Received: 16 July 2020 | Revised: 6 September 2020 | Accepted: 8 September 2020

DOI: 10.1111/pedi.13120

ISPAD WILEY

Response heterogeneity to lifestyle intervention among Latino adolescents

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Funding information
Institute of Education Sciences, Grant/Award Number: R305D190011; Maternal and Child Health Bureau, Grant/Award Number: T79MC31884; National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award Number: R01DK107579 and R01DK107579-03S1; National Institute on Minority Health and Health Disparities, Grant/Award Numbers: P20MD002316 and U54MD002316

Abstract

Objective: To characterize the heterogeneity in response to lifestyle intervention among Latino adolescents with obesity.

Methods: We conducted secondary data analysis of 90 Latino adolescents (age 15.4 ± 0.9 y, female 56.7%) with obesity (BMI% 98.1 ± 1.5%) that were enrolled in a 3 month lifestyle intervention and were followed for a year. Covariance pattern mixture models identified response phenotypes defined by changes in insulin sensitivity as measured using a 2 hour oral glucose tolerance test. Baseline characteristics were compared across response phenotypes using one-way ANOVA and chi-square test.

Results: Three distinct response phenotypes (PH1, PH2, PH3) were identified. PH1 exhibited the most robust response defined by the greatest increase in insulin sensitivity over time (β ± SE, linear 0.52 ± 0.17, $P < .001$; quadratic −0.03 ± 0.01, $P = .001$). PH2 showed non-significant changes, while PH3 demonstrated modest short-term increases in insulin sensitivity which were not sustained over time (linear 0.08 ± 0.03, $P = .002$; quadratic −0.01 ± 0.002, $P = .003$). At baseline, PH3 (1.1 ± 0.4) was the most insulin resistant phenotype and exhibited the highest BMI% (98.5 ± 1.1%), 2 hours glucose concentrations (144.0 ± 27.5 mg/dL), and lowest beta-cell function as estimated by the oral disposition index (4.5 ± 2.8).

Conclusion: Response to lifestyle intervention varies among Latino youth with obesity and suggests that precision approaches are warranted to meet the prevention needs of high risk youth.

KEYWORDS

diabetes prevention, insulin resistance, non-responder, precision medicine, responder

1 | INTRODUCTION

Disparities in the prevalence of type 2 diabetes among Latino youth[1] are the result of interactions between genetic factors and lifestyle behaviors.[2,3] Insulin resistance (ie, decreased insulin sensitivity), is an early pathological predictor of type 2 diabetes[4] and disproportionately impacts Latino youth.[5] Lifestyle intervention remains the cornerstone for preventing type 2 diabetes among high-risk adults,[6] and pediatric studies have demonstrated increases in insulin sensitivity and improvements in glucose tolerance following lifestyle intervention.[7,8] However, there is considerable heterogeneity in the response to intervention among youth with obesity[9] yet few studies have rigorously evaluated this phenomenon in the pediatric population with respect to changes in insulin sensitivity.

Precision medicine is an approach for tailoring medical interventions to individual traits to maximize prevention efforts, and this

concept has recently been extended to lifestyle interventions.[10] The application of precision medicine to pediatric obesity has been limited[11] but provides an important framework for understanding why some youth experience success with interventions and others do not.[12]

A major impediment in understanding heterogeneity in response to intervention is the need for alternative statistical methodology for use in clinical trials.[13] Structural equation modeling techniques provide a platform for understanding response heterogeneity by identifying "latent classes" of individuals that change similarly over time. Latent class growth models and growth mixture models are commonly used to identify classes of responders and can be applied to interventions.[14] Specifically, covariance pattern mixture modeling (CPMM) demonstrates better performance and circumvents estimation issues of other latent class methods with the sample sizes that are typical in intervention studies.[15] With this context, the purpose of this study is to apply CPMM to characterize response heterogeneity following a 3 month lifestyle intervention among Latino youth with obesity.[7]

2 | METHODS

2.1 | Participants

The current study is a secondary analysis from a randomized control trial that tested the efficacy of a 3 month lifestyle intervention to increase insulin sensitivity (primary physiologic outcome) among Latino youth with obesity.[16,17] For purposes of this analysis, data from youth enrolled in the intervention arm were used. A complete description of the study, participants, and the primary and secondary outcomes from the intervention have been reported elsewhere.[7] In short, 91 Latino youth were recruited from a network of schools, community centers, and clinics and enrolled in the lifestyle intervention arm of the study. NOTE: One participant did not have insulin sensitivity data for any time point and was thus excluded from the present analysis. Participants met the following inclusion criteria: (a) self-identification as Latino, (b) ages 14 to 16 years at enrollment, and (c) obesity as defined as BMI ≥95th percentile (BMI%) for age and sex or BMI ≥30 kg/m^2 and were excluded if they were (a) taking medication(s) or diagnosed with a condition that influences carbohydrate metabolism, physical activity, or cognition, (b) had a diagnosis of type 2 diabetes, (c) enrolled in a formal weight loss program within the 6 months prior to the start of the study period, or (d) diagnosed with depression or any other condition that may impact quality of life.

The lifestyle intervention included 3 months of moderate-vigorous physical activity (3 days/week) and 1 day of nutrition education and health behavior skills training. Following the intensive, 3 month intervention period, booster sessions were held once per month for three additional months to reinforce and support health behavior changes. Youth were subsequently followed for six additional months to assess the long-term changes in insulin sensitivity. All participants and a parent/guardian provided informed consent and assent. This study was approved by the Arizona State University (ASU) Institutional Review Board.

2.2 | Procedures

All outcomes were collected and assessed at the ASU clinical research unit. Height and weight were measured to the nearest 0.1 cm and 0.1 kg to calculate BMI and BMI% according to CDC Growth Charts. Severe obesity was defined as a BMI 120% of the 95th percentile for age and sex or BMI ≥35 kg/m^2.[18] Pubertal growth stage was estimated by the pubertal development scale.[19] Family history of type 2 diabetes including in utero exposure to gestational diabetes was measured by parental report. Body fat percent (Fat %) was estimated by bioelectric impedance scale (TBF-300A; Tanita Corporation of America, Arlington Heights, Illinois). A 75 g oral glucose tolerance test (OGTT) was administered after an overnight fast to assess insulin sensitivity as estimated by the whole-body insulin sensitivity index (WBISI) from glucose and insulin concentrations at 0′, 30′, 60′, 90′, and 120′.[20,21] Data were collected at baseline (T1), 3 months (T2), 6 months (T3), and 12 months (T4) with the following study visit/completion rates: 100%, 86.6%, 83.3%, and 84.4%, respectively.

2.3 | Analytical approach

Waterfall plots were used to depict individual changes in insulin sensitivity following lifestyle intervention with Figure 1 demonstrating changes from T1 to T2 (Panel A) and from T1 to T4 (Panel B). A quadratic CPMM with a class-specific unstructured covariance matrix was fit to these data to identify response phenotypes over the 12 month period. CPMMs combine covariance pattern models for estimating growth trajectories with latent class analysis to identify unobserved, latent groups of response phenotypes. These latent groups serve a similar function as including a moderator variable (eg, sex) such that different growth trajectories are estimated for each group. The difference with CPMMs is that the groups are not represented by a variable in the data but rather are determined by a probabilistic classification algorithm that groups individuals based on similarities in growth trajectories. Each identified response phenotype exhibits its own estimated growth trajectory.

Because the response phenotypes are unobserved, the first step in latent class analyses is to determine how many response phenotypes are most plausible. We tested models with between one and four latent response phenotypes using the Sample-Size Adjusted BIC (SA-BIC) information criterion to compare models. Lower SA-BIC values indicate more parsimonious fit and were used because they discriminate well with data similar to those in this study.[22] The bootstrapped likelihood ratio test and classification likelihood criteria were also used as supporting evidence for comparing models with 2 or more classes. Full information robust maximum likelihood was used to account for missing data such that all participants could be retained in the analysis, assuming that data were missing at random.[23] This estimator also protects against moderate deviations from normality. To prevent convergence to a local solution, 100 initial stage starts and 10 final stage optimizations were used when estimating the model.[24]

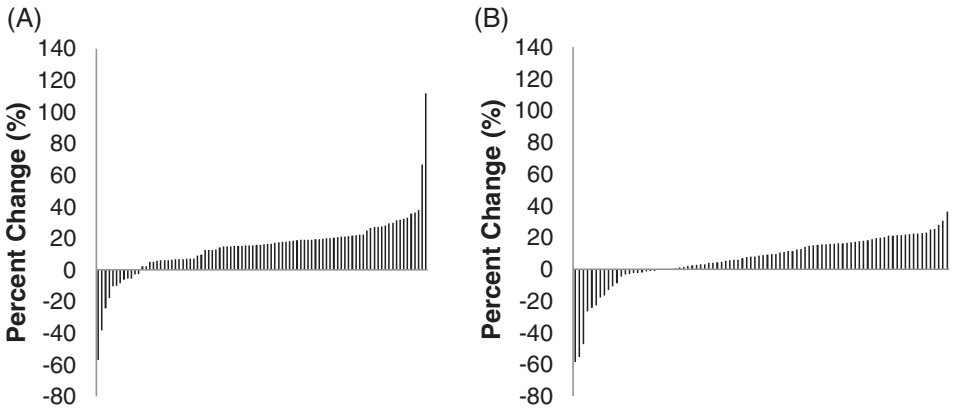

FIGURE 1 Individual response of insulin sensitivity to lifestyle intervention from T1 to T2 (Panel A) and from T1 to T4 (Panel B)

Once the number of response phenotypes was identified, baseline characteristics and type 2 diabetes risk factors were compared across phenotypes. A one-way ANOVA with Bonferroni adjustments was applied to compare baseline characteristics (demographic, anthropometric, and cardiometabolic risk) across response phenotypes. This approach was also used to compare intervention adherence, as measured by attendance, intervention fidelity, as measured by average heart rates during exercise sessions, and exercise response as baseline adjusted fitness at T2. Effect sizes from T1 to T4 for each response phenotype were calculated as the change in insulin sensitivity divided by the SD of change. Data from the CPMM analysis are presented as β ± SE with *P*-values, and baseline characteristics are reported as mean ± SD. Chi-square tests with Bonferroni adjustments were used to correct for multiple comparisons when comparing categorical variables across response phenotypes. Categorical variables are presented as sample size (N) and percentage (%). SAS 9.4 (Cary, NC), Mplus 8.4 (Los Angeles, CA), and SPSS Version 25 (Chicago, IL) were used to run analyses with significance set at the 0.05 alpha level.

3 | RESULTS

A total of 90 Latino youth (age 15.4 ± 0.9 y, BMI% 98.1 ± 1.5%, female 56.7%) were included in the current analysis.

Table 1 depicts the log-likelihood, SA-BIC, classification likelihood criteria, bootstrapped likelihood ratio test, and entropy (a measure of class separation) for models with different numbers of response phenotypes. All measures suggested three response phenotypes. The 4-class model is not shown since it would not converge likely due to having many parameters relative to sample size. CPMM of three distinct insulin sensitivity response phenotypes exhibited the best fit (Figure 2). Phenotype 1 (PH1) demonstrated the most pronounced increase in insulin sensitivity up to 1 year follow-up (linear 0.52 ± 0.13, $P < .001$; quadratic −0.03 ± 0.01, $P = .001$). Phenotype 2 (PH2) showed an overall negative but non-significant response that plateaus by 1 year (linear: −0.18 ± −0.095, $P = .059$; quadratic: 0.01 ± 0.006, $P = .094$). Phenotype 3 (PH3) demonstrated significant short term increases in insulin sensitivity before returning to baseline levels by 1 year follow-up (linear 0.08 ± 0.03, $P = .002$; quadratic −0.01 ± 0.002, $P = .003$). Overall effect sizes from T1 to T4 for PH1, PH2, and PH3 were 2.14, −0.63, and 0.30, respectively. No significant differences were found in program attendance (88.3 ± 10.5%, 78.0 ± 25.7%, 70.5 ± 31.5%, $P = .075$) or average heart rates during physical activity sessions (155.4 ± 9.7, 154.8 ± 9.2, 157.5 ± 9.5, beats/min $P = .471$), between PH1, PH2, and PH3. Further, fitness after the lifestyle intervention was not significantly different across phenotypes (3021.2 ± 46.0, 2962 ± 34.5, 3009.3 ± 31.6 mL/min, $P = .495$).

TABLE 1 Model fit for 1-, 2-, and 3-class models

Measure	1 Class	2 Classes	3 Classes
Loglikelihood	−403.57	−341.51	−312.67
SA-BIC	825	719	680
Relative Entropy	—	0.732	0.756
CLC	—	716	674
BLRT	—	124.1	76.6
BLRT *P*-value	—	<.001	.02

Note: Lower values of SA-BIC and CLC indicate better fit. A significant BLRT indicates the model fits better than a model with one fewer class. Relative Entropy, CLC, and BLRT require multiple classes to be computed and are undefined for the 1-class model.
Abbreviations: BLRT, bootstrapped likelihood ratio test; CLC, classification likelihood criteria; SA-BIC, sample size adjusted BIC.

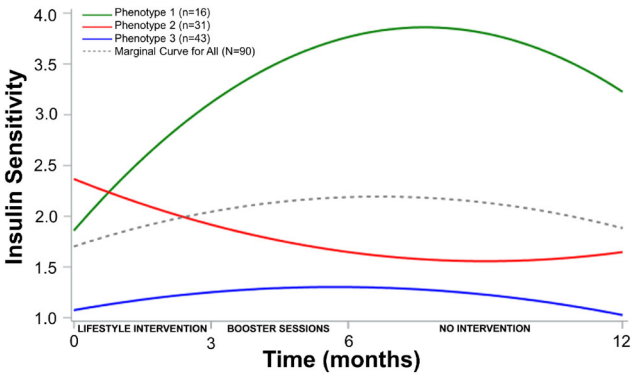

FIGURE 2 Response curves for 3 distinct phenotypes: PH1, PH2, PH3

TABLE 2 Comparison of baseline characteristics between three distinct response types

Parameter	PH1 (N = 16)	PH2 (N = 31)	PH3 (N = 43)	*P*-value
Age, y	**15.4 ± 1.1**	**15.4 ± 0.9**	**15.3 ± 0.9**	**.893**
Female, N (%)	8 (50%)	21 (67.7%)	22 (51.2%)	.306
PDS	2.7 ± 0.5	2.7 ± 0.5	2.5 ± 0.5	.362
Weight-specific QOL	59.1 ± 23.1	67.1 ± 23.8	61.8 ± 24.3	.489
GDM, N (%)	0 (0%)	3 (9.7%)	5 (11.6%)	.371
Family history[a], N (%)	10 (62.5%)	24 (77.4%)	28 (65.1%)	.440
Anthropometrics/adiposity				
BMI, kg/m^2	33.5 ± 5.4	33.3 ± 4.9	35.5 ± 5.1	.152
BMI%	97.8 ± 1.8	97.6 ± 1.7*	98.5 ± 1.1	.022
WC, cm	107.3 ± 9.9	105.1 ± 13.7	111.0 ± 12.1	.128
Fat %	45.3 ± 10.7	43.9 ± 5.9	45.6 ± 6.6	.577
Severe obesity[b]	8 (50%)	17 (54.8%)	17 (39.5%)	.410
Glucose regulation				
Prediabetes[c], N (%)	6 (42.9%)	8 (25.8%)	23 (53.5%)	.059
G_0, mg/dL	95.2 ± 6.8	91.3 ± 4.9	93.4 ± 8.1	.195
G_{60}, mg/dL	156.6 ± 27.3	137.1 ± 24.6*	163.0 ± 30.0	.001
G_{120}, mg/dL	131.3 ± 30.4	120.7 ± 18.0*	144.0 ± 27.5	.001
I_0, uIU/mL	21.4 ± 11.9*	16.7 ± 8.7*	32.0 ± 13.6	<.001
I_{60}, uIU/mL	234.2 ± 124.5	181.8 ± 101.3*	304.3 ± 110.9	<.001
I_{120}, uIU/mL	228.9 ± 172.5*	220.6 ± 169.0*	418.3 ± 185.2	<.001
HOMA-IR	5.1 ± 3.0*	3.9 ± 2.0*	7.5 ± 3.4	<.001
IGI	2.9 ± 1.2	3.7 ± 2.8	4.4 ± 2.7	.158
WBISI	1.8 ± 1.1*	2.4 ± 1.2*	1.1 ± 0.4	<.001
oDI_{WBISI}	4.7 ± 2.6	8.0 ± 5.9*	4.5 ± 2.8	.002
Glucose metabolism and insulin dynamics				
Total G_{AUC}	17 337.4 ± 2619.1**	15 373.7 ± 1992.3*	17 692.1 ± 2379.9	<.001
Total I_{AUC}	24 160.1 ± 11 718.8*	19 434.5 ± 10 930.8*	33 332.0 ± 10 059.8	<.001

Note: Continuous data presented as estimated marginal means±SD.

Abbreviations: BMI%, BMI percentile; Fat %, fat percentage; G, glucose (subscripts correspond to OGTT timepoint); G_{AUC}, total glucose area under the curve; GDM, exposure to gestational diabetes mellitus in utero; HOMA-IR, homeostatic model assessment of insulin resistance; I, insulin (subscripts correspond to ogtt timepoint); I_{AUC}, total insulin area under the curve; IGI, insulinogenic index; oDI, oral disposition index; PDS, pubertal development scale, QOL, quality of life; WBISI, whole-body insulin sensitivity index; WC, waist circumference.

[a]Family history as defined by a parent or sibling having been diagnosed with type 2 diabetes.

[b]As defined by 120% of the 95th percentile for each individual or BMI≥35 kg/m^2.

[c]As defined by ADA criteria (fasting glucose >100 mg/dL and/or 2-hour glucose during OGTT >139 mg/dL).

*Significantly different than PH3 ($P < .05$).

**Significantly different than PH2 ($P < .05$).

Comparison of baseline anthropometrics, type 2 diabetes, and cardiometabolic risk factors across phenotypes are shown in Table 2 and Supplementary Table S1. Overall, PH3 demonstrated the lowest insulin sensitivity (M ± SD, 1.1 ± 0.4) which was significantly lower than PH1 (1.8 ± 1.1, $F_{2,82}$ = 21.5, P = .028) and PH2 (2.4 ± 1.2, $F_{2,82}$ = 21.5, $P < .001$). No differences in insulin sensitivity were found between PH1 and PH2 ($F_{2,82}$ = 21.5, P = .103). In addition, PH3 showed significantly higher BMI% (98.5 ± 1.1% vs 97.6 ± 1.7%, $F_{2,87}$ = 4.0, P = .027), 2 hours glucose concentrations during OGTT (144.0 ± 27.5 vs 120.7 ± 18.0 mg/dL, $F_{2,87}$ = 7.8, P = .001), and lower oral disposition index (4.5 ± 2.8 vs 8.0 ± 5.9, $F_{2,80}$ = 6.6, P = .002) compared with PH2 with no significant differences between PH1 and PH3. Glucose area under the curve was significantly lower in PH2 (15 373.7 ± 1992.3 mg-h/dL) compared to PH1 (17 337.4 ± 2619.1 mg-h/dL, $F_{2,81}$ = 9.0, P = .038) and PH3 (17 692.1 ± 2380.0 mg-h/dL, $F_{2,81}$ = 9.0P = <.001) with no differences between PH1 and PH3. Differences in cholesterol (total, LDL, and HDL), liver enzymes (ALT and AST), and blood pressure percentiles are presented in Supplementary Table S1 and demonstrate that PH3 exhibited a significantly more adverse cardiometabolic profile compared to PH1 and PH2 at baseline. There were no significant differences in age, puberty, sex, exposure to gestational diabetes, or family history of type 2 diabetes across phenotypes.

4 | DISCUSSION

In order to inform precision approaches for diabetes prevention in high-risk youth, it is important to identify how individuals and/or groups respond to various prevention efforts. Using data from a completed trial that demonstrated significant increases in insulin sensitivity following lifestyle intervention, we were able to identify three distinct response phenotypes over the course of a year. PH1 showed the most robust response; PH2 did not respond to the lifestyle intervention; and, PH3 showed significant modest effects in the short-term but failed to sustain improvements by 1 year. These results support previous work on response heterogeneity of cardiometabolic risk factors among youth after lifestyle intervention, and further reinforce the need to develop and implement precision approaches for preventing type 2 diabetes among high-risk populations.[9]

The complex pathophysiology of diabetes makes it challenging to identify potential predictors of response to an intervention.[25] Physiologically, insulin sensitivity is impacted by numerous factors, including variations in glucose absorption, the incretin effect, insulin secretion, body composition, inflammation, and oxidative stress.[26-29] From the standpoint of behaviors, insulin sensitivity is affected by physical activity and dietary habits which were key behaviors targeted during the intervention.[30,31] Unfortunately, accurate assessments of habitual behaviors that may explain heterogeneity among youth were not available in this study. However, the fact that we did not observe any differences in fitness between phenotypes following the intervention suggests alternative mechanisms such as biological variability[32] may be operational. Given the multiplicity of factors that influence insulin sensitivity and the comprehensive nature of the intervention, it is impossible to identify whether the observed heterogeneity is the result of biological or behavioral factors or likely some interaction.

Previous studies have identified higher risk phenotypes that have exhibited less favorable responses to lifestyle interventions. In the Tuebingen Study of adults with prediabetes, a higher risk phenotype defined by low insulin sensitivity with non-alcoholic fatty liver disease showed the least improvements in 2 hours glucose concentrations compared to a lower risk phenotype following a 9 month lifestyle intervention.[33] The Diabetes Prevention Program showed that low insulin secretion and insulin sensitivity at baseline were predictive of greater incidence of diabetes during long-term follow up.[34] The DPP also demonstrated an attenuated response of insulin sensitivity among individuals with increased visceral and liver fat.[35] Similarly, our analysis revealed a higher risk phenotype, PH3, which was the most insulin resistant at baseline compared to the other phenotypes and only modestly increased insulin sensitivity in the short-term. It is particularly interesting that PH2 did not respond to the intervention given that PH2 started with similar levels of insulin sensitivity as the most robust responders (PH1). These results should be followed up in larger samples and highlight the need for intensive phenotyping at baseline to identify predictors of response to lifestyle interventions. Additionally, more aggressive and sustained interventions may yield greater physiologic effects. Whether variations in response to lifestyle intervention are explained by distinct biological processes is an interesting notion that warrants future investigation.

Although PH1 exhibited the most favorable response (effect size = 2.14), only 17.8% youth in our sample were in this group. Lifestyle intervention remains the cornerstone approach to preventing diabetes in high-risk populations, but the optimal combination of intervention targets (eg, nutrition, physical activity/inactivity, sleep) that influence type 2 diabetes risk remain largely unknown. Furthermore, social determinants of health are also operational and perhaps even more so among racial and ethnic minority groups.[36] As such, ecological factors outside of intervention targets may contribute to response heterogeneity.[37] Thus, it is important for future studies to consider the sociocultural context of the priority population and consider a more comprehensive array of factors that may help predict response to lifestyle intervention.

The current study advances the science by identifying distinct response phenotypes of an important type 2 diabetes biomarker among Latino adolescents with obesity following lifestyle intervention. We used robust statistical methods (ie, CPMM) to analyze longitudinal data from youth enrolled in a lifestyle intervention as part of a randomized control trial, which is novel to the field of pediatric obesity. CPMMs circumvent issues that other latent class analyses do not; therefore, this study introduces an appealing analytical technique to the field of pediatric obesity for examining heterogeneity of longitudinal data. Further, our study focuses on a vulnerable population at high risk of developing type 2 diabetes.[38] We acknowledge that the current study is not without the following limitations. Insulin sensitivity was the primary physiologic outcome in the parent study and was the sole dependent variable used to differentiate response phenotypes in the current analysis. This outcome measure was selected as a proximal risk factor for type 2 diabetes in youth[39] that is sensitive to change with lifestyle intervention.[40] The estimate of insulin sensitivity used in the present study is not the gold-standard hyperinsulinemic euglycemic clamp but has been validated in both youth with obesity and adults.[20,21] Our sample size for each phenotype was relatively small which may have influenced study results, and a larger sample size may more clearly illustrate differences in risk profiles across phenotypes. Further, physical activity and eating patterns were not included in the analysis as the self-reported instruments used to assess these behaviors in the parent study did not provide valid or reliable data. Thus, it remains plausible that changes in physical activity and nutrition explained the observed heterogeneity. Lastly, the current study included a distinct population of Latino youth with obesity, which limits generalizability.

In conclusion, a 3 month diabetes prevention program that included physical activity, nutrition education, and behavioral skills training induced a heterogeneous response in terms of changes in insulin sensitivity among Latino adolescents with obesity. The insulin response to glucose among Latino youth with obesity is variable with some youth showing a more favorable and sustained response to lifestyle intervention than others. Future research is warranted to understand the physiologic, genetic, psychosocial, environmental, and behavioral predictors of response to lifestyle intervention to inform precision medicine approaches to addressing pediatric obesity and related disorders.

ACKNOWLEDGEMENTS

We are grateful to all the research participants and families who devoted their time and energy to making this research possible. We would also like to thank Drs Joon Young Kim (Syracuse University) and Justin Ryder (University of Minnesota) for comments and critical feedback on the manuscript. This work was supported by grants from the National Institute on Minority Health and Health Disparities (P20MD002316 and U54MD002316) and the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK107579 and R01DK107579-03S1). A portion of time preparing this manuscript was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of Maternal Child Health Bureau Nutrition Training Grant, The TRANSCEND Program in Maternal Child Health Nutrition and Childhood Obesity Prevention (T79MC31884; PI: Bruening) and by an Institute for Educational Sciences (IES) statistical methodology grant (R305D190011; PI: McNeish). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, IES or the U.S. Government.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Gabriel Q. Shaibi, Micah L. Olson, and Armando Peña performed the research. Gabriel Q. Shaibi and Micah L. Olson designed the original research study. Armando Peña and Daniel McNeish analyzed the data. Daniel McNeish, Micah L. Olson, Stephanie L. Ayers, Kiley B. Vander Wyst, Allison N. Williams, and Gabriel Q. Shaibi provided advisement on the analysis and interpretation. Armando Peña wrote the first draft of the manuscript with revisions from Daniel McNeish, Micah L. Olson, Stephanie L. Ayers, Kiley B. Vander Wyst, Allison N. Williams, and Gabriel Q. Shaibi.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13120.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Peña A, McNeish D, Ayers SL, et al. Response heterogeneity to lifestyle intervention among Latino adolescents. *Pediatr Diabetes*. 2020;21:1430–1436. https://doi.org/10.1111/pedi.13120