



Green Space and Built Environment

Hotspots of childhood obesity in a large metropolitan area: does neighbourhood social and built environment play a part?

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Abstract

Background: Effective place-based interventions for childhood obesity call for the recognition of the high-risk neighbourhoods and an understanding of the determinants present locally. However, such an approach is uncommon. In this study, we identified neighbourhoods with elevated prevalence of childhood obesity ('hotspots') in the Porto Metropolitan Area and investigated to what extent the socio-economic and built environment characteristics of the neighbourhoods explained such hotspots.

Methods: We used data on 5203 7-year-old children from a population-based birth cohort, Generation XXI. To identify hotspots, we estimated local obesity odds ratios (OR) and 95% confidence intervals (95%CI) using generalized additive models with a non-parametric smooth for location. Measures of the socio-economic and built environment were determined using a Geographic Information System. Associations between obesity and neighbourhood characteristics were expressed as OR and 95%CI after accounting for individual-level variables.

Results: At 7 years of age, 803 (15.4%) children were obese. The prevalence of obesity varied across neighbourhoods and two hotspots were identified, partially explained by individual-level variables. Adjustment for neighbourhood characteristics attenuated the ORs and further explained the geographic variation. This model revealed an association between neighbourhood socio-economic deprivation score and obesity (OR = 1.014, 95%CI 1.004–1.025), as well as with the presence of fast-food restaurants at a walkable distance from the residence (OR = 1.37, 1.06–1.77).

Conclusions: In our geographic area it was possible to identify neighbourhoods with elevated prevalence of childhood obesity and to suggest that targeting such high-priority neighbourhoods and their environmental characteristics may help reduce childhood obesity.

Key words: Spatial analysis, childhood obesity, built environment, socio-economic factors, neighbourhoods

Key Messages

- Childhood obesity is a major public health concern and may be attributed to both individual- and neighbourhood-level determinants.
- Effective place-based interventions for childhood obesity call for the recognition of the high-risk neighbourhoods and an understanding of the determinants present locally.
- This study from a large birth cohort showed that the geographic distribution of childhood obesity at 7-years-old is not random.
- We identified several neighbourhoods located in two regions where the prevalence of obesity was above the area average.
- Neighbourhood socio-economic deprivation and greater availability of fast-food outlets partially explained the presence of these areas of increased prevalence of obesity.

Introduction

Childhood obesity is a major public health issue that usually progresses into adulthood obesity¹ and it is independently associated with adverse health outcomes.² Being obese in childhood is associated with greater risk of chronic diseases such as diabetes, hypertension and heart disease^{2,3} and adverse psychosocial consequences, such as poor self-esteem, social exclusion and depression.^{3,4} Worldwide, the prevalence of childhood obesity has risen dramatically during the past three decades.^{5,6} The global prevalence of obesity increased from 0.7% in 1975 to 5.6% in 2016 in girls, and from 0.9% in 1975 to 7.8% in 2016 in boys. According to the European Childhood Obesity Surveillance Initiative, the national prevalence of childhood obesity in 2015–17 was 12% and 11% in boys and girls, respectively, a value that ranks Portugal in the group of nations with the highest prevalence of childhood obesity.⁷

Childhood obesity has a complex multifactorial aetiology.⁵ It has a genetic basis, but it is also influenced by behavioural and contextual exposures that condition individual choices.^{8,9} Although systematic reviews on the topic reported small-to-moderate effects of neighbourhood environment on childhood obesity, suggesting that individual- and family-level factors play a bigger role in its aetiology, contextual factors might affect child weight status as a result of their influence on parenting practices and children's daily eating and activity behaviours.^{10–12} However, there are large between-neighbourhood variations in the

prevalence of childhood overweight and obesity^{13–17} and certain neighbourhood features are associated with increased risk of becoming obese.⁸ Walkability,¹⁸ land-use mix,¹⁹ presence of green space and other recreational facilities,^{17,20,21} socio-economic deprivation,^{14,15} safety²² and availability of certain types of food outlets^{23,24} are among the most consistent neighbourhood correlates of childhood obesity. However, these findings have limited public health utility, as very few investigations have identified where the neighbourhoods of greatest risk ('hotspots') are located, and even fewer have tried to explain why these geographical hotspots exist. The geographic demarcation of neighbourhoods of elevated risk favours more objective, cost-effective and place-oriented policies.^{16,17} This is particularly relevant in Portugal, which for nearly a decade faced wage/pension cuts, spending cuts in the National Health Service and the freezing of public investment.²⁵ The effectiveness of place-based policies requires a detailed characterization of high-risk neighbourhoods and an understanding of all the social, cultural, demographic, physical and economic attributes that may contribute to the observed excess risk.²⁶

In this study, we used georeferenced data on 7-year-old children from a large birth cohort to identify areas of elevated prevalence of childhood obesity ('hotspots') in the Porto Metropolitan Area and analyse the contribution of the built and socio-economic neighbourhood environment to explain geographic variations.

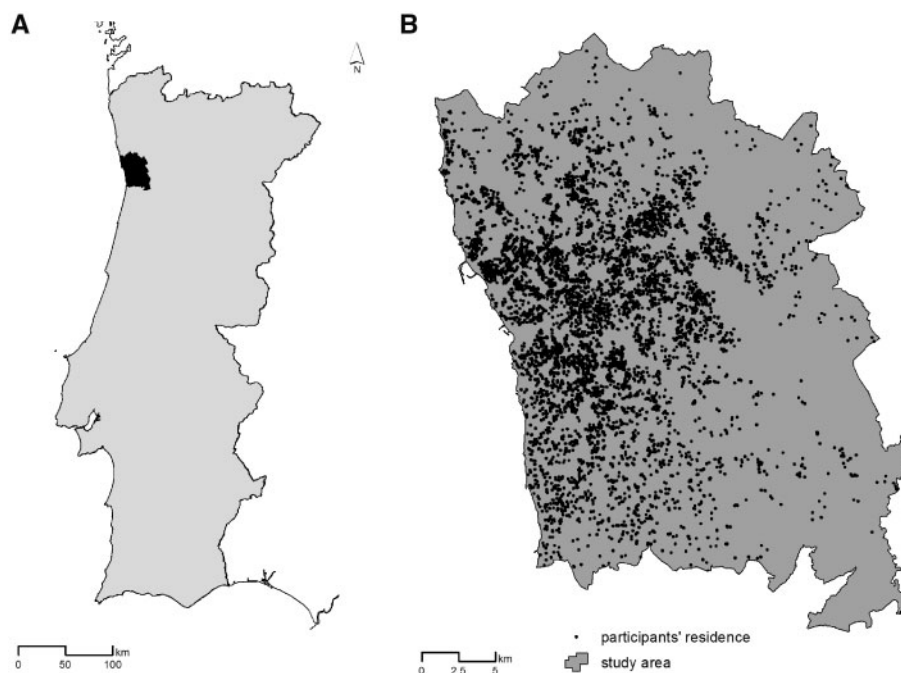


Figure 1. Location of the study area in Portugal (A) and spatial distribution of participants' residence locations across the study area (B).

Methods

Participants

This investigation uses data from Generation XXI (G21), a population-based birth cohort of 8647 newborns recruited in 2005/06 in the Porto Metropolitan Area (municipalities of Porto, Gondomar, Matosinhos, Valongo, Maia, Vila Nova de Gaia), Northern Portugal (Figure 1).²⁷

Recruitment occurred in the five public tertiary care maternity units providing obstetric and neonatal care, where 95% of the births of the metropolitan area occurred. During the hospital stay, women delivering live births were invited to participate, and 92% of mothers agreed. In 2012/2014 the cohort was invited for the 7 years of age follow-up and 6889 (80% of the initial cohort) participated, but anthropometric measures obtained under the same standardized protocol were only available for 5826 participants. Children who were not included belonged to families with lower education levels, as measured by maternal education ($P = 0.003$; primary education 42.5% excluded vs 40.0% included), but they were similar regarding demographic characteristics (age and sex).

The study was approved by the University of Porto Medical School/Hospital S. João Ethics Committee and signed informed consent was obtained from the legal guardian of all participants. All phases of the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki.

Obesity outcome

Anthropometric measures were taken by trained technicians. Participants were evaluated in underwear and bare feet. Weight was measured to the nearest one-tenth of a kilogram with the use of a digital scale (Tanita®), and standing height was measured to the nearest one-tenth of a centimetre with the use of a wall stadiometer (Seca®). Body mass index (BMI) was calculated by dividing weight (kg) by squared height (m). BMI was transformed into age- and sex-specific z-scores using the World Health Organization (WHO) standards.²⁸ Children were considered obese if their BMI z-score was >2 standard deviations (SD) above the WHO standard median.

Address georeferencing

The residential address of participants at age 7 were georeferenced using ArcGIS Online World Geocoding Service and Google Earth, as it was found to have good positional accuracy.²⁹ Poor quality address information prevented us from georeferencing 12 participants.

Characteristics of the socio-economic and built environment

Measures about the socio-economic and built environment were gathered using different methods and data sources and were organized in a geodatabase in ArcGIS 10.5.

Selection of the variables to include was based on an extensive literature review about the neighbourhood correlates of childhood obesity. We included neighbourhood socio-economic deprivation,³⁰ dwelling density, proportion of mixed-use buildings (as a proxy measure of land-use mix), greenness [normalized difference vegetation index (NDVI)], street connectivity, and pedestrian access to non-residential destinations (services, educational and cultural facilities, healthcare), to green spaces,^{31–33} to sports facilities and to fast-food restaurants. NDVI, street connectivity and pedestrian access to facilities were measured at the individual-level, using the residential georeferenced point-location of each child. Dwelling density, proportion of mixed-use buildings and neighbourhood deprivation were measured at census block level (mean area of 0.34 km² and 293 inhabitants) and were then assigned based on the child's census block of residence. To measure pedestrian access, we used a 400 m street-network buffer, as this is considered a reasonable walking distance to neighbourhood resources.^{33,34} Although geospatial data collection was conducted in 2016, we only included facilities that existed during the period of the cohort evaluation. Details about the included variables are summarized in [Table 1](#).

Data on the neighbourhood environment were collected for the municipalities of Porto, Gondomar, Matosinhos, Valongo, Maia, Vila Nova de Gaia and for some parishes from the surrounding municipalities, comprising roughly 85% of the metropolitan area population. Therefore, we excluded all the participants who did not live in this area ($n = 611$), leading to a final sample size of 5203 individuals. A flow-chart depicting the participants' selection process is shown in [Supplementary data](#), available at *IJE* online.

Individual-level characteristics

As a potential confounder for the geographic analysis, we included maternal education. Maternal education is a widely used indicator of socio-economic position and it is associated with both neighbourhood of residence and obesity.³⁵ Maternal education captures material resources and the knowledge-related assets of a person and influences the likelihood of them engaging in health compromising behaviours that may be deleterious to healthy child development.³⁶ Maternal education was categorized according to three classes: primary (≤ 9 years of education, ISCED, International Standard Classification of Education 2011 classes 0–2), which corresponds to the compulsory education in Portugal in the age-cohort of the G21 parents; secondary (10–12 years, ISCED = 3) and tertiary (13 years or more, ISCED = 4–6). Although we acknowledge that physical activity, diet and general health constitute

important mediators in the association between neighbourhood characteristics and obesity, to estimate direct effects avoiding over-adjustment, we only considered well-established confounders in our model.^{37,38}

Statistical analysis

We estimated local obesity odds using generalized additive models (GAMs), a form of non-parametric or semi-parametric regression with the ability to analyse binary outcome data.^{39,40} The model is semi-parametric because it has both non-parametric (smooth function) and parametric components (covariates). We modelled location using a bivariate smooth (S) of latitude (x_1) and longitude (x_2) (equation 1).

$$\text{logit} [p(x_1, x_2)] = \alpha + S(x_1, x_2) + z \quad (\text{equation 1})$$

Here the left-hand side is the log of the obesity odds at location (x_1, x_2), α is an intercept, z is a vector of covariates (individual- and/or neighbourhood-level). Without the smooth function, $S(x_1, x_2)$, the model becomes an ordinary logistic regression on the covariates. The plot of the surface $S(x_1, x_2)$ reveals the relationship between location and outcome, $\text{logit}(p)$. We used loess smoothing which adapts to changes in population density. The amount of smoothing depends on the percentage of the data points in the neighborhood, referred to as the span size.⁴¹ We used the optimal span that minimized the AIC (Akaike information criteria) identified by analysing the AIC curves,⁴¹ which was 0.2. This means that 20% of the data closest to the point of interest was used in the smoothing process.

We created a grid covering the study area using the minimum and maximum latitude and longitude coordinates from the dataset. We estimated the odds ratio (OR) and 95% confidence intervals (95%CI) at each location on the grid relative to the overall study population using the function 'modgam' in the R package MapGAM.⁴² The 95% CIs were used to delineate areas of high (local OR >1) and low (local OR <1) prevalence of obesity, shown as contour lines on the maps. The 'modgam' function also calculates the effect estimates and standard errors for any parametric covariates included in the GAM.

Three sequential models were fitted: Model 0, only including the latitude and longitude; Model 1, adjusted for maternal education; and Model 2, adjusted for maternal education and for the characteristics of the neighbourhoods. Accordingly, three maps were created as well to assess the impact of the successive adjustments, and the OR and 95%CI for the association between each covariate and obesity are presented. To guarantee that we were not

Table 1. Data sources and procedures used for assessing the characteristics of the built and socio-economic environment of the neighbourhoods

Variable	Datasets	Data source	Year	GIS and statistical procedure	Values	Min–Max	Median (IQR)
European deprivation index ³⁰	Census 2011 EU-SILC 2011	Statistics Portugal and EUROSTAT	2011	Weighted sum of the following standardized variables at census block group level: % non-owned households, % households without indoor flushing, % households with ≤5 rooms, % blue-collars, % residents with low education level, % of self-employed or employees, % unemployed looking for a job and % foreign residents.	Continuous score	–10.34 –26.79	–0.22 (2.80)
Dwelling density	Census	Statistics Portugal	2011	–	Dwellings per hectare	0.0–36.4	3.2 (5.5)
Proportion of mixed-use buildings	Census	Statistics Portugal	2011	–	Proportion (%) of buildings that are not exclusively for residence	0.0–100.0	4.0 (13.3)
Street connectivity	StreetMap for ArcPad Portugal TomTom	ESRI	2013	Intersections of ≤2 streets were removed, as well as intersections of motorways	Intersections with ≥3 intersecting streets per square kilometer within each census block	0.00–9.36	0.31 (0.42)
Pedestrian access to destinations, including educational facilities (<i>n</i> = 888), churches (<i>n</i> = 130), libraries and museums (<i>n</i> = 87), post offices (<i>n</i> = 154), banks (<i>n</i> = 444), supermarkets (<i>n</i> = 234), shopping centres (<i>n</i> = 144), pharmacies (<i>n</i> = 298) and health services (<i>n</i> = 109)	Created by the authors	Institutional websites, online business directories, TLA	2012/14	Number of destinations within 400 m of the residence assessed using the ArcGIS Network Analyst extension	Number of destinations	0–30	2 (4)
Pedestrian access to sports facilities (<i>n</i> = 962)	Created by the authors	Institutional websites, online business directories, TLA	2012/14	Number of sports facilities within 400 m of the residence assessed using the ArcGIS Network Analyst tool	Number of sports facilities	0–9	0 (1)
Pedestrian access to urban green spaces (<i>n</i> = 226)	Created by the authors ^{31–33}	TLA	2012/14	Number of green spaces within 400 m of the residence assessed using the ArcGIS Network Analyst tool	Number of green spaces	0–4	0 (0)
Normalized difference vegetation index (NDVI)	Vegetation Analysis	Landsat 8	2012/14	Average within 400 m of the residence	Values from –1 (less green) to 1 (more green).	0.07–0.44	0.22 (0.08)
Pedestrian access to fast-food restaurants (<i>n</i> = 94)	Created by the authors	Online business directories	2012	Count of within 400 m of the residence assessed using the ArcGIS Network Analyst tool	Number of fast-food restaurants	0–5	0 (0)

ESRI, Environmental Systems Research Institute; TLA, Territorial Local Area; EU-SILC, The European Union Statistics on Income and Living Conditions; IQR, interquartile range; GIS, Geographic Information System.

violating independence assumption, the presence of spatial autocorrelation was investigated. Moran's I global spatial autocorrelation was 0.034 ($P = 0.195$) showing low levels of autocorrelation.

Sensitivity analysis

To account for residential mobility, we conducted a sensitivity analysis, where we computed the local OR excluding the participants that changed neighbourhood between the ages of 4 and 7, since their period of exposure to the 7 years of age neighbourhood was shorter and, therefore, neighbourhood effects could be weaker in magnitude.⁴³ To evaluate to what extent the chosen 400 m threshold distance used to measure pedestrian access was driving our results, a sensitivity analysis was conducted with the distance cut-off of 800 m (often used in the literature³³).

Results

In the studied sample of 5203 children, 51.6% were male, 40.6% had mothers with the lowest education class, compared with 30.3% and 29.1% at the mid and highest education classes, respectively. The overall prevalence of obesity was 15.4% ($n = 803$).

We observed wide differences in the distribution of obesity across the study area (Figure 2A) and identified two areas of elevated prevalence of childhood obesity. One hotspot was located in the intersection of three parishes (Guifões, Santa Cruz do Bispo and Custóias) from Matosinhos municipality and presented an average childhood obesity prevalence of 20.1%, and the other in the parishes of Sobrado and Valongo from Valongo

municipality with an average prevalence of 26.7%. These hotspots were all located in the outer region of Porto city. No areas of reduced prevalence of obesity were identified. Results remained unchanged after excluding movers from the analysis (Supplementary data are available at *IJE* online).

After adjustment for maternal education, the differences in the prevalence of obesity were attenuated (Figure 2B) but the hotspots remained. From this model, as shown in Table 2 (Model 1), we observed that there was a graded association between obesity and maternal education, so that children of mothers with secondary (OR = 0.82, 95%CI 0.69–0.97) and tertiary (OR = 0.54, 95%CI 0.44–0.66) education had lower odds of obesity, as compared with children of the least educated women.

Figure 2C shows the local OR of obesity after accounting for neighbourhood characteristics. There was a reduction in the size and number of the hotspots. Table 2 (Model 2) shows the association between obesity and each neighbourhood characteristic. Among the studied neighbourhood correlates of obesity, the only variables associated with the odds of a child being obese were neighbourhood deprivation (OR = 1.014, 95%CI 1.004–1.025) and the availability of fast-food outlets within 400 m from the child's residence (OR = 1.37, 95%CI 1.06–1.77). It is important to note, though, that this association was not found in the sensitivity analysis we conducted using the 800 m distance threshold (Supplementary data are available at *IJE* online). The remaining variables were not associated with obesity, but the OR followed the expected direction. For instance, NDVI and pedestrian access to green space and sports facilities were negatively associated with obesity.

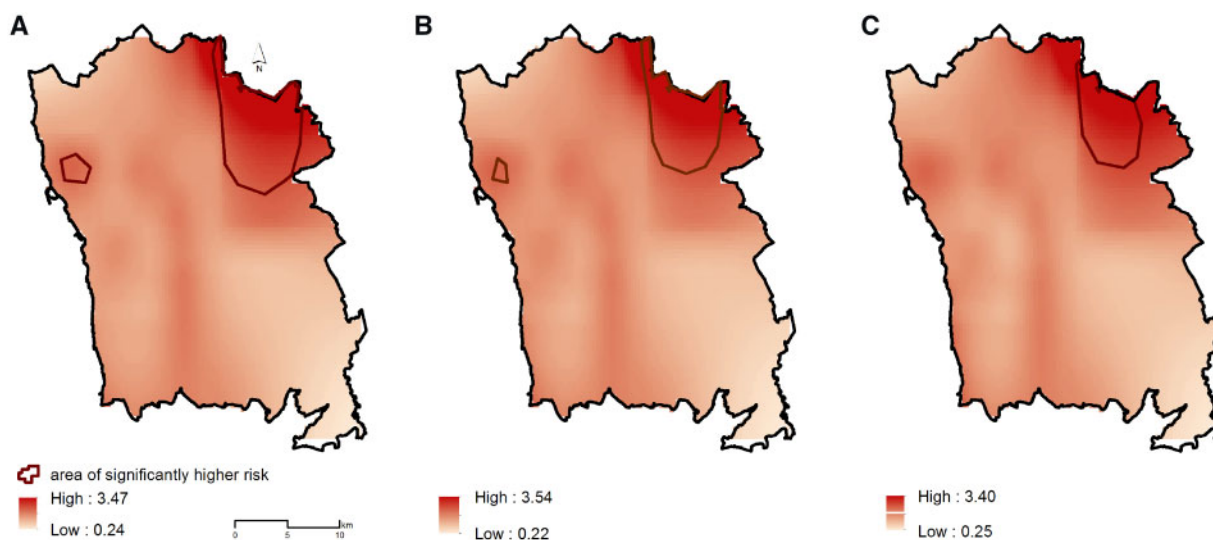


Figure 2. Spatial distribution of the odds ratio of obesity at 7 years of age across Porto Metropolitan Area. (A) Unadjusted model; (B) adjusted for maternal education; (C) adjusted for maternal education and neighbourhood socio-economic and built environment characteristics.

Table 2. Associations between childhood obesity, individual-level variables and neighbourhood characteristics

Variables	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Individual-level		
Maternal education (ref: primary)		
Secondary	0.82 (0.69–0.97)	0.84 (0.70–1.01)
Tertiary	0.54 (0.44–0.66)	0.57 (0.46–0.70)
Neighbourhood-level		
Socio-economic deprivation (score)		1.014 (1.004–1.025)
Dwelling density (dwellings/ha)		1.00 (1.00–1.00)
Proportion of mixed-use buildings (%)		1.00 (1.00–1.00)
Street connectivity (intersections/ha)		1.00 (1.00–1.00)
Pedestrian access to destinations (no. within 400 m)		1.01 (0.98–1.04)
Pedestrian access to sport facilities (no. within 400 m)		0.97 (0.89–1.06)
Pedestrian access to urban green spaces (no. within 400 m)		0.89 (0.73–1.08)
Pedestrian access to of fast-food restaurants (no. within 400 m)		1.37 (1.06–1.77)
Normalized difference vegetation index		0.92 (1.0 × 10 ⁻⁸ –8.2 × 10 ⁷)

OR, odds ratio (interquartile range-standardized for continuous variable); 95% CI, 95% confidence interval.

Discussion

This study from a large birth cohort showed that the geographic distribution of childhood obesity at 7 years old is not random. We identified several neighbourhoods located in two regions where the prevalence of obesity was above the area average. Adjustment for neighbourhood characteristics partially explained the observed geographical patterns, but only two variables—neighbourhood deprivation and pedestrian access to fast-food restaurants—influenced the odds of a child being obese.

Similar to other studies, we found well-defined geographical areas with increased prevalence of childhood obesity.^{14,16,44} We identified two areas of increased childhood obesity prevalence, both located in the outer regions of Porto metro area (suburbs). Davila-Payan *et al.* found that the mean prevalence of overweight among Georgia (USA) census tracts varied from 27 to 40% among children and adolescent populations.¹⁴ In Peru, substantial between-area differences were also observed among 3–5-year-old children, with obesity prevalence rates ranging from 0.8% to 5.3%.¹⁶ Also, in Uganda, several hotspots of obesity were identified among children <5 years old.⁴⁴

One important limitation of the previously mentioned studies on between-neighbourhood differences in childhood obesity is the lack of individual-level information that can explain geographical differentials. This methodological issue can be addressed using the richer data from cohort studies, such as the one we used. It is important to note that the previous studies were conducted using aggregated data, rather than individual-level data with continuous risk surfaces to delineate areas of increased risk, which prevents us from making any kind of comparison. Indeed, to the best of our knowledge, no other study has looked at

the geographic distribution of childhood obesity within urban settings in a European country.

We adjusted our results for maternal education, a classic indicator of socio-economic position. Although the inclusion of this variable reduced the size of the observed hotspots, they remained present in the adjusted analysis, suggesting that place-related variables may play an additional role in the risk of obesity, as we initially hypothesized. Although this study was focused on contextual determinants, we must also acknowledge that personal socio-economic characteristics play a major role in the development of childhood obesity and that place-based interventions may be particularly beneficial for disadvantaged individuals, as they tend to lack health-promoting resources at the individual-level and rely on the services in the local environment.^{45,46}

The next step was to assess if the neighbourhood environment influenced obesity risk and explained the presence of such hotspots. We found that the influence of these neighbourhood variables was rather modest. They partially explained the observed hotspots but only two of the nine variables were associated with the odds of being obese—neighbourhood socio-economic deprivation and pedestrian access to fast-food restaurants. This link between neighbourhood deprivation and obesity has been demonstrated by other studies both in children^{47,48} and adult populations.⁴⁹ Neighbourhood deprivation may affect childhood obesity through different, and still poorly studied, mechanisms. Wealthy neighbourhoods tend to attract beneficial facilities, such as healthy food shops and cultural and recreational places, and ward off environmental harms such as air and soil contaminants, which are often disproportionately concentrated in disadvantaged areas.^{46,50,51}

Furthermore, the socio-economic structure of neighbourhoods also influences behaviours, aspirations and social norms shared by residents.³⁴ We observed that the availability of fast-food restaurants in the proximity of residences was associated with higher odds of child obesity. Similar findings have been reported, with higher availability of fast-food restaurants being associated with higher risk of obesity.^{23,24} An obesogenic environment, where unhealthy foods high in fat and sugar are readily available and easily accessible, may facilitate the higher risk of obesity.²³

It is important to note though that variability in the odds of obesity remained even after accounting for the studied individual- and neighborhood-level variables. Various non-measured factors may contribute to the observed geographic pattern. On the one hand, it is plausible that social norms that operate at neighbourhood-level influence weight status and intentions for weight control. As demonstrated elsewhere,^{52,53} overweight individuals who have more social contacts who are also overweight were more likely to maintain their weight status and less likely to try losing weight. On the other hand, there are numerous environmental stressors with well-known links to obesity, namely local air pollution⁵⁴ and lack of safety,⁵⁵ which may play a role in the observed patterns. Unfortunately, data were not available at neighbourhood-level to investigate any of these factors.

The public health implications of our findings are noteworthy. The spatial approach allowed us to clearly demarcate priority areas that might benefit from policies to reduce obesity risk. Also, we identified factors that partially explained the presence of hotspots of obesity, which may help to delineate targeted and tailored interventions at the local level. Furthermore, our results identified clear differences in prevalence estimates between neighbourhoods of a single metropolitan area, which supports the importance of generating estimates for small areas.

Our study has a number of strengths and limitations. The strengths include the fact that we considered the space as a continuum, free from administrative delimitation, to identify the areas of increased risk, contrasting with most studies measuring clustering and between-neighbourhood variation in obesity using area-based methods. Those methods suffer from the modifiable areal unit problem (MAUP),^{56,57} i.e. low spatial resolution and the use of arbitrary census/administrative geographic divisions. The patterns we revealed may have not been identified based on administrative boundaries solely. We used objective and standardized measures of height and weight to compute BMI, whereas most of the studies on the topic rely on self-reported data prone to misclassification errors.⁵⁸ We conducted this study based on data from a large birth cohort,

which is the only available data source to produce prevalence estimates at the neighbourhood-level in Portugal. The use of this dataset provides confidence in our estimates, as data are collected under strict quality procedures, and allowed us to control our results for usually unconsidered issues such as residential mobility. It is also important to note that, due to data unavailability, we could not include all neighbourhood correlates of childhood obesity, more specifically those related to microenvironmental features (e.g. street maintenance, aesthetics), pollution, safety and the transportation network. Moreover, we did not measure population perceptions about the residential environment, which is important complementary information to understand community needs.⁵⁹ Another limitation is that some data on the neighbourhood characteristics did not temporally coincide with the study period. Data on deprivation, proportion of mixed-use buildings and dwelling density were only available for 2011 (Portuguese censuses occur every 10 years). Nonetheless, we found moderate-to-strong correlations ($P=0.73$, $P=0.90$ and $P=0.89$, respectively) between the same variables in 2011 and 2001, which shows temporal consistency and suggests that in 2012/14 those variables would not be substantially different. Finally, our results and our conclusion are based on the assumption that children spent most of their time in the home surroundings and use the resources in these environments, which might not be true.^{51,60}

In summary, using data from a large birth cohort we found wide geographic disparities in the prevalence of childhood obesity in a large metropolitan area. We delineated neighbourhoods with higher prevalence of childhood obesity and found that neighbourhood socio-economic deprivation and greater availability of fast-food outlets partially explained the presence of these areas of increased prevalence of obesity. Based on these findings, targeting these high-priority areas and developing tailored interventions may contribute to reduce childhood obesity in this particular urban setting.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

A.I.R. conceptualized the study and wrote the initial draft of the manuscript. A.I.R. and V.M.V. conducted the analysis. A.C.S. and V.M.V. reviewed and edited the final version of the manuscript. H.B. conceptualized the study, conducted the cohort study, supervised the study and reviewed and edited the final version of the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Conflict of interest: None declared.

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