



Full length article



Exposure to green spaces, cardiovascular risk biomarkers and incident cardiovascular disease in older adults: The Seniors-Enrica II cohort

Cara Scheer^{a,1}, Elena Plans-Beriso^{b,c,d,1}, Roberto Pastor-Barriuso^{c,d}, Rosario Ortolá^{d,e}, Mercedes Sotos-Prieto^{d,e,f,g}, Verónica Cabañas-Sánchez^{d,e}, Pedro Gullón^{h,i}, Carlos Ojeda Sánchez^j, Rebeca Ramis^{c,d}, Pablo Fernández-Navarro^{c,d}, Fernando Rodríguez-Artalejo^{c,d,g}, Esther García-Esquinas^{c,d,*}

^a Fulda University of Applied Sciences. Fulda, Germany

^b Public Health and Epidemiology Research Group, School of Medicine, Universidad de Alcalá, 28871 Madrid, Spain

^c Department of Chronic Diseases, National Center of Epidemiology, Carlos III Health Institute, Madrid, Spain

^d CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain

^e Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid. Madrid, Spain/ CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain

^f Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

^g IMDEA Food Institute. CEI UAM+CSIC, Madrid, Spain

^h Department of Surgery, Social and Medical Sciences. School of Medicine and Health Sciences, Universidad de Alcalá. Alcalá de Henares, Madrid, Spain

ⁱ Centre for Urban Research, RMIT University, Melbourne, Australia

^j Guadalajara University Hospital. Guadalajara, Spain

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ABSTRACT

Introduction: The impact of residential green spaces on cardiovascular health in older adults remains uncertain. **Methods:** Cohort study involving 2114 adults aged ≥ 65 years without cardiovascular disease (CVD), residing in five dense municipalities (Prince et al., 2015) of the Madrid region and with detailed characterization of their socioeconomic background, health behaviors, CVD biological risk factors, and mental, physical, and cognitive health. Greenness exposure was measured using the Normalized Difference Vegetation Index (NDVI) at varying distances from participants' homes. Traffic exposure, neighborhood environment, neighborhood walkability, and socioeconomic deprivation at the census level were also assessed. Serum N-terminal pro-B-type natriuretic peptide (NT-ProBNP), high-sensitivity troponin T (hs-TnT), interleukin 6 (IL-6), and Growth Differentiation Factor 15 (GDF-15) were measured at baseline, and incident CVD events identified through electronic medical records (International Classification of Primary Care-2 codes K74, K75, K77, K90, and K92). **Results:** After adjusting for sex, age, educational attainment, financial hardship and socioeconomic deprivation at the census level, an interquartile range (IQR) increase in NDVI at 250, 500, 750, and 1000 m around participants' homes was associated with mean differences in ProBNP of -5.56% (95%CI: $-9.77; -1.35$), -5.05% ($-9.58; -0.53$), -4.24% ($-8.19; -0.19$), and -4.16% ($-7.59; -0.74$), respectively; and mean differences in hs-TnT among diabetic participants of -8.03% (95%CI: $-13.30; -2.77$), -9.52% ($-16.08; -2.96$), -8.05% ($-13.94; -2.16$) and -5.56% ($-10.75; -0.54$), respectively. Of similar magnitude, although only statistically significant at 250 and 500 m, were the observed lower IL-6 levels with increasing greenness. GDF-15 levels were independent of NDVI. In prospective analyses (median follow-up 6.29 years), an IQR increase in residential

Abbreviations: AADT, Annual Average Daily Traffic; BMI, Body Mass Index; CVD, Cardiovascular Disease; eGFR, estimated glomerular filtration rate; GDF-15, Growth differentiation factor 15; GDS, Geriatric Depression Scale; HDL, High-Density Lipoprotein; hs-TnT, High sensitivity troponin T; IHD, Ischemic Heart Disease; IQR, Interquartile range; IL6, Interleukin 6; MCS, Mental Composite Score; METs, Metabolic Equivalents of Tasks (METs); MMSE, Mini-Mental State Examination; MVPA, Moderate-to-Vigorous Physical Activity; NDVI, Normalized Difference Vegetation Index; NT-ProBNP, N-terminal pro-B-type natriuretic peptide; PA, Physical Activity; PANES, Physical Activity Neighborhood Environment Scale; PCS, Physical Composite Score; TV, Television; SDI, Social Deprivation Index; SPPB, Short Physical Performance Battery.

* Corresponding author at: Department of Chronic Diseases, National Center for Epidemiology, Carlos III Institute of Health, 28029, Madrid, Spain.

E-mail address: egarciag@isciii.es (E. García-Esquinas).

¹ These authors contributed equally to the manuscript.

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greenness at 500, 750, and 1000 m was associated with a lower risk of incident CVD. The variables that contributed most to the apparent beneficial effects of greenness on CVD were lower exposure to traffic, improved cardiovascular risk factors, and enhanced physical performance. Additionally, neighborhood walkability and increased physical activity were notable contributors among individuals with diabetes.

Conclusion: Increased exposure to residential green space was associated with a moderate reduction in CVD risk in older adults residing in densely populated areas.

1. Introduction

According to the latest United Nations (UN) estimates, 1 in 6 people will be 65 years of age or older in 2050 (United Nations. United Nations., 2019). Given that 23 %, and up to 50 % in high-income countries, of the total global disease burden is attributable to disorders in people in this age group (Prince et al., 2015), a considerable increase in health care spending is to be expected in the next 30 years (Directorate-General for Economic and Financial Affairs. The, 2021). Healthy aging is therefore becoming an international priority. This importance is reflected in partnerships such as the UN “Decade of Healthy Aging (2021–2030)” initiative, which aims to empower and support people to lead healthy and active lives within their communities, thereby reducing the years of life spent in poor health (Decade of healthy aging, 2022).

The well-being of older adults is significantly influenced by their residential environment, where they tend to spend more time compared to younger individuals, mainly due to retirement or age-associated mobility limitations. For this reason, it is interesting to study the potential influence of specific components of the built environment on the health of the elderly, enabling the design of strategies to support their participation in healthy activities. One specific component of the built environment is the availability of green spaces. Previous research has shown that living in neighborhoods with more green spaces is positively associated with several aspects of health, including improved mental health and self-perceived general health, and reduced morbidity and mortality (Kondo et al., 2018; Nguyen et al., 2021; Twohig-Bennett and Jones, 2018). Focusing on cardiovascular disease (CVD), a leading cause of death and disability in older adults, several systematic reviews and meta-analyses have suggested some protective effects of urban green spaces on traditional cardiometabolic biological risk factors - i.e. hypertension (Lai et al., 2023; Zhao et al., 2022), diabetes (Twohig-Bennett and Jones, 2018; Ccami-Bernal et al., 2023; De la Fuente et al., 2020), dyslipidemia (Fernández Núñez et al., 2022), or increased adiposity (De la Fuente et al., 2020; Teixeira et al., 2021; Shen et al., 2022) -, as well as on ischemic heart disease (IHD), stroke, and overall CVD mortality (Liu et al., 2022; Bianconi et al., 2023). However, the few studies evaluating the specific effects of residential green spaces on cardiovascular health in older adults have yielded mixed results (Yuan et al., 2021). Moreover, there is often a lack of adequate data to determine whether the observed associations can be attributed to behavioral, psychosocial or environmental factors (Markevych et al., 2017).

A wide range of cardiovascular risk biomarkers are currently available, including N-terminal prohormone BNP (NT-ProBNP), high sensitivity Troponin T (hs-TnT), interleukin 6 (IL-6), and Growth Differentiation Factor 15 (GDF-15). Specifically, circulating NT-proBNP, serves as a biomarker indicating increased stress on the heart, providing to be a strong predictor for cardiovascular events, particularly heart failure, in individuals without a history of CVD (Echouffo-Tcheugui et al., 2022; Daniels et al., 2015). Hs-TnT, which functions as a marker of cardiac muscle injury, emerges as a predictive indicator of cardiovascular events and cardiovascular mortality in the general population (Aimo et al., 2022), and has been suggested as a biomarker of subclinical myocardial damage in the context of primary prevention (Muscente and De Caterina, 2021). IL-6, implicated in atherosclerosis and increased inflammation associated with ageing, has been found to predict global CVD, including coronary heart disease, stroke, and heart failure, after adjusting for other inflammation and subclinical myocardial injury

biomarkers such as high sensitivity C-reactive protein (hs-CRP), interleukin 18 (IL-18), NT proBNP, and hs-TnT (Jia et al., 2023). Finally, GDF-15, a systemic biomarker reflecting cellular aging, oxidative stress and systemic inflammation, has gained recognition as a predictor of CVD events, even after adjusting for hs-CRP, natriuretic peptides, and cardiac troponins (di Candia et al., 2021), and provides information on aspects of CVD development, progression, and prognosis that may not be covered by traditional risk predictors (di Candia et al., 2021; Wollert et al., 2017).

The present study aims to assess the association between residential greenness and concentrations of the abovementioned CVD risk biomarkers in older adults without a history of CVD. Additionally, it examines the association between residential greenness and CVD incidence after a mean follow-up of six years, as well as the potential pathways driving the observed associations, using a well-characterized cohort of older adults residing in the city of Madrid and four surrounding large municipalities. Given that 68 % of the world’s population is expected to live in urban areas by 2050, the study of the influence of green spaces in cities takes on even greater importance.

2. Methods

2.1. Study population

The Seniors-ENRICA-2 cohort study comprised 3,273 individuals aged ≥ 65 years recruited between 2015 and 2017 from the community-dwelling population in the Madrid Autonomous Region, including the cities of Madrid (with a population density of around 5,264 inhabitants/km²), Alcorcón (5,008 inhabitants/km²), Torrejón de Ardoz (3,948 inhabitants/km²), Getafe (2,268 inhabitants/km²) and Alcalá de Henares (2,205 inhabitants/km²) (Supplementary Fig. 1) (de la Comunidad, 2023). The selection process involved sex- and district-based stratified random sampling among individuals holding a national healthcare card, representing approximately 99 % of the population (García-Esquinas et al., 2021).

Invitations to participants were sent through the post mail and through direct telephone contacts, and those who accepted to be included in the study gave written informed consent. In order to thoroughly characterize the cohort, trained personnel collected information from participants using standardized protocols at different stages (García-Esquinas et al., 2021; Rodríguez-Artalejo et al., 2011). First, a telephone interview was conducted on sociodemographic factors, health behaviors, self-rated health, and chronic morbidities. Then, during a home visit, trained nurses performed physical examinations (i.e., blood pressure, bioelectrical impedance, anthropometric measurements, grip strength, lower limb strength and balance) and collected blood samples (García-Esquinas et al., 2021). Finally, during an additional participant’s home visit, they obtained an electronic and validated dietary history (Rodríguez-Artalejo et al., 2011). Participants were also equipped with an ambulatory blood pressure monitor (Carrasco-Rios et al., 2023) and a wrist-worn accelerometer (Cabanas-Sánchez et al., 2020). The median time between telephone interviews and physical examinations was 24 days. Participants were re-interviewed by phone in 2020 to update health-related information during COVID-19 confinement (García-Esquinas et al., 2021).

The study protocol was approved by the Clinical Research Ethics Committees of the “La Paz” University Hospital (Protocol #HULP-PI

1793) and the Carlos III Health Institute (Protocol #CEI PI 26_2021).

2.2. Study variables

2.2.1. Exposure to green spaces

The Normalized Difference Vegetation Index (NDVI) is an indicator of vegetation density based on satellite imagery. It measures the amounts of near-infrared and red light reflected by vegetation. On a scale from -1 to $+1$, the NDVI indicates the presence of greenness. Negative values indicate an absence of vegetation, such as roads, buildings, or other structures. Conversely, the higher the positive values, the denser and healthier the vegetation (Pettorelli et al., 2005). A zero on the scale represents blue spaces on the ground (Yengoh et al., 2014). Participants' geocoded home locations were used to estimate residential NDVI (30m resolution) within buffers for different Euclidian distances (250, 500, 750, and 1,000 m) using 2014 images from the Earth Observation study with 0 % cloud cover (<https://earthdata.nasa.gov/learn/discipline/land/>). The NDVI was determined by computing the median NDVI values from raster layers with cloud cover below 5 % during the months between May and September, corresponding to the growing season. This timeframe aligns with the period when trees typically retain their foliage, ensuring a more accurate representation of vegetation dynamics.

2.2.2. Study outcomes

2.2.2.1. CVD biomarkers. Fasting blood samples were collected from each participant in rapid serum tubes with thrombin-based clot activator

and polymer gel (Becton Dickinson). Tubes were centrifuged at 3,000 rpm for 10 min, and serum was aliquoted, frozen at -80°C , and stored in the Department of Preventive Medicine and Public Health at Universidad Autónoma de Madrid. NT-ProBNP, hs-TnT, IL-6, and GDF-15 were measured at the Department of Laboratory Medicine of 'La Paz' University Hospital by an electrochemiluminescence Elecsys® immunoassay method using a cobas® 6000 analyser (Roche Diagnostics).

2.2.2.2. Prevalence and incidence of CVD. Both at baseline and during the 2020 interview, participants reported medical diagnoses of congestive heart failure, coronary heart disease, angina or stroke. To complement information on CVD, we used the primary health care electronic health records from January 1, 1980 to December 31, 2022; and CVDs were defined using the International Classification of Primary Care-2 (ICPC-2) codes, which led to the inclusion of the following conditions: IHD (K74), myocardial infarction (K75), congestive heart failure (K77), stroke (K90), and atherosclerosis and peripheral vascular disease (K92). Thus, prevalent CVD cases in this study, which were excluded from the analyses, were all cases diagnosed before the study entry (either through self-report or through primary health care records), while incident CVD events were all cases that occurred from baseline to December 31, 2022 (median follow-up time of 6.29 years; IQR: 5.99–6.76).

2.2.3. Other variables

2.2.3.1. Sociodemographic and socioeconomic factors. Information was collected on age sex, educational attainment (primary, secondary,

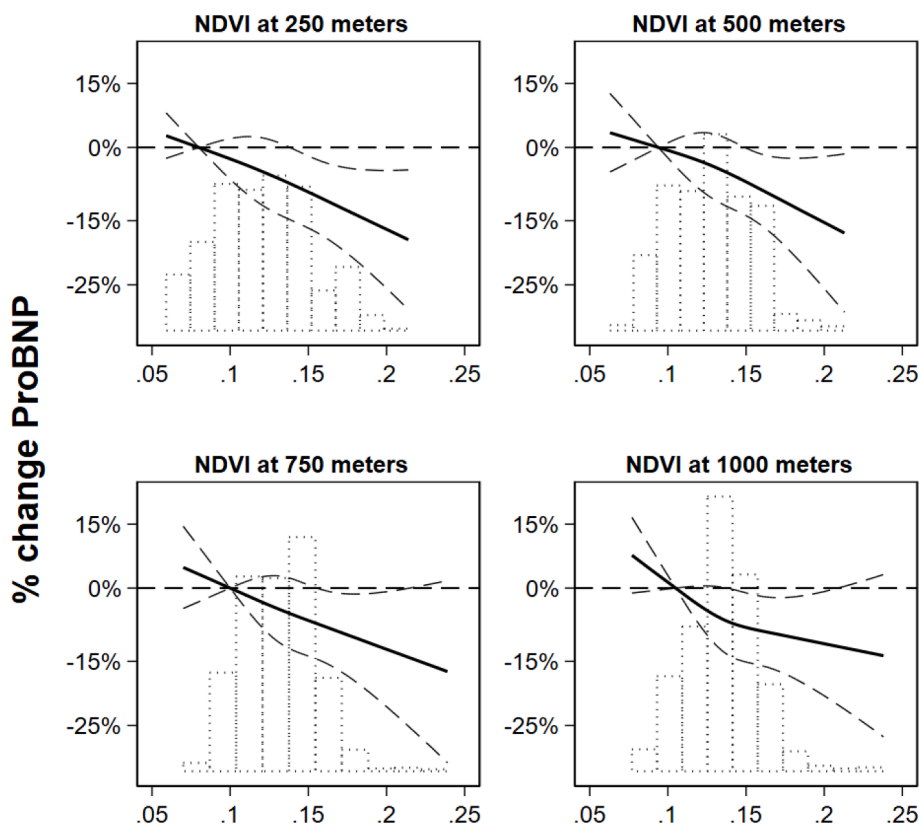


Fig. 1. Percentage change in ProBNP according to residential greenness (Normalized Difference Vegetation Index, NDVI) with buffer zones at 250, 500, 750, and 1000 m. Thick lines represent percentage changes and dotted lines their 95% confidence intervals. Analyses are based on restricted cubic splines for log-transformed NDVI with knots at the 10th, 50th and 90th percentiles of the distribution. The reference value was set at the 10th NDVI percentile. Percentage changes were obtained from linear regression models adjusted for sex, age, age-squared, educational level, degree of difficulty in making end meets, and social network score, and included a random-effect for the Deprivation Index at the census tract to account for clustering of individuals residing within neighborhoods with similar socio-economic characteristics. P-values for non-linear and global tests were 0.417 and 0.016 at 250 m, 0.491 and 0.050 at 500 m, 0.864 and 0.084 at 750 m, and 0.703 and 0.051 at 1000 m, respectively.

≥high school), ability to make ends meet (with great difficulty, with some difficulty, with some ease, easily, very easily) and home ownership (no/yes).

At the census level, socioeconomic status was assessed with the Socioeconomic Deprivation Index (SDI) from the Spanish Society of Epidemiology, derived from the Spanish 2011 census (Duque et al., 2021). This index includes six indicators: (a) population of manual workers, (b) population in casual salaried jobs, (c) unemployment rate, (d) individuals ≥ 16 years of age with primary education or less, (e) individuals between 16 and 29 years of age with primary education or less, and (f) main dwellings without Internet access (Duque et al., 2021). For ease of interpretation, note that areas are usually classified as low deprivation if they have an SDI below -0.86 , as medium–low deprivation if between -0.86 and -0.27 , as medium deprivation if between -0.27 and 0.21 , as medium–high deprivation if between 0.21 and 0.82 , and as high deprivation if above 0.82 .

2.2.3.2. Social cohesion and social network. Social cohesion was assessed using information on the frequency of attendance at club meetings (e.g., book clubs), senior centers, or volunteer centers (e.g., Caritas). A social network index was constructed with eight questions on: (a) marital status, (b) cohabitation, (c) frequency of contacts with relatives other than those with whom participants lived, (d) frequency of contacts with friends and neighbors, (e) amount of time spent alone at home, (f) availability of someone to go for a walk with, (g) receipt of emotional support (i.e. having someone to talk to, share feelings or problems with), (h) receipt of instrumental support (i.e. having someone who can take care of important things in case of illness). Being married, cohabiting, having daily/almost daily contact with family, friends or neighbors, being alone less than two hours a day, having someone to go for walks with, as well as someone to take care of important things in case of illness, were assigned 0 points (and the opposite, 1 point). An overall social network index was calculated as the sum of points for each item and ranged from 0 (better) to 8 (worse) (Leon-Gonzalez et al., 2021).

2.2.3.3. Lifestyle-related factors. Data on smoking (never, former, current smoker), alcohol intake (never, moderate, heavy, former drinker), usual time spent watching TV (hours/day), and physical activity were gathered Nurses' Health Study questionnaire validated in Spain (Martínez-González et al., 2005). Recreational physical activity, comprising walking, cycling, and sports, was assessed with the EPIC-Spain cohort questionnaire (Pols et al., 1997). In a subset, accelerometers were worn for a 24-hour activity cycle assessment, including sleep parameters (Cabanas-Sánchez et al., 2020; van Hees et al., 2013). Sleep quality was evaluated using a scale based on eight sleep disturbance symptoms (Leon-Gonzalez et al., 2021). Furthermore, food consumption details were collected through a validated diet history, and adherence to the Mediterranean diet was measured with the MEDAS score (Ortolá et al., 2021). For a more thorough understanding of these variables, please refer to the **Supplementary Methods**.

2.2.3.4. Cardiovascular disease biological risk factors. Weight and height were measured with standardized procedures. The body mass index (BMI) was calculated as weight in kilograms (kg) divided by squared height in meters (m), and individuals categorized as “normal weight” (<25 kg/m²), “overweight” (25–29.9 kg/m²), or “obese” (≥ 30 kg/m²). Blood pressure was determined three times at 1–2 min intervals with standardized procedures and the mean of the last two readings was used for analysis. Participants also reported the use of antihypertensive, lipid-lowering and antidiabetic drugs, which was verified against drug packages during the home visits. Twelve-hour fasting blood creatinine, glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured with colorimetric enzymatic methods using an Atellica Solution analyzer (Siemens Healthineers). Type-2

diabetes (T2DM) was defined as a participant-reported medical diagnosis, fasting glucose ≥ 126 mg/dl or use of antidiabetic medication. Glomerular filtration rate was estimated from serum creatinine values using the CKD-EPI 2009 equation (eGFR). Finally, a score based on the Framingham Heart Study was calculated to assess the individual 10-year risk of having a cardiovascular disease event (Linden, 2017).

2.2.3.5. Mental, physical and cognitive health. Global mental and physical health were assessed with the mental and composite scores (MCS and PCS) of the SF-12 questionnaire validated for the Spanish population (Vilagut). In addition, depressive symptoms were assessed with the 10-item Geriatric Depression Scale (GDS) (Yesavage et al., 1982 1983), well-being with the Cantril Ladder of Life Scale (Glatzer and Gulyas, 2014), and self-perception of aging with a 5-item Likert scale (Gale and Cooper, 2018). Lower extremity performance was assessed with the Short Physical Performance Battery (SPPB) (Guralnik et al., 1994), which combines information on balance (i.e., the ability to maintain a standing position with three hierarchical feet positions), gait speed, and chair standing (i.e., the ability and time required to rise from a chair five times consecutively without using the arms); and individuals scoring below 9 were considered low performers. Global cognitive health was assessed with the Mini-Mental Examination State (Folstein et al., 1975), and those scoring below 24 were considered cognitively impaired.

2.2.3.6. Other neighborhood characteristics. Traffic exposure was evaluated using Annual Average Daily Traffic (AADT) within 500 and 1000 m of participants' homes, calculated as the daily traffic volume on nearby highways, roads, and streets, expressed in vehicles per day. Navteq mapping, combined with traffic density data from the Spanish Ministry of Public Works, facilitated this assessment (del Río et al., 2024). Neighborhood characteristics were measured using the Physical Activity Neighborhood Environment Survey (PANES) (Sallis et al., 2010), covering housing type, retail availability, public transportation stops, sidewalk presence, bicycle facilities, recreational facilities, crime perception, traffic density impact on walking, interesting sights while walking, and walkable areas. Responses were recoded into “strongly agree/agree” vs. “disagree/strongly disagree,” except for housing type, dichotomized into detached single-family homes (lower residential density) vs. others (higher residential density).

Additionally, a walkability index, based on Creatore et al.'s work (Creatore et al., 2016), and modified according to European recommendations (Grasser et al., 2016), was established for participants in Madrid. The index considered residential density, population density, retail destinations, and street connectivity (Gullón et al., 2017). Data for 2014 were used, except for the Spanish Census, which was available for 2011. For further details, please refer to the **Supplementary Methods**.

3. Statistical analyses

3.1. Association of greenness with biomarkers of CVD risk

The association of greenness with biomarkers of CVD risk was evaluated using linear regression models, where the studied biomarkers were log-transformed. The exposure variable (i.e., NDVI) was modeled using quartiles, continuous log-transformed values with results expressed per interquartile range (IQR) increase, or restricted cubic splines with knots at the 10th, 50th and 90th percentiles. The ratios of the biomarker geometric means (with their 95 % confidence intervals) were obtained by exponentiating the β coefficients and standard errors from the regression models, while the mean percentage differences were calculated by subtracting 1 from the exponentiated β coefficients and multiplying the result by 100. Two initial models adjusted for potential confounders including sex, age and age-squared (Model 0), or the same three variables plus educational level, degree of difficulty in making end meets, and social network index (Model 1). In addition, models 0 and 1

included a random-effect for the census-based SDI to account for the clustering of individuals residing in neighborhoods with similar socioeconomic characteristics.

We evaluated effect modification by including in Model 1 interaction terms between NDVI and the following variables: sex, age (<70/≥70), educational attainment (<high school/≥high school), financial stress (whether or not having difficulties in making ends meet), meeting MVPA recommendations (no/yes), obesity (no/yes), T2DM (no/yes), hypertension (no/yes), Framingham CVD risk (≤30 %/>30 %), depression (GDS ≤ 5/>5), functional impairments (SPPB < 9/≥9), cognitive impairments (MMSE < 24/≥24), social deprivation (tertiles of SDI), AADT (≤75th percentile /> 75th percentile), and neighborhood walkability (≤25th percentile/> 25th percentile). Also, since the effect of greenness on hs-TnT varied according to diabetic status, with a dose–response association observed only among participants with T2DM, stratified results for this biomarker in this sub-group of participants were presented in all tables.

3.2. Mediation analyses of the association of greenness with biomarkers of CVD risk

In a second step, we fitted eight additional models beyond Model 1 to identify potential mediators for the observed associations through the *difference method* (VanderWeele, 2016). These models, which build on the variables in Model 1, included information on social cohesion (Model 2), lifestyle-related factors (Model 3, covering smoking, alcohol

intake, MEDAS score, TV viewing time, self-reported PA, and sleep quality), CVD biological risk factors (Model 4, encompassing BMI, systolic blood pressure, T2DM, medication use, lipid levels, and eGFR), well-being (Model 5, considering SF-12 scores, or alternative scales such as the Geriatric Depression Scale or Cantril Ladder), physical performance (Model 6), cognition (Model 7), residential traffic density (Model 8), neighborhood attributes (Model 9), and neighborhood walkability (Model 10, applicable to a subset of participants). A modified version of Model 3 adjusted for daily time in moderate-to-vigorous PA using information from the 2020 participants who wore the accelerometer. We then calculated the percentage reduction in the effect estimate in the various models compared to Model 1. For sensitivity analyses, we also employed the *product method* (Valeri and Vanderweele, 2013). For this approach, we decomposed the effect of greenness on each biomarker of CVD risk into a direct and mediating component (Supplementary Fig. 2).

3.3. Association of greenness with CVD incidence

To assess whether the observed changes translated into a decreased risk of CVD, we evaluated the prospective association between greenness and incidence of CVD (CIAP2 codes K74, K75, K77, K90, and K92) using Cox-proportional hazard models with age as time scale and individual starting follow-up times (age at baseline) treated as staggered entries. The assumption of hazards proportionality was evaluated based on the smoothed association between age and scaled Schoenfeld

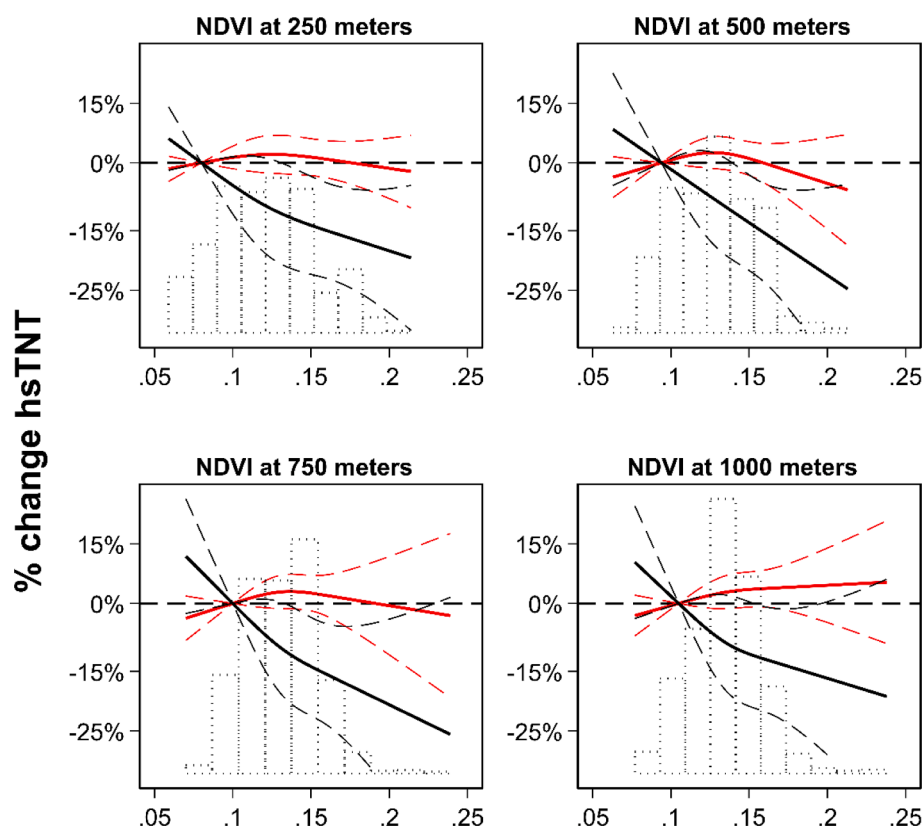


Fig. 2. Percentage change in hs-TnT according to residential greenness (Normalized Difference Vegetation Index, NDVI) with buffer zones at 250, 500, 750, and 1000 m. Black lines represent results for participants with Type-2 Diabetes, while red lines represent results for the overall population. Thick lines represent percentage changes and dotted lines their 95% confidence intervals. Analyses are based on restricted cubic splines for log-transformed NDVI with knots at the 10th, 50th and 90th percentiles of the distribution. The reference value was set at the 10th NDVI percentile. Percentage changes were obtained from linear regression models adjusted for sex, age, age-squared, educational level, degree of difficulty in making end meets, and social network score, and included a random-effect for the Deprivation Index at the census tract to account for clustering of individuals residing within neighborhoods with similar socioeconomic characteristics. In diabetics (black lines), P-values for non-linear and global tests were 0.731 and 0.011 at 250 m, 0.612 and 0.014 at 500 m, 0.914 and 0.020 at 750 m, and 0.76 and 0.092 at 1000 m, respectively. In the overall population (red lines), P-values for non-linear and global tests were, respectively, 0.167 and 0.3721 at 250 m, 0.130 and 0.301 at 500 m, 0.316 and 0.397 at 750 m, and 0.621 and 0.287 at 1000 m.

residuals, with no major departures from proportionality. NDVI was again modeled using quartiles and continuous log-transformed values with results expressed per IQR increase. All Cox proportional hazard models accounted for sex, educational level, degree of difficulty in making ends meet, social network index, and Deprivation Index.

3.4. Mediation analyses of the association of greenness with CVD incidence

To evaluate the mediating effect of the studied biomarkers of CV risk on the association between residential greenness and CVD incidence, we calculated the percentage reduction in the effect estimates after introduction of the studied biomarkers. For sensitivity analyses, we also employed the *product method* (VanderWeele, 2011).

Statistical analyses were performed using STATA Software V.18.

4. Results

From the initial sample of 3,273 participants, we excluded 672 individuals with a previous diagnosis of CVD, 10 without data on individual socioeconomic variables, 378 lacking at least one lifestyle-related variable and 69 with no information on traditional CV biological risk factors. This resulted in a final analytical sample of 2,144 participants. Additionally, for the analysis of each biomarker, subjects with no information on the corresponding biomarker were excluded (11 for NT-ProBNP, 12 for hs-TnT, 12 for IL-6 and 10 for GDF-15).

Of the final sample, 51.2 % lived in the city of Madrid, 18.3 % in Torrejón de Ardoz, 13.1 % in Alcorcón, 12.1 % in Getafe, and 5.2 % in Alcalá de Henares. The average SDI at the census tract was -0.55 . The mean age of study participants was 71.4 years (range 65–93), 45 % were men, 64.2 % had less than secondary education, 64.2 % made ends meet easily or very easily, and 95 % owned the house in which they lived (Table 1). Participants who lived surrounded by greater amounts of green space were, on average, younger, showed higher educational attainment and higher social network index, were more frequent moderate alcohol drinkers, had lower adherence to the Mediterranean Diet, slept better, had lower SBP and triglyceride levels, better mental health (i.e., lower GDS and higher MCS scores) and physical health (i.e., higher SPPB and PCS scores), and less frequent cognitive impairment. Additionally, those living in areas with higher NDVI were more physically active, watched less TV, and showed lower BMI. Residential greenness was also inversely associated with SDI and traffic exposure (information divided into Table 1 and Supplementary Table 1 due to space constraints).

After adjusting for age, sex, SDI, and sociodemographic variables (model 1, Table 2), an IQR increase in NDVI at 250, 500, 750 and 1000 m buffers from the study participants' home was associated with a 5.56 % (95 %CI: -9.77 ; -1.35), 5.05 % (-9.58 ; -0.53), 4.24 % (-8.19 , -0.19), and 4.16 % (-7.59 ; -0.74) lower NT-ProBNP concentrations, respectively. Levels of hs-TnT were not associated with residential green space density in the overall sample; however, greater greenness was inversely related to levels of this biomarker in participants with T2DM (p -interaction: <0.01) with mean differences of -8.03 % (-13.30 ; -2.77), -9.52 % (-16.08 ; -2.96), -8.05 % (-13.94 , -2.16) and -5.56 % (-10.75 ; -0.54) per IQR increase in NDVI at 250, 500, 750 and 1000 m, respectively. Of similar magnitude, although only statistically significant at 250 and 500 m, were the observed differences in IL-6 with increasing greenness; -6.35 % (-11.09 ; -1.61) at 250 m, -5.67 % (-11.25 ; -0.08) at 500 m, -4.06 % (-9.12 ; 1.00) at 750 m, and -3.50 % (-7.59 ; 0.60) at 1000 m. At all distances analyzed, the distribution of GDF-15 was independent of NDVI. Figs. 1 to 4 modeled the dose-response curves and revealed no major departures from linearity for the studied associations.

Table 3 presents the results of models addressing the influence of individual and neighborhood-related variables on the associations studied, using the *difference in coefficients method*. For most buffers, the

reduction in effect estimates for NT-ProBNP was most substantial in the following order of magnitude of decline: physical performance (model 6), traffic exposure (model 8), cognitive function (model 7) and CVD biological risk factors (model 4). For hs-TnT in diabetic participants, the association mostly attenuated when accounting for neighborhood walkability (model 10b vs. 10a), followed by lifestyle behaviors (model 3), especially PA in one-for-one adjustments (i.e., in the subsample with accelerometry, adjustment for MVPA provided the following percentage changes: 29.76 %, 22.31 %, 19.65 %, and 20.94 % for buffer distances 250, 500, 750 and 1000 m, respectively, data not shown in tables). Of note, the association of NT-ProBNP with NDVI in diabetics also decreased substantially when adjusted for accelerometer-based PA (22.4 %, 12.5 %, 8.7 %, 7.2 % for NT-ProBNP in 250, 500, 750 and 1000 m buffers, respectively), which is a larger decrease than that observed for the overall sample. Finally, in the case of IL-6, this was the variable that benefited most from adjustment for individual socioeconomic variables. Furthermore, the association between NDVI and IL-6 was notably attenuated when adjusting for physical performance (model 6), neighborhood walkability (model 10b vs 10a), CVD biological risk factors (model 4) and traffic exposure (model 8), separately. Similar findings were observed for the product method (Supplementary Table 2).

Supplementary Figs. 3-7 show stratified results by participants' characteristics. The impact of greenness on NT-ProBNP, GDF-15 and IL-6 was very similar for all categories of the studied variables and for all distances evaluated, except for obese participants, who showed more pronounced decreases in NT-ProBNP with NDVI, and for those with higher Framingham risk score, who showed somewhat higher decreases in IL-6. As mentioned above, stratified analyses revealed an inverse association between NDVI and hs-TnT in participants with T2DM (Supplementary Fig. 4), with those meeting recommendations for MVPA or living in the most disadvantaged areas (with the highest SDI) showing the greatest reductions in this biomarker (Supplementary Figure 5).

During a mean follow-up time of 6.3 years, 127 persons experienced a CVD event. Mean (SD) baseline concentrations of NT-ProBNP, hsTnT, GDF-15 and IL-6 were higher among those who developed CVD than those who did not (Supplementary Table 3). The Hazard Ratios (95 % CI) for cardiovascular incidence were 1.02 (0.60; 1.74), 0.62 (0.38; 1.00), 0.63 (0.38, 1.03) and 0.57 (0.33; 0.99) comparing participants in the highest vs the lowest quartile of the distribution of NDVI at 250, 500, 750, and 1000 m (Table 4). Despite borderline p -values, the association between NDVI and lower risk appeared to be more pronounced among women and older participants (Supplementary Figure 7).

In mediation analyses using the *difference method*, adjustment for Pro-BNP, Hs-TnT and IL6 provided a 33.4 %, 19.4 % and 14.6 % reduction in effect estimates for residential NDVI at 500, 750 and 1000 m, respectively. Because the incidence of cardiovascular disease was low during the follow-up period, the *product method* yielded similar results (VanderWeele, 2011). The indirect-to-total effects ratio revealed that 26.4 %, 14.7 % and 13.0 % of the total effect for residential NDVI at 500, 750 and 1000 m, respectively, was explained by these biomarkers.

5. Discussion

In this cohort of older adults residing in densely populated areas of the Community of Madrid and with no previous history of CVD, increased availability of green spaces was cross-sectionally associated with small linear reductions in serum NT-ProBNP and IL-6 in the entire sample, as well as with reduced levels of hs-TnT in those with T2DM. Furthermore, residential greenness was prospectively associated with a modest reduction in mid-term CVD incidence.

It has previously been proposed that exposure to green spaces is beneficially associated with cardiovascular morbidity and mortality in young and middle-aged adults. For example, in a meta-analysis of 12 studies in 7 countries, a 0.1 increase in NDVI was associated with a 2–3 % lower odds of CVD, IHD, and stroke incidence and prevalence (Liu et al., 2022). Another meta-analysis with 6 of the 12 aforementioned

Table 1

Distribution of socioeconomic variables, lifestyle-related behaviors, cardiovascular risk factors, quality of life, functional impairments and traffic exposure, according to vegetation density at 250, 500 and 1000 m from the residence of 2144 community-dwelling older adults with no previous history of cardiovascular disease.

	Total	NDVI 250 m					NDVI 500 m					NDVI 1000 m				
		Q1	Q2	Q3	Q4	p-val	Q1	Q2	Q3	Q4	p-val	Q1	Q2	Q3	Q4	p-val
N	2144	517	530	518	579		522	521	525	576		513	524	561	546	
Age, mean (SD)	71.4 (4.4)	72.4 (4.8)	71.3 (4.2)	71.4 (4.3)	70.8 (4.0)	**	72.6 (4.8)	70.7 (4.2)	71.5 (4.2)	71.0 (4.0)	**	72.6 (4.8)	71.0 (4.0)	71.0 (4.2)	71.2 (4.2)	**
Male,%	44.9	42.2	40.8	47.3	48.9	*	42.7	43.8	45.3	47.4	0.4	40.9	46.0	45.5	46.9	0.2
Educational level,%						**					**					**
Primary	64.2	71.2	77.4	66.2	44.0		70.5	74.1	67.6	46.4		68.0	68.3	58.5	62.5	
Secondary	18.5	18.0	13.8	19.1	22.6		17.6	18.0	18.5	19.6		20.1	18.9	17.3	17.8	
≥High school	17.4	10.8	8.9	14.7	33.3		11.9	7.9	13.9	34.0		11.9	12.8	24.2	19.8	
Deprivation index, mean (SD)	-0.6 (0.7)	-0.3 (0.5)	-0.3 (0.6)	-0.5 (0.7)	-1.2 (0.6)	**	-0.4 (0.6)	-0.2 (0.5)	-0.5 (0.6)	-1.2 (0.6)	**	-0.4 (0.6)	-0.3 (0.6)	-0.8 (0.8)	-0.8 (0.7)	**
Meeting ends, %						**					**					*
With great difficulty	3.8	5.1	3.8	3.9	2.4		4.6	3.5	4.1	2.8		4.2	4.4	3.9	2.6	
With some difficulty	9.6	12.2	13.6	8.5	4.5		12.1	12.5	9.5	4.7		12.3	10.9	7.0	8.4	
With some ease	22.5	26.3	27.2	22.8	14.5		28.2	24.4	22.9	15.3		25.0	23.7	19.4	22.2	
Easily	56.2	48.5	50.0	58.1	67.0		47.5	54.9	57.0	64.6		50.9	54.6	60.2	58.6	
Very easily	8.0	7.9	5.5	6.8	11.6		7.7	4.8	6.5	12.7		7.8	6.5	9.4	8.2	
Social network score, mean (SD)	5.0 (1.6)	4.8 (1.6)	5.1 (1.5)	5.0 (1.6)	5.1 (1.5)	**	4.8 (1.6)	5.2 (1.5)	5.0 (1.6)	5.1 (1.5)	**	4.8 (1.5)	5.1 (1.5)	4.9 (1.6)	5.2 (1.5)	**
Smoking,%						0.2					0.5					*
Never	54.0	56.7	55.8	53.7	50.1		57.1	53.9	53.7	51.4		59.8	52.7	54.0	49.6	
Former	36.7	32.9	35.3	37.3	40.9		33.0	36.9	37.1	39.6		31.4	39.3	36.2	39.7	
Current	9.3	10.4	8.9	9.1	9.0		10.0	9.2	9.1	9.0		8.8	8.0	9.8	10.6	
Drinking,%						**					**					**
Never drinker	19.3	21.9	21.7	18.3	15.5		22.0	20.5	19.2	15.6		24.6	17.2	19.4	16.1	
Moderate drinker	69.6	65.8	64.7	71.6	75.6		64.6	67.2	71.0	75.0		62.0	71.2	71.5	73.3	
Heavy drinker	5.0	4.6	5.7	4.6	5.0		5.4	5.2	3.6	5.7		4.1	4.6	5.0	6.2	
Ex drinker	6.2	7.7	7.9	5.4	3.8		8.0	7.1	6.1	3.6		9.4	7.1	4.1	4.4	
Recreational PA, METs-h/week	28.5 (19.4)	26.7 (18.6)	28.3 (19.2)	29.5 (21.4)	29.2 (18.4)	0.1	26.8 (18.9)	29.1 (19.5)	28.0 (20.3)	29.0 (18.9)	*	26.5 (18.5)	30.0 (20.2)	29.3 (20.4)	28.0 (18.4)	*
† MVPA, h/d, mean (SD)	0.92 (0.6)	0.88 (0.6)	0.91 (0.6)	0.95 (0.6)	0.95 (0.6)	0.1	0.88 (0.6)	0.92 (0.6)	0.91 (0.5)	0.97 (0.6)	*	0.87 (0.6)	0.92 (0.5)	0.94 (0.6)	0.96 (0.6)	*
TV viewing, h/d, mean (SD)	3.2 (1.5)	3.3 (1.7)	3.3 (1.6)	3.1 (1.5)	2.9 (1.4)	**	3.3 (1.7)	3.2 (1.4)	3.1 (1.5)	3.0 (1.4)	**	3.2 (1.6)	3.2 (1.5)	3.1 (1.5)	3.1 (1.5)	0.2
BMI, mean (SD)	27.6 (4.4)	27.6 (4.1)	28.4 (4.7)	27.7 (4.4)	27.1 (4.1)	**	27.6 (4.3)	28.5 (4.5)	27.4 (4.2)	27.1 (4.4)	**	27.8 (4.4)	27.6 (4.1)	27.6 (4.7)	27.6 (4.3)	0.9
MEDAS index, mean (SD)	7.1 (1.7)	7.3 (1.6)	7.2 (1.7)	7.1 (1.7)	7.0 (1.8)	**	7.3 (1.6)	7.2 (1.8)	7.1 (1.7)	6.9 (1.8)	**	7.3 (1.5)	7.4 (1.6)	6.8 (1.8)	7.0 (1.8)	**
Poor sleep quality,%	17.1	22.5	18.7	14.9	12.8	**	20.2	20.0	16.4	12.4	**	19.2	16.8	17.0	15.6	0.5
Night sleep time; min, mean (SD)	602 (59)	600 (58)	607 (61)	606 (59)	591 (57)	**	601 (58)	602 (560)	601 (61)	597 (58)	*	601 (61)	598 (59)	603 (60)	604 (56)	0.3
SBP, mean (SD)	135 (18.0)	136 (18.6)	135 (18.3)	136 (17.8)	133 (17.0)	**	137 (19.1)	134 (17.5)	135 (17.8)	133 (17.1)	**	137 (19.0)	135 (18.1)	132 (16.7)	135 (17.6)	**
HT treatment, %	48.7	49.5	51.9	48.6	45.3	0.2	50.4	50.5	47.2	47.0	0.5	49.7	49.6	44.9	50.9	0.2
Total cholesterol, mean (SD)	194 (33.2)	194 (32.1)	193 (33.9)	195 (35.2)	193 (31.8)	0.8	191.8 (32.7)	193 (33.9)	196 (33.3)	194 (33.0)	0.3	194 (33.2)	191 (32.8)	196 (33.6)	194 (33.2)	0.1
Triglycerides, mean (SD)	114 (51.7)	116 (52.1)	118 (55.1)	111 (47.1)	111 (51.8)	0.1	115.4 (52.1)	119 (56.7)	110 (47.5)	111 (49.6)	**	116 (50.9)	115 (55.9)	116 (56.7)	109 (41.4)	0.1
HDL cholesterol, mean (SD)	54.8 (14.2)	54.6 (14.4)	55.2 (14.6)	54.4 (13.7)	54.9 (14.1)	0.8	54.4 (14.7)	54.3 (14.1)	55.1 (14.0)	55.3 (13.9)	0.6	54.5 (14.7)	53.9 (14.1)	55.3 (14.1)	55.4 (13.8)	0.3
Lipid lowering drugs,%	23.0	36.6	25.3	19.7	11.7	**	37.0	23.4	20.2	12.5	**	39.0	25.4	17.6	11.2	**
Type-2 diabetes, %	18.9	19.6	21.4	18.2	16.8	0.3	21.3	19.5	16.6	18.4	0.3	20.3	17.8	19.1	18.6	0.8
eGFR, mean (SD)	81.4 (12.4)	79.0 (13.2)	81.4 (12.5)	82.9 (12.1)	82.2 (11.6)	**	78.2 (13.3)	82.8 (12.0)	82.9 (11.7)	81.6 (12.1)	**	78.1 (13.3)	82.7 (12.4)	82.3 (11.0)	82.4 (12.3)	**
Framingham score > 20 %, %	44.4	45.3	43.4	45.9	43.0	0.8	48.7	43.0	43.2	42.7	**	48.9	42.9	41.5	44.3	0.1

(continued on next page)

Table 1 (continued)

	Total	NDVI 250 m					NDVI 500 m					NDVI 1000 m				
		Q1	Q2	Q3	Q4	p-val	Q1	Q2	Q3	Q4	p-val	Q1	Q2	Q3	Q4	p-val
GDS, mean (SD)	0.8 (1.6)	0.9 (1.8)	1.0 (1.8)	0.8 (1.5)	0.7 (1.4)	**	0.9 (1.7)	0.9 (1.7)	0.9 (1.6)	0.7 (1.4)	*	0.9 (1.7)	0.8 (1.5)	0.9 (1.8)	0.7 (1.4)	0.2
Quality Life MCS, mean (SD)	53.9 (9.4)	53.8 (9.3)	52.9 (10.8)	53.9 (8.8)	55.0 (8.5)	**	54.1 (9.6)	53.3 (10.1)	53.6 (9.7)	54.7 (8.2)	0.1	53.8 (9.9)	53.6 (10.0)	53.8 (9.1)	54.5 (8.7)	0.5
Quality Life PCS, mean (SD)	46.6 (10.5)	45.5 (11.5)	46.0 (10.9)	47.5 (9.6)	47.4 (9.6)	**	45.2 (11.4)	46.1 (10.7)	47.2 (10.4)	47.9 (9.2)	**	45.1 (11.8)	46.7 (10.2)	47.1 (9.9)	47.5 (9.8)	**
SPPB, mean (SD)	9.9 (1.7)	9.3 (1.7)	9.8 (1.7)	10.1 (1.7)	10.5 (1.5)	**	9.3 (1.8)	9.9 (1.5)	10.2 (1.6)	10.4 (1.7)	**	9.4 (1.7)	9.8 (1.6)	10.0 (1.8)	10.5 (1.6)	**
MMSE, mean (SD)	28.0 (2.0)	27.7 (1.9)	27.5 (2.0)	28.1 (2.0)	28.5 (2.0)	**	27.6 (1.9)	27.4 (2.0)	28.3 (1.8)	28.5 (2.1)	**	27.6 (2.0)	27.9 (1.8)	28.1 (2.3)	28.3 (1.9)	**
AADT at 500 m, mean (SD)	551 (644)	837 (791)	524 (626)	415 (474)	441 (566)	**	743 (788)	516 (635)	551 (548)	406 (1935)	**	751 (809)	613 (613)	417 (549)	439 (524)	**
AADT at 1000 m, mean (SD)	2680 (2994)	3601 (2898)	2375 (2762)	2462 (3118)	2330 (3009)	**	3283 (3328)	2486 (2884)	3089 (325)	1935 (226)	**	3689 (422)	2848 (269)	2086 (221)	2180 (221)	**
PNE, mean (SD)	10.3 (1.5)	9.9 (1.7)	10.6 (1.4)	10.2 (1.4)	10.4 (1.4)	**	9.9 (1.7)	10.4 (1.5)	10.4 (1.4)	10.4 (1.3)	**	10.0 (1.71)	10.6 (1.5)	10.2 (1.4)	10.4 (1.4)	**
† Walkability, median (IQR)	1.5 (4.2)	2.1 (1.9)	2.4 (1.9)	3.0 (2.7)	-1.4 (4.0)	**	1.9 (2.2)	2.4 (1.4)	2.7 (1.6)	-1.4 (3.1)	**	1.9 (2.2)	-2.0 (4.0)	-0.4 (3.3)	2.1 (3.9)	**

AADT: Annual Average Daily Traffic; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; GDS: Geriatric Depression Scale; HDL: High-Density Lipoprotein; HT: Hypertension; IQR: Interquartile range; MCS: Mental Component Score of the SF-12; METs: Metabolic Equivalents; MMSE: Mini-Mental State Examination; MVPA: Moderate-to-vigorous physical activity as estimated with the accelerometer; PA: Physical activity; PCS: Physical Component Score of the SF-12; PNE: Perceived Neighborhood Environment; SD: Standard Deviation; SBP: Systolic Blood Pressure; SPPB: Short Physical Performance Battery; TV: Television. P-values were obtained from ANOVA tests for continuous outcomes and chi-square tests for categorical outcomes. *p-value < 0.05; **p-value < 0.01.

†Subsample of 2020 participants with an accelerometry-based measures.

††Subsample of 1072 participants with this information available.

Table 2

Percentage change (95%Confidence Interval) in biomarkers of cardiovascular disease risk according to residential greenness (buffer zones at 250, 500, 750, and 1000 m).

	NDVI	At 250 m		At 500 m		At 750 m		At 1000 m	
		n	% change (95 %CI)	N	% change (95 %CI)	n	% change (95 %CI)	n	% change (95 %CI)
Pro-BNP	Q1	514	Ref.	522	Ref.	517	Ref.	512	Ref.
	Q2	526	-2.94 (-10.94; 5.07)	516	-5.89 (-14.51; 2.73)	523	-5.90 (-14.91; 3.21)	520	-7.21 (-15.92; 1.51)
	Q3	515	-6.89 (-15.55; 1.77)	520	-4.19 (-12.92; 4.54)	537	-7.71 (-16.78; 1.35)	558	-8.28 (-16.80; 0.24)
	Q4	578	-10.83 (-19.61; -2.04)	575	-9.02 (-17.76; -0.27)	556	-9.18 (-17.58; -0.77)	543	-9.41 (-17.92; -0.90)
	p-trend		<0.01		0.06		0.03		0.03
hs-TnT	Per IQR	2133	-5.56 (-9.77; -1.35)	2133	-5.05 (-9.58; -0.53)	2133	-4.24 (-8.19; -0.19)	2133	-4.16 (-7.59; -0.74)
	Q1	513	Ref.	522	Ref.	517	Ref.	512	Ref.
	Q2	526	2.21 (-2.29; 6.70)	515	3.11 (-1.27; 7.48)	522	0.14 (-4.54; 4.82)	519	2.19 (-2.23; 6.61)
	Q3	515	-0.50 (-5.48; 4.49)	520	1.71 (-2.65; 6.07)	537	5.09 (0.63; 9.56)	558	3.25 (-1.06; 7.55)
	Q4	578	0.68 (-3.62; 4.98)	575	1.21 (-3.85; 6.27)	556	1.29 (-3.90; 6.48)	543	1.56 (-3.56; 6.68)
*hsTnT, T2DM	p-trend		0.93		0.79		0.33		0.51
	Per IQR	2132	-0.24 (-2.01; 2.50)	2132	-0.20 (-2.90; 2.50)	2132	0.75 (-1.71; 3.22)	2132	1.51 (-0.46; 3.47)
	Q1	100	Ref.	111	Ref.	105	Ref.	104	Ref.
	Q2	111	-3.21 (-15.65; 0.24)	99	-1.73 (-13.32; 9.87)	92	-4.10 (-16.87; 8.67)	91	-2.47 (-14.08; 9.14)
	Q3	94	-11.29 (-24.15; -1.56)	86	-7.78 (-19.99; 4.43)	99	-6.89 (-17.09; 3.30)	106	-7.38 (-18.45; 3.68)
IL-6	Q4	97	-12.83 (-23.83; -1.83)	106	-15.75 (-26.79; -4.72)	106	-13.66 (-25.53; -1.78)	101	-10.95 (-23.02, 1.12)
	p-trend		<0.01		<0.01		0.01		0.04
	Per IQR	402	-8.03 (-13.30; -2.77)	402	-9.52 (-16.08; -2.96)	402	-8.05 (-13.94; -2.16)	402	-5.65 (-10.75; -0.54)
	Q1	514	Ref.	521	Ref.	516	Ref.	511	Ref.
	Q2	525	-5.21 (-14.16; 3.73)	516	-2.61 (-11.25; 6.02)	523	-6.93 (-14.59; 0.72)	520	-7.52 (-15.30; 0.27)
GDF-15	Q3	515	-2.76 (-11.50; 5.98)	520	-1.14 (-9.62; 7.35)	537	-7.04 (-16.08; 2.00)	558	-9.48 (-18.63; -0.34)
	Q4	578	-12.31 (-21.21; -3.40)	575	-12.13 (-23.25; -1.02)	556	-11.23 (-21.86; -0.60)	543	-10.49 (-20.69; -0.29)
	p-trend		0.01		0.04		0.03		0.04
	Per IQR	2132	-6.35 (-11.09; -1.61)	2132	-5.67 (-11.25; -0.08)	2132	-4.06 (-9.12; 1.00)	2132	-3.50 (-7.59; 0.60)
	Q1	515	Ref.	522	Ref.	517	Ref.	512	Ref.
GDF-15	Q2	526	5.21 (-0.28; 10.70)	517	-0.22 (-5.26; 4.82)	524	-1.09 (-6.26; 4.08)	520	1.08 (-4.37; 6.53)
	Q3	515	-0.46 (-5.60; 4.68)	520	-1.43 (-6.73; 3.88)	537	3.98 (-0.85; 8.80)	559	1.82 (-3.36; 7.00)
	Q4	578	2.69 (-1.88; 7.26)	575	1.51 (-3.25; 6.27)	556	1.73 (-3.05; 6.52)	543	2.71 (-2.21; 7.64)
	p-trend		0.73		0.67		0.20		0.26
	Per IQR	2134	0.101 (-2.14; 2.30)	2134	1.10 (-1.41; 3.60)	2134	1.64 (-0.59; 3.87)	2134	1.57 (-0.42; 3.55)

IQR: Interquartile range; NVDI: Normalized Difference Vegetation Index; T2DM: Subpopulation with type-2 diabetes. *The association between proximity to green spaces and levels of hs-TnT was modified by diabetic status. Results for participants without diabetes were virtually the same as those in the overall sample and are not shown in the tables.

All models were adjusted for sex, age, age squared, educational level, degree of difficulty in making end meets and social network score; moreover a random-effect for the Deprivation Index at the census tract was included to account for clustering of individuals residing within neighborhoods with similar socioeconomic characteristics.

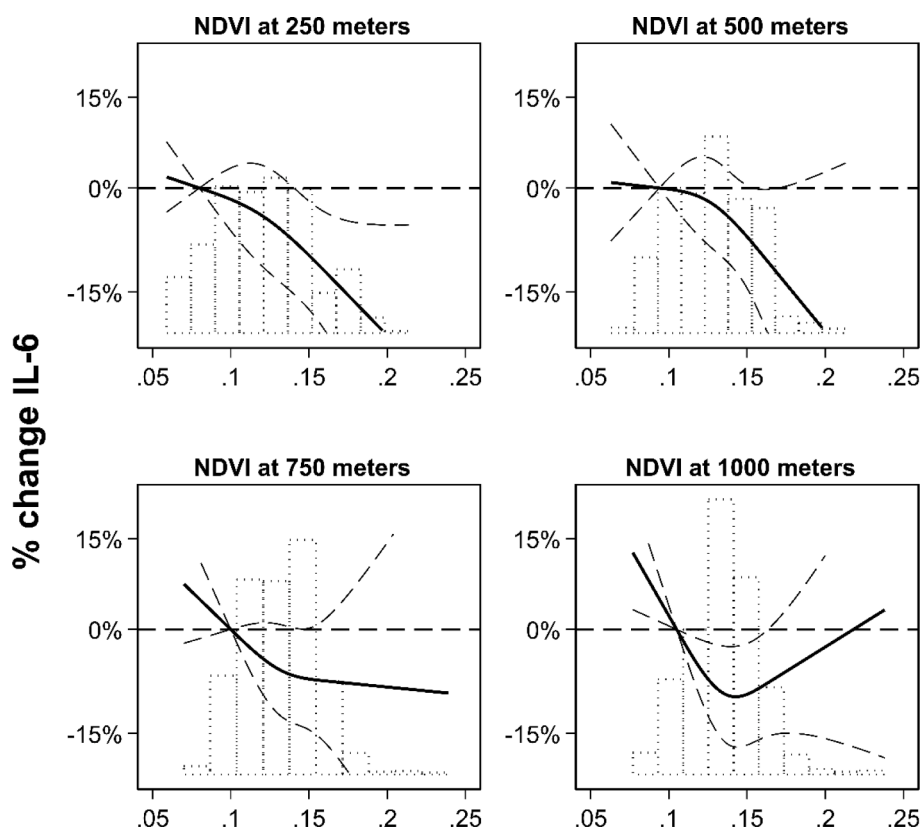


Fig. 3. Percentage change in IL-6 according to residential greenness (Normalized Difference Vegetation Index, NDVI) with buffer zones at 250, 500, 750, and 1000 m. Thick lines represent percentage changes and dotted lines their 95% confidence intervals. Analyses are based on restricted cubic splines for log-transformed NDVI with knots at the 10th, 50th and 90th percentiles of the distribution. The reference value was set at the 10th NDVI percentile. Percentage changes were obtained from linear regression models adjusted for sex, age, age-squared, educational level, degree of difficulty in making end meets, and social network score, and included a random-effect for the Deprivation Index at the census tract to account for clustering of individuals residing within neighborhoods with similar socioeconomic characteristics. P-values for non-linear and global tests were 0.279 and 0.018 at 250 m, 0.242 and 0.110 at 500 m, 0.857 and 0.177 at 750 m, and 0.119 and 0.048 at 1000 m, respectively.

studies, obtained analogous results and showed a 4–6 % reduction in CVD, IHD, and stroke mortality risk per IQR increase in NDVI (Bianconi et al., 2023). This findings are further supported by studies showing an inverse association between residential greenness and changes in cardiometabolic risk biomarkers, such as decreased arterial (Zhao et al., 2022) and central (Lane et al., 2017; Liu et al., 2021) blood pressure, improved lipid profile (Fernández Núñez et al., 2022; Mei et al., 2023; Plans et al., 2019); lower glycated hemoglobin levels (HbA1c) among non-diabetics (Fiffer et al., 2023), decreased levels of sympathetic activation (Geary et al., 2023), decreased oxidative stress biomarkers (Yeager et al., 2018), lower inflammation scores (Egorov et al., 2017; Iyer et al., 2022), and improved angiogenic profile (Yeager et al., 2018). However, regarding the cardiovascular biomarkers analyzed in our study, research is limited and inconclusive, such that: (i)–no study has previously investigated the relationship between NDVI and ProBNP or GDF-15, leaving this area of research largely unexplored; (ii)– only one study has examined the connection between NDVI and cardiac troponin. It found that living in areas with higher greenness was associated with decreased levels of troponin I in patients who had suffered a myocardial infarction (Wu et al., 2023); and (iii)– only a few studies have evaluated the association between NDVI and IL-6, with some (Mao et al., 2012), but not all (Yang et al., 2021; Egorov et al., 1987), detecting lower levels of IL-6 with higher green exposure.

The evidence on the effect of green space exposure on cardiovascular outcomes in older adults is also scarce, heterogeneous, and with inconsistent results (Yuan et al., 2021). In particular, among those studies using NDVI as the measure of green space exposure, some show clear benefits on CVD incidence and mortality (Orioli et al., 2019; Wang

et al., 2017), but when *meta-analyzed* with others, they only show a reduction in the risk of stroke mortality, and not CVD or IHD (Yuan et al., 2021). Moreover, when studies combine information from different age groups and stratify their results by age, they tend to show stronger protective effects among younger participants (Liu et al., 2022). Unfortunately, most of these studies only consider area-level data, which may lead to ecological fallacies, and the few that take into account individual variables usually refer only to sex, age, and socioeconomic status, which precludes the systematic investigation of individual mediators or modifiers of the associations of interest.

In the literature, it appears that the health benefits of green spaces are greater for people with low socioeconomic status and for those residing in more deprived neighborhoods (Rigolon et al., 2021), as well as for women (Sillman et al., 2022). In our study, we found similar effects on biomarkers of cardiovascular stress across strata defined by sex, educational level, and financial stress, although we observed a non-significant lower risk of CVD in women exposed to higher greenness compared with men. Likewise, when stratifying by SDI at the census level, we found greater reductions in hs-TnT among people with T2DM who lived in more deprived areas.

Previous investigations consistently report that the protective influence of surrounding greenness on cardiovascular disease tends to be more pronounced within smaller buffers, typically up to 250 m (Liu et al., 2022). Unexpectedly, however, our findings indicate an absence of a significant association with cardiovascular incidence within the 250-meter buffer. This observation aligns with the results of a previous study conducted in the city of Madrid, involving the analysis of primary healthcare electronic medical records from 437,513 individuals (Gullón

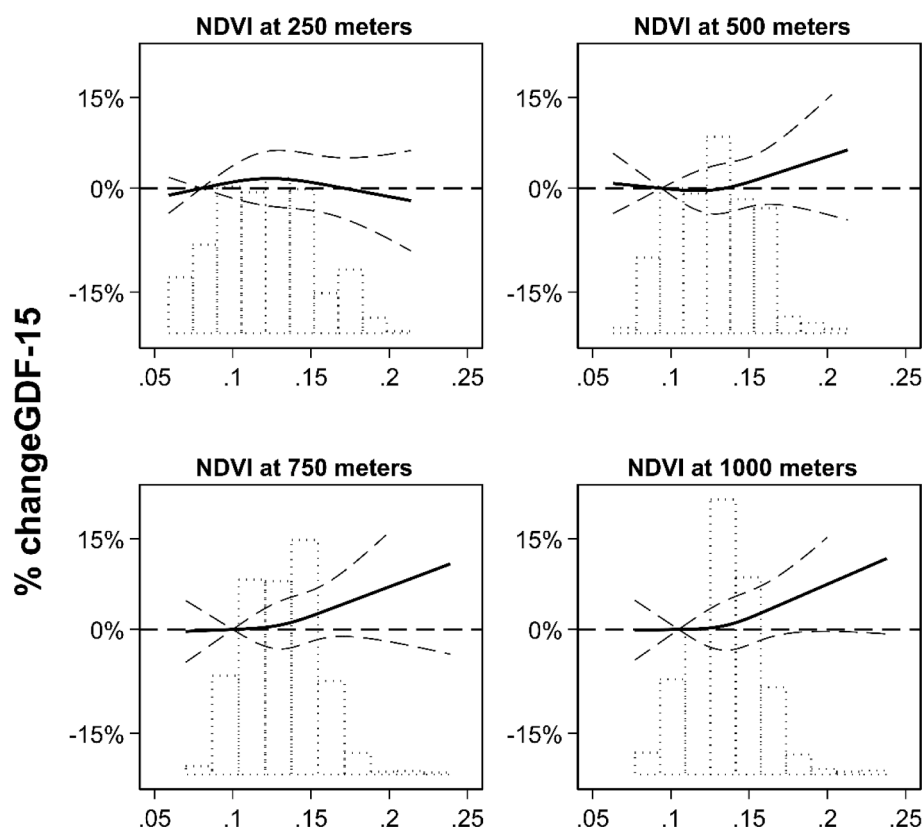


Fig. 4. Percentage change in GDF-15 according to residential greenness (Normalized Difference Vegetation Index, NDVI) with buffer zones at 250, 500, 750, and 1000 m. Thick lines represent percentage changes and dotted lines their 95% confidence intervals. Analyses are based on restricted cubic splines for log-transformed NDVI with knots at the 10th, 50th and 90th percentiles of the distribution. The reference value was set at the 10th NDVI percentile. Percentage changes were obtained from linear regression models adjusted for sex, age, age-squared, educational level, degree of difficulty in making end meets, and social network score, and included a random-effect for the Deprivation Index at the census tract to account for clustering of individuals residing within neighborhoods with similar socio-economic characteristics. P-values for non-linear and global tests were 0.463 and 0.757 at 250 m, 0.438 and 0.590 at 500 m, 0.515 and 0.348 at 750 m, and 0.380 and 0.237 at 1000 m, respectively.

et al., 2023). In their data, the researchers noted a lack of association in close buffers, attributing it to potentially distinct causal pathways for each buffer size. Although the reasons for these lack of associations are unclear, our investigation did not yield consistent evidence in support of this hypothesis.

Among the mechanisms that have been suggested to explain the association between exposure to green spaces and reduced CVD risk are the adoption of healthier lifestyles, increased social cohesion, a restorative capacity, or reduction of air pollution, noise, and heat (Markevych et al., 2017). Even though we recognize the limitations of exploring casual associations using cross-sectional data (Maxwell and Cole, 2007), we wanted to take advantage of the detailed information we have on the individuals in the cohort, and attempted to shed light upon different candidate pathways. These included adoption of healthy behaviors (including both self-reported habitual PA and one-week accelerometry records), well-being and good mental health, improvements in physical and cognitive function or decreased exposure to residential traffic. The temporal relationship supporting the association between green space exposure and these mediators finds validation in existing evidence. For example, a 10-year longitudinal study involving 2.4 million adults in Wales showed that residential greenness was associated with a lower risk of common mental health disorders (Geary et al., 2023). Similarly, in the Nurses Health Study, older women living in greener environments experienced a lower risk of depression during follow-up (315,548 person-years) (Banay et al., 2019). Increasing evidence also suggests that exposure to green space among older adults reduces the risk of cognitive and functional decline. In particular, residential greenness has shown protective effects against cognitive decline in the Whitehall II cohort (de

Keijzer et al., 2018), the Nurses Health Study (Jimenez et al., 2022), or the Chinese Longitudinal Healthy Longevity Survey (CLHLS); or against dementia in the Ginkgo Evaluation of Memory Study (Slawsky et al., 2022) and the UK Biobank (Hu et al., 2023). Furthermore, in the CLHLS, residential greenness was associated with a lower risk of frailty (Zhu et al., 2020) and disability (Zhu et al., 2019). In terms of lifestyles, prospective evidence supports the positive effect of residential greenness on physical activity and sleep quality. For example, the European Prospective Investigation of Cancer Norfolk, with 15,672 individuals followed from 1993 to 2009, revealed that older adults residing in greener neighborhoods experienced a smaller decline in physical activity compared to those living in less green areas (Dalton and Jones, 2020). Also, in a prospective analysis involving 17,834 people with no previous diagnosis of type-2-diabetes and 260 new cases of T2D in Australia, it was found that changes in walking and moderate-to-vigorous physical activity increased with a higher percentage of greenspace within 1 and 2 km buffers among new cases, supporting the idea that green spaces can be a facilitating element when making lifestyle modifications (Chong et al., 2019). The Swedish Longitudinal Occupational Survey of Health (SLOSH), a population-based sample of adults in Sweden with 43,062 observations, indicated that greater availability of greenspace in the immediate residential surroundings was associated with fewer sleep difficulties (Stenfors et al., 2023). Finally, residential green spaces have been prospectively and inversely associated with cardiometabolic risk factors, such as elevated fasting glucose levels, large waist circumference, elevated triglyceride levels, low high-density lipoprotein cholesterol, or hypertension.

Some of our results are consistent with the literature showing that

Table 3

Percentage change (95% confidence interval) in biomarkers of cardiovascular disease risk according to residential greenness (buffer zones at 250, 500, 750, and 1000 m), and percentage change in the magnitude of the observed effects relative to model 1. Results are expressed by increasing interquartile range in greenness.

		NDVI 250 m		NDVI 500 m		NDVI 750 m		NDVI 1000 m	
		% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*
Pro-BNP n = 2132	M1SES	-5.56 (-9.45; -1.50)		-5.05 (-9.58; -0.53)		-4.23 (-8.03; -0.28)		-4.15 (-7.36; -0.82)	
	M2 (M1 + Cohesion)	-5.56 (-9.45; -1.50)	-0.01	-5.05 (-9.58; -0.53)	-0.02	-4.24 (-8.04; -0.28)	-0.23	-4.16 (-7.39; -0.83)	-0.42
	M3 (M1 + Lifesyles)	-4.97 (-9.40; -0.55)	10.60	-4.61 (-9.46; 0.24)	8.69	-3.98 (-8.24; 0.28)	5.88	-3.89 (-7.43; -0.35)	6.17
	M1sub accel [†]	-5.41 (-9.78; -1.04)		-5.01 (-9.72; -0.30)		-4.33 (-8.52; -0.15)		-4.37 (-7.93; -0.82)	
	M3b (M1sub + accel ^{††})	-4.86 (-9.44; -0.28)	10.18	-4.51 (-9.45; 0.43)	9.99	-4.03 (-8.48; 0.32)	6.96	-4.08 (-7.75; -0.42)	6.67
	M4 (M1 + CVR)	-5.15 (-9.32; -0.98)	7.35	-4.44 (-9.01; 0.14)	12.17	-3.78 (-7.89; 0.33)	10.54	-3.80 (-7.26; -0.34)	8.32
	M5 (M1 + Mental)	-5.49 (-9.66; -1.32)	1.30	-4.99 (-9.49; -0.49)	1.17	-4.20 (-8.23; -0.18)	0.64	-4.13 (-7.52; -0.75)	0.31
	M6 (M1 + SPPB)	-4.48 (-8.64; -0.33)	19.82	-3.78 (-8.24; -0.68)	25.58	-3.06 (-6.24; 0.86)	28.18	-3.31 (-6.50; -0.02)	20.43
	M7 (M1 + MMSE)	-5.22 (-9.39; -1.05)	6.31	-4.59 (-9.03; -0.16)	9.25	-3.82 (-7.54; 0.05)	9.86	-3.90 (-7.06; -0.63)	6.16
	M8 (M1 + Traffic)	-4.96 (-8.89; -0.85)	11.16	-4.60 (-8.89; -0.12)	9.06	-3.79 (-7.71; 0.29)	10.53	-3.64 (-7.02; -0.13)	12.53
*hsTnT, T2DM n = 402	M9 (M1 + PNE)	-5.38 (-9.34; -1.24)	3.41	-4.88 (-9.13; -0.43)	3.47	-4.11 (-7.94; -0.11)	3.01	-4.04 (-7.30-0.67)	2.65
	M1sub walk [†]	-5.36 (-9.88; -0.61)		-5.42 (-10.62; 0.08)		-4.25 (-8.96; 0.71)		-3.75 (-7.74; 0.42)	
	M10 (M1sub + Walk)	-5.16 (-10.24; 30.21)	3.86	-4.88 (-10.53; 1.10)	10.31	-3.83 (-8.61; 1.22)	1.08	-3.57 (-7.55; 0.58)	4.83
	M1SES	-8.03 (-12.75; -3.06)		-9.52 (-15.26; -3.38)		-8.05 (-13.94; -2.16)		-5.65 (-10.35; -0.71)	
	M2 (M1 + Cohesion)	-7.85 (-12.57; -2.87)	2.36	-9.36 (-15.07; -3.28)	1.70	-7.88 (-13.71; -2.05)	2.08	-5.46 (-10.13; -0.54)	3.37
	M3 (M1 + Lifesyles)	-7.45 (-12.81; -2.08)	7.29	-9.00 (-15.40; -2.53)	5.78	-7.53 (-13.24; -1.82)	6.50	-5.04 (-9.96; -0.12)	7.59
	M1sub accel [†]	-7.54 (-13.08; -2.00)		-9.47 (-16.41; -2.54)		-8.23 (-14.36; -2.11)		-6.02 (-11.19; -0.86)	
	M3b (M1sub + accel ^{††})	-5.34 (-10.81; 0.13)	29.18	-7.78 (-14.20; -1.36)	17.87	-7.00 (-12.62; 1.36)	15.16	-5.20 (-9.88; -0.52)	13.65
	M4 (M1 + CVR)	-7.84 (-12.93; -2.76)	2.34	-9.08 (-15.11; -3.06)	4.56	-5.48 (-10.26; 0.71)	2.96	-5.48 (-10.26; -0.71)	2.96
	M5 (M1 + Mental)	-7.73 (-13.01; -2.44)	3.81	-9.31 (-15.83; -2.79)	2.22	-7.92 (-13.75; -2.08)	1.68	-5.52 (-10.54; -0.49)	2.35
IL6 n = 2132	M6 (M1 + SPPB)	-7.83 (-12.53; -2.88)	2.64	-9.26 (-14.94; -3.19)	2.87	-7.80 (-13.04; -2.24)	3.23	-5.42 (-10.12; -0.47)	4.08
	M7 (M1 + MMSE)	-7.91 (-12.63; -2.93)	1.64	-9.37 (-15.10; -3.25)	1.67	-7.92 (-13.18; -2.34)	1.72	-5.54 (-10.27; -0.55)	1.99
	M8 (M1 + Traffic)	-9.11 (-13.95; -4.00)	-12.4	-9.98 (-15.58; -4.01)	-5.14	-8.42 (-13.52; -3.03)	-5.05	-6.12 (-10.64; -1.38)	-9.16
	M9 (M1 + PNE)	-7.97 (-12.72; -2.95)	0.87	-9.44 (-15.23; -3.26)	0.84	-7.99 (-13.31; -2.35)	0.72	-5.59 (-10.33; -0.59)	1.06
	M1sub walk [†]	-4.02 (-10.41; 2.82)		-5.90 (-13.97; 2.92)		-4.21 (-11.52; 3.70)		-2.95 (-8.90; 3.40)	
	M10 (M1sub + Walk)	1.56 (-7.11; 11.0)	69.2	-1.81 (-11.13; 8.47)	69.8	-1.70 (-9.32; 6.58)	60.2	-1.60 (-7.46; 4.26)	46.0
	M1SES	-6.35 (-11.69; -1.80)		-5.67 (-10.79; -0.25)		-4.06 (-8.79; 0.92)		-3.50 (-7.37; 0.54)	
	M2 (M1 + Cohesion)	-6.36 (-11.67; -1.84)	-0.09	-5.66 (-10.78; -0.24)	0.15	-3.96 (-8.69; 1.02)	2.47	-3.36 (-7.20; 0.63)	3.94
	M3 (M1 + Lifesyles)	-6.72 (-11.26; -2.18)	-5.85	-6.18 (-11.59; -0.76)	-8.90	-4.38 (-9.31; 0.55)	-7.80	-3.72 (-7.71; 0.27)	-6.41
	M1sub accel [†]	-6.57 (-11.31; -1.83)		-5.41 (-11.02; 0.20)		-3.74 (-8.90; 1.41)		-3.14 (-7.32; 1.05)	
M3b (M1sub + accel ^{††})	-7.06 (-11.64; -2.49)	-7.47	-5.89 (-11.30; -0.47)	-8.75	-4.13 (-9.13; 0.88)	-10.27	-3.44 (-7.56; 0.67)	-9.77	
M4 (M1 + CVR)	-5.38 (-9.84; -0.92)	15.33	-4.15 (-9.36; 1.07)	26.86	-2.80 (-7.48; 1.88)	31.03	-2.58 (-6.32; 1.15)	26.14	
M5 (M1 + Mental)	-6.36 (-11.11; -1.61)	-0.14	-5.67 (-11.27; -0.08)	-0.13	-4.06 (-9.12; 0.99)	-0.06	-3.50 (-7.59; 0.59)	-30.05	
M6 (M1 + SPPB)	-4.17 (-8.54; 0.41)	35.09	-3.18 (-8.11; 2.03)	44.68	-1.73 (-6.26; 3.02)	57.89	-1.83 (-5.60; 2.09)	48.05	
M7 (M1 + MMSE)	-6.19 (-10.54; -1.62)	2.62	-5.46 (-10.66; 0.06)	3.85	-3.86 (-8.66; 1.19)	4.91	-3.38 (-7.29; 0.69)	3.47	

(continued on next page)

Table 3 (continued)

	NDVI 250 m		NDVI 500 m		NDVI 750 m		NDVI 1000 m	
	% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*	% change (95 %CI)	% vsM1*
M8 (M1 + Traffic)	-5.44 (-9.92; -0.74)	14.75	-5.02 (-10.23; 0.49)	11.67	-3.41 (-8.25; 1.68)	16.20	-2.68 (-6.64; 1.45)	23.69
M9 (M1 + PNE)	-6.15 (-10.56; -1.53)	3.20	-5.49 (-10.69; 0.00)	3.16	-3.93 (-8.72; 1.11)	3.20	-3.38 (-7.29; 0.68)	3.32
M1sub walk [†]	-9.65 (-15.22; -3.72)		-9.75 (-16.03; -2.99)		-7.09 (-11.13; -0.64)		-4.48 (-9.03; 0.30)	
M10 (M1sub + Walk)	-5.21 (-15.24; 1.69)	47.29	-5.58 (-12.23; 1.57)	43.97	-5.04(-11.02; 1.36)	29.79	-3.68 (-8.20; 1.06)	18.17

Accel: accelerometry; CI: Confidence interval; CVR: Cardiovascular Disease Risk factors; MMSE: Mini-Mental Examination Test; NDVI: Normalized Difference Vegetation Index; SES: Socio-economic factors; SPPB: Short-Physical Performance Battery; T2DM: Subpopulation with type-2 diabetes; Walk: Walkability.

*%vsM1: Percentage change in the magnitude of observed effects relative to model 1.

[†]Models 3sub and 10sub are as model 1 in subsample with information on accelerometry (n = 2020) or walkability (n = 1072), respectively.

^{††}The percentage changes in the magnitude of observed effects for models 3b and 10b was estimated relative to models 3sub and 10asub respectively.

All models included a random-effect for the Deprivation Index at the census tract to account for clustering of individuals residing within neighborhoods with similar socioeconomic characteristics. Adjustment variables are indicated below:

Model 1: Adjusted for sex, age, age squared, educational level, degree of difficulty in making end meets, and social network score.

Model 2: As model 1 + further adjusted for social cohesion.

Model 3: As model 1 + further adjusted for lifestyle-related factors including smoking status (never, former, current), alcohol drinking (never, former, moderate drinker, current drinker), diet quality (MEDAS index), self-reported PA (Mets/h-week), time watching TV (h/day), sleep time (h/day) and poor sleep quality.

Model 3sub: Model 3 in subsample with information on accelerometry (n = 2020).

Model 3b: Model 3 in subsample with information on accelerometry (n = 2020) with adjustment for time in moderate-to-vigorous physical activity.^{††} The percentage change in the magnitude of observed effects for model 3b was estimated relative to model 3sub.

Model 4: As model 1 + further adjusted for cardiovascular risk factors including BMI (normal weight, overweight, obese), systolic blood pressure (continuous), treatment for hypertension (no/yes), blood total and HDL cholesterol (continuous), triglycerides (continuous), treatment with lipid lowering drugs (no/yes) and glomerular filtration rate (continuous).

Model 5: As model 1 + further adjusted for the presence of depression.

Model 6: As model 1 + further adjusted for physical performance (SPPB score).

Model 7: As model 1 + further adjusted for cognitive impairments (MMSE score).

Model 8: As model 1 + further adjusted for residential traffic exposure.

Model 9: As model 1 + further adjusted for other neighborhood characteristics (PNE scale).

Model10sub: Model 1 in the subsample with information on walkability (n = 1072).

Model 10b: Model 1 in the subsample with information on walkability with adjustment for walkability (n = 1072).^{††} The percentage change in the magnitude of observed effects for model 10b was estimated relative to model 10sub.

Table 4

Hazard Ratios (95% confidence interval) for cardiovascular disease incidence during six years of follow-up according to residential greenness (buffer zones at 250, 500, 750, and 1000 m) among participants with all biomarkers available.

CVD	At 250 m		At 500 m		At 750 m		At 1000 m	
	n/total		n/total		n/total		n/total	
Q1	33/513	Ref.	43/521	Ref.	40/516	Ref.	37/511	Ref.
Q2	27/525	0.81 (0.48; 1.37)	20/515	0.51 (0.28; 0.95)	30/522	0.77 (0.44; 1.35)	36/519	1.04 (0.60; 1.81)
Q3	32/515	0.94 (0.57; 1.54)	36/520	0.88 (0.54; 1.45)	30/537	0.80 (0.50; 1.26)	32/558	0.92 (0.55; 1.53)
Q4	35/578	1.02 (0.60; 1.74)	28/575	0.62 (0.38; 1.00)	27/556	0.63 (0.38; 1.03)	22/543	0.57 (0.33; 0.99)
p-trend		0.78		0.20		0.06		0.03
Per IQR	127/2131	0.96 (0.75; 1.25)	127/2131	0.83 (0.63; 1.10)	127/2131	0.79 (0.61; 1.01)	127/2131	0.80 (0.65; 0.97)

CI: Confidence interval; NDVI: Normalized Difference Vegetation Index; Q: Quartile.

All models were adjusted for sex, age, age squared, educational level, degree of difficulty in making end meets and social network score; moreover a random-effect for the Deprivation Index at the census tract was included to account for clustering of individuals residing within neighborhoods with similar socioeconomic characteristics.

reduced traffic exposure could partly mediate the observed decrease in CVD risk (Markevych et al., 2017). They also suggest that PA might be a particularly important mediator in the association between NDVI and decreased cardiovascular risk among participants with T2DM, which are at much higher risk of CVD (Damaskos et al., 2020). In fact, only diabetics who met the recommendations for MVPA showed reductions in hs-TnT with greenness. Regarding the mediating effects of reduced residential traffic among diabetics, we should acknowledge that air pollution has been associated with the risk of diabetes and its complications, and some of the specific pathways by which diabetics have an increased cardiovascular risk may be particularly benefited by a reduction in air pollution levels in areas with increased greenness (Pedersen et al., 2019; Gorini et al., 2021). On the other hand, according

to our analyses, improved mental health and social cohesion probably account for little of the beneficial effects of green spaces on cardiovascular health in older adults.

As a novel finding, the present results highlight the importance of functional status when examining the relationship between residential characteristics and cardiovascular health. Adjusting for the SPPB score attenuated the protective impact of green spaces across all analyzed outcomes. This implies that residential areas with more green spaces might safeguard the cardiovascular system by enhancing functional capacity among older adults. In this regard, there is evidence that the SPPB might be linked to CVD through mechanisms beyond low PA and traditional CVD risk factors, such as increased oxidative stress and DNA damage, inflammation, or endocrine dysregulation (Bellettiere et al.,

2020). Moreover, some research has previously found that green spaces exert a protective impact on the functionality of older adults (Zhu et al., 2020; Zhu et al., 2019; de Keijzer et al., 2019).

Some discrepant results between the studied outcomes may be due to their different nature. ProBNP is released in response to increased pressure and stress in the heart, particularly in heart failure or hypertension, while hs-TnT indicates heart muscle injury. On the other hand, IL-6 and GDF-15 are cytokines with a central role in the inflammatory cascade, and although they have shown to predict CVD risk (Kato et al., 2023), they are less specific to cardiovascular conditions. In particular, GDF-15 indicates chronic subclinical inflammation that is characteristic in old age (Liu et al., 2021). In this sense, an interesting hint in our study was that among those with a low SPPB (score below 9 points, a usual cut-off point for measuring frailty), greater greenness was associated with higher levels of GDF-15, and to a lesser extent, higher levels of IL-6. This suggests potentially adverse health influences of green spaces on individuals with low functional capacity, which need to be further studied (Markevych et al., 2017).

Within the limitations of the present study, we were unable to completely eliminate the risk of residential self-selection (i.e., healthier people tending to choose to live in greener places) (Markevych et al., 2017). However, our participants are residentially stable, most (95 %) owned the house where they lived, and when a subsample of the cohort (n = 1468) was asked about changes in residential address, less than 5 % reported changes during the previous years. As a second limitation, although we examined a great number of potential confounders and mediators, the selection of some indicators (i.e., social cohesion) may not have been optimal, and we lacked information on air pollutants and noise, so we could not evaluate their impact on the studied associations. Another limitation was the use of a vegetation index, as these do not differentiate between structured (i.e. parks) and unstructured (i.e. street trees) vegetation. However, in our population around 95 % of participants had a park within 500 m as estimated using the Spanish Land Use Information System (SIOSE) database from 2011 (data not shown) (Ojeda Sánchez et al., 2023). Finally, the cross-sectional nature of the analyses with cardiovascular biomarkers precluded differentiation between the confounding and mediating effect of some of the studied factors (Bellettiere et al., 2020).

6. Conclusion

Increased exposure to residential green space is associated with a moderate reduction in CVD risk in older adults residing in densely populated areas. This study identifies some potential mediators for this association, including lower exposure to traffic, enhanced physical performance, and a lower prevalence of CVD biological risk factors. Future longitudinal studies should further evaluate the cardiovascular benefits of green spaces in older adults according to their baseline functional status.

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CRedit authorship contribution statement

Cara Scheer: Writing – original draft. **Elena Plans-Beriso:** Formal analysis, Visualization, Writing – review & editing. **Roberto Pastor:** Methodology, Software, Writing – review & editing. **Rosario Ortola:** Data curation, Writing – review & editing. **Mercedes Sotos-Prieto:** Writing – review & editing. **Verónica Cabañas-Sánchez:** Funding

acquisition, Writing – review & editing. **Pedro Gullón:** Writing – review & editing. **Carlos Ojeda Sánchez:** Data curation, Writing – review & editing. **Rebeca Ramis:** Writing – review & editing. **Pablo Fernández-Navarro:** Investigation, Writing – review & editing. **Fernando Rodríguez-Artalejo:** Funding acquisition, Investigation, Writing – review & editing. **Esther García-Esquinas:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing – original draft, 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

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108570>.

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