Health & Place 95 (2025) 103522

Contents lists available at ScienceDirect

Health and Place

journal homepage: www.elsevier.com/locate/healthplace

Neighbourhood greenness might impact thyroid hormone levels in children, adolescents, and young adults

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ARTICLE INFO

Keywords:
Neighbourhood greenness
Thyroid hormone
Cohort study
Children and adolescents
Healthy cities

ABSTRACT

Background: Growing attention has been paid to the health benefits of neighbourhood greenness in urban cities, whereas the potential impacts on thyroid hormone levels remain unclear, particularly among children, adolescents, and young adults.
Methods: This longitudinal cohort study included 57,198 participants aged 6–25 years from an open cohort in Taiwan, observed from 2000 to 2017. Individual thyroid stimulating-hormone (TSH) and free thyroxine (FT4) levels were measured using immunoassay analysers. The annual average of Normalized Difference Vegetation Index (NDVI) was derived for each participant's address. Linear mixed models were used to investigate the associations between neighbourhood greenness and TSH and FT4, with analyses conducted separately for males and females. The modifying effects and potential mediators were also evaluated.
Results: 49690 participants with 71715 observations were included in this study. Among them, 42.7 % of participants were females. Negative association was found between neighbourhood greenness exposure and TSH level for both females and males, while a positive association was found with FT4 levels only among females. Women exposed to the third quartile of NDVI had lower TSH levels ($-7.84e^{-2}$ μIU/ml, 95 % CI: $-15.01e^{-2}$, $-0.67e^{-2}$) compared with those in the first quartile of NDVI. Decreased TSH levels of $4.56e^{-2}$ μIU/ml (95 % CI: $-8.53e^{-2}$, $-0.59e^{-2}$) and $7.24e^{-2}$ μIU/ml (95 % CI: $-12.19e^{-2}$, $-2.29e^{-2}$) were found in males exposed to the third and fourth quartile of NDVI, respectively. Regarding FT4 levels, women exposed to the second quartile of NDVI had increased FT4 levels ($2.01e^{-2}$ ng/dl, 95 % CI: $0.19e^{-2}$, $3.82e^{-2}$). Each SD increase of NDVI was associated with $0.65e^{-2}$ ng/dl (95 % CI: $0.15e^{-2}$, $1.15e^{-2}$) increase of FT4.
Conclusion: Our study provided evidence on the impacts of neighbourhood greenness on thyroid hormone levels among young populations. These findings may reveal potential biological mechanisms and contribute to urban planning and public health strategies.

1. Introduction

Thyroid hormones (THs) are essential chemical messengers that regulate growth and early brain development throughout childhood and adolescence (Bettendorf, 2002; Hanley et al., 2016), playing a vital role in maintaining both physiological and psychological health (Rovet, 2014). Abnormal thyroid hormone production in the thyroid gland is associated with thyroid dysfunctions (e.g. hyperthyroidism and hypothyroidism), contributing to serious health consequences, such as an increased risk of thyroid cancer (Cabanillas et al., 2016), early-onset

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https://doi.org/10.1016/j.healthplace.2025.103522
Received 5 November 2024; Received in revised form 5 July 2025; Accepted 22 July 2025
Available online 16 August 2025
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type 2 diabetes (Bardugo et al., 2021) and anxiety disorders (Luo et al., 2024).

Previous studies have demonstrated that multiple factors may influence the long-term variation of thyroid hormone levels within individuals, including genetics (Hansen et al., 2004), demographic factors (Yao et al., 2021), and lifestyle choices (Feng et al., 2022). Recent research increasingly highlighted the impact of environmental factors on thyroid hormone regulation (Liu et al., 2023). For example, emerging evidence suggested an association between air pollutants and the concentration of multiple THs (Irizar et al., 2021; Kim et al., 2024), such as free thyroxine (FT4) and Thyroid-stimulating hormone (TSH) (Zhou et al., 2024). Climate variables such as precipitation may affect TSH level (Zeng et al., 2021). These findings underscore the necessity of exploring the potential effects of living environments to inform large-scale population-level intervention strategies (Street et al., 2024).

Among various living environmental factors, neighbourhood greenness has shown protective effects on general physical and mental health (Paoin et al., 2023; Wang et al., 2024). The potential mechanism underlying the health benefits primarily include encouraging physical activity (McMorris et al., 2015), improving psychological restoration (Mennis et al., 2018), reducing air pollution (Diener and Mudu, 2021), alleviating perceived noise disturbances (Dzhambov and Dimitrova, 2015), and facilitating social cohesion (Jennings and Bamkole, 2019). However, the health impacts of neighbourhood greenness on THs and thyroid function remain unclear because most of studies applied ecological and cross-sectional designs, which are prone to ecological fallacy (Wang et al., 2022) and limited causal inference (Liu et al., 2025). Additionally, inconsistent findings were reported. For example, while spatial analyses covering 27.6 % of the total population in China found that more greenness was linked to a lower risk of thyroid cancer (Huo et al., 2022), another nationwide study indicated that greenness was associated with lower prevalence of thyroid nodules (Liu et al., 2025), other ecological study has yielded no health benefits of greenness on thyroid cancer (Wang et al., 2022). Nevertheless, the potential mechanisms underlying these associations are still not fully understood. Therefore, further research with longitudinal design at individual level is necessary to explore the associations between greenness and thyroid health. Such research could reveal the potential biological mechanism and contribute to urban planning and public health strategies (Liu et al., 2025).

Furthermore, previous research on greenness and thyroid health has focused more on general population (Liu et al., 2025), while the impacts on young population remained unexplored. The developmental immaturity of thyroid systems among young population renders them more susceptible to thyroid dysfunction than adult counterparts (Bettendorf, 2002). During the period from 1999 to 2014, cancer of the thyroid and other endocrine glands ranked as the second leading cancer causing death among children and adolescents aged 1–19 years (Curtin SC and Anderson, 2016). The importance to investigate environmental factors in this vulnerable demographic is underscored.

Considering the existing research gaps, this study aimed to investigate the impact of neighbourhood greenness on thyroid hormone levels among children, adolescents, and young adults aged between 6 and 25 years, using a retrospective cohort in Taiwan. We examined the hypothesis that higher exposure to neighbourhood greenness is associated with lower TSH and higher FT4 level among children, adolescents, and young adults.

2. Methodology

2.1. Study population

This study included participants from the MJ cohort in Taiwan, which has been detailed in previous publications (MJ Health Research Foundation, 2016; Guo et al., 2019; Wu et al., 2017). Briefly, this ongoing longitudinal cohort was established by the MJ Health Management Institution as part of a health screening programme and has enrolled general residents since 1994. All the participants are encouraged to visit the clinical centres periodically, where they receive a comprehensive physical examination service and complete a standard self-administered questionnaire. The address of each participant at each visit is recorded through sending the medical examination report. Quality control measures for physical examinations are elaborated upon in the technical report from MJ Health Research Foundation (MJ Health Research Foundation, 2016). Consent form is required to be signed by each participant before joining this programme. The Human Research Ethics Committee of the University of Hong Kong has approved this study (EA230618).

Fig. S1 illustrates the participants selection procedure for our study. A total of 57,198 participants aged 6–25 between 2000 and 2017 (Velayutham et al., 2015). 619 participants were excluded due to missing address information or because they were located outside the main island of Taiwan. Additionally, 6889 participants without covariate information were excluded, resulting in 49,690 participants with 71715 observations for the following analyses. Ultimately, 40,079 participants with 60,319 visits were included for TSH analysis, and 11,931 participants with 16,268 observations were included for FT4 analysis. We explored the potential gender differences in the greenness-THs associations by comparing the coefficients of the main model between males and females (Clogg et al., 1995). The Z-test equation (1) is:

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{(SE\beta_1)^2 + (SE\beta_2)^2}} \tag{1}$$

The results suggested no significant differences between genders in the association between THs and greenness ($Z = 0.014$ and $P = 0.989$ for TSH; $Z = 0.014$ and $P = 0.989$ for FT4). However, given the natural gender differences in thyroid hormone levels and vulnerability of thyroid disease (Calcaterra et al., 2020; Kuzmenko et al., 2021), all analyses were still performed separately for males and females.

2.2. Outcome variables and procedures

In the present study, the major health outcomes included TSH and FT4. Blood samples were collected in the morning and stored at −20 °C. Immunoassay analysers (ABBOTT; IMX, AxSYM, and I2000) were used to measure the levels of TSH and FT4. Both hormones are commonly recognised as biomarkers for diagnosing thyroid dysfunction and related diseases. In this study, the normal reference ranges were established as 0.47–5 μIU/ml for TSH and 0.7–1.48 ng/dl for FT4 (MJ Health Research Foundation, 2016).

Following the guideline of the American Thyroid Association and previous clinical studies, thyroid dysfunction was defined based on the abnormal level of TSH and FT4 (Ross, 2001; Surks et al., 2004; The American Thyroid Association). In short, a TSH level outside the normal range typically suggests hypothyroidism if elevated, and hyperthyroidism if lower. A FT4 level within the normal range can indicate subclinical hyperthyroidism or hypothyroidism, while a FT4 level outside the normal range points to overt thyroid dysfunction (Sterenborg et al., 2024). In this study, we included subclinical hypothyroidism (TSH >5 μIU/ml & FT4 within 0.7–1.48 ng/dl) or hypothyroidism (TSH >5 μIU/ml & FT4 < 0.7 ng/dl), and subclinical hyperthyroidism (TSH <0.47μIU/ml & FT4 between 0.7 and 1.48 ng/dl) or hyperthyroidism (TSH <0.47μIU/ml & FT4 > 1.48 ng/dl) in the sensitivity analysis.

2.3. Neighbourhood greenness

We used the Normalized Difference Vegetation Index (NDVI) to assess neighbourhood greenness. NDVI is a satellite-derived index based on atmospherically corrected reflectance in the visible red light (RED) and near-infrared light (NIR). The following equation was employed: NDVI=(NIR−RED)/(NIR + RED). NDVI values range from −1 to 1, with higher values indicating more abundant vegetation, while negative or zero values representing the presence of water bodies and built-up areas (Braun and Herold, 2004).

We derived NDVI metrics through an imagery dataset archived from Google Earth Engine (GEE), a cloud computing-based platform incorporating remotely sensed imagery and geospatial datasets (Tamiminia et al., 2020). We obtained 30-m resolution images from the United States Geological Survey (USGS) Landsat 7 Level 2, Collection 2, Tier 1 dataset for our study period (January 1, 2000, to December 31, 2017). Landsat 7 is characterized by an approximately 710 km sun-synchronous circular orbit inclined at 98.2°, which allows for a regular image collection every 16 days (Teillet et al., 2001). Landsat 7 was thus selected due to its long-term and large-scale coverages. Surface reflectance products were generated by the Landsat 7 ETM + sensor using the Landsat Ecosystem Disturbance Adaptive Processing System (LEDAPS) algorithm (version 3.4.0). We used the pixel quality attributes generated from CFMask algorithm for cloud and cloud shadow detection (Foga et al., 2017), and supplemented missing data post-cloud masking with the resampled 250-m NDVI from Moderate-resolution Imaging Spectroradiometer (MODIS) Terra (Feng et al., 2006). All NDVI raster data were generated and exported from GEE. The annual average NDVI were computed for the main analysis. Additionally, we examined annual maximum NDVI to assess the robustness of the health impacts related to different greenness indices. Negative values were removed, the average NDVI within buffer zones were calculated to represent neighbourhood greenness.

We considered both 500 m and 1000 m Euclidean radius buffers around the participants' addresses for each visit year in this study. Previous studies on neighbourhood greenness suggested that a 500 m buffer commonly represents the immediate neighbourhood environment, where residents undertake physical activities and mitigate exposure to air pollution (Su et al., 2019; Yang et al., 2019). Therefore, the health impacts of NDVI within a 500 m buffer were highlighted as the main results. Analyses included both the per standard deviation (SD) and quartiles of greenness.

To evaluate the robustness of our findings across different vegetation indices, we also included Enhanced Vegetation Index (EVI) in the sensitivity analysis. EVI is generated from the NIR, Red and Blue bands, and ranges from −1.0 to 1.0 (Huete et al., 2002). The equation of EVI is expressed as follows: $EVI = G * (NIR - RED)/(NIR + C_1 * RED - C_2 * BLUE + L)$, where G represents a gain or scaling factor, L is the canopy background adjustment, and C_1 and C_2 are the coefficients of the aerosol resistance term. Compared to NDVI, EVI was developed by incorporating a feedback-based approach to decouple the canopy background signal and reduce the atmospheric influences. As a result, EVI could offer improved sensitivity to regions with high biomass and changes in vegetation (Matsushita et al., 2007). Similarly, EVI was obtained from the MODIS Combined 16 Day product through the Land Processes Distributed Active Archive Center (LP DAAC) at a resolution of 250 m^2. The coefficients adopted for the MODIS EVI algorithm are, $L = 1$, $C_1 = 6$, $C_2 = 7.5$, and $G = 2.5$ (Didan et al., 2015).

2.4. Covariates

In the present study, covariates were selected mainly based on previous literature (Babic Leko et al., 2021; Rugge et al., 2015). We divided the covariates into four categories:

Demographic factors. Demographic factors include age, body mass index (BMI; kg/m^2), educational level (high school or lower/college or university or above).

Lifestyle factors. Smoke status (never or ever/current), alcohol intake (irregular: <3 times a week/regular: ≥ 3 times a week), weekly exercise intensity [Inactive or low-intensity (e.g. walking); Moderate or high-vigorous exercise (e.g. jogging, skipping)], vegetable/fruit intake (infrequent: ≤ 2 servings per day/frequent: >2 servings per day) were assessed as categorical variables.

Medical factors. A history of using hormone medications (yes/no) were recorded.

Environmental factors. Natural environment includes annual average air pollution ($PM_{2.5}$, NO_2, and O_3) (continuous variable) (Ghassabian et al., 2019; Ilias et al., 2020), annual average precipitation and temperature. Social environment includes neighbourhood-level (township in Taiwan) education and household income. Built environment includes street connectivity (road length and number of intersections), and distance to transit (number of transit stations).

Since most covariates were recorded at each visit, we also derived environmental indicators through the following process. The assessment of $PM_{2.5}$, NO_2, and O_3 has been described in previous studies (Geng et al., 2021; Guo et al., 2022; Wu et al., 2021; Zhang et al., 2017). In short, the satellite-derived aerosol optical depth (AOD) data obtained from the U.S. National Aeronautics and Space Administration were utilized to estimate the daily $PM_{2.5}$ concentration through a spatio-temporal model. Daily NO_2 and O_3 concentration were estimated using image data from the Tropospheric Monitoring Instrument (TROPOMI) through a geographically and temporally weighted regression (Wu et al., 2021). All three air pollutants were estimated at a resolution of one km^2, and annual average concentrations were calculated. Because NO_2 and O_3 were unavailable before 2005, missing data were imputed using the estimates in the year 2005. The air pollution estimates were subsequently assigned to each participant based on the nearest distance to their locations.

Precipitation data at a resolution of 5.6 km^2 was obtained from the Climate Hazards Group InfraRed Precipitation with Station data (CHIRPS). Temperature data at a resolution of 1 km^2 was obtained from the MOD11A1 V6.1 Terra land surface temperature product. The precipitation data were further resampled to one km^2 resolution using bilinear interpolation method to maintain consistent spatial resolution (Appendix. A). Finally, the meteorological data were matched with participants based on their addresses.

Parental socioeconomic status (SES) information, including parental education and income, was unavailable in this study. We thus included neighbourhood-level SES indicators as proxies of parental information (Alwahaibi and Zeka, 2016) and as measures of the social environment. Neighbourhood SES indices were assigned to each participant based on their geocoded addresses. Neighbourhood-level education (the proportion of college or above educated residents, %) was obtained from the Statistical Map of the National Population Database, managed by the Department of Household Registration in Taiwan. Annual median household income (1000 NTD) was sourced from the Income Tax Statistics, managed by the Fiscal Information Agency, Ministry of Finance of Taiwan.

We included several important built environmental features as contextual characteristics underlying the potential confounding pathways related to health behaviours such as walkability (van den Berg et al., 2015). We adjusted street connectivity and distance to transit in our study. The number of intersections and road length were assessed as proxies for street connectivity (Knight and Marshall, 2015). Number of transit stations in buffers were calculated to represent the distance to transit. Due to a lack of historical data, information on road network and transit stations was extracted from the OpenStreetMap (OSM) datasets of Taiwan in 2017 using Python package *OSMnx* (Boeing, 2017). This is a promising source for basic geographical information, and the quality of OSM road network in Taiwan has been validated (Jianhong et al., 2024). We excluded highways and trunk ways which are less accessible to pedestrians when calculating built environment indicators (Deng et al., 2020; Xue et al., 2020). The transit stations within pedestrian catchment areas included categories coded as "bus station", "bus stops", "ferry terminal", "railway halt", "railway station", and "tram stop" (Kartschmit et al., 2020). We then assigned the built environment indicators to the participants based on a 500 m buffer around their addresses for each visit.

2.5. Examination of spatial dependency

To address possible spatial autocorrelation effects of the study samples, we calculated Global Moran's I statistics (Moran, 1948). Global Moran's I is a robust measure of spatial clustering patterns, the value closer to −1 or 1 indicates a dispersion or clustering. The results revealed statistically weak spatial dependence across all baseline strata: TSH female group (Moran's I = 0.003, p = 0.369), TSH male group (Moran's I = 0.016, p = 0.083), FT4 female group (Moran's I = 0.020, p = 0.053), and FT4 male group (Moran's I = 0.019, p = 0.110).

2.6. Statistical analysis

2.6.1. Association between neighbourhood greenness and thyroid hormone

We used Spearman's correlation to check for potential multicollinearity between NDVI and other variables. Covariates that exhibited a high association ($p \geq 0.7$) with NDVI were excluded from the main models. Linear mixed models (LMMs) were used to assess the associations of NDVI with TSH and FT4. A random intercept for each participant was included to account for intra-individual correlation arising from repeated measurements. The abovementioned covariates were sequentially included in the following models: Model 1 was a crude model; Model 2 was adjusted for age, educational level, BMI, smoking status, alcohol intake, intensity of exercise, vegetable/fruit intake, and community-level education; and Model 3 was further adjusted for precipitation, temperature, $PM_{2.5}$, NO_2, O_3, number of intersections, and number of transit stations. The Variance inflation factor (VIF) was used to check the multi-collinearity issues. The estimated associations with the corresponding 95 % confidence intervals (95 % CIs) were reported.

The linearity of the dose-response associations was examined using likelihood ratio test. For nonlinear dose-response associations between NDVI and thyroid hormone levels, natural cubic spline functions were used with the 25th percentile as a reference level (Fang et al., 2024). Natural cubic splines, a commonly used approach in epidemiological studies (Elhakeem et al., 2022; Fang et al., 2024), can well fit the non-linear associations (Perperoglou et al., 2019). The degree of freedom was selected based on the minimum Akaike Information Criterion (AIC) value (Appendix. B).

2.6.2. Stratified analyses

In this study, the following potential modifiers were considered: age (children and adolescents: 6–17 years old; and young adults: 18–25 years old) (Witte et al., 2015), BMI (non-obesity: <25 kg/m^2; and obesity: ≥ 25 kg/m^2) (World Health Organization, 1995), weekly exercise intensity [Inactive or low-intensity (e.g. walking); Moderate or high-vigorous exercise (e.g. jogging, skipping)], $PM_{2.5}$ (Low; and High), NO_2 (Low vs. High), and O_3 (Low vs. High). Cutoff points for air pollutants were determined by the median values. Interaction terms between NDVI and each modifier were included in the main model separately to examine whether the NDVI-THs associations were modified. Stratified analyses were then performed by the statistically significant modifiers (P interaction <0.1).

2.6.3. Causal mediation analyses

To explore the potential mechanistic pathways underlying the associations between neighbourhood greenness and THs, we employed causal mediation analyses (Zhang et al., 2016), specifying a potential biological linkage through air pollution ($PM_{2.5}$, NO_2, O_3), metabolic regulation (BMI), and physical activity (exercise intensity). All the covariates in Model 3 except for the target mediators were adjusted. Statistical analyses were performed with 1000 bootstrap simulations (Tingley et al., 2014). The average causal mediation effect (ACME), average direct effect (ADE), and the proportion of the mediating effects were calculated.

2.6.4. Sensitivity analyses

To evaluate the robustness of our primary findings, we performed multi-dimensional sensitivity analyses:

1) *Vegetation metrics consistency.* To evaluate whether the associations were consistent across different vegetation indices, we examined the associations between EVI and thyroid hormone levels using LMMs with an adjustment for the covariates specified in Model 3.
2) *Longitudinal and temporal consistency.* To examine the stability of cumulative greenness impact, we extended the exposure window to 2-year (visit year and the previous year) average NDVI. To reduce the influence of extreme seasonal effect in single year, we examined the annual maximum value of NDVI and its associations with thyroid hormone levels. To assess the consistency of the longitudinal association aligning with baseline patterns, we examined cross-sectional analyses for baseline observations of the cohort using a linear regression model.
3) *Spatial scale dependency.* To examine whether the associations are consistent across different spatial scales, we examined the health impacts of NDVI exposure within 1000 m buffer.
4) *Clinical translation validity.* To validate whether the hypothesised protective effect of greenness remained stable when translating continuous indicators into clinically meaningful outcomes, we further investigated the associations with thyroid dysfunction (i.e., hypothyroidism/subclinical hypothyroidism and hyperthyroidism/subclinical hyperthyroidism) using a mixed-effects logistic regression model, adjusting for the Model 3 covariates.
5) *Causality robustness examination.* To enhance understanding of potential causal associations, we applied an inverse probability weighting (IPW) approach to mitigate potential confounders (Rosenbaum and Rubin, 1983). We fitted multivariable linear regression model with NDVI as the outcome to create the propensity score, the covariates in Model 3 were included in the models. Finally, we employed weighted linear regression models to determine the association between neighbourhood greenness and thyroid hormone in each cohort.
6) *Physical activity sensitivity.* Leisure-time Physical Activity (LTPA) level from the surveys (metabolic equivalent of task, MET) was adjusted to replace the exercise intensity to examine the robustness of physical activity indicator. The assessment and categorising of LTPA were described in previous study (Wen et al., 2011).

ArcGIS Pro 3.0.0 was used to perform participants address matching and assess neighbourhood NDVI and EVI. All statistical analyses were conducted using R software (version 4.2.3). The threshold for statistical significance was preset at < 0.05.

3. Results

3.1. Descriptive statistics

The characteristics of all participants at baseline were presented in Table 1. A total of 49690 participants with 71715 visits were included in the main analyses for thyroid hormone levels. The median follow-up time was 3.41 years (range: 0.33–17.08) and 2.50 years (range: 0.58–8.42) for TSH and FT4 group, respectively. In the TSH group, at baseline, the average age was 20.73 years (SD: 4.74) for females and 19.74 years (SD: 4.92) for males. 60.3 % of females and 50.0 % of males attained a college/university or higher level of education. The average BMI was 20.09 kg/m^2 (SD: 2.41) for females and 22.03 kg/m^2 (SD: 4.32) for males. Among the participants included in the TSH analysis (n = 40,079), 1630 (7.7 %) females and 4127 (21.9 %) males were smokers at baseline, while 260 (1.2 %) females and 356 (1.9 %) males reported current alcohol consumption. Additionally, 30.7 % female participants engaged in moderate or high-vigorous exercise, while the proportion was 63.0 % for male group. A small number of participants used

Table 1
Baseline characteristics of participants.

Characteristics	Thyroid-Stimulating Hormone (TSH)		Free Thyroxine (FT4)	
	Female (n = 21,240)	Male (n = 18,839)	Female (n = 6181)	Male (n = 5750)
	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)
Demographic factors				
Age	20.73 (4.74)	19.74 (4.92)	21.29 (3.48)	20.56 (3.59)
College or university and above	12,804 (60.3)	9425 (50.0)	4308 (69.7)	3463 (60.2)
BMI (kg/m^2)	20.09 (2.41)	22.03 (4.32)	20.59 (3.47)	22.78 (4.46)
Lifestyle factors				
Current smokers	1630 (7.7)	4127 (21.9)	392 (6.3)	1001 (17.4)
Regular drinkers	260 (1.2)	356 (1.9)	97 (1.6)	102 (1.8)
Frequent intake of vegetable/fruit	7920 (37.3)	7400 (39.3)	2595 (42.0)	2743 (47.7)
Moderate or high-vigorous exercise	6523 (30.7)	11,867 (63.0)	1769 (28.6)	3752 (65.3)
Medical factors				
Use hormone drug	229 (1.0)	19 (0.1)	85 (1.4)	6 (0.1)
Environmental factors				
NDVI (500 m buffer)	0.172 (0.08)	0.176 (0.09)	0.182 (0.09)	0.182 (0.09)
$PM_{2.5}$ (μg/m^3)[a]	24.04 (4.22)	23.95 (4.32)	23.66 (3.64)	23.69 (3.70)
NO_2(μg/m^3)[a]	43.34 (17.25)	42.58 (17.47)	38.13 (15.09)	37.59 (15.20)
O_3 (μg/m^3) [a]	51.53 (8.14)	51.98 (8.05)	55.54 (7.00)	56.07 (6.78)
Precipitation (mm/d)	5.88 (1.43)	5.88 (1.43)	5.69 (1.07)	5.64 (1.04)
Temperature (°C)	30.78 (1.98)	30.73 (1.98)	30.66 (1.83)	30.59 (1.80)
Neighbourhood-level education, college or university and above (%)	28.98 (0.11)	28.17 (0.11)	37.15 (0.10)	36.35 (0.10)
Neighbourhood-level median household income (K NTD)	608.16 (92.55)	602.69 (90.38)	626.32 (96.32)	619.93 (96.05)
Number of intersections	104.30 (60.37)	101.70 (59.95)	100.00 (59.40)	95.87 (57.33)
Road length (km)	16.92 (7.58)	16.45 (7.37)	16.68 (7.73)	16.01 (7.187)
Number of transit stops	12.65 (9.48)	12.16 (9.39)	12.71 (9.60)	11.99 (9.25)
TSH (μIU/ml)	1.74 (2.14)	1.70 (1.12)	–	–
FT4(ng/dl)	–	–	1.11 (0.19)	1.14 (0.17)

[a] Air pollutant concentration. $PM_{2.5}$: Fine particulate matter. NO_2: Nitrogen dioxide, O_3: Ozone.

hormone medication (1.0 % of females and 0.1 % of males). The main characteristics of the participants in FT4 group were generally comparable to those of TSH group. The mean TSH level was 1.74 μIU/ml (SD: 2.14) for females and 1.70 μIU/ml (SD: 1.12) for males. The mean FT4 level was 1.11 ng/dl (SD: 0.19) for females and 1.14 ng/dl (SD: 0.17) for males. TSH levels were generally decreased over age (Fig. 1), with a much higher rate of decline observed in children and adolescents compared to adults. In contrast, FT4 level increased significantly with age.

Fig. 2(A) shows the spatial distribution of average NDVI across the main island of Taiwan between 2000 and 2017. The gradient green colour represented the NDVI values classified using the Jenks natural breaks, while the blue colour indicated water body. The distribution of NDVI in Taiwan main island depicted a diverse landscape with varying greenness condition. Higher NDVI values were mainly observed among central mountain covered by forest. In contrast, the western and coastal regions exhibited a relatively lower NDVI, indicating a higher level of urbanization and reduced natural vegetation cover. Fig. 2 (B) illustrates the participants distribution, showing that the majority of participants were located in regions characterized by relatively lower NDVI. Fig. 3 demonstrates that NDVI levels were generally stable during the study period.

3.2. *Main analyses*

The longitudinal associations between neighbourhood greenness and THs were shown in Table 2. We found significantly negative associations between NDVI and TSH levels in both females and males. After fully adjusted for covariates, compared to females exposed to the first quartile of NDVI, those exposed to the third quartile had lower TSH levels ($-7.84e^{-2}$ μIU/ml, 95 % CI: $-15.01e^{-2}$, $-0.67e^{-2}$). Males exposed to the third and fourth quartile of NDVI also had decreased TSH levels of $4.56e^{-2}$ μIU/ml (95 % CI: $-8.53e^{-2}$, $-0.59e^{-2}$) and $7.24e^{-2}$ μIU/ml (95 % CI: $-12.19e^{-2}$, $-2.29e^{-2}$), respectively. By contrast, women exposed to the second quartile of NDVI had increased FT4 levels compared to those exposed to the first quartile ($2.01e^{-2}$ ng/dl, 95 % CI: $0.19e^{-2}$, $3.82e^{-2}$). Each SD increase of NDVI was associated with $0.65e^{-2}$ ng/dl (95 % CI: $0.15e^{-2}$, $1.15e^{-2}$) increase of FT4 in males. For each model, there were minor multicollinearity issues among the predictor variables with all VIF values < 3. The R square values of full models were between 0.498 and 0.574 in this study, the RMSE were between 0.080 and 1.070 (Table S1).

The exposure-response associations between neighbourhood greenness and thyroid hormone levels are depicted in Fig. 4. The fitted curves indicate a decreasing trend in the greenness-TSH response and an increasing pattern in the greenness-FT4 gradient, both of which are consistent with the estimates obtained from linear mixed regression analysis. The predominantly linear associations between greenness and TSH-females and FT4 are demonstrated (TSH-female group: $p = 0.190$, FT4-female group: $p = 0.664$, FT4-male group: $p = 0.181$). Notably, TSH-male group exhibits a U-shaped curve (Nonlinear $p = 0.013$) (Fig. 4), with insignificant health impacts as NDVI ≥ 0.280.

3.3. *Stratified analyses*

Following the examination of interaction items between NDVI and potential modifier (Table S2), only age for TSH male group ($p = 0.085$), $PM_{2.5}$ for TSH female group ($p = 0.021$), and O_3 for FT4 male group ($p = 0.058$) were selected for further stratified analyses. Fig. 5 and Table S3 illustrates the stratified associations between neighbourhood greenness and thyroid hormone levels. After stratified by age, a negative association between NDVI and TSH was observed in both age groups, while the estimated associations were relatively stronger in children and adolescents' group compared to adults. Additionally, we identified stronger negative effects of NDVI on TSH levels among female participants in area with higher $PM_{2.5}$, as well as pronounced positive effects on FT4 levels among males in area with lower O_3 concentration, respectively.

3.4. *Causal mediation analysis*

The causal mediation analysis revealed that $PM_{2.5}$ and O_3 significantly mediated the association between neighbourhood greenness and FT4 levels in male group (Fig. 6, Table S4). Specifically, $PM_{2.5}$ had an average mediation proportion of -23.85 % ($p = 0.030$), suggesting a suppressive effect on the associations between greenness and FT4, while O_3 mediated 33.72 % ($p < 0.001$) of NDVI-FT4 associations. No

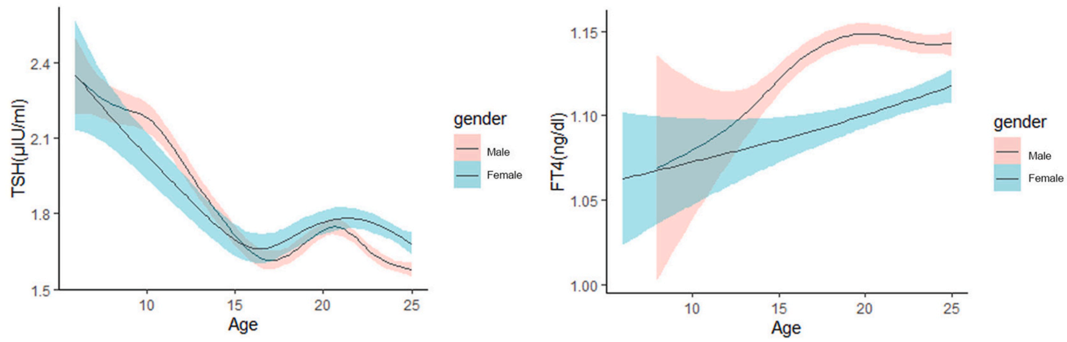

Fig. 1. Variations of thyroid stimulating-hormone and free thyroxine by age.

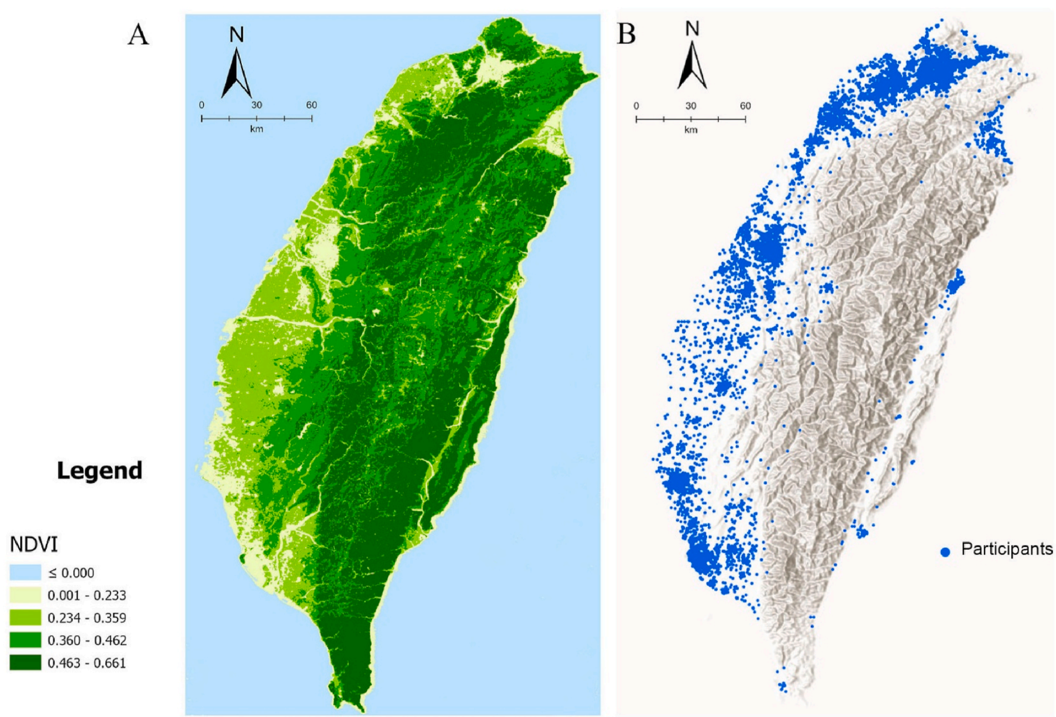

Fig. 2. (A) Spatial distribution of annual mean NDVI between 2000 and 2017; (B) Spatial distribution of participants' addresses.

statistically significant mediating effects were found for BMI or physical activity in the associations between greenness and THs in this study.

3.5. Sensitivity analyses

The robustness of the association between neighbourhood greenness and THs could be strengthened by the sensitivity analyses (Table S5-S6). There was a strong agreement on the negative effects of NDVI on TSH, as well as the positive effects of NDVI on FT4. Specifically, the association of NDVI on FT4 in female groups was less relevant in 1000 m buffers. Moreover, linear regression adjusted with IPW showed comparable results with main analyses. We also checked the covariate balance before and after the IPW analysis (Fig. S2), and the overall balance of the confounders was achieved. Additionally, we found that NDVI was associated with a lower prevalence of (subclinical) hypothyroidism and (subclinical) hyperthyroidism in both males and females (see Table S6).

4. Discussion

To the best of our knowledge, this is the first longitudinal cohort study that examined the association between neighbourhood greenness and thyroid hormone levels among children, adolescents, and young adults. By leveraging a large-scale representative database in Taiwan, we found that neighbourhood greenness may contribute to the regulation of TSH and FT4 levels in young population. Age and air pollution may modify the associations. $PM_{2.5}$ and O_3 may be the potential mediators. Overall, this study further provides scientific insights into the biological mechanism underlying the associations between greenness and the growth and development of children and adolescents.

Neighbourhood greenness was negatively associated with TSH and positively associated with FT4 in this study. While direct investigations of greenness-THs associations remain scarce, our findings bridge existing indirect evidence linking greenness with metabolic and psychological health - both domains profoundly influenced by TSH. A cross-sectional study found negative associations between greenness and the risk of hypertension among children in China (Xiao et al., 2020). Ittermann et al. (2012) found that serum TSH level was associated with a higher risk of hypertension in children and adolescents. Additionally, previous studies found that greenness was associated with lower odds of metabolic syndrome (MetS) (Li et al., 2022; Yang et al., 2020), which may abnormally elevated TSH level among euthyroid young women (Oh et al., 2013). Similarly, another study by Persson et al. (2018) found that

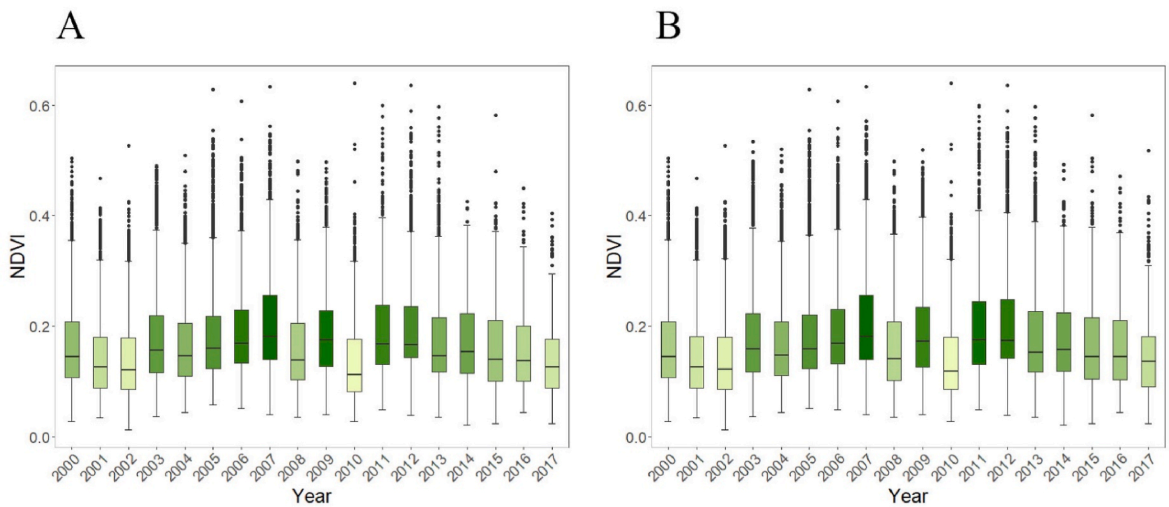

Fig. 3. Temporal pattern of NDVI in main island of Taiwan
*Panel A: Temporal distribution of annual mean NDVI in 500 m buffer at baseline;
*Panel B: Temporal distribution of annual mean NDVI in 500 m buffer for all medical visits.

exposure to greenness was associated with a lower risk of central adiposity, while TSH receptors had been linked to fat tissue, enabling the regulation of TSH on lipolysis and insulin signalling (Teixeira et al., 2020). The exposure-response association between NDVI and TSH in males exhibited a U-shaped pattern (Fig. 4). The increasing trend in its health impacts is partially attributed to the relatively small number of participants residing in regions with dense vegetation coverage. In addition, our findings suggest that an NDVI value of 0.280 may represent a potential threshold for the health impacts of NDVI on TSH in males. This specific threshold aligned closely with NDVI of 0.3 as a threshold proposed for assessment of green infrastructure in previous research (Jürgens and Meyer-Heß, 2020). Therefore, our findings may fill the knowledge gap by providing scientific evidence for the mechanism underlying the health impacts of greenness on metabolic and psychological health.

In our study, we observed subtle differences in effect size and patterns between genders, which may be attributed to inherent gender disparities in thyroid health, as highlighted in previous research. A national study in the United States reported that men exhibit a comparatively lower prevalence of thyroid dysfunction compared to women (Aoki et al., 2007). Additionally, among disease-free populations, females were found to have higher TSH levels than males (Hollowell et al., 2002), indicating that women may be a more vulnerable subgroup concerning thyroid health. Another contributing factor could be gender differences in outdoor activity patterns, leading to varied levels of greenness exposure. For instance, a study involving college students from Brazil and the U.S. revealed that although women expressed a higher preference for outdoor recreation, their actual engagement in nature-based activities was lower (Rosa et al., 2023). Factors such as safety concerns may restrict women's willingness to visit open spaces (Thompson et al., 2007). Consequently, given the vulnerability of women, future studies should focus on women's thyroid health and promote their engagement with natural environments to enhance greenness exposure.

Our exposure assessment employed a 500-m radius, which reflects approximately a 10-min walking distance (Villeneuve et al., 2012) to capture the environmental interactions of young people, particularly children and adolescents, who typically have lower mobility compared to adults. Additionally, sensitivity analysis with 1000 m buffers yielding the robustness of our findings, however, no statistically significant association was found between greenness and FT4 levels in females at larger scale. This suggests that small radius may be more suitable for capturing the biological impact within this population. Empirical evidence supports various buffers for evaluating surrounding greenness for young people. For instance, several studies used 500-m buffer to examine the effects of residential greenness on metabolic health outcomes (Villeneuve et al., 2018; Yang et al., 2020). A study on preschool children used a 1000-m buffer to assess residential greenness, based on the average distance between homes and kindergartens, as well as estimated daily walking distances (H. Chen et al., 2024). Another study also used a 1000-m buffer, guided by the 15-min community-life circle principle (Y. Chen et al., 2024). Multiple buffer scales ranged from 100 m to 1000 m were also employed to compare outcomes across different distances (Dadvand et al., 2014). Future work could refine measures of neighbourhood greenness, such as network-based buffers, to disentangle greenness exposure pathways of young people.

We observed age-related differences in the association between thyroid hormone levels and greenness in the present study. Specifically, children and adolescents generally had stronger greenness-TSH associations as compared to adults. One explanation for this finding is that thyroid hormone levels undergo significant changes throughout early life, continuously declining from birth to adulthood (Kapelari et al., 2008). Another contributing factor may be the higher metabolic activity level of the thyroid during childhood (Walsh, 2022), which may render thyroid hormone more susceptible to environmental influences during this developing age. Relevant studies also highlighted the age-relevant differences in the impacts of other environmental factors on thyroid hormones in children and adolescents (Kim et al., 2024; Yang et al., 2023). Therefore, the age-specific associations between greenness and thyroid health warrant further exploration, with a focus on multiple life stages.

The mechanisms underlying the impacts of neighbourhood greenness on thyroid hormone levels have yet to be established. In our analyses, $PM_{2.5}$ and O_3 were identified as significant mediators, which were indicated to be risk factors of thyroid dysfunction in previous studies. Exposure to air pollutants was significantly associated with change of TSH and FT4 levels (Kim et al., 2024; Xu et al., 2025). Oxidative stress (OS) and inflammatory response triggered by inhaling air pollutants have been suggested as potential mechanisms (Mancini et al., 2016). Furthermore, BMI and physical activity, which were linked to the health benefits of greenness, have also been frequently mentioned as predictors of thyroid health in previous studies. For instance, a randomized controlled trial compared the effectiveness of high- and moderate-intensity interval training programs on thyroid hormone

Table 2
Longitudinal associations between NDVI and thyroid hormone levels.

Models [a]	Thyroid-Stimulating Hormone (TSH) in female						Thyroid-Stimulating Hormone (TSH) in male					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*
Each SD increase	0.85 (−1.62, 3.33)	0.500	0.82 (−1.66, 3.31)	0.516	−2.89 (−6.45, 0.66)	0.110	−0.28 (−1.67, 1.12)	0.698	0.11 (−1.28, 1.49)	0.879	−1.68 (−3.63, 0.027)	0.092
AIC	128265		128235		128214		85391		84799		84794	
Ref: Q1[b]	–		–		–		–		–		–	
Q2	−0.37 (−6.42, 5.67)	0.904	−0.74 (−6.77, 5.30)	0.811	−1.83 (−8.01, 4.34)	0.560	−1.34 (−4.68, 2.00)	0.431	−1.74 (−5.06, 1.57)	0.303	−2.74 (−5.74, 0.93)	0.113
Q3	−3.73 (−10.16, 2.70)	0.256	−3.66 (−10.08, 2.75)	0.263	**−7.84 (-15.01, -0.67)**	**0.032**	−1.71 (−5.30, 1.88)	0.350	−1.66 (−5.22, 1.89)	0.359	**−4.56 (-8.53, -0.59)**	**0.024**
Q4	3.82 (−2.94, 10.58)	0.268	3.68 (−3.08, 1.04)	0.286	−3.77 (−12.79, 5.24)	0.412	−2.76 (−6.55, 1.02)	0.153	−1.82 (−5.58, 1.93)	0.342	**−7.24 (-12.19, -2.29)**	**0.004**
AIC	128264		128234		128215		85393		84802		84793	

Models[a]	Free Thyroxine (FT4) in female						Free Thyroxine (FT4) in male					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*	β(95 %CI) (e^{-2})	*p*
Each SD increase	−0.04 (−0.70, 0.61)	0.897	0.16 (−0.52, 0.84)	0.643	0.54 (−0.39, 1.47)	0.258	0.08 (−0.29, 0.46)	0.660	0.07 (−0.31, 0.46)	0.706	**0.65 (0.15, 1.15)**	**0.010**
AIC	2966.9		2959.1		2934.1		−7536.6		−7680.9		−7740.3	
Ref: Q1[c]	–		–		–		–		–		–	
Q2	**1.82 (0.02, 3.62)**	**0.047**	**1.85 (0.05, 3.66)**	**0.044**	**2.01 (0.19, 3.82)**	**0.030**	−0.46 (−1.39, 0.46)	0.327	−0.49 (−1.41, 0.43)	0.293	−0.31 (−1.24, 0.62)	0.518
Q3	0.21 (−1.62, 2.03)	0.823	0.43 (−1.40, 2.26)	0.684	0.95 (−1.03, 2.93)	0.347	0.11 (−0.88, 1.09)	0.753	0.08 (−0.95, 1.01)	0.953	0.68 (−0.38, 1.75)	0.206
Q4	0.18 (−1.67, 2.02)	0.852	0.63 (−1.25, 2.52)	0.511	1.28 (−1.12, 3.68)	0.295	−0.17 (−1.20, 0.87)	0.754	−0.14 (−1.26, 0.82)	0.682	1.08 (−0.20, 2.35)	0.098
AIC	2965.8		2958.8		2934.6		−7534.1		−7678.4		−7735.7	

[a] Linear mixed regression models were used. Model 1: crude model.Model 2: Adjusted for age, educational level, BMI, smoking status, alcohol intake, intensity of exercise, vegetable/fruit intake, and neighbourhood-level education.Model 3: Adjusted for age, educational level, BMI, smoking status, alcohol intake, intensity of exercise, vegetable/fruit intake, neighbourhood-level education, $PM_{2.5}$, NO_2, O_3, precipitation, temperature, number of intersections, and number of transit stops.

[b] Cut points of NDVI quartiles for females: 0.113, 0.155 and 0.221; males: 0.115, 0.159 and 0.227.

[c] Cut points of NDVI quartiles for females: 0.117, 0.161 and 0.230; males: 0.118, 0.165 and 0.234.

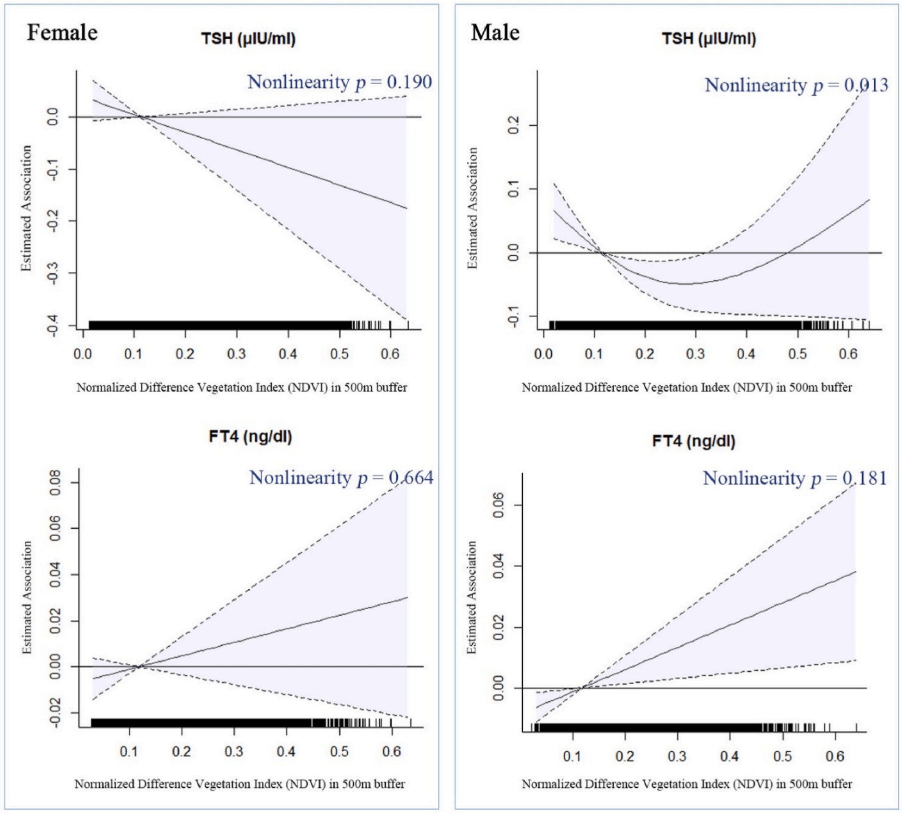

Fig. 4. Concentration-response associations between normalized difference vegetation index and thyroid hormone levels.
*The black solid lines represent the estimated associations, and the dashed lines are the corresponding 95 % confidence levels.

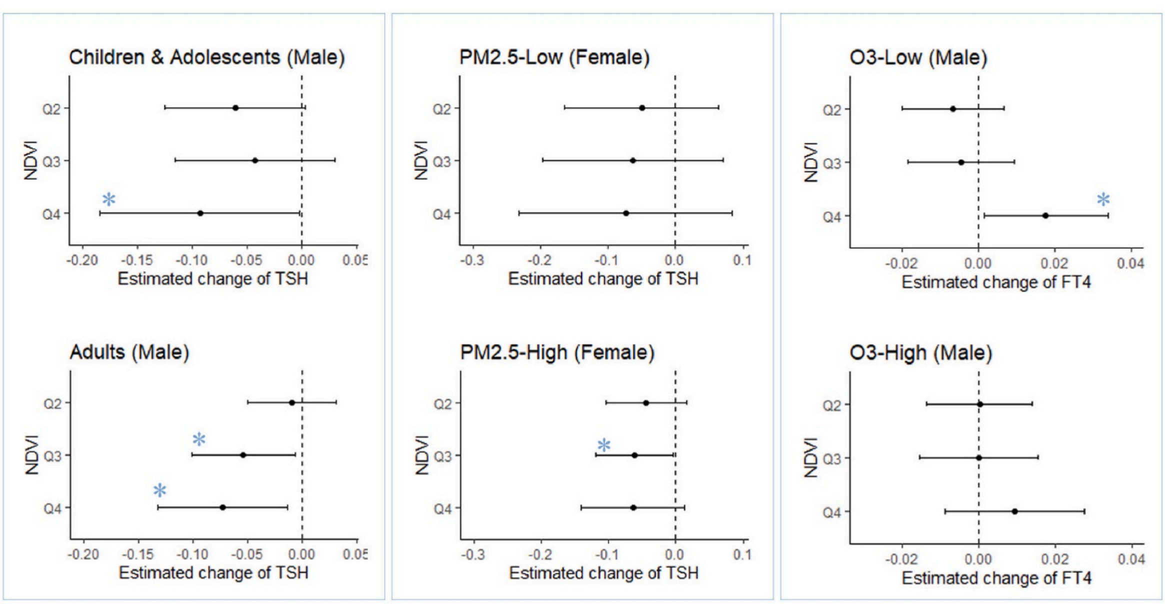

Fig. 5. Stratified association between NDVI and thyroid hormone levels
* represents statistically significant interaction terms (P value < 0.05)
*Cut point for $PM_{2.5}$: 24.4 μg/m^3
*Cutpoint for O3: 56.8 μg/m^3
*Sample size for each group: TSH-male, children&adolscents v.s. adults: 5575, 15091; TSH-female, PM2.5 low v.s. high: 11427, 11516; FT4-male, O_3 low v.s. high: 3124, 3001.

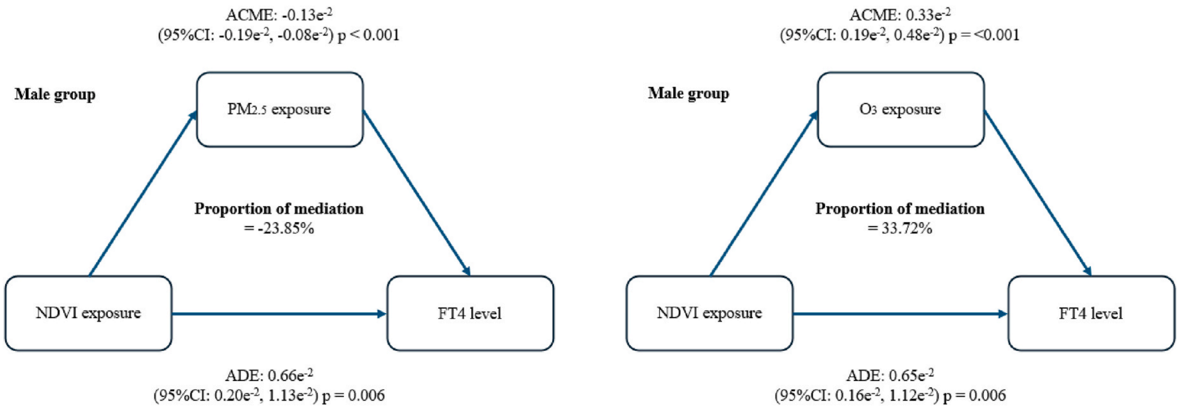

Fig. 6. Mediation effects of air pollution underlying the association between NDVI and thyroid hormone levels.

levels among adolescent girls, finding a significant decrease in TSH levels in the high-intensity group (Abassi et al., 2020). Similarly, existing documentation linked obesity to inflammatory markers that affect iodide uptake and thyroid function (Song et al., 2019). However, the mediating effects of BMI and physical activities were still not clear in our study. One plausible explanation is that while NDVI objectively quantifies greenness, it may fail to capture the type, quality, accessibility, or perceived usability of green spaces. This aligns with a meta-analysis by Marcilla-Toribio et al. (2025), reported no significant association between NDVI and the level of physical activity. Further studies are needed to comprehensively investigate the causal pathways and relevant modifiers between greenness and THs.

Our findings suggested that greenness might provide protective effects against thyroid dysfunction. Thyroid dysfunction is potentially related to various environmental pollutants and stressors, which would result in damage of thyroid follicular cells due to increased bioaccumulation of harmful substances, thereby leading to adverse effects on thyroid gland and abnormal levels of thyroid hormones (Gianì et al., 2021). For example, exposure to toxic metals were related to both hyperthyroidism and hypothyroidism (Rezaei et al., 2019). Greenness may play a protective role by mitigating harmful pollutant exposure, ultimately contributing to thyroid health. Despite that greenness was negatively associated with TSH in our study, the health benefits of greenness in relation to thyroid dysfunction - especially for subclinical hyperthyroidism - may extend beyond subtle regulation.

To date, the present study is the first to explore the longitudinal associations between neighbourhood greenness and thyroid hormone levels among children, adolescents, and young adults. The large sample size and long-term follow up empowered us to detect solid results. Our research findings offered insights into the biological mechanisms underlying the linkages between greenness and the growth and development of these population, thereby addressing the research gap in the greenness-THs associations. Moreover, our results highlighted the importance of integrating green space planning into urban development policies to promote thyroid health among young population.

However, several limitations should be acknowledged. First, although we employed long-term longitudinal data, adjusted for a wide range of covariates, and conducted robustness examination on causality, the observational nature of this study, along with potential residual biases may limit our ability to fully establish a causal association between greenness and thyroid hormone levels. Second, the mechanisms underlying the association between greenness and thyroid function are not yet fully understood. The constraints of data availability on potential mediators may contribute to the limitation. Future research should validate our findings through more comprehensively investigation on behavioural, environmental, and other aspects of mediators. Third, despite adjusting for key covariates, unaccounted built environment effect modifiers, such as building density, urban land use patterns, and other 3D urban morphology metrics, are warranted. Fourth, the actual individual contact with greenness remains unmeasured, potentially leading to exposure misclassification. However, we have applied multiple strategies, including using different greenness indices (NDVI and EVI) with different buffer zones (500m and 1000m), with the hope that can minimize this effect. Research with more comprehensive indicators of greenness (such as landscape pattern, perceived quality, and green view) is necessary to provide a fully understanding of its health benefits on thyroid function. Fifth, due to data limitations, we did not include other thyroid hormones, such as free triiodothyronine and information on other anti-thyroid autoantibodies (thyroid stimulating hormone receptor antibodies, thyroglobulin antibody, and thyroid peroxidase antibody). However, TSH and FT4 have been suggested to be the most representative thyroid hormones in previous studies (Zhao et al., 2019). Future research with comprehensive thyroid hormone measurements could provide a more holistic understanding of the dynamic associations between greenness and thyroid health. Sixth, parental information on SES was not available in current cohort study. To address this limitation, we incorporated neighbourhood-level (township) SES indicators as proxies. These indicators have been shown to effectively capture the contextual effects (Lin et al., 2004) and reflect broader population-level SES characteristics (Burra et al., 2009). Furthermore, empirical studies also suggested that neighbourhood SES have significant impacts on health-related behaviours and outcomes among children and adolescents (Hsieh et al., 2019; Liu et al., 2019).

5. Conclusion

In summary, our study found that neighbourhood greenness was associated with reduced TSH levels and increased FT4 levels among children, adolescents, and young adults. Age and air pollution serve as major modifying factors in the greenness-THs associations. $PM_{2.5}$ and O_3 were identified as potential mediators. This pioneering longitudinal research offered insights into the biological mechanism underlying the health benefits of greenness on the growth and development of children and adolescents. This study further underscores the importance of integrating urban development strategies into health promotion in young population.

CRediT authorship contribution statement

Yiling Zheng: Writing – review & editing, Writing – original draft, Conceptualization. **Siyi Chen:** Writing – review & editing. **Yufei Liu:** Writing – review & editing. **Yuanyuan Yi:** Writing – review & editing. **Jun Ma:** Writing – review & editing. **Changqing Lin:** Writing – review & editing. **Alexis Kai Hon Lau:** Writing – review & editing. **Ta-Chien**

Chan: Writing – review & editing. **Dongze Wu:** Writing – review & editing, Supervision. **Cui Guo:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4-o to improve language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Sources of funding

This work was in part supported by HKU Seed Fund for Collaborative Research (2207101523) and National Natural Science Foundation of China Young Scientists Fund (4240070121).

Conflict of interest

The authors declare that they have no conflicting interests related to this manuscript.

Acknowledgment

Part of the data used in this research was authorized by the MJ Health Research Foundation (Authorization Code: MJHRF2022008A). Any interpretation or conclusion described in this paper does not necessarily represent the views of MJ Health Research Foundation.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.healthplace.2025.103522.

Appendix

A. Bilinear interpolation

The bilinear interpolation resampling technique was used in this study. Bilinear interpolation uses the weighted average value of the four nearest input cell centres to determine the output value on the raster. This method is preferred for data which is phenomena represented with continuous surface.

B. AIC results of different degrees of freedom for natural cubic spline functions

AIC	TSH-female	TSH-male	FT4-female	FT4-male
df = 2	128612	85071	2931.4	−7746.1
df = 3	128612	85072	2932.1	−7745.0

Data availability

The data that has been used is confidential.

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