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Is residential greenness associated with individual levels of glycated haemoglobin in the Portuguese population?

Master’s in Public Health

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic and preventable disease with multiple risk factors. A higher residential greenness has been shown to be associated with a lower prevalence of T2DM in several epidemiological studies. Nevertheless, there is still a lack of evidence regarding the use of more objective outcomes such as Glycated haemoglobin (HbA1c). Therefore, in this study we explored the association between residential greenness and HbA1c in adults without a previous diagnosis of diabetes.

Methods: Health data from a representative sample of the Portuguese adult population, the National Health Examination Survey (INSEF) 2015 was used. Residential greenness was obtained using the annual average normalized difference vegetation index (NDVI) of 2014 on a 300 m circular buffer around each participant´s residence and categorized into tertiles. A linear regression was used to estimate the association by adjusting for selected confounding variables. Sensitivity analysis with a 1000 m buffer and effect modification analysis with sex and rural/urban living were also performed.

Results: In the fully adjusted models results show that living in the greenest areas significantly reduced the average HbA1c levels (Exp(β) = 0.985; 95% CI: 0.971, 0.999) compared to the least green areas. The association was weaker and not statistically significant for areas with medium greenery (Exp(β) = 0.994; 95% CI: 0.975, 1.012). Results remained the same with a larger buffer size and no evidence of effect modification was found.

Conclusions: This study provides evidence of a protective association between greenness and HbA1c, suggesting that public health interventions in the built environment can have beneficial effects on T2DM prevention.

Keywords: NDVI; HbA1c; Diabetes; Portugal; Greenness; Population-based

Resumo

Introdução: A Diabetes Mellitus tipo 2 (T2DM) é uma doença crónica e prevenível, contendo múltiplos fatores de risco. Estudos epidemiológicos têm vindo a demonstrar que uma maior densidade de vegetação se encontra associada a uma menor prevalência de T2DM. Contudo, verifica-se ainda a falta de evidência desta associação utilizando variáveis objetivas de saúde, como a hemoglobina glicada (HbA1c). Neste estudo, será investigada a associação entre a densidade de vegetação da área de residência e a HbA1c em adultos portugueses sem diagnóstico prévio de diabetes.

Métodos: Foram utilizados dados de saúde de uma amostra representativa da população adulta portuguesa, o Inquérito Nacional de Saúde com Exame Físico (INSEF) de 2015. A densidade de vegetação residencial foi obtida através da média anual do índice de vegetação (NDVI) de 2014 num buffer circular de 300m ao redor da residência de cada participante e categorizado em tercis. Foi utilizada uma regressão linear para estimar a associação, ajustando para variáveis de confundimento. Foi também realizada uma análise de sensibilidade com um buffer de 1000m e uma análise de modificação de efeito pelo sexo e tipologia de área urbana ou rural.

Resultados: Nos modelos totalmente ajustados, os resultados mostram que viver em áreas mais verdes reduziu significativamente os níveis médios de HbA1c ($Exp(\beta)$ = 0,985; IC 95%: 0,971, 0,999) em comparação com as áreas menos verdes. A associação revelou-se mais fraca e não estatisticamente significativa para as zonas com níveis médios de verde ($Exp(\beta)$ = 0,994; IC 95%: 0,975, 1,012). Os resultados das análises de sensibilidade não mostraram alterações relevantes e não se verificou existência de modificação de efeito.

Conclusões: Este estudo evidencia a existência de uma associação protetora entre residir em áreas mais verdes e a HbA1c, sugerindo que as intervenções de saúde pública no ambiente construído podem ter efeitos benéficos na prevenção do T2DM.

Palavras-Chave: NDVI; HbA1c; Diabetes; Portugal; Vegetação; Populacional

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List of abbreviations and acronyms

AIC	Akaike's information criterion
BMI	Body Mass Index
DAG	Directed Acyclic Graph
DM	Diabetes Mellitus
EDI - PT	Portuguese Version of the European Deprivation Index
EDTA	Ethylenediaminetetraacetic Acid
EHES	European Health Examination Survey
GLM	Generalized Linear Models
HbA1c	Glycated Haemoglobin
INSEF	National Health Examination Survey
IQR	Interquartile Range
NDVI	Normalized Difference Vegetation Index
PA	Physical Activity
RNU	National Health Registry
SDG	Sustainable Development Goals
SES	Socioeconomic Status
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

General Introduction to the study

Diabetes Mellitus (DM) is a chronic, non-communicable disease of high transcendence and magnitude, and its prevalence and disease burden have been increasing on a global scale (1). Studies have shown that exposure to green spaces has an effect on reducing the risk of type 2 DM, and it seems promising to integrate more green spaces into urban spaces as a measure to prevent this disease (2,3). However, only few studies have explored the relationship between green spaces with objective and quantitative indicators of type 2 DM such as HbA1c (4–6), although these studies did not find consistent results. The HbA1c level in the blood is a predictor of average glucose concentration and is recommended by the World Health Organization (WHO) for diagnosing and monitoring DM. An HbA1c level over 6.5% is suggested as the diagnostic threshold (7).

The prevention of diabetes and the importance of natural environments, such as green spaces, are referred, as relevant commitments in the areas of health, environment, and climate change in, the Sustainable Development Goals (SDGs), which are perhaps the most important strategic objectives on a global scale, with almost all member states of the United Nations having committed to trying to achieve (8). They emphasise the importance of promoting health, preventing chronic disease, preserving the natural environment and creating healthy and sustainable urban environments. The study of the effects of greenness on T2DM may contribute to SDG 3, 15 and 11, considering their targets: **SDG 3, Quality Health** (Target 3.4): 'By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment(…)'; **SDG 15**, **Protect terrestrial life** (Target 15.2): '(...)promote the implementation of sustainable management of all types of forests, halt deforestation, restore degraded forests and substantially increase afforestation and reforestation globally'; and **SDG 11, Sustainable Cities and Communities** (Target 11.7): 'By 2030, provide universal access to safe, inclusive, affordable and green public spaces, particularly for women and children, older persons and persons with disabilities.'

This study aims to estimate the association between residential greenness and HbA1c levels in the adult Portuguese population without previous diagnosis of diabetes, controlling for individual and aggregate socioeconomic confounding factors, stratified by degree of urbanisation and estimating the effect modification of sex and of urban or rural living.

We hope that our results will contribute to the creation of evidence to support decision-making, and the formulation of health policies related to the built environment in order to prevent T2DM.

Research Question

Is residential greenness associated with the levels of glycated haemoglobin in the Portuguese adult population without previous diagnosis of diabetes?

Objectives

General Objective

To estimate the association between residential greenness and individual levels of glycated haemoglobin in the Portuguese adult population without previous diagnosis of diabetes in 2015.

Specific Objectives

1- To describe the glycated haemoglobin values of the Portuguese adult population without a previous diagnosis of DM in 2015;

2- To describe the demographic, socioeconomic and behavioural characteristics of the Portuguese adult population without a previous diagnosis of DM in 2015;

3 - To estimate the association between green space and glycated haemoglobin levels in the Portuguese population without previous diagnosis of diabetes in 2015, aged between 25 and 74, adjusted for confounding;

4- To study the effect modification of sex and degree of urbanisation on the association between green space density and glycated haemoglobin levels in the Portuguese population without previous diagnosis of diabetes in 2015, aged between 25 and 74, adjusted for confounding.

Draft of the submitted scientific article

1. Introduction

Diabetes Mellitus (DM) is a chronic, non-communicable disease of significant importance, given its magnitude and disease burden. In 2021, approximately 529 million people were living worldwide with diabetes, 6 out of 100 people, and a recent projection estimates that its prevalence will rise to 9 out of every 100 people by 2050 (1).

Type 2 DM (T2DM) is the most prevalent type of diabetes, accounting for 96% of all cases (1), and is strongly associated with individuals' lifestyles, thereby having a high potential for prevention and risk mitigation (9). In Portugal, the self-reported prevalence of diabetes in individuals over 15 years old was 9.3% in 2014 and 9.9% in 2019 according to the last two National Health Surveys (10,11), while another study called PREVADIAB conducted in 2009 with objective measurements of glucose and glycated haemoglobin (HbA1c) estimated a prevalence of diabetes of 11.7% in individuals aged between 20 and 79 years (12) and estimated an increase to 13.6% in 2018 (13). Portugal is the second European country with the highest prevalence of diabetes, above the European average of 7%, according to data from *Health at a Glance Europe 2022* (14). Therefore, it is imperative to prevent the occurrence of diabetes in Portugal. On one hand, through primary prevention policies/actions/initiatives, acting on the main known modifiable risk factors. On the other hand, it is essential to obtain new knowledge about health determinants that act upstream of these modifiable risk factors, namely environmental and social factors, thus increasing the potential for prevention.

Exposure to green spaces has been associated with a wide range of physical and mental health benefits through proposed mechanisms such as threat reduction (e.g., thermoregulatory effect, filtration of pollutant particles), restoration (e.g., reduction of stress and mental fatigue), and enhanced opportunities for physical activity and social cohesion (15–19).

In particular, there is a significant body of research on the association between green spaces and T2DM, suggesting that there is an inverse relationship between green space exposure and diabetes risk (2,3,20). However, very few studies have focused on the relationship between green spaces and metabolic markers used for the diagnosis of T2DM such as HbA1c (4–6,21) and even fewer are population-based, nationwide, using representative samples (6). Only one of these studies found a statistically significant reduction of the HbA1c levels of 0.27% (95% CI: 0.05%, 0.49%) for each interquartile increase of green space (5). The HbA1c level in the blood is a predictor of average glucose concentration and is recommended by the World Health Organization (WHO) for diagnosing and monitoring DM. An HbA1c level over 6.5% is suggested as the diagnostic threshold (7).

Studying the association between the density of green spaces in residential areas with HbA1c levels on individuals without a previous diagnosis of diabetes is relevant as it might shed light on the preventive potential of exposure to residential green spaces on T2DM. Therefore, in this study, we aimed to estimate this association in the Portuguese adult population without diabetes diagnosis, controlling for individual and aggregated confounding factors. Additionally, we explored the effect modification of these associations by sex and degree of urbanisation.

2. Materials and Methods

2.1 Data sources and study population

This is a cross-sectional study having as study population the 2015 Portuguese National Health Examination Survey (INSEF 2015) that aimed to represent the adult population of Portugal. The details of the sampling methods and recruitment have been described elsewhere (22). Individuals were selected from the National Health Registry (RNU) via a sampling process that involved a two-step probabilistic cluster design with Community Health Centres serving as the primary sampling units (49 in total), stratified based on region and urbanization level. In total, there were 4911 participants selected, all between 25 and 74 years old and living in Portugal for more than 12 months in 2015. Data were collected in health centres and included: i) a general health questionnaire; ii) physical examination with measurements of blood pressure, height, weight, hip, and waist circumferences; and iii) blood collection for analysis of lipid profile, HbA1c, and erythrocyte count. The procedures of the European Health Examination Survey (EHES) were followed (23).

For the present study, the sample was restricted to individuals who were not pregnant, did not have a self-reported diagnosis of diabetes, and were not taking antidiabetic medication in the two weeks prior to the interview. The exclusion of these individuals allowed controlling for changes in HbA1c levels that are due to factors other than those we wish to study. Pregnancy was considered an exclusion criterion due to physiological changes that decrease HbA1c levels during early and late pregnancy (24). Thus, excluding these variables allows for the identification of factors that influence HbA1c levels before the onset of the disease. Additionally, individuals without a 7-digit postal code that allows for reliable geocoded data and whose values of glycated haemoglobin were missing were also excluded from the subsample analysed. From the initial total of 4911 individuals, 591 were excluded, of which, 119 did not have HbA1c data, 25 did not have data on self-reported medication for diabetes or medical diagnosis, 429 had self-reported diagnosis of diabetes or were taking antidiabetic medication, 31 were pregnant and 3 did not have postal code data (Figure 1). Some individuals had more than 1 exclusion criterion.

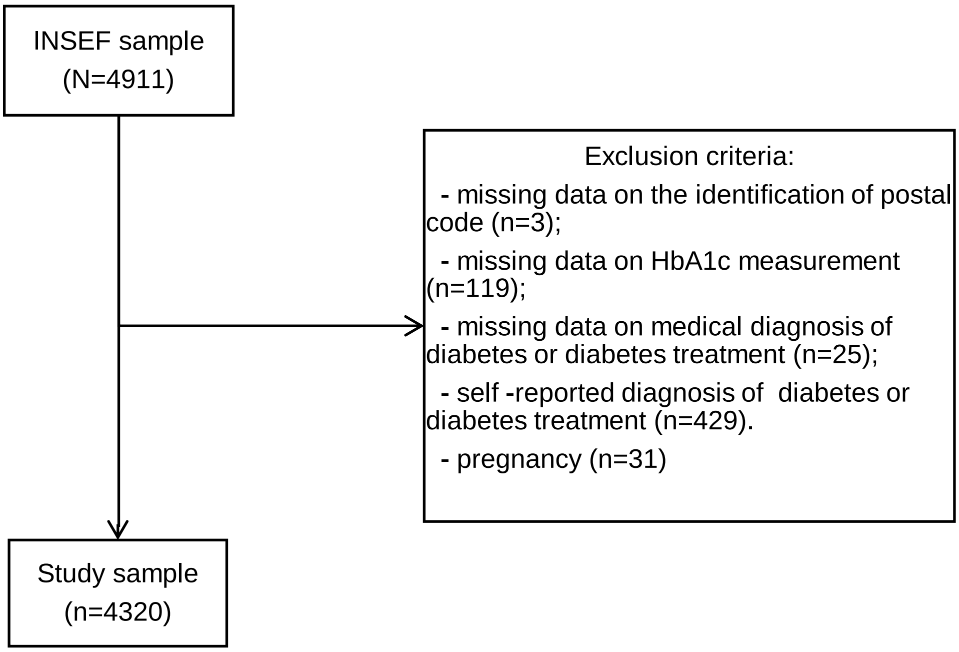

Figure 1. Study sample flow diagram

2.2 Residential greenness

Surrounding greenness was calculated using the average of the Normalized Difference Vegetation Index (NDVI) for each residential area based on a 300-meter Euclidian circular buffer around the geocoded residential address of each participant based on their 7-digit postal code. The NDVI is an indicator of vegetation density obtained through remote sensing, ranging from −1 to +1 (maximum green) based on the land reflectance of red and near-infrared light bands (25). NDVI was calculated using Google Earth Engine for the Portuguese mainland and autonomous regions with images from the Landsat 8 satellite obtained during the whole year of 2014 (one year before the fieldwork of INSEF 2015). Results represent the average NDVI for that entire year in a 30m x 30m resolution. To provide more accurate results, we only used images with less than 20% cloud cover (26).

2.3 Outcome assessment

The medium levels of HbA1c were obtained in INSEF 2015 via blood samples. Blood was collected in health centres of the Portuguese National Health Service by nurses or laboratory technicians using the Clipse® system (27). A tube with 2mL of ethylenediaminetetraacetic acid (EDTA) was used to count erythrocytes and to assess glycated haemoglobin, which was then measured by high-performance liquid chromatography. Laboratory analyses were conducted in various regional laboratories, since the results needed to be available within 24 hours after blood sample collection. The collection procedures followed the recommendations of the European Health Examination Survey (EHES) (23) and puncture procedures followed guidelines created by the World Health Organization (27). An internal quality assurance scheme was in place comparing results from all participating laboratories (22).

2.4 Covariates

INSEF 2015 collected important individual-level variables. We considered several socio-demographic covariates such as age group (25–34, 35–44, 45–54, 55–64, 65–74); sex (male, female); highest level of education attained (no education/1st cycle, 2nd/3rd cycle, secondary and tertiary); type of occupation (high skilled white collar, low skilled white collar, high skilled blue collar, low skilled blue collar); and household economic status (based on being able to pay an unexpected expense of 434€ - more affluent, less affluent). We additionally adjusted for risk factors for T2DM such as Body Mass Index (BMI) (under/normal weight; overweight; obese) and Physical Activity (PA) (no activity; 1-2 times a week; 3 or more times a week). BMI was calculated using the height and weight measured during the physical examination part of the survey.

We also considered area-level covariates, namely, a socioeconomic deprivation index and a walkability index. For the area-level deprivation index we used the Portuguese version of the European Deprivation Index (EDI-PT) whose methodology has been described elsewhere (28). We used the index at the parish level and examined it in tertiles from T1 (least deprived) to T3 (most deprived). This is a relevant variable since it allows for the assessment of deprivation in an aggregated level and has been shown to be a sensitive measure of health inequalities between parishes (28).

The Walkability index used in this study has also been described elsewhere (29) and was created for the whole Portuguese territory using the methodology described by Frank et al. (2005)(30). This index allows for the measurement of characteristics in the built environment that influence how walkable that area is such as: residential density, road connectivity and diversity in soil use. In this study this index was used at the parish level and was categorized in tertiles from T1 (least walkable) to T3 (most walkable).

2.5 Statistical analysis

Descriptive statistics included mean and standard error for continuous variables and frequency data for categorical variables. Comparison between groups was done using Chi-Square test. Comparison of the distribution of HbA1c between groups was performed using nonparametric tests (i.e., Mann-Whitney or Kruskal-Wallis), giving the non-normality of distributions observed.

The normality of the HbA1C distribution was assessed using the Shapiro-Wilk and skewness test that indicated the absence of a Gaussian distribution. Since no transformation was able to normalize the distribution, we ran several single level Generalized Linear Models (GLM) with different distributions (normal, lognormal, gamma) and used Akaike's Information Criterion (AIC) to assess the models' goodness of fit (31). We selected the GLM with a Gaussian distribution as it showed the lowest AIC value (31) and used the log link to help transform the distribution of the outcome more symmetrical and handle heteroscedasticity.

We ran a linear regression with a log link to quantify the association between the NDVI (categorized in tertiles from least green to greenest) with the levels of HbA1c. Since coefficients are exponentiated and shown as exp(β), we interpreted them in mean percentage of change in HbA1c: $(\exp(\beta) - 1) \times 100$.

The selection of confounding variables to adjust in multivariate analysis was based on literature review and a Directed Acyclic Graph (DAG), built in DAGitty v3 (Supplementary Fig. 3). We analysed the association using five different models, in a forward fashion: (1) with the exposure (NDVI) and outcome (HbA1c); (2) additionally with demographic variables such as sex and age group (4,5,21,32–37); (3) additionally with individual-level socioeconomic variables (highest education level attained, occupation type and household economic status) (4,6,32,34–36); (4) additionally with area level socioeconomic deprivation and walkability indexes (4–6,21,29,32,33,35–38); (5) finally in the last model we additionally controlled for T2DM risk factors, namely, BMI and physical activity (5,32,35,36,39).

We conducted an effect modification analysis by sex and urbanization level to explore whether the association would be significantly different for males and females and between living in a rural or an urban area. We also ran a sensitivity analysis for a 1000m buffer to assess consistency and robustness of results.

Sampling weights were used throughout the analysis to account for the complex sampling design (40). All statistical methods were performed in Stata® Version 15 using *svy* package for survey data. All analyses, calculations and graphs were made using Stata® version 15, with a statistical confidence level of 95%.

3. Results

3.1 Characteristics of the study sample

Table 1 shows the main characteristics of the study population overall and by tertile of NDVI. In brief, this sample has a lower proportion of males (45.46%) and most individuals were between 35 and 44 years old (25.42%). Most participants had attained at least the second or third cycle of education (33.94%) and most of them (61.36%) were able to afford an unexpected expense of 434€. Regarding area level variables we notice that most live in areas with the highest level of deprivation (47.04%), but also in the most walkable ones (59.79%). Participants were equally distributed between tertiles of greenness (33.33%) for each group. Bivariate analysis (table 1) shows significant differences according to tertiles of greenness between groups of level of education, household economic status, occupation type, area-level socioeconomic deprivation and walkability. We see striking differences in walkability as most participants in the least green tertile live in the most walkable areas (76.94%), also in area-level deprivation we see more noticeable differences in the least green tertile where most participants live in higher deprivation areas (61.60%).

Table 1. Characteristics of the study sample (N =4320)

Characteristics	n	%	Least Green n (%)	Medium Green n (%)	Greenest n (%)	*P* value
Sex						
Female	2356	54.54	795 (55.21)	785 (54.51)	776 (53.89)	0.776
Male	1964	45.46	645 (44.79)	655 (45.49)	664 46.11)	
Age groups (years)						
25-34	676	15.65	230 (15.97)	239 (16.60)	207 (14.37)	0.298
35-44	1098	25.42	365 (25.35)	350 (24.31)	383 (26.60)	
45-54	1079	24.98	343 (23.82)	363 (24.21)	373 (25.90)	
55-64	884	20.46	288 (20.00)	309 (21.46)	287 (19.93)	
65-74	583	13.50	214 (14.86)	179 (12.43)	190 13.19)	
Education						
No education/1st cycle	1207	27.97	304 (21.16)	402 (27.92)	501 (34.82)	<0.001
2nd/3rd cycle	1465	33.94	491 (34.17)	488 (33.89)	486 (33.77)	
Secondary	860	19.93	303 (21.09)	301 (20.90)	256 (17.79)	
Tertiary	784	18.16	339 (23.59)	249 (17.29)	196 (13.62)	
Household economic status						
Less affluent	1647	38.64	502 (33.43)	554 (38.96)	591 (41.53)	0.004
More affluent	2615	61.36	915 (64.57)	868 (61.04)	832 (58.47)	

Occupation type						
High skilled white collar	1048	26.75	446 (33.56)	341 (25.99)	261 (20.44)	<0.001
Low skilled white collar	1406	35.89	486 (36.57)	485 (36.97)	435 (34.06)	
High skilled blue collar	714	18.22	188 (14.15)	240 (18.29)	286 (22.40)	
Low skilled blue collar	750	19.14	209 (15.73)	246 (18.75)	295 (23.10)	
Area socioeconomic deprivation (tertiles)						
1st (least deprived	990	22.92	171 (11.88)	360 (25.00)	459 (31.87)	<0.001
2nd	1298	30.05	382 (26.53)	433 (30.07)	483 (33.54)	
3rd (most deprived)	2032	47.04	887 (61.60)	647 (44.93)	498 (34.58)	
Walkability						
1st (less walkable)	724	16.76	165 (11.46)	236 (16.39)	323 (22.43)	<0.001
2nd	1013	23.45	167 (11.60)	331 (22.99)	515 (35.76)	
3rd (most walkable)	2583	59.79	1108 (76.94)	873 (60.62)	602 (41.81)	
BMI						
Under/ normal weight	1416	32.93	525 (36.61)	470 (32.82)	421 (29.36)	0.002
Overweight	1698	39.49	540 (37.66)	566 (39.53)	592 (41.28)	
Obese	1186	27.58	369 (25.73)	396 (27.65)	421 (29.36)	
Physical Activity						
No activity	2803	64.93	885 (61.54)	947 (65.76)	971 (67.48)	0.001
1-2 times a week	787	18.23	264 (18.36)	274 (19.03)	249 (17.30)	
3 or more times a week	727	16.84	289 (20.10)	219 (15.21)	219 (15.22)	

P value refers to the Chi2 test for differences in the distribution of the variables according to the greenness tertiles. Statistical significance was set at p<0.05.

The mean HbA1c level was 5.36% (CI: 5.34-5.37) and the median was 5.4% (25th percentile = 5.1%; 75th percentile = 5.6%). Descriptive analysis of Hba1c shows lower values for females, younger age groups, higher level of education attained and a more speciallized ocupation type. Higher tertiles of walkability also present lower levels of Hba1c. There are significant differences in the mean Hba1c level between groups in all confunding variables except for sex (supplementary Table 2).

3.2 Association between greenness and HbA1c levels

The results of the multivariate gaussian regression are shown in Figure 2. The first model we ran, not adjusted for confounding, did not show a statistically significant association between greenness and the mean levels of HbA1c despite the confidence interval being close to be significant and the coefficients being bellow one [Exp(β) = 0.997 (95% CI 0.979, 1.015) for medium-green and Exp(β) = 0.994 (95% CI 0.981, 1.008) for the greenest tertile], showing prospects of a negative association. In model 2 we controlled for demographic variables and observed very similar not statistically significant results. In model 3 individual-level socioeconomic variables were added and the regression coefficients increased but there is still little change in the confidence intervals [Exp(β) = 0.996 (95% CI 0.978, 1.014) for the second tertile and Exp(β) = 0.988(95% CI 0.975, 1.002) for the greenest area]. Finally, in model 4 we added the area-level socioeconomic deprivation and the walkability indexes and in model 5 we added BMI and Physical Activity. Again, we see an increase of effect size in both tertiles and more interestingly a statistically significant association between the greenest tertile and the mean levels of HbA1c [Exp(β) = 0.985 (95% CI: 0.971, 0.999)]. In both the 4th and in the fully adjusted model, living in the greenest area compared to the least green area significantly reduced the mean levels of HbA1c by 1.5%. A similar reduction is found when comparing living in a medium green area to the least green, showing a reduction of about 1%, though it is not statistically significant.

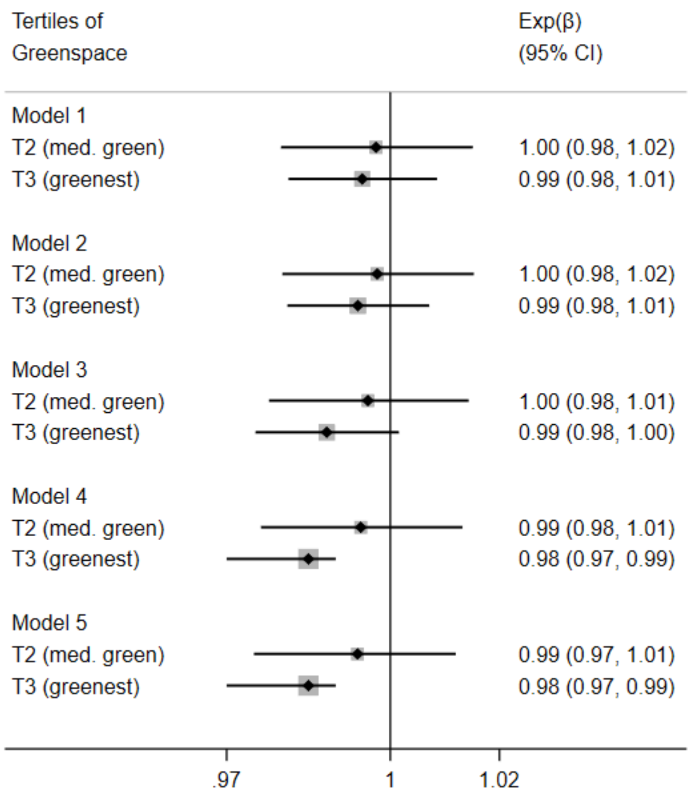

Figure 2. Regression results on the association between greenness (NDVI tertiles) and HBA1c levels in 5 different models sequentially adjusted for confounding.

Abbreviations: CI - confidence interval; T2 - 2nd tertile; T3 - 3rd tertile; Med. - Medium; NDVI – Normalized Difference Vegetation Index.

Model 1: Unadjusted analysis; Model 2: Adjusted for sex and age; Model 3: Adjusted for the previous variables plus education, occupation type and household economic status; Model 4: Adjusted for the previous variables plus area-level socioeconomic deprivation and walkability. Model 5: Adjusted for previous variables plus BMI and Physical Activity. The first tertile was used as reference and is omitted.

3.3. Sex and rural/urban living as effect modifiers

We tested if the association between greenness and HbA1c would be different between sexes and living in a rural or urban area. Considering interactions with a $p < 0.5$, our results show the absence of effect modification in this association for sex [p value for interaction = 0,86] or living in an urban/rural environment [p value for interaction = 0,32].

3.4. Sensitivity analysis

To test the robustness of our results we ran a sensitivity analysis with a larger buffer of 1000m and the results obtained in the fully adjusted model were very similar to the ones obtained with the 300m buffer, despite not being statistically significant. For the 2nd tertile (medium green) and the 3rd tertile (greenest) we observed exponentiated coefficients of 0.996(95% CI: 0.987, 1.005) and of 0.988(95% CI: 0.973, 1.002), respectively.

4. Discussion

In this study we used a sub-sample of a representative sample of the Portuguese population living in Portugal in 2015 and we ran a multivariate gaussian regression model with a log link to access the association between greenness and HbA1c levels. We observed that living in the greenest areas was significantly associated with lower mean levels of HbA1c.

In the final model after adjusting for all selected confounding variables (demographical, socioeconomical and area-level walkability and deprivation indexes, and risk factors), we found that living in the greenest areas (3rd tertile of NDVI) significantly reduces the mean levels of HbA1c by -1.5% (95% CI -3.9%, -0.1%) compared to living in the least green areas (1st tertile of NDVI). Additionally, living in the medium green areas compared to the least green areas seems to indicate that there is a reduction in the mean HbA1c levels, although results were not statistically significant -1.6% (95% CI -3,4%, 1,3%). We also checked for effect modification from sex and rural/urban living, and we did not find evidence of any effect modification from those variables.

To our knowledge few studies use the same exposure and outcome as ours. One such study by Fiffer *et al.* (2023) showed a 0.27% decrease in HbA1c levels for each interquartile range (IQR) increase of average NDVI in a 1230 m buffer but did not show statistically significant results with a smaller buffer size and in multi-exposure analysis (5). Two other similar studies, by Bloemsma *et al.* (2019) and by Gallo *et al.* (2022), did not find statistically significant results (4,6). These studies were cohorts, did not use a population-based representative sample of a country and did not have the same exclusion criteria as ours which might help explain differences in results from our study.

On the other hand, literature reviews and meta-analyses on the association between green space and T2DM do include studies where HbA1c is used as a diagnostic criterion for T2DM (using the binary variable of having or not the disease diagnosis), but not as the sole outcome variable (as a continuous variable) as in our study. The consensus from the literature is that there is evidence of protective effect of greenness on T2DM prevalence and incidence (2,3,20). A meta-analysis of 40 studies on this association found a reduced risk of T2DM from living with more green space of OR = 0.90 (95% CI,0.8–1.0) (20).

Our study population was well defined, and we used a representative population-based sample from the entire country, that to our knowledge, no other study on this association has used. Also, we focused on individuals that did not have T2DM diagnosis and were not on medication, not only to exclude any potential bias from medication use that could lower HbA1c levels, but also to give new insights regarding diabetes prevention. We believe that knowing if green space affects HbA1c levels before reaching values established for diagnosis will allow to obtain useful knowledge for early action to prevent diabetes. Therefore, effect size obtained in this study was expected to be much lower than the one reported in the above-mentioned meta-analysis (20).

We adjusted our explanatory model for several important risk factors, as well as demographic and socioeconomic covariates, both at the individual level and parish level, which strengthens our confidence in the results obtained in the fully adjusted model. When we introduced physical activity (PA) and BMI in our fifth model, we observed that the inclusion of these variables did not significantly change the effect size, or the confidence interval compared to previous models without those variables. These results suggest that in this study, the association likely does not depend on these variables. There is still an absence of consensus on literature regarding how these variables may be involved in this association (2), and some authors have explored the potential roles of PA and BMI as mediators but did not find a mediation role from these variables (41,42).

The main strengths of this study are: i) the use of an objective measure of the outcome, as we used HbA1c levels collected via blood samples by health professionals as a continuous variable; ii) the use of an objective measure of the exposure variable, considering we used geocoded data to calculate year-average NDVI around each participants residence allowing for more precise and less subjective assessment of green exposure; iii) the adjustment for the Portuguese version of the European Deprivation Index (EDI-PT), allowing for replicability in other European studies, as well controlling for both the effects of group and individual-level socioeconomic variables; iv) the adjustment for the walkability index, not commonly used in these studies even though there is available evidence on its effects on HbA1c levels (29) and on greenness (38) and finally v) the restriction of the analysis to individuals without a prior diagnosis of diabetes and not taking medication, which strengthens the evidence for the potential of diabetes prevention through green space interventions.

One limitation of this study is the cross-sectional study design. Hence, our results should be carefully interpreted considering bias commonly involved in this type of study design, namely, reverse causality bias. Another limitation of the study is the use of only one metric for evaluating green space, the NDVI, which does not consider factors such as accessibility or qualitative aspects of green spaces that might influence how people use and perceive them (43–45). However, in a nationwide study like ours this proves to be very difficult to measure (22). Several other studies have also suggested that larger buffers than the one we used (up to 3000 meters) may be more suitable for measuring associations between green spaces and health outcomes (46,47), However we did use a 1000m buffer for our sensitivity analysis and the results remained similar.

5. Conclusions

The results of this study are relevant because they provide evidence that residential greenness could be beneficial to metabolic health, specifically by reducing medium HbA1c levels in individuals undiagnosed for diabetes. Therefore, these findings support the potential role of green spaces in contributing to prevention of T2DM. More research into how environmental exposures might affect T2DM behavioural risk factors and metabolic markers is needed.

6. References

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7. Supplementary materials

7.1 DAG

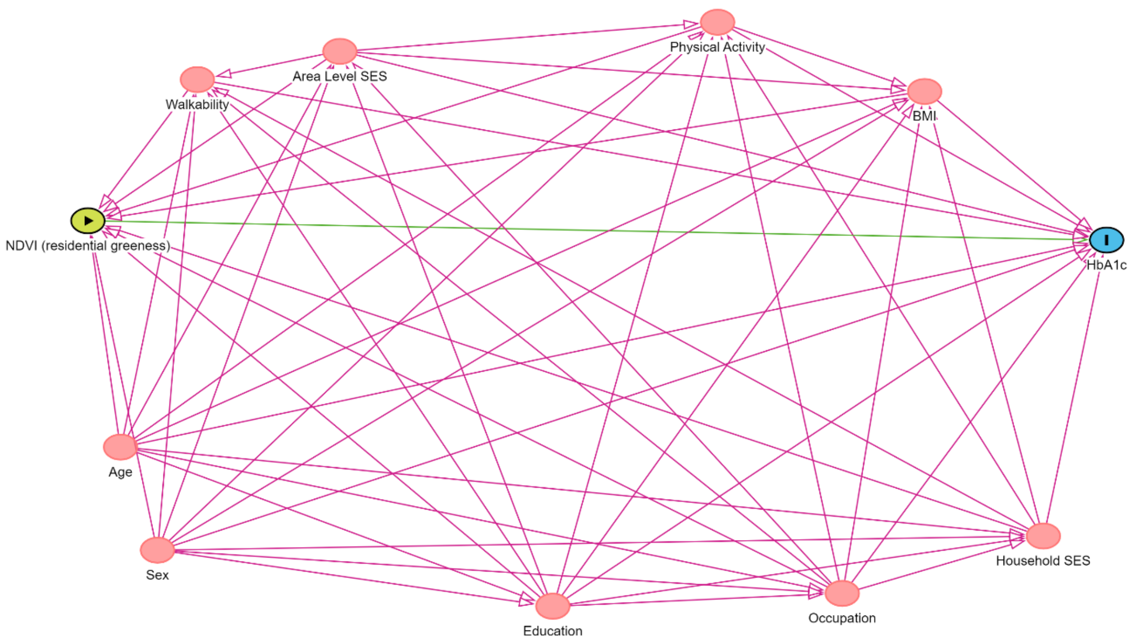

Figure 3. Directed Acyclic Graph (DAG) representing the relationships between selected variables

7.2. Distribution of HbA1c values (%) according to the sample characteristics

Table 2. Distribution of HbA1c values (%) according to the sample characteristics

Characteristics	HbA1c mean	Standard error	CI (95%)		*p-value*
Sex					
Male	5.33817	.0185405	5.30053	5.375809	
Female	5.34615	.0192076	5.307156	5.385144	0.040*
Age groups (years)					
25-34	5.137514	.0302468	5.07611	5.198918	
35-44	5.218609	.0200229	5.177961	5.259258	
45-54	5.387329	.0240225	5.338561	5.436097	
55-64	5.521234	.0389617	5.442137	5.60033	
65-74	5.560024	.0386258	5.481609	5.638438	<0.001
Education					
No education/1st cycle	5.503699	.0369064	5.428775	5.578623	
2nd/3rd cycle	5.347843	.0202832	5.306665	5.38902	
Secondary	5.256783	.0201938	5.215787	5.297778	<0.001

Tertiary	5.227265	.0284127	5.169584	5.284946	
Occupation type					
High skilled white collar	5.240638	.0207314	5.198551	5.282725	
Low skilled white collar	5.343642	.0221002	5.298777	5.388508	
High skilled blue collar	5.399462	.0375951	5.32314	5.475784	
Low skilled blue collar	5.407181	.0271765	5.35201	5.462353	<0.001
Area socioeconomic deprivation (tertiles)					
1st (least deprived	5.322633	.0266834	5.268463	5.376803	
2nd	5.364847	.0247837	5.314533	5.41516	
3rd (most deprived)	5.332824	.0179389	5.296406	5.369242	0.020
Household economic status					
Less affluent	5.374607	.0199115	5.334184	5.415029	
More affluent	5.325028	.0171771	5.290157	5.3599	<0.001*
Level of urbanization					
Rural	5.336574	.0217586	5.292402	5.380746	
Urban	5.34386	.0189178	5.305454	5.382265	<0.001*
Walkability					
1st (least walkable)	5.445051	.0601086	5.323024	5.567078	
2nd	5.332575	.0242354	5.283374	5.381775	
3rd (most walkable)	5.336985	.017457	5.301545	5.372424	0.020
Physical Activity					
No activity	5.379653	.019728	5.339603	5.419702	
1 or 2 times per week	5.281608	.0163893	5.248336	5.31488	
3 or more times per week	5.257604	.0202555	5.216483	5.298725	<0.001
BMI					
Underweight	5.21009	.0210403	5.167376	5.252804	
Overweight	5.354183	.0199216	5.31374	5.394626	
Obese	5.498729	.0208327	5.456436	5.541022	<0.001

Abbreviations: CI, confidence interval; BMI, body mass index
P-value referring to the test of differences (Kruskal-Wallis) between various groups regarding the distribution of glycated haemoglobin. The null hypothesis is that there is no difference in the medians between the groups. *Mann-Whitney: The null hypothesis is that there are no differences in the means between the group.

7.3 Ethics Statement

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

Instituto Nacional de Saúde Doutor Ricardo Jorge

Comissão de Ética Instituto Nacional de Saúde Doutor Ricardo Jorge

Comissão de Ética para a Saúde

Parecer sobre o Projeto: ***ASSOCIAÇÃO ENTRE A DENSIDADE DE ESPAÇO VERDE NA ÁREA DE RESIDÊNCIA E OS NÍVEIS DE HEMOGLOBINA GLICADA DA POPULAÇÃO PORTUGUESA***

Investigador INSA Responsável: Daniel Saldanha Aguiar Resendes - INSA-DEP.

Outros Investigadores: Mafalda Sousa Uva Resendes - INSA-DEP& ENSP-UNL; Carlos Matias Dias - INSA-DEP & ENSP-UNL;

Instituições envolvidas no projeto: Instituto Nacional de Saúde Dr Ricardo Jorge; Escola Nacional de Saúde Pública (ENSP).

Financiamento: INSA

Data de submissão à CES: 26 fev 2024

Data de início do projeto: 12/02/2024

Data de fim do projeto: 15/07/2024

Após análise e apreciação do projeto supracitado, na reunião da Comissão de Ética para a Saúde (CES) no passado dia 12/03/2024, envia-se abaixo o parecer emitido por esta Comissão.

Objetivo Geral:

- Estimar a associação entre a densidade de espaços verdes na área de residência e os níveis individuais de hemoglobina glicada na população adulta portuguesa sem diagnóstico prévio de DM, em 2015.

Objetivos Específicos:

- Descrever os valores de hemoglobina glicada, da população adulta portuguesa sem diagnóstico prévio de DM, em 2015;
- Descrever as características demográficas, socioeconómicas, de comportamentos e estilos de vida da população adulta portuguesa sem diagnóstico prévio de DM, em 2015;
- Estimar a associação entre densidade de espaços verdes e os níveis de hemoglobina glicada na população residente em Portugal em 2015 com idade entre 25 e 74 anos ajustada para o confundimento;
- Estimar a associação entre densidade de espaços verdes e os níveis de hemoglobina glicada na população residente em Portugal em 2015 com idade entre 25 e 74 anos, ajustada para o confundimento e estratificada por grau de urbanização;

• Estimar a mediação de efeito da atividade física e o Índice de Massa Corporal (IMC) na associação entre a densidade de espaços verdes e os níveis de HbA1C.

Declaração de interesses e transparência:

• Apresenta respostas compatíveis com ausência de conflito de interesses.

Informação ao Participante e Declaração de Consentimento Informado e Esclarecido:

• Não aplicável, pois trata-se de utilização secundária de dados do Projeto INSEF que teve anteriormente parecer positivo da CE-INSA.

Metodologia:

• Será realizado um estudo transversal com recurso a dados do Inquérito Nacional com Exame Físico (INSEF) de 2015;

• Os dados do inquérito incluem características sociodemográficas, de estilo de vida e bioquímicas dos participantes;

• Outras variáveis como o índice de caminhabilidade e de privação socioeconómica ao nível da freguesia serão também incluídas na análise;

• Os indicadores das áreas verdes serão calculados numa área de 1km da residência dos participantes. As associações serão estimadas através de modelos de regressão logística.

Propriedade Intelectual dos dados e dos resultados do estudo: INSA

Valor e impacte social e científico do Projeto:

• Esta investigação tem como finalidade aumentar o conhecimento na área da Saúde Pública.

Parecer dos Coordenador dos Departamentos:

• Apresenta parecer favorável do representante do Coordenador do DEP.

Parecer do Encarregado de Proteção de Dados do INSA: Não aplicável.

Análise:

• O projeto tem mais-valias e é inovador.

Parecer da CES-INSA:

• Tudo visto e ponderado, delibera a Comissão de Ética sugerir a correção da informação de que será usado sangue para o estudo. Trata-se de um equívoco relacionado com o uso de material biológico no Projeto INSEF. O presente utiliza essa informação já obtida, isto é, há a utilização secundaria de dados, e não há colheita de material biológico;

• É desejável, possível e eficaz prosseguir investigação científica e os estudos, nomeadamente os conducentes à elaboração de trabalhos académicos;

• Verificado o que antecede, estão reunidas as condições para que possa ser considerado justificado o uso secundário dos dados nesta investigação.

Instituto Nacional de Saúde
Doutor Ricardo Jorge

Neste sentido, é deliberado pela CES INSA pronunciar-se favoravelmente relativamente à realização do projeto "***ASSOCIAÇÃO ENTRE A DENSIDADE DE ESPAÇO VERDE NA ÁREA DE RESIDÊNCIA E OS NÍVEIS DE HEMOGLOBINA GLICADA DA POPULAÇÃO PORTUGUESA".***

Recomendações gerais à Equipa de Investigação:

- Qualquer alteração ao desenho do estudo agora apresentado carece de um pedido de reapreciação ética por esta CES. O atual parecer da CES INSA apenas é válido mantendo-se o projeto sem qualquer alteração metodológica ou procedimental.
- Caso seja aplicável o Regulamento Geral de Proteção de Dados, recomenda-se que seja dado conhecimento do presente Parecer ao Encarregado de Proteção de Dados do INSA, solicitando-se reciprocidade quanto ao respetivo parecer que venha a ser emitido.
- O endereço eletrónico institucional da CES_INSA (comissao.etica@insa.min-saude.pt) , deverá ser transmitido, para obter esclarecimentos, se necessário, ou disponibilizar os contactos adequados para esse efeito : i) aos Participantes do estudo, através do documento de Informação aos Participantes; ii) aos profissionais de saúde envolvidos em projetos de investigação.
- Deverá proceder-se à revisão regular dos projetos, em particular, dos projetos com duração prolongada, com vista à sua atualização, (por exemplo, por motivos de alteração do quadro legal, requisitos de autodeterminação dos participantes, proteção de dados, declarações de interesses, entre outras).
- Deve ser mencionada a importância de fazer constar nos processos clínicos, o registo, realizado pelos profissionais de saúde, do consentimento inicial do participante, bem como da posterior manutenção do interesse em participar na investigação clínica.

Por último, solicita-se que, ao abrigo do disposto no nº23 da atual versão da Declaração de Helsínquia, dê igualmente conhecimento à CES INSA do relatório final com as conclusões do estudo, de eventuais alterações ao protocolo de investigação e demais informações tidas por relevantes.

Aproveitamos ainda para desejar o maior sucesso no desenvolvimento deste trabalho.

Lisboa, 18 de março de 2024
Com os melhores cumprimentos,

P'A Comissão de Ética para a Saúde do INSA, I.P.

(Nina de Sousa Santos)

7.4 Proof of submission of article to an indexed journal