cohort in China.

Various interconnected mechanisms are thought to mediate the association between urban greenness exposure and human health, including modifications in exposure to air pollution (Lee et al., 2021), noise (Jarvis et al., 2021), and heat (Jaganmohan et al., 2016), promotion of outdoor physical activity (McMorris et al., 2015), lower risk of obesity (Villeneuve et al., 2018), and improved mental health (Abraham Cottagiri et al., 2022). Although a few efforts have attempted to clarify the relationship between urban greenness and lung cancer mortality (Table S1), the potential intermediate mechanisms remain unclear. In recent decades, only one study (Rodriguez-Loureiro et al., 2022) has attempted to clarify the mediation mechanisms underlying the association between greenness exposure and lung cancer mortality. However, limited evidence has primarily focused on the role of air pollution while ignoring other potential pathways (e.g., ambient heat, physical activity, and body mass index (BMI)) (Table S1). A comprehensive understanding of the potential mediation pathway between urban greenness exposure and lung cancer mortality is important but still lacking.

In this study, we aimed to assess the causal links between urban greenness exposure and lung cancer mortality, utilizing a doubly robust approach within a large-scale cohort comprising almost 0.6 million individuals in southern China with a follow-up period over 12 years. We further applied a general multiple mediation method to assess the potential mediation role of various factors, including particulate matter, temperature, physical activity, and BMI on the effect. By shedding light on the complex relationship between urban greenness and lung cancer mortality, our ultimate goal is to contribute valuable insights to the field of sustainable cities, facilitating evidence-based urban planning and policy-making initiatives.

2. Method

2.1. Study population

The data used in the present study is part of the National Project of Community-based Collaborative Innovation hepatitis B virus (CCI-HBV) in China (Ruan et al., 2019b). The CCI-HBV project, a nationwide prospective study, consisted of over 5 million participants. The primary focus of this project was to identify the influencing factors and develop community-level prevention strategies for hepatitis B and HBV carriers. Further details regarding the CCI-HBV project have been previously described (Ruan et al., 2019a). This present study used data from a sub-cohort of individuals who reside in Guangzhou, China (Zhang et al., 2023). Briefly, the sub-cohort enrolled a total of 654,115 participants (48.12 % male, 51.88 % female; average age at enrollment: 44.06 [SD: 20.63] years) between January 2009 and December 2015 from 35 randomly selected communities in Guangzhou, a megacity and an important economic center in southern China. Participants under 18 years ($n = 72{,}330$) were excluded, leaving 581,785 adults eligible for the final analysis. We collected various types of variable information through electronic questionnaires and physical examination, including demographic, socioeconomic, and behavioral characteristics. Ethics approval (IRB No. L201703) from the Human Ethics Committee at Sun Yat-sen University and written informed consent were obtained for all participants.

2.2. Outcome

The outcome data were ascertained through linkage to the Mortality Register records provided by the Guangzhou Center for Disease Control and Prevention (CDC) using the national identification number. The mortality records contained information on the date and cause of death (from Jan 1st, 2009 to Dec 31st, 2020). Causes of death were coded by the *International Classification of Diseases, Ten Revision* (ICD-10). The outcome in the present study was lung cancer mortality (ICD-10: C34) and survival time from diagnosis. Individuals who were alive or died due to causes other than lung cancer were censored either at the last follow-up (Dec 31st, 2020) or the date of death, respectively.

2.3. Assessment of residential greenness

We utilized a normalized difference vegetation index (NDVI) to characterize the residential greenness exposure. The NDVI represents the normalized ratio of near-infrared radiation (NIR) to red reflectance (Red), and it can be mathematically expressed as $\mathrm{NDVI} = \mathrm{NIR} - \mathrm{Red}/\mathrm{NIR} + \mathrm{Red}$(Jimenez et al., 2022). The NDVI values range from -1.0 (water) to $+1.0$ (dense green space), with a larger value corresponding to greater vegetation coverage. The NDVI dataset was derived from the Terra Moderate Resolution Imaging Spectro-Radiometer Vegetation indices (MOD13Q1) in the existing National Oceanic and Administration-Advanced Very High-Resolution Radiometer (Didan et al., 2015). The products were generated every 16 days at a spatial resolution of 250 m. To minimize estimation bias due to blue space, pixels with values below 0 were excluded from the analysis (McDougall et al., 2022). Geocoding was performed for each participant according to their residential address at baseline, and the average NDVI values within buffer zones surrounding each participant were calculated. Three buffer zones (including 250 m, 500 m, and 1000 m radius) commonly used in previous studies were considered in our study to address the uncertainty regarding the optimal spatial scale for assessing residential greenness (Rojas-Rueda et al., 2019; Twohig-Bennett & Jones, 2018). We defined long-term greenness exposure as the three-year moving average NDVI values preceding the endpoint (Yu et al., 2023b).

2.4. Assessment of mediators

In this study, we considered multiple mediators including particulate matters (PM_1, $PM_{2.5–1}$, $PM_{10–2.5}$), temperature, physical activity, and BMI, the association of which with both greenness (Bell et al., 2008; Chaudhuri & Kumar, 2022; McMorris et al., 2015; Wang et al., 2021) and lung cancer mortality (Brenner et al., 2016; Gourd, 2022; Mittal & Rajala, 2020; Yang et al., 2013) were previously reported.

The annual average concentrations of $PM_{2.5}$ and PM_{10} at a spatial resolution of 1 km^2 were extracted from a Long-term Gap-free High-resolution Air Pollutants concentration dataset (LGHAP) in China. Concentrations were estimated using a random forest regression model (Bai et al., 2022). These estimations exhibited well agreement with ground measurements, yielding R^2 values of 95 % and 94 %, and root mean square errors (RMSE) of 12.03 μg/m^3 and 19.56 μg/m^3, respectively. Also, annual average concentrations of PM_1 (1 km × 1 km resolution) were extracted from the China High Air Pollutants (CHAP) database (Wei et al., 2019). The space-time extremely randomized trees (STET) were developed to drive PM_1 concentration with R^2 value of 77 % and RMSE of 14.6 μg/m^3. A monthly air temperature dataset (2009–2020) at a resolution of 1 km^2 was generated using the delta spatial downscaling method, previously described in detail (Peng et al., 2019). Additionally, we assigned the average concentrations of PM_1, $PM_{2.5}$, PM_{10}, and temperature over the three years preceding the endpoint to each participant according to their residential address coordinates. We further calculated $PM_{2.5–1}$ (difference between $PM_{2.5}$ and PM_1) and $PM_{10–2.5}$ (difference between PM_{10} and $PM_{2.5}$) concentration. Information on physical activity was collected through a self-report questionnaire and assessed by exercise frequency (never, occasionally, more than once a week, everyday). BMI (kg/m^2) calculated as the ratio of weight (in kilograms) to the square of standing height (in square meters), was obtained through physical examination conducted at baseline.

2.5. Covariates other than exposure and mediators

We collected information on demographic characteristics, lifestyle factors, and environmental covariates. Details regarding the selection of potential confounders in the main and mediation analysis are provided in the *Statistical Analysis* section. Demographic characteristics and lifestyle covariates were recorded in the baseline survey. These included age at baseline (in years), sex (male, female), ethnicity (Han, ethnic minority [defined as non-Han ethnicity]), education (primary or below, secondary, high, college or greater than college), marital status (not married, married, widowed, divorced), medical insurance (medical insurance for urban workers, medical insurance for urban residents, the new rural cooperative medical insurance, others), smoking status (never, quit, current smoker), and alcohol consumption (never, occasionally, more than once a week, everyday). Missing values were handled using multiple imputations by chained equation (van Buuren & Groothuis-Oudshoorn, 2011). Regarding environmental confounders, we obtained the monthly precipitation (PRE) dataset (2009–2020) at 1 km^2 resolution as previously described (Peng et al., 2019). The night-time light (NTL) satellite dataset was extracted from an extended time-series (2000–2020, 500 m × 500 m resolution) of Suomi National Polar-orbiting Partnership Visible Infrared Imaging Radiometer Suite (NPP-VIIRS) like NTL data (Chen et al., 2021). We also calculated the three-year moving average exposure values prior to the endpoint for PRE and NTL.

2.6. Statistical analysis

2.6.1. Main analysis

We applied a doubly robust (DR) approach (Funk et al., 2011) to estimate the causal relationship between greenness exposure and the mortality risk of lung cancer. Overall, the main analysis involved two steps. First, we constructed a model that relates the exposure (i.e., NDVI) to confounders (i.e., the propensity score). This relationship was used to mimic a randomized trial, thereby creating a pseudo-population where the exposure and confounders are independent. Second, we further addressed confounding by incorporating the confounders into the outcome regression model. The DR approach offers a key advantage by allowing unbiased effect estimates to be obtained, even if only one of the two models is correctly specified. The fundamental assumptions necessary for conferring a causal interpretation on the effect estimate include consistency, exchangeability, positivity, and stable unit treatment value assumption (SUTVA).

In the aforementioned first step, we calculated stabilized inverse-probability weights (IPWs) for each greenness exposure in different buffers (i.e., 250 m, 500 m, and 1000 m) conditional on the potential confounders. To determine the preferable weighting method, we considered three methods in the calculation of IPW, including generalized linear modeling (Naimi et al., 2014), generalized boosted modeling (McCaffrey et al., 2013), and entropy balancing (Hainmueller, 2012). To address outliers, the weights exceeding the upper percentile were replaced with the value at the 99th percentile, while the weights falling below the lower percentile were assigned the value at the 1st percentile (Yazdi et al., 2021). Covariate balance was assessed using the average absolute correlation (AC), with a value <0.1 indicating a desirable balance (Zhu et al., 2015). The entropy balancing was selected for further analysis due to the lowest AC values observed (Fig. S1).

In the aforementioned second step, we performed the Cox proportional hazard (PH) model to assess the causal relationship between greenness exposure and lung cancer mortality, given the confounders and individuals weighted by the IPW obtained in the preceding step. HRs and corresponding 95 %CIs were calculated for each inter-quartile range (IQR) increment in NDVI values. Despite observing some indication of nonproportionality, we opted for the fixed-time Cox PH model as it offers a weighted average of the time-varying HRs, effectively summarizing the exposure effect (Stensrud & Hernán, 2020). According to the directed acyclic graph (DAG) (Fig. S2), we identified the minimal sufficient adjustment set necessary to estimate the total effect of greenness on the lung cancer mortality risk using the backdoor criteria (Brewer et al., 2017; Tennant et al., 2021). We developed the following three models: (1) Age-adjusted model: adjusted for age at the baseline; (2) Minimum-adjusted model: incorporated the minimum sufficient set of adjusted variables determined by DAG (age at baseline, sex, ethnicity, education, marital status, NTL, and PRE); (3) Full-adjusted model: adjusted all potential confounders (minimal sufficient adjustment set and additional inclusion of smoking, drinking, and medical insurance). Following the principles of causal inference theory (Pearl, 2009), we selected the minimum-adjusted model as the main model. We applied a bootstrap-based method with 200 replicates to simultaneously account for the uncertainty of estimations of both weighting and exposure-outcome association (Austin, 2016). To assess the potentially nonlinear relationship between greenness exposure and lung cancer mortality, we additionally applied a weighted Cox PH model with the penalized spline smoothing method ($df = 3$) (Malloy et al., 2009).

2.6.2. Stratified analysis

We further performed a stratified analysis to examine effect-measure modification (EMM). Based on prior studies, modifier variables considered in our study included age (<65; ≥ 65 years old), sex (female; male), marital status (not married; divorced; widowed; married), education (primary or below; secondary school; high school; university or above) and NTL (Quartile1- Quartile4). The EMM was tested using a partial likelihood ratio test (with and without the interaction term).

2.6.3. Multiple mediation analysis

We applied a multiple mediation analysis (MMA) approach, as proposed by Yu et al., to examine the potential effects of various mediators [particulate matters (PM_1, $PM_{2.5-1}$, $PM_{10-2.5}$), temperature, BMI, and physical activity] in the causal pathway between greenness exposure and lung cancer mortality (Yu et al., 2019). The joint effect from PM_1, $PM_{2.5-1}$, and $PM_{10-2.5}$ instead of any individual effect was considered due to their strong intercorrelation and potential causal relationship.

The MMA approach enables simultaneous consideration of multiple correlated mediators in the pathway analysis. The MMA considered all potential confounders in the associations between exposure, mediators, and outcome, including age at baseline, sex, ethnicity, education, marital status, smoking status, alcohol consumption, medical insurance, NTL, and PRE. First, we assumed a multivariate normal distribution for multiple mediators and employed a generalized linear model to examine the relationship between multiple mediators and greenness conditional on potential confounders. Second, we used the Cox PH model to estimate the association between lung cancer mortality and all other predictors (i.e., greenness exposure, multiple mediators, and potential confounders). Finally, we decomposed the average total effect into the average direct effect (ADE) and average indirect effect (ATE) through each mediator. The AIE is defined as the average change in the outcome mediated by a certain mediator with an IQR increase in greenness. The ADE represents the lung cancer mortality risk associated with a greenness that cannot be explained by the mediators. We used the bootstrap method with 200 replicates to estimate the uncertainty.

2.7. Sensitivity analysis

Several sensitivity analyses were conducted to evaluate the robustness of the results, we (1) calculated E-value (Haneuse et al., 2019) for the DR approach to evaluate the robustness of our causal results against potential unmeasured confounding. It can be calculated without making any assumptions regarding unmeasured confounders and helps estimate the overall strength of potential unmeasured confounding that could affect our causal findings; (2) compared the findings using the imputed cohort against those using the complete cohort data which excluded the missing values; and (3) alternatively treated multiple mediators as confounders rather than mediators to further support the findings in MMA. All data analyses were performed using R version 4.2.0.

3. Results

3.1. Descriptive characteristics

We identified 581,785 individuals with 3,303 deaths from lung cancer over 4,480,441 person-years of follow-up (Jan 2009–Dec 2020). Table 1 presents the baseline characteristics of our cohort stratified by lung cancer mortality. The mean age of the overall cohort at baseline was 48.36 (SD: 17.56) years, with 47.48 % of participants being male, 77.17 % being married, and 64.61 % with a high school or higher education degree. Larger lung cancer mortality was observed among elderly, male, individuals who have a lower education level, are current smokers, or have abnormal weight. The demographic characteristics of the cohort by greenness exposure are shown in Table S2.

Table 2 displays the distribution of environmental exposure variables. The median (P25, P75) of NDVI in the pooled cohort was 0.214 (0.189, 0.249), 0.214 (0.189, 0.252), and 0.215 (0.188, 0.256) in the 250 m, 500 m, and 1000 m grid, respectively. The Spearman correlation matrix showed that NDVI at different buffers was all negatively correlated with PM_1 (r: −0.39 to −0.42), PM_{25} (r: −0.41 to −0.43), and PM_{10} (r: −0.47 to −0.48) while demonstrating a positive correlation with NTL (r: 0.31 to 0.36) (Table S3). The distribution of lung cancer mortality by quartile of NDVI is shown in Table S4.

Table 1
Characteristics of the participants based on lung cancer mortality (N = 581,785 with 3,303 deaths of lung cancer over 4,480,441 person-years of follow-up, 2009–2020).

	Overall (n = 581,785)	Non-death of lung cancer (n = 578,482)	Death of lung cancer (n = 3,303)	P value
Age, mean (SD)	48.36 (17.56)	48.25 (17.53)	67.78 (11.90)	<0.001
Age groups, n (%)				
18–44	254,237 (43.70)	254,162 (43.94)	75 (2.27)	<0.001
45–64	217,205 (37.33)	215,970 (37.33)	1,235 (37.39)	
≥65	110,343 (18.97)	108,350 (18.73)	1,993 (60.34)	
Sex,n (%)				<0.001
Female	305,548 (52.52)	304,425 (52.62)	1,123 (34.00)	
Male	276,237 (47.48)	274,057 (47.38)	2,180 (66.00)	
Ethnicity, n (%)				<0.001
Han Chinese	570,811 (98.11)	567,541 (98.11)	3,270 (99.00)	
Ethnic minority	10,974 (1.89)	10,941 (1.89)	33 (1.00)	
Marital status, n (%)				<0.001
Not Married	108,494 (18.65)	108,303 (18.72)	191 (5.78)	
Married	448,945 (77.17)	446,145 (77.12)	2,800 (84.77)	
Widowed	17,396 (2.99)	17,137 (2.96)	259 (7.84)	
Divorced	6,950 (1.19)	6,897 (1.19)	53 (1.60)	
Medical insurance, n (%)				<0.001
Medical insurance for urban workers	355,100 (61.04)	352,936 (61.01)	2,164 (65.52)	
Medical insurance for urban residents	164,444 (28.27)	163,490 (28.26)	954 (28.88)	
New rural cooperative medical insurance	6,452 (1.11)	6,448 (1.11)	4 (0.12)	
Others	55,789 (9.59)	55,608 (9.61)	181 (5.48)	
Education, n (%)				<0.001
Primary school or below	74,239 (12.76)	73,301 (12.67)	938 (28.40)	
Secondary school	131,644 (22.63)	130,696 (22.59)	948 (28.70)	
High school	266,807 (45.86)	265,574 (45.91)	1,233 (37.33)	
College or greater than college	109,095 (18.75)	108,911 (18.83)	184 (5.57)	
Physical activity, n (%)				0.014
Never	322,723 (55.47)	321,031 (55.50)	1,692 (51.23)	
Occasionally	73,249 (12.59)	72,828 (12.59)	421 (12.75)	
More than once a week	68,953 (11.85)	68,586 (11.86)	367 (11.11)	
Everyday	116,860 (20.09)	116,037 (20.06)	823 (24.92)	
Smoking status, n (%)				<0.001
Never smoking	506,285 (87.02)	503,715 (87.08)	2,570 (77.81)	
Quit smoking	6,753 (1.16)	6,625 (1.15)	128 (3.88)	
Current smoking	68,747 (11.82)	68,142 (11.78)	605 (18.32)	
Alcohol consumption, n (%)				0.135

(continued on next page)

Table 1 (*continued*)

	Overall (n = 581,785)	Non-death of lung cancer (n = 578,482)	Death of lung cancer (n = 3,303)	P value
Never	516,143 (88.72)	513,289 (88.73)	2,854 (86.41)	
Occasionally	18,921 (3.25)	18,768 (3.24)	153 (4.63)	
More than once a week	5,851 (1.01)	5,791 (1.00)	60 (1.82)	
Everyday	40,870 (7.02)	40,634 (7.02)	236 (7.15)	
BMI, *n* (%)				<0.001
Low weight	30,369 (5.22)	30,166 (5.21)	203 (6.15)	
Normal	444,649 (76.43)	442,242 (76.45)	2,407 (72.87)	
Overweight	106,767 (18.35)	106,074 (18.34)	693 (20.98)	

Data are n (%), mean (SD); Abbreviations: NDVI, normalized difference vegetation index; BMI, body mass index; SD, standard deviation.

3.2. Associations between greenness exposure and lung cancer mortality

The estimated HRs for the risk of lung cancer mortality associated with NDVI are presented in Fig. 1 and detailed in Table S5. We observed a decreased risk of lung cancer mortality with increased greenness exposure across all models: age-, minimum-, and full-adjusted models. Compared to the age-adjusted model, the adjustments for minimum or full covariates attenuated the protective effects of NDVI. HRs for different buffer sizes of NDVI, for minimum or fully adjusted showed consistent results. In the minimum adjusted model, an IQR increase in $NDVI_{250m}$, $NDVI_{500m}$, and $NDVI_{1000m}$ were inversely associated with lung cancer mortality, yielding HRs (95 %CI) of 0.91 (0.87, 0.97), 0.89 (0.83, 0.96), and 0.88 (0.79, 0.98), respectively.

We observed non-linear exposure-response relationships (P for non-linear < 0.05) between long-term greenness exposure and lung cancer mortality risk across different NDVI buffer sizes (Fig. 2). The non-linear curve indicated that the protective effect of greenness on lung cancer mortality increased with higher levels of greenness, but the tendency flattened out.

3.3. Stratified analysis

Table 3 presents the results of the stratified analysis. We observed significant effect modifications by education ($P < 0.001$), marital status ($P = 0.002$), and NTL ($P < 0.001$), and these findings were similar across NDVI within different buffer sizes (250 , 500 , and 1000 m buffer). Participants with an education level of high school or above (HRs: 0.77 to 0.84) exhibited a stronger protective effect of greenness against lung cancer mortality compared to their counterparts (HRs: 0.95 to 1.03). Married participants showed a stronger association between greenness and lung cancer mortality (HRs: 0.86 to 0.89) relative to participants who were not married, widowed, or divorced (HRs: 1.03 to 1.06). Moreover, the protective effect of greenness was stronger among the participants with higher NTL exposure levels.

Table 2
Distribution of environmental exposure variables.

	Mean (SD)	Percentiles					IQR
		Min	25th	50th	75th	Max	
NDVI							
250 m	0.223 (0.044)	0.074	0.189	0.214	0.249	0.522	0.060
500 m	0.224 (0.043)	0.102	0.189	0.214	0.252	0.544	0.063
1000 m	0.224 (0.043)	0.123	0.188	0.215	0.256	0.542	0.068
Particulate matter (μg/m^3)							
PM_1	15.46 (2.02)	13.13	14.17	15.34	16.04	29.22	1.87
$PM_{2.5}$	30.25 (2.43)	27.33	29.00	29.33	30.33	44.00	1.33
PM_{10}	52.54 (3.45)	47.67	50.33	52.33	53.67	74.33	3.33
Temperature (°C)	22.73 (0.14)	21.70	22.71	22.77	22.80	22.95	0.09
Precipitation (mm)	1486.72 (27.51)	1186.11	1474.78	1493.22	1501.78	1599.53	27.00
NTL (nW cm^{-2} sr^{-1})	35.52 (8.11)	9.91	29.51	34.08	39.98	82.59	10.47

Abbreviations: NDVI, normalized difference vegetation index; PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, fine particulate matter; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; IQR, inter-quartile range; NTL, nighttime light; Min, minimum; Max, maximum.

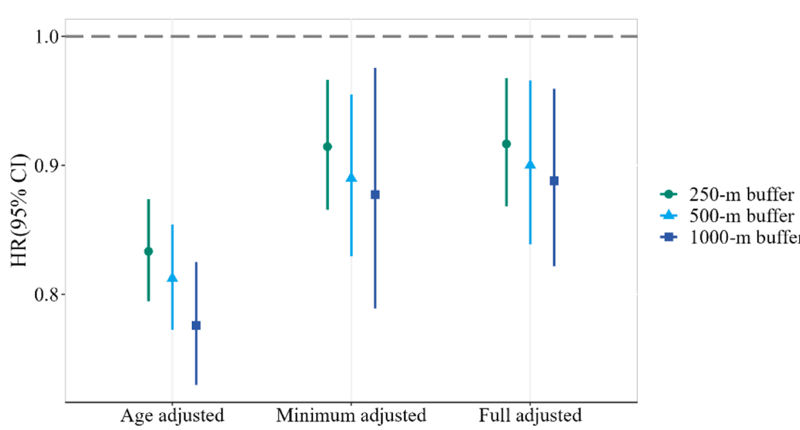

Fig. 1. The effect of greenness on the mortality of lung cancer with each IQR increase in NDVI within the different buffers (250 m, 500 m, 1000 m). Age-adjusted model: adjusted for age; Minimum-adjusted model, adjusted the minimum sufficient variables set (age, sex, ethnicity, education, marital status, nighttime light, and precipitation); Full-adjusted model: minimum sufficient adjustment set + medical insurance, smoking, and drinking. Abbreviation: HRs, hazard ratios; CI, confidence interval; IQR, inter-quartile range; NDVI, normalized difference vegetation index.

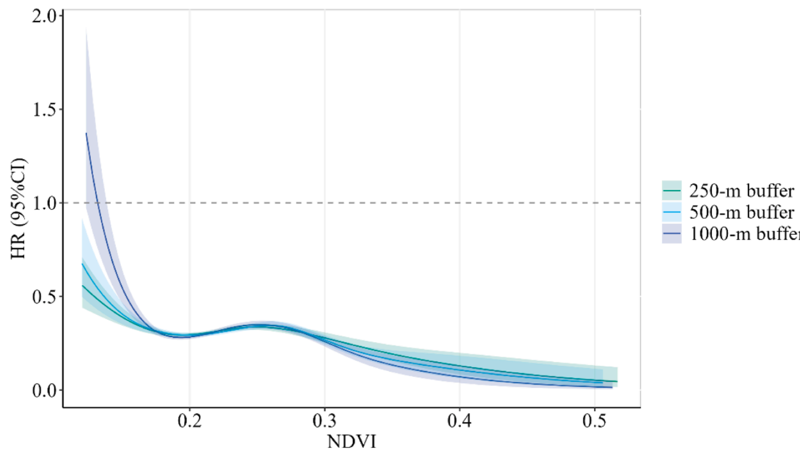

Fig. 2. Exposure-response association for greenness exposure in different buffers and mortality risk of lung cancer in southern China, 2009–2020. HRs (solid lines) and 95 %CI (shaded areas) are estimated from the weighted Cox PH model with the penalized spline smoothing method ($df = 3$) and adjusted for age at the baseline visit, sex, ethnicity, education, marital status, nighttime light, and precipitation. Abbreviation: HRs, hazard ratios; CI, confidence interval; NDVI, normalized difference vegetation index.

3.4. Multiple mediation analysis

Table 4 presents the estimation of mediating effect (HRs), the values of which indicate the average change in the outcome mediated by a certain mediator with an IQR increase in greenness. Results from mediation analyses showed that the association between greenness and lung cancer mortality might be mediated by particulate matter, temperature, and physical activity, with an estimated total average indirect effect of 0.841 (95 % CI: 0.789, 0.896), 0.826 (95 % CI: 0.769, 0.887), and 0.748 (95 % CI: 0.668, 0.837) for $NDVI_{250m}$, $NDVI_{500m}$, and $NDVI_{1000m}$, respectively. We observed that the protective effect of greenness on lung cancer mortality was primarily mediated by particulate matter. For NDVI in a 500 m radius, an IQR increase in greenness might reduce 36.7 % (95 %CI: 32.8, 40.4 %) mortality risk of lung cancer by modifying particulate matter exposure. In contrast, greenness in 500 m buffer might increase the mortality risk of lung cancer through both the temperature and physical activity pathways, with a stronger mediating effect of temperature (HR = 1.306, 95 % CI: 1.283, 1.329) than physical activity (HR = 1.015, 95 % CI: 1.011, 1.018). These findings were consistent for NDVI in a 250 m or 1000 m radius. The coefficient estimations of the outcome model are shown in Table S6.

3.5. Sensitivity analysis

Our conclusions were robust for all sensitivity analyses. First, the E-values for the point estimate of the minimum adjusted model were from 1.43 (1.25) to 1.50 (1.16), representing that our estimates would be robust unless there exists an unmeasured covariate that has a relative risk association as large as 1.43–1.50 with both greenness and lung cancer mortality. It is less likely true, especially given that it exceeds the effect observed for most risk factors for lung cancer (Table S6). Second, consistent associations between NDVI and lung cancer mortality were observed with the complete case dataset (Table S7). Third, we observed that the protective associations between greenness and lung cancer mortality were greatly weakened when we further adjusted for particulate matter (PM_1, $PM_{2.5–1}$, or $PM_{10–2.5}$) as a confounder (Fig. S3). These findings further verify that particulate matter was an important mediator in such a protective association of greenness. In contrast, as expected, these protective effects of greenness became slightly strengthened when we further adjusted for the temperature or physical activity while the mediation conclusion also remains unchanged (Fig. S3).

4. Discussion

This large-scale community-based prospective cohort demonstrated that each IQR increment in long-term greenness exposure could reduce the risk for lung cancer mortality by 9–12 %. These inverse associations were stronger among participants who were more educated, married, and had higher NTL exposure levels. Furthermore, the association tended to be mediated by particulate matter, temperature, and physical activity. Notably, particulate matter showed the strongest mediation effect.

4.1. Causal link of greenness exposure against lung cancer mortality

We observed a robust protective effect of residential greenness against lung cancer mortality risk. Consistent protective associations were also reported in other cohort studies, including the Beijing registered-based cohort (per 0.1-unit in $NDVI_{250m}$, HR = 0.93, 95 % CI: 0.92, 0.95) (Yang et al., 2021), the Dutch national cohort (per IQR increase in $NDVI_{300m}$, HR = 0.93, 95 %CI: 0.92, 0.94) (Klompmaker et al., 2019), the Belgian register-based cohort (per IQR increase in $NDVI_{300m}$, HR = 0.95, 95 %CI: 0.92, 0.97) (Rodriguez-Loureiro et al., 2022), the Taiwan retrospective longitudinal cohort (per 0.1 unit increase in NDVI, HR = 0.95, 95 % CI: 0.91, 0.99) (Huang et al., 2022), and Israel registry-based cohort (per IQR increase in $NDVI_{300m,}$ HR = 0.75, 95 % CI: 0.66, 0.85) (Kayyal-Tarabeia et al., 2022). These consistent findings somewhat support our conclusions and indicate the beneficial role of residential greenness exposure against lung cancer mortality.

However, many studies conducted across the world suggested a null assoc iation between greenness and lung cancer mortality, such as New Zealand (Richardson et al., 2010), the United Kingdom (Richardson & Mitchell, 2010), the United States (Coleman et al., 2022), the and Japan (Li et al., 2008). These inconsistencies may be attributed to several factors, including differences in study design, sample size, vegetation structure, and statistical modeling. Compared with cohort design, ecological fallacy and exposure misclassification for these cross-sectional or system-registered data could potentially lead to such a negative result. Also, prior cohort studies have indicated that insufficient samples or follow-up time may also lead to a reduced statistical power to detect association (Klompmaker et al., 2019; Rodrigue-z-Loureiro et al., 2022). Furthermore, even with the same increment in greenness exposure, the heterogeneity in green space structure and vegetation types may influence the estimation of greenness-associated health effects (Nguyen et al., 2021). For example, tree canopy, and forests may exert a greater influence on mean NDVI exposure values

Table 3
Associations between greenness (per IQR increase in NDVI) and the risk of lung cancer mortality, stratified by potential modifiers.

Subgroup	NDVI exposure					
	250 m buffer [HRs (95 % CI)][a]	P [b]	500 m buffer [HRs (95 % CI)][a]	P [b]	1000 m buffer [HRs (95 % CI)][a]	P [b]
Age		0.281		0.191		0.076
18–65 years	0.92 (0.80, 1.06)		0.93 (0.73, 1.18)		1.01 (0.73, 1.39)	
≥65 years	0.85 (0.80, 0.91)		0.83 (0.77, 0.89)		0.81 (0.66, 0.99)	
Sex		0.088		0.074		0.182
Male	0.87 (0.82, 0.93)		0.86 (0.79, 0.93)		0.83 (0.71, 0.98)	
Female	1.02 (0.91, 1.13)		1.00 (0.88, 1.14)		1.00 (0.86, 1.15)	
Education		<0.001		<0.001		0.002
Primary or below	1.01 (0.91, 1.12)		0.99 (0.89, 1.10)		0.95 (0.85, 1.07)	
Secondary	1.03 (0.90, 1.16)		0.99 (0.83, 1.18)		0.99 (0.83, 1.19)	
High school	0.83 (0.76, 0.90)		0.82 (0.74, 0.91)		0.81 (0.71, 0.92)	
University or above	0.77 (0.57, 1.05)		0.81 (0.62, 1.05)		0.84 (0.53, 1.33)	
Marital status		< 0.001		0.002		< 0.001
Not married/ Widowed/ Divorced	1.06 (0.91, 1.25)		1.03 (0.88, 1.22)		1.04 (0.89, 1.23)	
Married	0.89 (0.84, 0.95)		0.88 (0.82, 0.95)		0.86 (0.79, 0.94)	
NTL		< 0.001		<0.001		<0.001
Quartile1	1.09 (0.96, 1.22)		1.11 (0.98, 1.25)		1.19 (1.05, 1.36)	
Quartile2	0.83 (0.71, 0.97)		0.85 (0.74, 0.98)		0.83 (0.72, 0.97)	
Quartile3	0.86 (0.79, 0.93)		0.82 (0.76, 0.89)		0.76 (0.69, 0.84)	
Quartile4	0.70 (0.60, 0.81)		0.61 (0.51, 0.72)		0.52 (0.42, 0.65)	

Abbreviations: NDVI, normalized difference vegetation index; IQR, interquartile range; NTL, nighttime light; HRs, hazard ratios; CI, confidence interval.
[a] The effects were estimated by the weighted Cox PH model adjusted for age at the baseline visit, sex, ethnicity, education, marital status, NTL, and precipitation.
[b] P values represent the interaction effects between NDVI and potential modifiers and were obtained by the likelihood ratio test.

(Martinez & Labib, 2023) and exhibit a more consistent association with better respiratory health compared to grass (Egorov et al., 2020). Notably, this study applied doubly robust estimation techniques to minimize bias risk due to model misspecification and enable causal estimates of exposure effect under specific assumptions (Funk et al., 2011). The DR approach yielded more powerful and robust results compared to previous studies using the traditional association approaches. Overall, it is suggested that more cohort studies with large sample sizes, long follow-up periods, and comprehensive vegetation-type information are warranted to confirm the causal association between residential greenness and lung cancer mortality in China.

Table 4
Summary of mediation effect estimations for the association between greenness (per IQR increase in NDVI) and lung cancer mortality [Hazard ratios (HRs) and 95 % confidence interval (CI)].

Mediators	250 m buffer	500 m buffer	1000 m buffer
Total AIE	0.841 (0.789, 0.896)	0.826 (0.769, 0.887)	0.748 (0.668, 0.837)
Particulate matter (μg/m^3)	0.649 (0.615, 0.685)	0.633 (0.596, 0.672)	0.547 (0.498, 0.600)
PM_1	0.614 (0.595, 0.633)	0.587 (0.570, 0.604)	0.541 (0.517, 0.567)
$PM_{2.5-1}$	0.958 (0.954, 0.962)	0.949 (0.944, 0.953)	0.949 (0.944, 0.955)
$PM_{10-2.5}$	1.103 (1.046, 1.163)	1.097 (1.035, 1.163)	1.063 (0.984, 1.150)
Temperature (°C)	1.297 (1.276, 1.318)	1.306 (1.283, 1.329)	1.368 (1.332, 1.405)
BMI (kg/ m^2)	1.000 (0.998, 1.001)	1.000 (0.998, 1.001)	1.000 (0.998, 1.002)
Physical activity	1.017 (1.013, 1.021)	1.015 (1.011, 1.018)	1.015 (1.010, 1.021)

Abbreviations: NDVI, normalized difference vegetation index; IQR, interquartile range; NTL, nighttime light; HRs, hazards ratios; CI, confidence interval; AIE, average indirect effect; PM_1, particulate matter with an aerodynamic diameter ≤ 1 μm; $PM_{2.5}$, fine particulate matter; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; $PM_{2.5-1}$, the difference between $PM_{2.5}$ and PM_1; $PM_{10-2.5}$, the difference between PM_{10} and $PM_{2.5}$.
HRs and 95 %CI were estimated by multiple mediation analyses with adjustment for age at the baseline visit, sex, ethnicity, education, marital status, NTL, and precipitation, smoking, drinking, medical insurance.

4.2. Modification effect

We demonstrated that participants with higher education attainment would benefit more from greenness exposure. In line with our findings, a registered-based cohort in Belgium also observed a significant modification effect of educational level on greenness-associated lung cancer mortality risk (Rodriguez-Loureiro et al., 2022). It has been well-documented that higher educational attainment has a direct impact on individual happiness and may indirectly improve happiness by increasing individual income (Yang et al., 2022). Better economic status may also be associated with higher community-level greenness and lower noise pollution. Additionally, we observed a higher protective effect of greenness among married participants. A meta-analysis of 7, 881,040 individuals reported that non-partnered people had a 33 % higher risk of cancer mortality compared with married couples (Wang et al., 2020). Non-partnered individuals have an elevated risk of mental disorders (Hossain et al., 2020), cognitive impairment (Liu et al., 2019), and lower healthcare utilization (Pandey et al., 2019), which could mask the effect of greenness. However, the modification role of marital status has not been consistently concluded across different participants' characteristics, primary outcomes, and study sample size. Further research is needed to confirm our findings.

Numerous studies have suggested a relationship between NTL and increased risk of cancer and adverse mental health outcomes (Al-Naggar & Anil, 2016; Paksarian et al., 2020). However, the role of NTL on the health effect of residential greenness remains poorly understood (Stanhope et al., 2021). By including NTL as confounding in the main model and comparing the benefits of residential greenness among different NTL quartile groups, we showed that more mortality benefits were observed in people exposed to higher levels of NTL. Physical activity at night may be a potential explanation for this phenomenon. People are more likely to move around in brightly lit places at night. A positive correlation between NTL and residential greenness ($r = 0.31$–0.36) was observed in our data, which indicated a higher residential greenness exposure for those people with higher levels of NTL. Moreover, we showed a non-linear effect of residential greenness on lung cancer mortality (Fig. 2), where more mortality benefits of greenness were observed in people exposed to higher levels of greenness, so the modification effect of NTL may be attributed to the diverse exposure to greenness levels. Due to limited evidence to date, it remains unclear whether other factors play a role in these phenomena and more in-depth research is needed.

4.3. Mediation effect

We observed that the protective effect of greenness against lung cancer mortality risk was mainly mediated by particulate matter. Previous evidence has demonstrated the mediating effect of particulate matter in other diseases, including blood pressure (Chen et al., 2022), depression (Zhang et al., 2022), and birth outcomes (Lee et al., 2021). Only one study (Rodriguez-Loureiro et al., 2022) has quantitatively assessed the mediating effect of particulate matter on greenness-associated lung cancer mortality risk, aligning with the present study findings (Proportion mediated by PM_{10}: 6 % [95 % CI: 1–12 %]). Consistent with previous evidence, we also observed a negative correlation between greenness and particulate matter (Table S3) and a positive marginal association of particulate matter with lung cancer mortality risk (Table S6). These findings suggest that greenness could alleviate the risk of lung cancer mortality by reducing particulate matter concentrations. Several potential biological mechanisms may explain the removal of particulate matter due to greenness exposure. In our study region with a southern subtropical monsoon climate, evergreen broad-leaved forests were predominantly the vegetation type. Plant stomata, microscopic pores on leaves, are known to efficiently remove particulate matter through the processes of deposition and adsorption (Kwak et al., 2020; Popek, et al., 2019). Furthermore, most emissions of primary pollutants may not be present in greenspace (e.g. the lack of traffic) (Su et al., 2011). The barrier or filtering effect of green space could also block pollutant flows and help attenuate the dispersion of traffic-related pollution (Abhijith et al., 2017).

Another contribution of our study is the statistically significant positive mediating effect of temperature (HR > 1), suggesting that greenness may increase the risk of lung cancer mortality through the temperature pathway. Based on a literature review, no previous study has investigated the extent to which the beneficial effects of greenness can be explained by temperature. Previous studies suggested that greenness could mitigate the UHI effect by solar radiation absorption and evapotranspiration, and thus influence the temperature-health association (Markevych et al., 2017). Since Guangzhou has a subtropical monsoon climate, the impact of vegetation on temperature may be negligible (Lamchin et al., 2018) and low-temperature present a higher mortality attribution fraction than the high temperature in the subtropical monsoon climate zone (Li et al., 2023). Moreover, we observed a statistically significant but relatively small mediating effect of physical activity on greenness-associated lung cancer mortality risk. Several studies have shown that physical activity could partially explain the beneficial effect of greenness on COPD incidence (Yu et al., 2023a), hypertension (Jia et al., 2018), and all-cause mortality (James et al., 2016). However, some studies reported no mediating effect for physical activity (Huang et al., 2021; Yang et al., 2020). Different measures of physical activity, mediation analysis models, and vegetation structures might be important reasons for these discrepancies. More studies are still needed to elucidate the potential mediating role of temperature and physical activity in greenness-associated health.

4.4. Strengths and limitations

Our study has several strengths. This study is the first to prospectively examine the causal links between urban greenness exposure and lung cancer mortality, employing state-of-the-art causal methodologies. Second, this is the first study to apply a multiple mediation analysis method considering inter-mediator correlations to quantify the multiple potential mediating pathways between urban greenness exposure and lung cancer mortality. Furthermore, this study is based on a large-scale cohort ($n = 581{,}785$) with a long follow-up period, which ensured sufficient statistical power.

Several limitations must be noted. First, the assessment of residential greenness exposure relied on an overall NDVI measure, which was unable to differentiate the reflectance between vegetation types (e.g., tree canopy, grass or shrubs/forbs). Several studies have indicated that different types of vegetation and the structural characteristics of green space may have heterogeneous effects on air pollution and human health (Nguyen et al., 2021). Due to limited data resources available for the study period (2009–2020), we were unable to obtain detailed information regarding the specific types of vegetation. Nevertheless, the robustness and consistency of our findings have also provided important insights into the potential protective effect against lung cancer mortality of overall urban greenness exposure. Further research is needed to elucidate the health effects of different vegetation types and explore the potential causal pathways. Second, the causal inference approaches inherently assume the absence of unmeasured confounders, which may not be true with the observational data. However, the E-values in the sensitivity analysis suggested that our estimates should be robust against the potential residual confounding issue. Future studies may collect more information on confounders such as household income and occupation (Klompmaker et al., 2019). Third, the physical activity used as a mediator in our study was collected from self-reported questionnaires. Such self-report measures may suffer from self-reporting bias (e.g., recall or response bias) and be not able to capture all forms of physical activity. The measurement errors in self-report data may attenuate the association between greenness exposure and physical activity, potentially resulting in an underestimation of the mediating effect. However, it is difficult to accurately quantify the physical activity for each of the 0.6 million participants and address these measurement errors through post hoc methods. Future studies need to collect direct measured data (e.g., accelerometers measured data) and validate the self-reported information. Furthermore, more comprehensive mediator measures such as mental health, and social cohesion may be considered in future research. Fourth, the exposure assessment was based on the geocoded residential addresses at baseline and we cannot guarantee the absolute stability of home locations throughout the study period. Additionally, the residential location considered in the present study possibly only accounts for a proportion of human activity spaces. However, collecting individualized time-activity information in large epidemiological studies, like our cohort with nearly 0.6 million participants, is a formidable challenge. The absence of such data limits our ability to assess personal greenness levels and understand how exposure patterns influenced the association. Future studies that incorporate real-time personal-level measurements of greenness and air pollution exposure are warranted.

5. Conclusion

In summary, this study is the first to prospectively examine the causal links and multiple mediation pathways between urban greenness exposure and lung cancer mortality using state-of-the-art causal methodologies and multiple mediation analysis methods. Based on the large community-based prospective cohort in southern China, we observed protective causal associations between urban greenness exposure and lung cancer mortality in southern China. The protective effect of greenness was particularly pronounced among participants with higher education levels, marital status, or greater exposure to NTL. Notably, the results of multiple mediation analyses indicated that the protective effect of urban greenness against lung cancer mortality could be achieved primarily by reducing the particulate matter concentration. The present study adds to the limited literature on causal links and potential mediation pathways between greenness and lung cancer mortality. These findings hold significant implications for urban planners, suggesting that green space planning can be a viable and effective strategy for palliating lung cancer, controlling urban air pollution, and promoting urban sustainable development. Future studies on the topic need to integrate more comprehensive data, including diverse vegetation types, additional mediation pathways (e.g., mental health), multiple measures of physical activity, and individuals' time-activity patterns, to provide more detailed insights for urban policy-making.

CRediT authorship contribution statement

Wenjing Wu: Writing – original draft, Conceptualization, Formal analysis, Visualization, Methodology, Investigation, Writing – review & editing. **Gonghua Wu:** Writing – original draft, Methodology, Investigation, Writing – review & editing. **Jing Wei:** Data curation, Project administration, Conceptualization, Resources, Investigation, Writing – review & editing. **Wayne R Lawrence:** Methodology, Investigation, Writing – review & editing. **Xinlei Deng:** Methodology, Investigation, Writing – review & editing. **Yuqin Zhang:** Methodology, Investigation, Writing – review & editing. **Shirui Chen:** Methodology, Investigation, Writing – review & editing. **Ying Wang:** Conceptualization, Investigation, Funding acquisition. **Xiao Lin:** Conceptualization, Investigation, Funding acquisition. **Dan Chen:** Conceptualization, Investigation, Writing – review & editing. **Xinling Ruan:** Conceptualization, Investigation, Writing – review & editing. **Qiaoxuan Lin:** Investigation, Funding acquisition. **Zhiqiang Li:** Conceptualization, Investigation, Writing – review & editing. **Ziqiang Lin:** Investigation, Writing – review & editing. **Chun Hao:** Conceptualization, Investigation, Writing – review & editing. **Zhicheng Du:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Investigation, Writing – review & editing. **Wangjian Zhang:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Investigation, Writing – review & editing. **Yuantao Hao:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.scs.2023.105079.

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