International Journal of Hygiene and Environmental Health 222 (2019) 283–290

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Associations of greenness with diabetes mellitus and glucose-homeostasis markers: The 33 Communities Chinese Health Study

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ARTICLE INFO

Keywords:
Greenness
Diabetes mellitus
Glucose
Insulin resistance
Cross-sectional
Mediation

ABSTRACT

Background: Residing in greener places may be protective against diabetes mellitus (DM) but evidence is scarce and comes mainly from developed countries.

Objectives: To investigate associations of residential greenness with DM prevalence and glucose-homeostasis markers in Chinese adults and whether these associations were mediated by air pollution, physical activity, and body mass index.

Methods: In 2009, a total of 15,477 adults from the cross-sectional 33 Communities Chinese Health Study provided blood samples and completed a questionnaire. We considered fasting and 2-h glucose and insulin concentrations, as well as the homoeostasis model assessment of insulin resistance and β-cell function, as glucose-homeostasis markers. DM was defined according to the American Diabetes Association's recommendations. Residential greenness was estimated by two satellite-derived vegetation indexes – Normalized Difference Vegetation Index (NDVI) and Soil Adjusted Vegetation Index (SAVI). Nitrogen dioxide and particulate matter

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https://doi.org/10.1016/j.ijheh.2018.12.001
Received 6 September 2018; Received in revised form 24 November 2018; Accepted 2 December 2018
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Abbreviations

ADA	American Diabetes Association
BMI	body mass index
CI	confidence interval
DM	diabetes mellitus
HOMA-B	the homeostasis model assessment of β-cell function
HOMA-IR	the homeostasis model assessment of insulin resistance index
NO_2	nitrogen dioxide
OGTT	oral glucose tolerance test
OR	odds ratio
$PM_{2.5}$	particulate matter less than or equal to 2.5 μg/m^3 in diameter
WHO	World Health Organization
33CCHS	33 Communities Chinese Health Study

≤ 2.5 μm were used as air pollution proxies. Associations were assessed by two-level adjusted logistic and linear regression models.

Results: A 0.1-unit increase in $NDVI_{500\ m}$ and $SAVI_{500\ m}$ was significantly associated with lower odds of DM by factors of 0.88 (95% Confidence Interval 0.82–0.94) and 0.80 (0.72–0.90), respectively. Higher greenness was also significantly associated with lower fasting and 2-h glucose levels, 2-h insulin level, as well as lower insulin resistance and higher β-cell function. Air pollution and body mass index significantly mediated 6.9–51.1% and 8.6–78.7% these associations, respectively, while no mediation role was observed for physical activity.

Conclusions: Higher residential greenness appears to be associated with a lower prevalence of DM. This association might be due to glucose and insulin metabolism and pancreatic β-cell function. Lower levels of air pollution and body mass index can be pathways linking greenspace to diabetes.

1. Introduction

The global prevalence of diabetes mellitus (DM) is rapidly increasing, with a near four-fold growth since 1980. This increase is steeper in low- and middle-income countries compared to high-income countries (World Health Organization (WHO), 2016). China too has experienced a notable shift in the prevalence of DM (Bragg et al., 2017). At the most recent national survey conducted in 2010, the prevalence of DM reached 11.6%, representing approximately 114 million Chinese adults with DM (Xu et al., 2013). Without urgent interventions, this number is estimated to reach 150 million by 2040 (WHO, 2016), which would ultimately lead to major health, social and economic consequences.

More greenspace, meaning higher greenness (i.e. vegetation level) or better availability of green spaces, has been shown to be protective against DM in several epidemiological studies (Astell-Burt et al., 2014a; Bodicoat et al., 2014; Brown et al., 2016; Clark et al. 2017; Dalton et al., 2016; Maas et al., 2009; Ngom et al., 2016). Additionally, three studies have reported beneficial associations of greenspace with glucose levels (Dadvand et al., 2018; Lee et al., 2017) and insulin resistance (Thiering et al., 2016). However, only one study has been conducted in developing countries, and none in China. Investigating the potentially protective health impact of greenspace on DM in China is urgent, given rapid urbanization and the attendant loss of greenspace, as well as the large population who could benefit from greenspace interventions.

Associations of greenspace with DM or glucose-homeostasis markers might be attributed to lower air pollution levels around greenspace, enhanced physical activity in greenspace, or reduced adiposity (Markevych et al., 2017). However, prior studies were mainly descriptive and rarely explored these or other potential mechanisms linking greenspace to DM or glucose-homeostasis markers (Dalton et al., 2016). In this study, we aimed to investigate whether residing in areas with higher greenness is linked to a lower prevalence of DM, as well as beneficial changes in glucose-homeostasis markers that are crucial for DM development. We further explored whether these associations were mediated by air pollution levels, physical activity, and body mass index (BMI).

2. Methods

2.1. Study design and participants

The current study is nested within the large community-based cross-sectional 33 Communities Chinese Health Study (33CCHS) that was conducted during 2009 in Liaoning province, Northeastern China (Dong et al., 2013; Yang et al., 2017, 2018). Using a random number generator, a four-stage stratified cluster sampling strategy was used to recruit study participants. First, three cities - Shenyang, Anshan, and Jinzhou - were randomly selected from the 14 cities in the Liaoning province. Second, from each city district (five districts in Shenyang and three in each of Anshan and Jinzhou), three communities were randomly selected, yielding 33 in total. The area of these communities ranged from 0.25 to 0.64 km^2. Third, from each study community, 700 to 1000 study households were randomly selected. Fourth, from each study household, one adult aged 18–74 years was randomly selected for study enrollment. Individuals with pre-existing severe diseases (e.g., cancers), pregnant women and people who resided at the current address for less than five years were not eligible.

A total of 28,830 participants were invited to take part in the study. A standardized study questionnaire was then used to collect information, including socio-economic status (e.g., occupation, household annual income and highest educational attainment), lifestyles (e.g., leisure time physical activity), current health problems and a family history of DM. 24,845 participants returned completed questionnaires (response rate = 86.2%). The current analysis is restricted to 15,477 participants (62.3% of all 33CCHS participants) who agreed to provide a blood sample and for whom information on socio-economic status, lifestyle and other covariates was complete. All study procedures and protocols were reviewed and approved by the Human Studies Committee of Sun Yat-Sen University. Written informed consent was obtained from all participants before data and sample collection.

2.2. Glucose-homeostasis markers and DM diagnosis

After overnight fasting (≥12 h), a standard 75-g oral glucose tolerance test (OGTT) was performed and blood samples were drawn at 0-h and 2-h after glucose intake. Fasting and 2-h glucose levels were determined by an enzymatic colorimetric method, using a hexokinase photometric assay. Fasting and 2-h insulin levels were quantified by an immune-assay. We employed the homeostasis model assessment of insulin resistance index (HOMA-IR), calculated as [(fasting insulin (μU/L) × fasting glucose (mmol/L)]/22.5, to estimate insulin resistance, and the homeostasis model assessment of β-cell function (HOMA-B), calculated as [20 × fasting insulin (μU/L)]/(fasting glucose (mmol/L) – 3.5), to measure β-cell function (Matthews et al., 1985). DM was defined based on the recommendations of the American Diabetes

Association (ADA) as fasting glucose ≥ 7.0 mmol/L or 2-h glucose ≥ 11.1 mmol/L or use of any anti-diabetic medication (ADA, 2014).

2.3. Residential greenness

Residential greenness was defined using two satellite-based vegetation indexes – Normalized Difference Vegetation Index (NDVI) (Tucker, 1979) and Soil Adjusted Vegetation Index (SAVI) (Huete, 1988). Derivations of both NDVI and SAVI are based on the difference of surface reflectance over absorbance in two vegetation-informative light wavelengths - visible red and near-infrared. SAVI is similar to NDVI but includes a correction factor to suppress soil pixels. NDVI and SAVI range from −1 (water) through 0 (barren areas) to +1 (completely vegetated areas). For our greenness calculations, we used two cloud-free Landsat 5 Thematic Mapper satellite images at a resolution of 30 m (http://earthexplorer.usgs.gov) obtained during August 2010. We selected images taken during the summer to grasp maximum vegetation contrasts and from the year closest in time to the health data collection. NDVI and SAVI were abstracted as mean values in circular buffers of 100 m, 500 m and 1000 m around each study community centroid. Informed by several recent studies (Markevych et al., 2014, 2016; Dadvand et al., 2014), we focused on the 500-m buffer for the main analysis. Results using other buffers are reported as well. These calculations were performed using ArcGIS 10.4 (ESRI, Redlands, CA, USA).

2.4. Ambient air pollution

Ambient concentrations of nitrogen dioxide (NO_2) were assigned using data from the nearest air monitoring stations that were located far from main roadways, industry or residential sources of air emissions in order to better reflect background pollution levels. All 33 study communities were located within approximately 1 km of air monitoring stations. A detailed description of the air monitoring stations has been published elsewhere (Dong et al., 2013; Yang et al., 2017) (supplemental methods: NO_2 assessment). Concentrations of particulate matter less than or equal to 2.5 μg/m^3 in diameter ($PM_{2.5}$) were predicted by spatiotemporal modelling, using $PM_{2.5}$ measurements from air monitoring stations, satellite $PM_{2.5}$ measurements, meteorology and land use characteristics (Yang et al., 2018; Chen et al., 2018) (supplemental methods: $PM_{2.5}$ assessment). Annual average NO_2 and $PM_{2.5}$ measurements from 2006 to 2008 were used as estimates of long-term air pollutant exposures.

2.5. Covariates and mediators

We built a directed acyclic graph (DAG, Fig. S1) representing the existing literature and expert knowledge to select a minimally sufficient set of variables to adjust for confounding (Greenland et al., 1999), employing DAGitty v1.0 software (www.dagitty.net). The following covariates were included: age (years), sex (male *vs.* female), ethnicity (Han *vs.* other), household annual income (≤5000 Yuan, 5001-10,000 Yuan, 10,001-30,000 Yuan, ≥ 30,000 Yuan), and highest educational attainment (no school, primary school, middle school, junior college or higher). Also, based on our DAG (Fig. S1), air pollution ($PM_{2.5}$ and NO_2), physical activity (yes: exercised ≥180min per week; no: exercised < 180 min per week), and BMI (kg/m^2) were selected as candidate mediators.

2.6. Statistical analysis

Normally distributed continuous variables, as tested by the Shapiro-Wilks test, are reported as arithmetic means ± standard deviations. Skewed continuous variables are reported as medians and 1st and 3rd quartiles. Categorical variables are reported as frequencies.

Based on previous literature (Brown et al., 2016; Clark et al., 2017; Dadvand et al., 2018; Thiering et al., 2016), we hypothesized a linear relationship between measures of greenness and diabetes in the main analysis. However, we also operationalized greenness as categorical variable in sensitivity analysis to evaluate non-linear associations. Associations between greenness and DM were assessed using a two-level binary logistic regression model where participants were the first-level units and study districts were the second-level units (Dong et al., 2013; Yang et al., 2017, 2018) (supplemental methods: detailed information on the two-level binary logistic regression model). The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) per a 0.1-unit increase in NDVI and SAVI. Linear regression models were applied to assess associations of greenness with fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, HOMA-IR and HOMA-B levels. Prior to regression analyses, all six glucose-homeostasis markers were naturally log-transformed to normalize the distributions. The effect estimates were then back-transformed from the log scale and are presented as percent changes in the outcome. We used two levels of covariate adjustments. Crude models were unadjusted. Main models were adjusted for age, sex, ethnicity, household income, and educational levels. Regression analyses were performed using the GLIMMIX procedure in SAS 9.2 (SAS Institute, Inc. Cary, NC).

As associations with greenness might differ in population subgroups (Markevych et al., 2017), we explored potential effect modification by age (≥45 years *vs* < 45 years, based on the definition of young people from the WHO) (WHO, 1982), sex (male *vs* female), and education levels (< 9 years *vs* ≥ 9 years, referring to no school/primary school/middle school *vs* junior college or higher, respectively) using stratified and interaction analyses.

We also used mediation analysis to explore whether air pollution, physical activity, and BMI could be mechanisms through which greenness affected DM and glucose-homeostasis markers. Proportions of the mediated effect were calculated following Baron and Kenny's steps for causal mediation (Baron and Kenny, 1986), using the function *mediate* implemented in the R package *mediation*. Briefly, the exposure effect estimate from the full model that includes the exposure, mediator and all covariates (additionally-adjusted model) was compared with the exposure effect estimate obtained from the mediation model (i.e. the univariate model where exposure is regressed on the mediator). Standard errors were generated by bootstrapping (500 simulations).

For statistical significance, we used an α level of 0.05.

3. Results

3.1. Study population characteristics

The mean age of participants was 45 years and there were slightly more men than women (53% *vs* 47%; Table 1). Most participants were of Han ethnicity (94%) and had at least a middle school education (85%). Twenty-nine percent of participants reported a higher household income, and 32% exercised regularly. The distribution of these characteristics was similar (though not exactly the same) between the included participants and those who were excluded from this study (Table S1). The prevalence of DM was 11%, which is similar to the general Chinese population (Xu et al., 2013). Participants with DM differed from participants without DM in terms of all sociodemographic and behavioral variables (Table 1).

Greenness levels differed markedly across the study communities (e.g., $NDVI_{500\text{-m}}$ ranged from 0.18 to 0.80; Fig. 1, Table 2). In addition, NDVI and SAVI were highly correlated (Spearman's correlation coefficient r ranged from 0.65 to 0.98) while their correlations with $PM_{2.5}$ and NO_2 were low (r < 0.43).

In bivariate analyses, $NDVI_{500\ m}$ levels were significantly higher in younger participants and women, and in participants with lower BMI, higher household income, or higher education levels compared to their counterparts. $NDVI_{500m}$ levels were modestly lower among participants who exercised less regularly and those of Han ethnicity (Table S2).

Table 1
Characteristics of study participants from the 33 Communities Chinese Health Study.

Characteristic	No diabetes mellitus	Diabetes mellitus	Total
	(n = 13,783)	(n = 1694)	(n = 15,477)
Age (years)[a,c]	43.9 ± 13.4	53.7 ± 10.8	45.0 ± 13.5
Sex[c]			
Men	7070 (51.3%)	1086 (64.1%)	8156 (52.7%)
Women	6713 (48.7%)	608 (35.9%)	7321 (47.3%)
Ethnicity[c]			
Han	12,936 (93.9%)	1618 (95.5%)	14,554 (94.0%)
Other	847 (6.1%)	76 (4.5%)	923 (6.0%)
Education[c]			
> Junior college	3359 (24.4%)	220 (13.0%)	3579 (23.1%)
Middle school	8479 (61.5%)	1075 (63.5%)	9554 (61.7%)
Primary school	1564 (11.3%)	299 (17.7%)	1863 (12.0%)
No school	381 (2.8%)	100 (5.9%)	481 (3.1%)
Family income per year[c]			
≤5000 Yuan	1016 (7.4%)	151 (8.9%)	1167 (7.5%)
5001-10,000 Yuan	1657 (12.0%)	320 (18.9%)	1977 (12.8%)
10,001-30,000 Yuan	7078 (51.4%)	791 (46.7%)	7869 (50.8%)
≥30,000 Yuan	4032 (29.3%)	432 (25.5%)	4464 (28.8%)
Exercise (more than 180 min/week) [c]			
No	9516 (69.0%)	1029 (60.7%)	10,545 (68.1%)
Yes	4267 (31.0%)	665 (39.3%)	4932 (31.9%)
Body mass index[c]			
≤25 kg/m^2	8546 (62.0%)	674 (39.8%)	9220 (59.6%)
26–30 kg/m^2	4536 (32.9%)	882 (52.1%)	5418 (35.0%)
≥30 kg/m^2	701 (5.1%)	138 (8.2%)	839 (5.4%)
Fasting glucose (mmol/L)[b,c]	5.1 (4.8–5.5)	7.3 (6.2–9.2)	5.2 (4.8–5.6)
2-h glucose (mmol/L)[b,c]	6.2 (5.3–7.4)	13.9 (12.0–17.7)	6.4 (5.4–8.0)
Fasting insulin (μU/L)[b,c]	8.2 (5.6–11.7)	9.9 (6.8–15.5)	8.3 (5.7–12.0)
2-h insulin (μU/L)[b,c]	32.9 (20.1–54.1)	35.8 (19.1–66.6)	33.0 (20.0–55.3)
HOMA-IR[b,c]	1.8 (1.3–2.7)	3.4 (2.2–5.6)	1.9 (1.3–2.9)
HOMA-B[b,c]	107.7 (73.9–160.0)	55.0 (30.9–90.4)	101.9 (68.6–153.9)

Abbreviations: HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance index.
[a] Mean ± standard deviation.
[b] Median (1st quartile-3rd quartile).
[c] Significant difference ($p < 0.05$).

3.2. Greenness and DM and glucose-homeostasis markers

A 0.1-unit increase in $NDVI_{500\ m}$ was significantly associated with a 12% lower odds for DM prevalence, as well as 1.14% lower fasting glucose, 2.03% lower 2-h glucose, 1.66% lower 2-h insulin, 1.17% lower HOMA-IR, and 3.33% higher HOMA-B levels (Table 3). These associations were slightly stronger for SAVI than for NDVI. No associations were detected with fasting insulin. Similar results were observed for $NDVI_{100\ m}$ (Table S3) and $NDVI_{1000\ m}$ (Table S4). In addition, we observed mostly linear dose-response trends when categorizing $NDVI_{500\ m}$ and $SAVI_{500\ m}$ into quartiles, in which the effect estimates were stronger for higher levels of $NDVI_{500\ m}$ and $SAVI_{500\ m}$ (Table S5).

3.3. Stratified results by age, sex, and education levels

When the analysis was stratified by age, the association for $NDVI_{500\ m}$ with DM prevalence was stronger in younger participants (Fig. 2, Table S6). No effect modification by age was observed for all the six glucose-homeostasis markers. Sex modified all associations, except for DM prevalence and 2-h glucose with $NDVI_{500\ m}$ as well as 2-h glucose with $SAVI_{500\ m}$, but the pattern of associations was mixed. For example, while the associations of $NDVI_{500\ m}$ and HOMA-B were stronger in women, associations with fasting glucose, fasting insulin, 2-h insulin and HOMA-IR were stronger in men. In stratified analyses by education levels, the associations with fasting insulin, 2-h insulin and HOMA-IR seemed to be stronger in those more educated, while for the remaining outcomes, no differences or an opposite trend was observed.

3.4. Potential mediation role of air pollution, physical activity, and BMI

Associations of greenness with HOMA-B were completely independent of air pollution levels (Table S7). Associations with fasting glucose, 2-h glucose and DM prevalence were only partially due to lower air pollution, explaining up to 18.2% of the associations. Nevertheless, NO_2 mediated large proportions of the associations with 2-h insulin (28.4%) and HOMA-IR (51.1%). Similarly, while a small proportion of associations with DM (16.6%), fasting glucose (8.6%), and 2-h glucose (16.2%) were mediated by BMI, it was estimated to explain 78.7%, 70.3%, and 24.0% of the associations with 2-h insulin, HOMA-IR, and HOMA-B, respectively. Physical activity did not mediate any of the associations (data not shown).

4. Discussion

The results of our cross-sectional analysis on 15,477 Chinese adults suggest that higher residential greenness may be beneficially associated with diabetes prevalence and glucose-homeostasis markers. These associations were partially mediated by air pollution and BMI and entirely independent of physical activity. While sex and education modified these associations, the patterns were mixed. To our knowledge, this is the most comprehensive study to date, to investigate the relationship between greenspace and DM and glucose-homeostasis markers, and the first such study in a developing country. Additionally, no prior study considered HOMA-B or explored potential mediation by air pollution and BMI.

In line with our findings, four large cross-sectional studies conducted in the Netherlands (Maas et al., 2009), the United Kingdom (Bodicoat et al., 2014), Australia (Astell-Burt et al., 2014b) and Canada (Ngom et al., 2016) have reported that participants who lived in greener neighborhoods (measured as a higher percentage of green space or a shorter distance to the nearest green space) had a lower risk of self-reported DM. Another cross-sectional study from the USA reported that a 2-SD increase in mean block-level NDVI was associated with a 14% lower DM prevalence (Brown et al., 2016). A longitudinal study from England showed a 19% lower relative hazard of developing DM for individuals living in the greenest compared to the least green quartile (Dalton et al., 2016). Another longitudinal analysis from Canada reported that a 0.12-unit increase in NDVI in a 100-m buffer was associated with 10% lower risk for incident DM (Clark et al., 2017). However, a Norwegian study did not observe any association between greenspace and DM (Ihlebæk et al., 2018). Additionally, one USA study observed cross-sectional (with DM prevalence), but not longitudinal (with DM incidence) associations (Lee et al., 2017). In the stratified analyses, we detected associations for greenness with DM prevalence only among younger participants and women. It is difficult to compare these stratified findings with others, as no published study explored effect modifications by age and sex on the association between greenness and DM. One might speculate that younger people, especially women, are more likely to visit and utilize outdoor greenspace but we have no data to validate this.

Fasting and post-loaded (2-h) glucose levels are important clinical indicators of DM. However, to date, only two studies have investigated associations between greenspace and these DM biomarkers (Dadvand et al., 2018; Lee et al., 2017). Dadvand et al. (2018) reported that more time spent in green spaces was associated with lower fasting glucose levels in Iranian children and adolescents. Lee et al. (2017) revealed that a higher percentage of greenspace in a census block group was linearly associated with lower fasting plasma glucose levels at the baseline, but not with a change of glucose levels over 6.4 years of

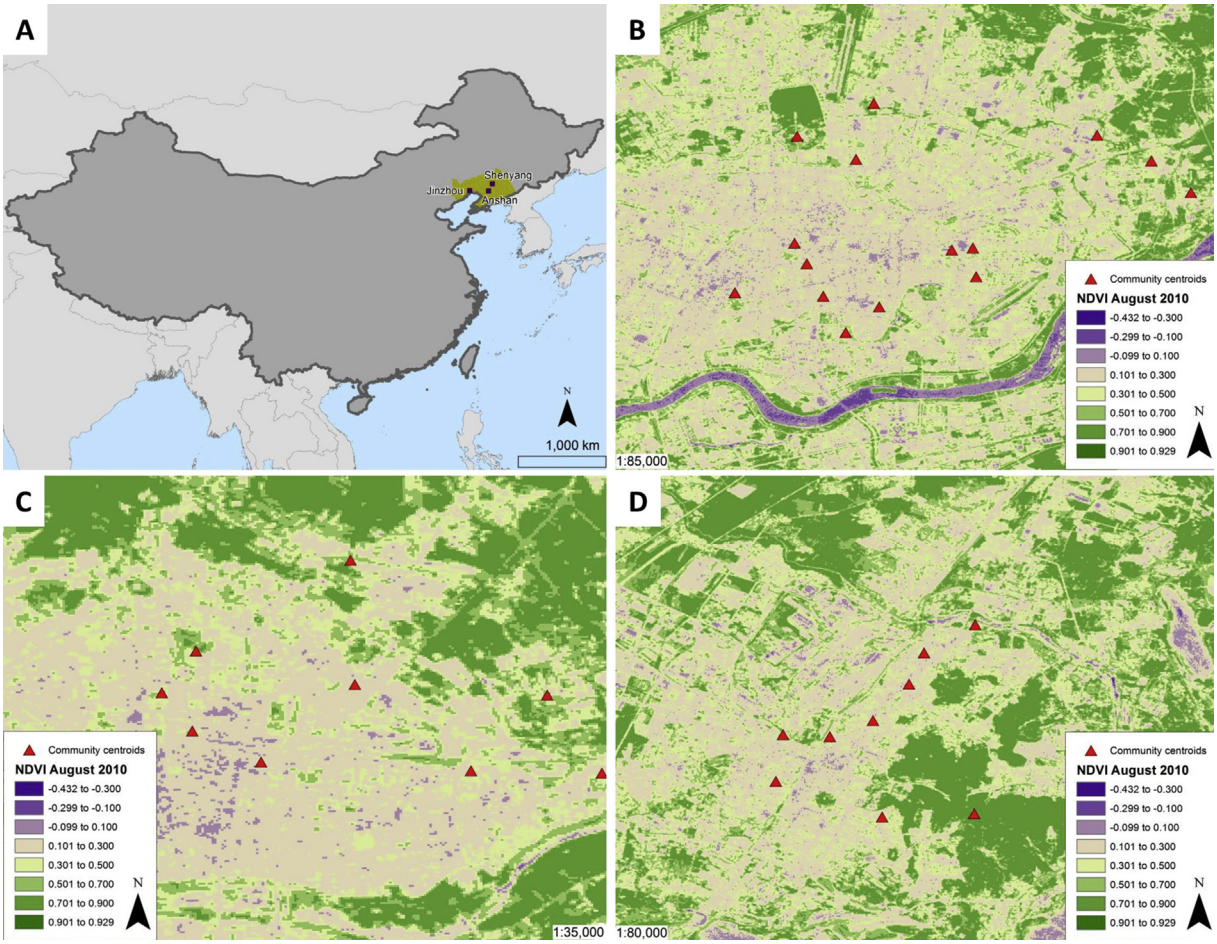

Fig. 1. Location of the study area on the map of China (panel A), as well as locations of the community centroids superimposed over the NDVI layer in the cities of Shenyang (panel B), Jinzhou (panel C) and Anshan (panel D).

follow-up. We observed similar cross-sectional associations for greenness with both fasting and 2-h glucose levels. Insulin levels and insulin resistance are also important markers of DM. We also observed inverse associations of greenness with 2-h glucose levels and HOMA-IR. Our findings are partially in line with a previous analysis of German adolescents that reported similar association between $NDVI_{1000\ m}$ and HOMA-IR, but the association disappeared after additional adjustment for NO_2 (Thiering et al., 2016).

Another novel finding of the current study is that higher greenness was associated with higher HOMA-B, an indirect indicator of β-cell function (Matthews et al., 1985). The primary functions of pancreatic β-cells are insulin synthesis, storage and secretion, events crucial to the pathogenesis of DM. Thus, our findings indicate that the lower odds of DM associated with greenness might reflect the beneficial effects on pancreatic β-cell function. Since no study so far has investigated the potential association between greenness and β-cell function, replication studies are needed to confirm our findings.

Several biopsychosocial pathways have been suggested to explain the health benefits of greenness (Markevych et al., 2017). A mounting body of evidence points towards a link between air pollution and DM (Thiering and Heinrich, 2015). Thus, it is logical to assume that air pollution confounds associations with DM and glucose-homeostasis markers due to spatial correlation. It can also mediate such associations since greenspace might actively filter out air pollutants. In particular,

Table 2
Distributions and inter-correlations (Spearman correlation coefficients) for NDVI, SAVI, and air pollutants at residential addresses of 33 Communities Chinese Health Study participants.

	Median (IQR)	Min	Max	$NDVI_{100\ m}$	$NDVI_{500\ m}$	$NDVI_{1000\ m}$	$SAVI_{100\ m}$	$SAVI_{500\ m}$	$SAVI_{1000\ m}$	$PM_{2.5}$	NO_2
$NDVI_{100\ m}$	0.26 (0.16)	0.12	0.82	1	0.77[a]	0.65[a]	0.97[a]	0.72[a]	0.66[a]	−0.34	−0.22
$NDVI_{500\ m}$	0.29 (0.17)	0.18	0.80		1	0.90[a]	0.78[a]	0.98[a]	0.89[a]	−0.32	−0.05
$NDVI_{1000\ m}$	0.31 (0.15)	0.20	0.75			1	0.66[a]	0.89[a]	0.97[a]	−0.39[a]	−0.08
$SAVI_{100\ m}$	0.14 (0.09)	0.06	0.50				1	0.76[a]	0.69[a]	−0.38[a]	−0.24
$SAVI_{500\ m}$	0.16 (0.11)	0.10	0.48					1	0.90[a]	−0.32	−0.06
$SAVI_{1000\ m}$	0.17 (0.10)	0.11	0.45						1	−0.43[a]	−0.07
$PM_{2.5}$ (μg/m^3)	73.00 (26.00)	64.00	104.00							1	0.61[a]
NO_2 (μg/m^3)	33.00 (9.00)	27.00	45.00								1

Abbreviations: IQR, interquartile range (computed by subtracting the 1st quartile from the 3rd quartile); Max, maximum; min, minimum; NO_2, nitrogen dioxide; NDVI, normalized difference vegetation index; $PM_{2.5}$, particle with aerodynamic diameter ≤2·5 μm; SAVI, soil adjusted vegetation index.
[a] Statistically significant correlation ($p < 0.05$).

Table 3
Results of regression models for associations of $NDVI_{500\ m}$ and $SAVI_{500\ m}$ around the residential address (per 0.1 increase) with diabetes mellitus and glucose-homeostasis markers.

Model	Diabetes mellitus OR (95% CI)	Fasting glucose % change (95% CI)	2-h glucose % change (95% CI)	Fasting insulin % change (95% CI)	2-h insulin % change (95% CI)	HOMA-IR % change (95% CI)	HOMA-B % change (95% CI)
$NDVI_{500\ m}$							
Crude	0.76 (0.71, 0.82)[b]	−1.29 (−1.55, −1.05)[b]	−2.43 (−2.89, −1.97)[b]	0.47 (−0.21, 1.15)	0.98 (−0.02, 2.00)	−0.86 (−1.61, −0.11)[b]	4.13 (3.23, 5.05)[b]
Adjusted[a]	0.88 (0.82, 0.94)[b]	−1.14 (−1.41, −0.89)[b]	−2.03 (−2.49, −1.57)[b]	−0.05 (−0.75, 0.65)	−1.66 (−2.67, −0.63)[b]	−1.17 (−1.94, −0.39)[b]	3.33 (2.40, 4.27)[b]
$SAVI_{500\ m}$							
Crude	0.64 (0.58, 0.72)[b]	−2.15 (−2.55, −1.75)[b]	−3.82 (−4.53, −3.08)[b]	0.28 (−0.80, 1.37)	1.41 (−0.20, 3.06)	−1.91 (−3.09, −0.72)[b]	6.40 (4.92, 7.90)[b]
Adjusted[a]	0.80 (0.72, 0.90)[b]	−1.93 (−2.34, −1.51)[b]	−3.19 (−3.91, −2.50)[b]	−0.56 (−1.68, 0.57)	−2.85 (−4.46, −1.21)[b]	−2.53 (−3.76, −1.28)[b]	5.12 (3.60, 6.64)[b]

Abbreviations: CI, confidence interval; HOMA-IR, the homeostasis model assessment of insulin resistance index; HOMA-B, the homeostasis model assessment of β-cell function; NDVI, normalized difference vegetation index; OR, odds ratio; SAVI, soil adjusted vegetation index.

[a] Adjusted for age, sex, ethnicity, education level, and family income.

[b] Statistically significant association ($p < 0.05$).

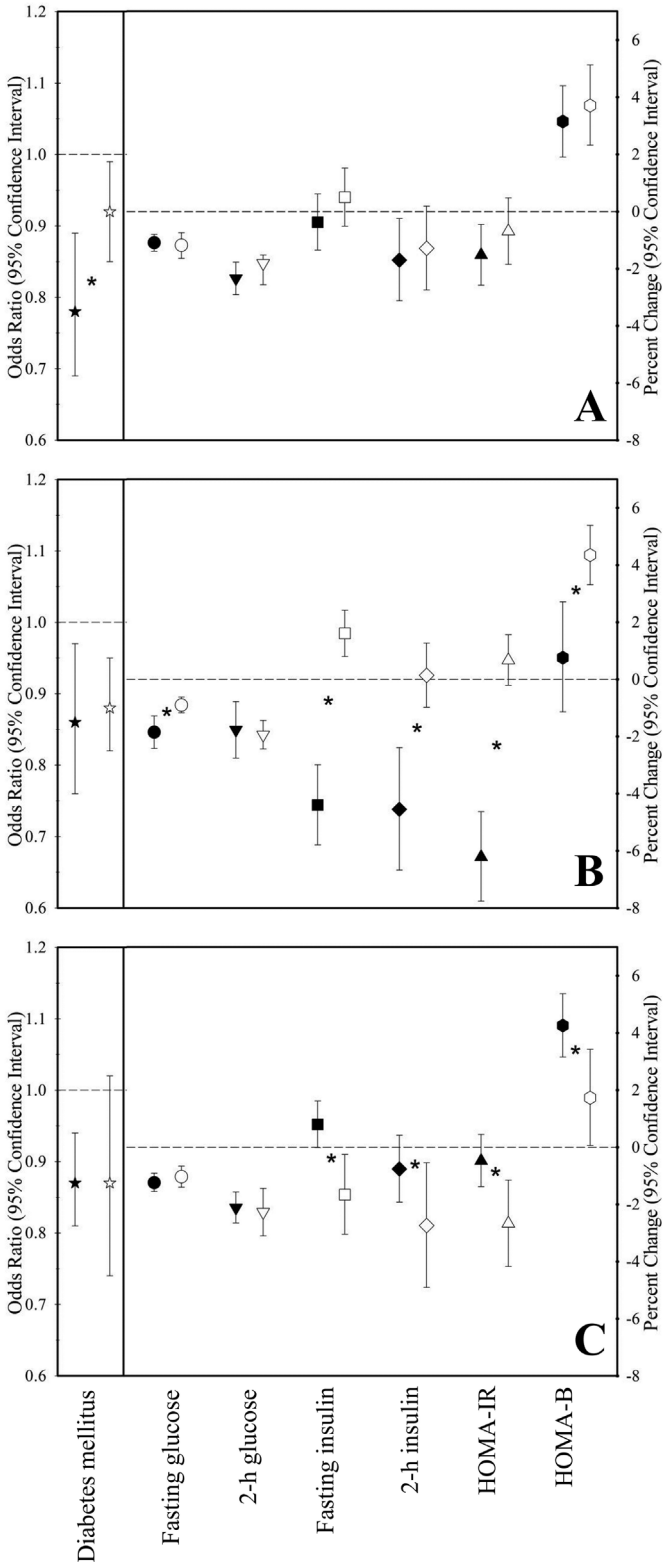

Fig. 2. Associations for $NDVI_{500\text{-}m}$ with diabetes mellitus, fasting glucose, 2-h glucose, fasting insulin, 2-h insulin, HOMA-IR and HOMA-B, stratified by age (panel A), sex (panel B) and education level (panel C). In panel A, black symbols represent participants < 45 years and white symbols represent those ≥ 45 years. In panel B, black symbols represent men and white symbols represent women. In panel C, black symbols represent participants with < 9 years of education and white symbols represent those with ≥ 9 years.

Thiering et al. (2016) reported that an observed association between greenness and insulin resistance disappeared after additional adjustment for NO_2. They concluded that the association might be attributable to the lower co-exposure to ambient air pollution. Our observations were very similar. In addition, air pollution, especially NO_2, partially mediated the associations with both HOMA-IR and 2-h insulin. This was also the case for glucose levels but to a much lesser extent. For HOMA-B no such evidence was present. This leads us to the conclusion that greenspace's association with DM might at least partially be due to lower air pollution and that air pollution is not only a spatial correlate in this case. Still, a large part of this association remains unexplained. Although in our study, participants who were physically active resided in greener places than their counterparts, we did not observe any mediation role of physical activity. This is consistent with the results of Astell-Burt et al. (2014b), Thiering et al. (2016), and Dalton et al. (2016), in which the associations for greenspace with DM and insulin resistance, respectively, were independent of physical activity. Evidence has suggested that exposure to higher greenness levels is associated with reduced obesity (Sarkar, 2017). Obesity is a major risk factor for DM (Kivimäki et al., 2017). Thus, it is also plausible to hypothesize that BMI might mediate the association between greenness and DM and diabetic traits. Our findings support this hypothesis in that BMI significantly mediated the associations of greenness with all studied glucose-homeostasis markers, especially with 2-h insulin and HOMA-IR. Unfortunately, we did not have data to explore other potential mechanisms, for example, psychological and physiological stress alleviation by greenspace or buffering noise effects.

Our study offers many strengths. Analysis was conducted in a large community-based cohort with a high response rate. Unlike previous studies of greenspace and DM that relied only on self-reported data, administrative databases or hospital discharge records, we employed an OGTT test to define DM following the recommendations of the American Diabetes Association. Moreover, we utilized data on six glucose-homeostasis markers, allowing for a comprehensive assessment of DM-associated outcomes. We also incorporated a large panel of covariates into the analyses that helped us to reduce the impact and extent of confounding. Finally, we used a formal mediation analysis to investigate pathways by which greenspace can be related to DM, namely air pollution, BMI, and physical activity.

Nevertheless, our study must be interpreted in the context of its limitations. First, this study was not specifically designed to investigate the association of greenness with DM and glucose-homeostasis markers. The cross-sectional design did not allow for establishing temporality between exposures and outcomes, and so we cannot rule out reverse causality. This particularly affects the results of our mediation analyses that are prone to overestimate existing mediation (Maxwell et al., 2011). Second, we did not have access to personal addresses, but rather to community centroids, nor to time-activity patterns describing time spent in the study community or use of greenspace over time. This lack of information may have introduced exposure measurement misclassification, leading to bias and residual confounding. However, evidence suggests that this kind of misclassification usually biases the effect estimates to null (Hutcheon et al., 2010), which indicates our results are probably conservative. Third, although vegetation indexes NDVI and SAVI provide reliable information on the general level of vegetation, they are not informative about structure (e.g., park *vs* street line trees), type (e.g., public *vs* private) and quality (e.g., well-maintained greenspace *vs* abandoned land overgrown with vegetation) of greenspace, which may be important and also lead to exposure misclassification. Fourth, our assessment of physical activity was crude, and may have misclassified some participants. In addition, participants with DM are likely to have modified their lifestyles as a part of a treatment plan (e.g., physical activity and weight loss), which unfortunately, could not be addressed due to cross-sectional nature of our study. Fifth, due to the multilevel structure of our data, we performed mediation analysis using Baron and Kenny's (1986) method. However, this method has been criticized on multiple grounds (Markevych et al., 2017; Pardo and Román, 2013). For example, according to Baron and Kenny (1986), a direct effect of exposure on an outcome is required. However, this may not be a logical prerequisite because the direct effect can be concealed by contradictory direct and mediated effects (e.g., opposite sign). In addition, Baron and Kenny's (1986) proposal in assessing the statistical significance of the indirect effect has technical limitations, such as lacking potency in assessing the indirect effect, and high type I error rate when null hypothesis is true (i.e., indirect effect is zero). Finally, there were some differences between the included participants and those who were excluded (e.g., education level and household income), which might have introduced selection bias and affected our effect estimates. Given all these limitations, our early findings should be perceived with caution and replicated by more definitive prospective studies.

5. Conclusion

In summary, higher residential greenness appears to be beneficially associated with both DM prevalence and glucose-homeostasis markers. Air pollution and BMI partially explained the observed associations. Our results should prove useful to policy makers and public health authorities for designing interventions to mitigate the growing diabetes epidemic in China.

Declaration of interests

None.

Acknowledgements

The research was funded by the National Natural Science Foundation of China (No. 81872582; No.91543208; No.81703179; No.81673128); the National Key Research and Development Program of China (No.2016YFC0207000); the Fundamental Research Funds for the Central Universities (No.16ykzd02; No.17ykpy16); the Guangdong Province National Science Foundation (No. 2018B05052007; No.2016A030313342; No. 2017A050501062); and Science and Technology Program of Guangzhou (No. 201807010032; No. 201803010054). YG was supported by the Career Development Fellowship of Australian National Health and Medical Research Council (No. APP1107107). The authors acknowledge the cooperation of participants in this study who have been very generous with their time and assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2018.12.001.

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