Research Article

Lifestyle Genomics

Lifestyle Genomics 2020;13:99–106
DOI: 10.1159/000505749

Received: July 20, 2019
Accepted: January 3, 2020
Published online: February 18, 2020

The Association of Parental Genetic, Lifestyle, and Social Determinants of Health with Offspring Overweight

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Keywords
Childhood · Predisposition · *MC4R rs17782313* · Obesity

Abstract
Introduction: In the UK, the number of comorbidities seen in children has increased along with the worsening obesity rate. These comorbidities worsen into adulthood. Genome-wide association studies have highlighted single nucleotide polymorphisms associated with the weight status of adults and offspring individually. To date, in the UK, parental genetic, lifestyle, and social determinants of health have not been investigated alongside one another as influencers of offspring weight status. A comprehensive obesity prevention scheme would commence prior to conception and involve parental intervention including all known risk factors. This current study aims to identify the proportion of overweight that can be explained by known parental risk factors, including genetic, lifestyle, and social determinants of health with offspring weight status in the UK. ***Methods:*** A cross-sectional study was carried out on 123 parents. Parental and offspring anthropometric data and parental lifestyle and social determinants of health data were self-reported. Parental genetic data were collected by use of GeneFiX saliva collection vials and genotype were assessed for brain-derived neurotrophic factor *(BDNF)* gene *rs6265*, melanocortin 4 receptor *(MC4R)* gene rs17782313, transmembrane protein 18 *(TMEM18)* gene *rs2867125*, and serine/threonine-protein kinase *(TNN13K)* gene *rs1514175*. Associations were assessed between parental data and the weight status of offspring. ***Results:*** Maternal body mass index modestly predicted child weight status ($p < 0.015$; $R^2 = 0.15$). More mothers of overweight children carried the *MC4R rs17782313* risk allele (77.8%; $p = 0.007$) compared to mothers of normal-weight children. Additionally, fathers who were not Caucasian and parents who slept for <7 h/night had a larger percentage of overweight children when compared to their counterparts

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($p = 0.039$; $p = 0.014$, respectively). ***Conclusion:*** Associations exist between the weight status of offspring based solely on parental genetic, lifestyle, and social determinants of health data. Further research is required to appropriately address future interventions based on genetic and lifestyle risk groups on a pre-parent cohort.

Introduction

Currently, more than 1.9 billion adults and 340 million children are overweight or obese worldwide; this has doubled since 1980 [1]. Obesity is associated with many comorbidities [2]. In the UK, the number of comorbidities seen in children has increased along with the worsening obesity rate [2, 3]. This has been shown to worsen into adulthood [2, 3]. Genome-wide association studies have highlighted an array of single nucleotide polymorphisms (SNPs) associated with both adulthood and childhood obesity [4]. Investigation of genetic variations in the form of SNPs for the risk of obesity is an expanding area of research [4–6]. This, along with the increase in prevalence of obesity, has revealed a sub-population of at-risk individuals based on genetic predisposition, which has the potential to contribute to an effective obesity prevention scheme [6, 7]. Obesity prevention has been highlighted globally [8]. However, in the UK, current prevention schemes are more akin to treatment schemes. These include family-based, lifestyle, and surgical intervention, which have resulted in only a modest effect on childhood weight loss [9]. A comprehensive prevention scheme for obesity would commence prior to conception and involve parental intervention including both genetic and lifestyle and social determinants of health (L&SD) risk factors [6, 7].

Many SNPs have been identified as being unequivocally associated with obesity-related traits, of which little is known beyond association [5, 6]. SNPs alone have not been reported to equate to clinical predictive worth [5]; however, when in combination with L&SD factors, predictive power reaches significance [6, 7, 10, 11]. The strongest predictive power has recently been reported by Khera et al. [6], using a Bayesian approach utilising over 2 million SNPs. Studies either predict weight status at the time of data collection (cross-sectionally) [6, 10] or longitudinally predict future weight status [11, 12].

Associations, causes, and trends of overweight and obesity differ between countries, and generally, the more westernised countries have the highest prevalence [13]. Therefore, we aimed to identify the proportion of overweight that can be explained by known parental genetic and L&SD risk factors only with offspring weight status in a UK cohort.

Materials and Methods

A cross-sectional study was carried out. Participants were required to be the biological parent of a child aged up to 16 years, be their primary carer, born and currently living in the UK, not to have any chronic disease (excluding overweight and obesity), and not to be following a weight loss programme. A power calculation for the number of variables included in the regression analysis [14, 15] with the anticipated medium effect size (f^2) of 0.18, a desired statistical power level of 0.8, a probability level of 0.05, and 18 predictors concluded that 127 participants were required [15, 16]. Attrition of 5% was accounted for, endeavouring to recruit 133 participants. A total of 130 parents were recruited, 3 of whom withdrew prior to genetic analysis, and a further 4 did not provide full data sets and were therefore excluded. Complete L&SD and SNP data were collected for 123 parents resulting in an estimated power of 0.78.

Anthropometric Measurements for Parents and Children

Parental and offspring data were self-reported by one or both parents. Height (m) and weight (kg) were collected for one or both parents and offspring. Pre-pregnancy maternal body weight was also collected. BMI was calculated for the mother (current and pre-pregnancy) and/or father (current) using the equation: weight (kg)/height $(m)^2$ [1]. Adult participants were categorised into normal-weight and overweight groups based on the World Health Organisation (WHO) criteria (≥25 kg/m^2) [1]. Childhood weight percentile was calculated using the WHO and UK90 criteria [17, 18]. Children aged 0–16 years were categorised into normal-weight and overweight groups (children aged 0–2 years ≥85th percentile, children aged 2–16 years ≥98th percentile) [17, 18].

Parental L&SD Variables

All variables were self-reported by the parent. Data were collected by use of the Bristol Online Survey platform (https://www.onlinesurveys.ac.uk/). The following parental L&SD risk factors used in the study by Morandi et al. [7] were assessed dichotomously: gender (male/female), single parenthood (yes/no), and smoking status (yes/no). The following variables were selected a priori, according to their association with obesity in the UK [19]: household status (whether privately owned), income (above/below GBP 32,000 – basic tax rate 2016) [20], hours of sleep per night (above/below 7 h per night), whether obtained higher education (yes/no), whether breastfed child (yes/no), method of birth of child (natural or caesarean section), and ethnicity (whether Caucasian or not).

Genetic Analysis

The following SNPs were chosen for final inclusion: brain-derived neurotrophic factor *(BDNF)* gene *rs6265* (effect sizes adult/children: 0.19/0.19), *FTO rs9939609* (0.38/0.39), melanocortin 4 receptor *(MC4R)* gene *rs17782313* (0.07/0.13), transmembrane protein 18 *(TMEM18)* gene *rs2867125* (0.31/0.31), and serine/threonine-protein kinase *(TNN13K)* gene *rs1514175* (0.07/0.07).

Table 1. Characteristics of the study cohort

	Mothers	Fathers	Daughters	Sons
Total cohort	76 (62)	47 (38)	41 (43)	54 (57)
Average age, years	38.4±6.5	39.7±7.9	6.8±4.5	8.8±4.5
Average BMI, kg/m^2	20.6±4.5	24.0±5.2	–	–
Average percentile	–	–	59	52
Non-overweight	66 (87)	34 (72)	30 (73)	42 (78)
Overweight	10 (13)	13 (28)	11 (27)	12 (22)

Values are presented as *n* (%) or mean ± SD as appropriate.

The following SNP selection process was carried out: firstly, SNPs were required to be associated with childhood and adulthood obesity independently in genome-wide association studies with a defined effect size (reported above) [21–24]. This was to ensure assessment of the life course development of obesity. SNPs were excluded if they had only been associated with either adulthood or childhood obesity, but not both. SNPs with the largest defined effect size for both childhood and adulthood obesity were included. These were all also ranked in the GIANT consortium as having some of the strongest associations with obesity [25]. Following this, of the SNPs selected, biological plausibility was assessed by the research team. For biological plausibility to be approved, the SNP was required to have a suggested mechanism that is indicative of body weight regulation. The following genes and SNPs met the inclusion criteria and were therefore included in the present study: *BDNF rs6265* [26], *FTO rs9939609* [27], *MC4R rs17782313* [28], *TMEM18 rs2867125* [29], and *TNN13K rs1514175* [30]. The scope of this study allowed inclusion of the top 5 SNPs after the selection process noted above.

Saliva samples (2 mL) were collected for DNA analyses from parents (GeneFiX; Isohelix, Kent, UK). DNA extraction was carried out through use of a PSP® SalivaGene 17 DNA Kit 1011 (STRATEC Molecular, Berlin). DNA quantification and quality control were assessed with spectroscopy (Nanodrop; ThermoFisher, Waltham, MA, USA). Genotyping was carried out using prepared TaqMan® SNP genotyping assays for *rs6265, rs9939609, rs17782313, rs2867125*, and *rs1514175* (ThermoFisher) and the StepOnePlus thermocycler (Applied Biosystems, CA, USA). All samples were analysed in duplicate in accordance with the manufacturer's protocol. Individual samples were accepted with a quality of more than 98%. All genetic analyses were carried out at St. Mary's University, Twickenham.

Statistical Analysis

To determine if data were normally distributed the Shapiro-Wilks test was used. Allele frequency in the total study cohort was assessed using the Hardy-Weinberg equilibrium. Allele frequency of the total cohort rather than controls (healthy weight) only was assessed due to the condition (overweight) being common [31, 32]. Following this, a logistic regression model was fitted to identify the proportion of offspring overweight that can be explained by parental genetic and L&SD variables together, specified in sections above. The variables included in the regression analysis are as follows: maternal and paternal age and BMI (Table 1), parental L&SD (Table 2), and SNPs as listed above. Further exploratory statistical analyses were carried out to assess associations between parental L&SD and genetic factors and dichotomous weight status of offspring (overweight: yes/no). The χ^2 test of association was used throughout the exploratory analysis. Each independent variable was dichotomised to represent high and low risk groups at the median or a defined cut-off as specified in the sections above and detailed in Tables 2 and 3. The χ^2 tests of association were carried out between each independent variable and offspring weight category: overweight (yes/no). Mothers and fathers were assessed together and alone. Maternal and paternal BMI was corrected for (included as a layer variable) where appropriate in each χ^2 test of association. Fisher's exact test results are reported where appropriate. SNPs were dichotomised by grouping the risk alleles, as per previous research [33–35]. All statistical analyses were carried out using SPSS

Table 2. Parental lifestyle factors analysed

Variable	Group	Mothers	Fathers
Ethnicity	Caucasian	54 (71)	36 (77)
	Non-Caucasian	22 (29)	11 (23)
Single parent	No	63 (83)	45 (96)
	Yes	13 (17)	2 (4)
Household status	Privately owned	54 (71)	33 (70)
	Not privately owned	22 (29)	14 (30)
Smoker	No	73 (93)	43 (91)
	Yes	3 (4)	4 (9)
Household income[1]	GBP >32,000	18 (24)	9 (19)
	GBP <31,999	58 (76)	38 (81)
Hours of sleep per night	>7 h	34 (45)	23 (49)
	<7 h	42 (55)	24 (51)
Whether child was breastfed	Yes	69 (91)	40 (89)
	No	9 (12)	5 (11)
Method of birth of child	Natural	57 (75)	34 (76)
	Caesarean	19 (25)	13 (29)

Values are presented as *n* (%). [1] Based on 2016 tax brackets [18].

Table 3. Parental genotypes for *BDNF rs6265*, *MC4R rs17782313*, *TMEM18 rs2867125*, and *TNNI3K rs1514175*

	BDNF	*MC4R*	*TMEM18*	*TNNI3K*
Genotypes				
HR	TT/CT	CC/CT	CC/CT	AA/AG
NR	CC	TT	TT	GG
Mothers				
HR	23 (30)	38 (50)	75 (100)	54 (71)
NR	53 (70)	38 (50)	0 (0)	22 (29)
Fathers				
HR	14 (30)	20 (43)	46 (98)	31 (66)
NR	33 (70)	27 (57)	1 (2)	16 (34)

Values are presented as *n* (%). HR, higher risk; NR, no risk; SNP, single nucleotide polymorphism; *BDNF*, brain-derived neurotrophic factor gene *rs6265* SNP; *MC4R*, the melanocortin 4 receptor gene *rs17782313* SNP; *TMEM18*, transmembrane protein 18 gene *rs2867125* SNP; *TNNI3K*, troponin I-interacting protein kinase gene *rs1514175* SNP.

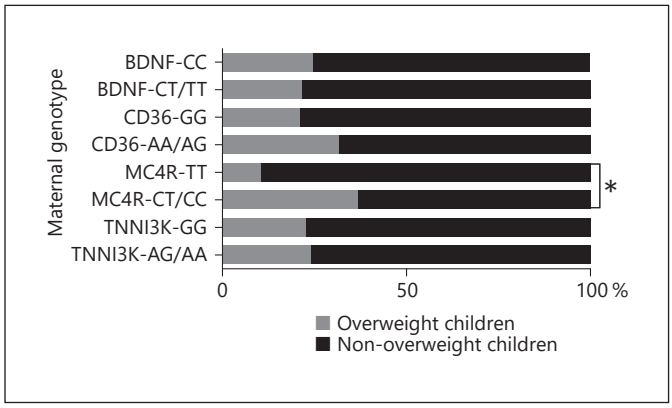

Fig. 1. Maternal genotype and offspring weight status. Values with an asterisk indicate a significant difference ($p < 0.05$). BDNF, brain-derived neurotrophic factor gene rs6265; MC4R, the melanocortin 4 receptor gene rs17782313; TNNI3K, troponin I-interacting protein kinase gene rs1514175 SNP.

(IBM SPSS Statistics for Windows, Version 24.0, released 2016; IBM Corp., Armonk, NY, USA). All tests were two-tailed, with a p value <0.05 considered statistically significant. For exploratory analysis, multiple testing was not corrected for in line with the reasons stated by Althouse [36]. Therefore, conclusions drawn are required to be confirmed by subsequent research with related hypotheses [36].

Results

Demographics

Tables 1 and 2 detail the study descriptors for the cohort. All SNPs, excluding *FTO rs9939609*, were within the Hardy-Weinberg equilibrium, according to χ^2 goodness of fit analysis ($p > 0.05$). *FTO rs9939609* was therefore excluded from further analysis. Table 3 details the genotype distribution within the cohort [31, 32].

Regression Analysis

Firstly, logistic regression (n = 123 parents) determined that only maternal BMI was significantly, although modestly, associated with the weight status of offspring ($p = 0.015$; adjusted $R^2 = 0.15$).

Exploratory Analysis: Parental Genetic and L&SD Factors and Child Weight Status

A higher percentage of mothers of overweight children ($n = 16$) carried the *MC4R rs17782313* higher-risk (C) allele (77.8%) compared to mothers of normal-weight children ($n = 60$) (41.4%; $p = 0.007$; $\chi^2 = 7.208$) (Fig. 1). When controlled for mother weight category, overall results remained significant ($p = 0.006$; $\chi^2 = 7.666$). A higher percentage of non-overweight mothers of overweight children (n = 11) carried the *MC4R rs17782313* higher-risk (C) allele (84.6%) compared to mothers of normal-weight children (n = 22) (42.3%; $p = 0.006$; $\chi^2 = 7.448$). No significance was seen between the percentage of overweight mothers and offspring weight category ($p > 0.05$). No other genetic associations were found among the SNPs selected for this study (data not shown).

Of the L&SD factors analysed, non-Caucasian fathers (n = 11) had a higher percentage of overweight children (45.5%) than Caucasian fathers ($n = 36$) (13.9%; $p = 0.039$; $\chi^2 = 5.012$). When controlling for father weight category, overall results remained significant ($p = 0.039$; $\chi^2 = 5.012$). A higher percentage of overweight non-Caucasian fathers (n = 4) had a higher percentage of overweight children (80 %) than overweight Caucasian fathers (n = 1) (20%; $p = 0.039$; $\chi^2 = 5.012$). No significance was seen between the percentage of non-overweight non-Caucasian fathers and offspring weight category ($p > 0.05$).

A higher percentage of parents who slept for less than 7 h per night (n = 66) had overweight children (38.6%) compared to those who slept for more than 7 h per night (n = 57) (13.6%; $p = 0.014$; $\chi^2 = 7.122$). When controlling for mother weight category, overall results remained significant ($p = 0.025$; $\chi^2 = 5.0.49$). A higher percentage of non-overweight mothers of offspring whose parents slept

for less than 7 h per night ($n = 10$) had overweight children (76.9%) compared to non-overweight mothers of offspring whose parents slept for more than 7 h per night ($n = 3$) ($p = 0.005$; $\chi^2 = 7.814$). No significance was seen between the percentage of overweight mothers of offspring whose parents slept for less than 7 h per night and overweight mothers of offspring whose parents slept for more than 7 h per night ($p > 0.05$). The data set was too small to control for father weight status. All L&SD data can be found in Tables 1 and 2. No other L&SD associations were found (data not shown).

Discussion

This study aimed to identify the proportion of overweight that can be explained by known parental genetic and L&SD risk factors with offspring weight status. We have demonstrated that only maternal BMI significantly, although modestly, predicted the weight status of offspring (accounting for a proportion of 15%); genetics did not contribute. Exploratory analysis provided the following hypothesis-generating results: maternal *MC4R* rs17782313 risk allele (C) is associated with overweight in offspring, along with maternal BMI, paternal ethnicity, and parental sleep duration. This is the only study to date that evaluates whether known parental L&SD and genetic risk factors are associated with the weight status of offspring in a UK cohort, in light of the prevention of obesity.

In order to confirm whether the association found between maternal *MC4R* rs17782313 risk allele and offspring weight status was independent of the association found between maternal and offspring weight status, maternal weight status was controlled for in the exploratory analysis. Despite the limitation of sample size discussed below, the results remained significant, specifically within the non-overweight maternal cohort. Demonstrating that when strong L&SD such as maternal weight status [37] are not apparent, genetic predisposition may play a role in obesity development [6]. Such information may contribute to personalised preventative health care. Although an association was reported here within the exploratory analysis, it is important to continue this preliminary research to draw stronger conclusions. To date, results have been inconclusive as to the contribution of genetic factors to weight gain. Initially, studies demonstrated that L&SD offer greater contribution to weight outcome [5, 7]. However, more recently, genetic contribution has been reported to be a large contributing factor [6, 10].

The biological plausibility of the *MC4R* gene influencing weight status has been reported in previous research, which complements the results of the present study. The *MC4R* gene plays a key role in the melanocortin system, which is one of the best characterised pathways for energy homeostasis and therefore plays an important role in regulating appetite [28]. *MC4R* knockout mice are obese, hyperphagic, and hyperinsulinemic [38]. In humans, the *MC4R* gene has been associated with dietary intake pattern, specifically control of appetite [39] and binge eating [40]. In addition to this, the *MC4R* rs17782313 SNP has been associated with adulthood and childhood polygenic obesity separately, although never from parent to offspring within the UK, in accordance with our findings. Loos et al. [23] showed that the risk allele (C) was associated with a difference in BMI of 0.049 Z-score units ($p = 2.8 \times 10^{-15}$) in adults and each additional copy of the risk allele (C) was associated with a BMI difference of between 0.10 and 0.13 Z-score units ($p > 7.3 \times 10^{-6}$) in children. Comparable results were found by Xi et al. [41] and Elks et al. [42]. All the above-mentioned studies use a cross-sectional or longitudinal design assessing an individual's own weight status, differing from the current study. This indicates that with further research, parental genetic analysis has the potential to provide insight into offspring outcome. Future research of this kind should endeavour to obtain offspring genotype data, as this will determine whether offspring genotype may be contributory to weight gain or whether parental genotype may be influencing parental weight and as a result impacting offspring weight status. The difference here is key to our understanding of genetic impact and its confounders towards heritable weight status.

An association was observed in the current study between parental sleep duration and offspring weight status. This is in line with other research [43, 44]. For example, Cappuccio et al. [43] (2008) in their meta-analysis reported that in children the pooled odds ratio for short duration of sleep and obesity was 1.89 (1.46–2.43; $p < 0.0001$) and in adults the pooled odds ratio was 1.55 (1.43–1.68; $p < 0.0001$). The authors, unlike the current study, did not investigate the relationship between adults and children. Parental habitual L&SD factors such as energy intake and voluntary energy expenditure (influencing BMI) and sleep pattern can influence offspring habit development [45, 46]. To confirm the association found in this current study was not the result of the potentially confounding factor parental weight status [37], as it was controlled for. Results remained significant in the non-overweight maternal cohort, indicating that parental sleep duration (an L&SD) may influence offspring weight status indepen-

dently of maternal weight status; however, maternal weight status is likely to be a more influential factor [37]. The ability to draw such a conclusion from an L&SD such as sleep duration may be beneficial in obesity prevention because it provides a target for intervention and subsequently less of a focus on offspring body image, an area well known to dissuade parents from participation [47]. Due to the limitations discussed below this must be considered preliminary research only. There are also other confounding factors when discussing the impact of sleep duration on obesity, namely other gene-environment interactions [48] and chronobiological factors [49]. Interestingly, Celis-Morales et al. [50] (2017) reported that genetic profile risk score has a stronger effect on obesity in participants who had short (less than 7 h) and long (more than 9 h) sleep duration per night. The scope of this study did not allow for the assessment of interaction between parental genetic predisposition and sleep patterns on offspring weight status. This warrants further research.

To date, research has been inconclusive as to whether parental ethnicity is associated with both offspring and/or own weight status. An association was observed in the current study between paternal ethnicity and offspring weight status. Results remained significant when paternal weight status was controlled for. In general, ethnicity is not shown to determine the risk of obesity alone, contrasting to the results in this current study [51, 52]. However, culture, specifically cultural practices, can become risk factors within countries where such practices are not used to, for example, food availability. There is also evidence to show that ethnic minority groups are often within the lower socioeconomic groups and are therefore more at risk of obesity and obesity-related comorbidities [53]. An interesting argument in relation to this, proposed by Dowse and Zimmet [54], is an evolutionary (genetic) adaptation influencing the ability to adjust to environmental changes, highlighting the possibility for an ethnicity-related genetic predisposition.

The results of this study need to be considered alongside its limitations. Primarily, the sample size allowed only for exploratory analysis. A larger cohort will be required to confirm these preliminary results, particularly when sub-cohort analyses were carried out. Additionally, the sample size would have prevented the *FTO rs9939609* SNP from reaching the Hardy-Weinberg equilibrium and caused a low number of high-risk genotypes for the other SNPs analysed, which may impact sub-group analyses. Moreover, due to the heterogeneity of the sample, further studies are required to demonstrate the reproducibility of the findings, especially regarding ethnicity, which poses a complex area of investigation because the UK is multicultural. Study groups were dichotomised to reduce heterogeneity, i.e., if one parent was not Caucasian the child was classified as non-Caucasian. This limits conclusions that could be drawn between different ethnic minority groups. In order to achieve this, within-couple ethnic homogeneity would need to be controlled for. Despite these limitations, obtaining significant results with a diverse cohort invites further exploration. Future research aiming for confirmatory analysis, as opposed to exploratory, should consider multiple testing. Here, offspring weight status was analysed against the 17 (18 excluding *FTO* rs9939609) parental variables. Lastly, the scope of this study did not allow for anthropometric data to be recorded by the researcher or for the analysis of offspring DNA. This was partially because the intention was to draw conclusions based on parents alone. However, future studies should use researcher-recorded body mass data and include further knowledge of offspring DNA to strengthen the conclusions drawn, in addition to accounting for confounding factors to distinguish whether there is a direct effect of parental genetics and L&SD on offspring weight status or whether parental genetics and L&SD indirectly impact offspring weight status, as discussed previously.

In summary, this study demonstrates that associations can be made between the weight status of offspring based solely on parental L&SD and genetic data, specifically, maternal rs17782313, maternal BMI, paternal ethnicity, and parental sleep duration. These results could be relevant in the development of strategies aimed at reducing obesity and combatting the increasing early-onset rate.

Statement of Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the St. Mary's University Ethics Committee (SMEC_2016–17_099). Written informed consent was obtained from all subjects/patients. This study is registered as "The Prediction of Overweight and Obesity Based on Lifestyle and Genetic Factors," corresponding information can be found at the following website: http://www.researchregistry.com/ (reference: researchregistry3423).

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No external funding was awarded for this study.

Author Contributions

C.A.M.G. assisted with the study design, interpretation of data, and writing of the manuscript and carried out recruitment, data collection, and data analysis. C.R.P. assisted with writing of the manuscript. G.H. assisted with the interpretation of data and carried out statistical analysis. S.L.-C. and P.G.-M. assisted with the interpretation of data and writing of the manuscript. Y.M. assisted with the study design, interpretation of data, and writing of the manuscript.

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