PEDIATRIC OBESITY: A FOCUS ON TREATMENT OPTIONS

EDITED BY: Fatima Cody Stanford and Angela K. Fitch
PUBLISHED IN: Frontiers in Pediatrics

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-940-7
DOI 10.3389/978-2-88945-940-7

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

PEDIATRIC OBESITY: A FOCUS ON TREATMENT OPTIONS

Topic Editors:
Fatima Cody Stanford, Massachusetts General Hospital and Harvard Medical School, United States
Angela K. Fitch, Massachusetts General Hospital and Harvard Medical School, United States

Cover image: Nina Rys/ Shutterstock.com

Obesity is the most prevalent chronic disease in the pediatric population. Despite continued efforts to prevent obesity in the population, obesity rates continue to climb, and there has been a dramatic increase in severe obesity (body mass index (BMI) >/=40). With the current concerns about obesity and adiposity related conditions on the health and quality of life, we should have treatment options that serve to reduce this burden on the patient population to improve morbidity and mortality. We need treatment options that are intensive, prescriptive, or deliverable in multidisciplinary settings (i.e. family, school, and medical environment).

Citation: Stanford, F. C., Fitch, A. K., eds. (2019). Pediatric Obesity: A Focus on Treatment Options. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-940-7

Table of Contents

II. REVIEWS

III. CASE REPORTS

frontiers in Pediatrics

EDITORIAL
published: 07 May 2019
doi: 10.3389/fped.2019.00177

Editorial: Pediatric Obesity: A Focus on Treatment Options

Fatima Cody Stanford[1,2,3]* *and Angela K. Fitch*[1,3,4]

[1] MGH Weight Center, Massachusetts General Hospital, Boston, MA, United States, [2] Neuroendocrine Unit, Division of Endocrinology, Departments of Medicine and Pediatrics, Boston, MA, United States, [3] Harvard Medical School, Boston, MA, United States, [4] Endocrine Unit, Division of Endocrinology, Department of Medicine, Boston, MA, United States

Keywords: obesity, pediatric obesity, nutrition, weight loss medications, weight loss surgery, bariatric surgery

Editorial on the Research Topic

Pediatric Obesity: A Focus on Treatment Options

Obesity is the most prevalent chronic disease in the United States with 17.8% of youth aged 2–19 with obesity and 5.8% with severe obesity (1). In 2015, it was noted that the average weight of children had risen an average of more than 5 kg within 3 decades, but it is also noteworthy that low-income and middle income countries have reported similar or even more rapid increases in the prevalence of obesity (2, 3). While it is important to continue efforts to promote prevention of obesity in children and adolescents, we must ensure that efforts also target the treatment of obesity to ensure that gains in life expectancy throughout the world do not decline due to the deleterious impacts of this chronic disease of obesity. Our issue seeks to address issues surrounding treatment of obesity in the pediatric population.

In our topic, there are three reviews on: (1) genetics and the role it plays in obesity, (2) vascular disease and atherosclerosis and its role in fatty liver in the pediatric population, and (3) the role of pediatric obesity in eating disorders. Genetics play a large role in the development of obesity, but its role in common (multifactorial/polygenic) obesity is less pronounced than in persons with monogenic and syndromic obesity (4). Mărginean and colleagues review genetic and obesogenic environmental factors and the roles they play in the prevalence of childhood obesity in their review, Mărginean et al. In Karjoo seeks to discern if there is a correlation between atherosclerosis and fatty liver disease in adolescents due to the early incidence of these entities in children and adolescents. Finally, De Giuseppe and colleagues evaluate the impact of multi-disciplinary treatment of eating disorders to decrease obesity in this population in De Giuseppe et al.

With the rise in obesity in the pediatric population, are patients being adequately referred for management of their obesity? Imoisili and colleagues seek to provide insights about childhood obesity referral types as it relates to clinicians, clinical practice, and patient characteristics in Imoisili et al. When pediatric patients with overweight and obesity are evaluated, is there a clear algorithm that clinicians may follow to ensure standardized care? Cuda and Censani present a pediatric algorithm for the care of patients with obesity in Cuda and Censani.

In Schumaker and Censani present the case of a 10 year old male with severe obesity who presented with growth failure and excessive weight gain and treatment strategies for the care of this patient. Outside of behavioral and lifestyle therapies, there is often minimal use of evidence-based treatments for pediatric patients with obesity in the US and around the world. In Fox and Kelly demonstrate the utility of weight loss medications in the treatment of obesity in the pediatric population. Dr. Campoverde Reyes and colleagues evaluate weight loss surgery utilization in adolescents and young adults in several academic institutions in Campoverde Reyes et al. to ascertain whether the most effective treatment for moderate to severe obesity, metabolic and bariatric surgery, is utilized in the patients most likely to garner benefit.

OPEN ACCESS

Edited by:
Andrew S. Day,
University of Otago, New Zealand

Reviewed by:
Hellas Cena,
University of Pavia, Italy

***Correspondence:**
Fatima Cody Stanford
fstanford@mgh.harvard.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *19 March 2019*
Accepted: *17 April 2019*
Published: *07 May 2019*

Citation:
Stanford FC and Fitch AK (2019) Editorial: Pediatric Obesity: A Focus on Treatment Options. Front. Pediatr. 7:177. doi: 10.3389/fped.2019.00177

When metabolic and bariatric surgery is utilized in adolescents and young adults, it is important to recognize that there is often an overestimation of resting energy expenditure (REE), a tool that may be utilized to govern behavioral strategies in the postoperative setting, as noted by Rickard et al.

It is well-known that racial and ethnic minority populations have disproportionately higher levels of obesity and subsequent lower levels of treatment compared to majority populations (5). As such, Srivastava and colleagues evaluated the feasibility of shared medical appointments (SMA) in African-American families with obesity in an urban safety net hospital in their original research, Srivastava et al. Thornton and colleagues also evaluated chronic disease management for diseases such as obesity in families and how it plays a role in adolescent family members and their health behaviors in Thornton et al. Finally, Showell and colleagues sought to examine the association between neighborhood factors and obesity in overweight in racial and ethnic minority preschool children in Showell et al.

With this issue, Stanford and Fitch we have presented a wide spectrum of work surrounding the diagnosis and treatment of obesity in diverse pediatric populations. Much is needed to ensure that children, adolescents, and young adults receive adequate care for overweight or obesity.

AUTHOR CONTRIBUTIONS

FS drafted and reviewed the manuscript. AF reviewed the manuscript.

FUNDING

National Institutes of Health NIDDK P30 DK040561 (FS) and L30 DK118710 (FS).

REFERENCES

1. Ogden CL, Fryar CD, Hales CM, Carroll MD, Aoki Y, Freedman DS. Differences in obesity prevalence by demographics and urbanization in us children and adolescents, 2013-2016. *JAMA*. (2018) 319:2410–8. doi: 10.1001/jama.2018.5158
2. Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA, et al. Child and adolescent obesity: part of a bigger picture. *Lancet*. (2015) 385:2510–20. doi: 10.1016/S0140-6736(14)61746-3
3. Imes CC, Burke LE. The obesity epidemic: the united states as a cautionary tale for the rest of the world. *Curr Epidemiol Rep*. (2014) 1:82–8. doi: 10.1007/s40471-014-0012-6
4. Rohde K, Keller M, la Cour Poulsen L, Bluher M, Kovacs P, Bottcher Y. Genetics and epigenetics in obesity. *Metabolism*. (2019) 92:37–50. doi: 10.1016/j.metabol.2018.10.007
5. Byrd AS, Toth AT, Stanford FC. Racial disparities in obesity treatment. Curr *Obes Rep*. (2018) 7:130–8. doi: 10.1007/s13679-018-0301-3

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer HC declared a past co-authorship with one of the authors, FS, to the handling Editor.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 12 December 2018
doi: 10.3389/fped.2018.00367

Referrals and Management Strategies for Pediatric Obesity—*DocStyles* Survey 2017

***Omoye E. Imoisili*[1,2]*, *Alyson B. Goodman*[2], *Carrie A. Dooyema*[2], *Sohyun Park*[2], *Megan Harrison*[2], *Elizabeth A. Lundeen*[2] *and Heidi Blanck*[2]**

[1] *Epidemic Intelligence Service, Office of Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention, Atlanta, GA, United States,* [2] *Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, United States*

Background: Childhood obesity care management options can be delivered in community-, clinic-, and hospital-settings. The referral practices of clinicians to these various settings have not previously been characterized beyond the local level. This study describes the management strategies and referral practices of clinicians caring for pediatric patients with obesity and associated clinician characteristics in a geographically diverse sample.

Methods: This cross-sectional study used data from the *DocStyles* 2017 panel-based survey of 891 clinicians who see pediatric patients. We used multivariable logistic regression to estimate associations between the demographic and practice characteristics of clinicians and types of referrals for the purposes of pediatric weight management.

Results: About half of surveyed clinicians (54%) referred <25% of their pediatric patients with obesity for the purposes of weight management. Only 15% referred most (≥75%) of their pediatric patients with obesity for weight management. Referral types included clinical referrals, behavioral referrals, and weight management program (WMP) referrals. Within these categories, the percentage referrals ranged from 19% for behavioral/mental health professionals to 72% for registered dieticians. Among the significant associations, female clinicians had higher odds of referral to community and clinical WMP; practices in the Northeast had higher odds of referral to subspecialists, dieticians, mental health professionals, and clinical WMP; and clinics having ≥15 well child visits per week were associated with higher odds of referral to subspecialists, mental health professionals, and health educators. Not having an affiliation with teaching hospitals and serving low-income patients were associated with lower odds of referral to mental health professionals, and community and clinical WMP. Compared to pediatricians, family practitioners, internists, and nurse practitioners had higher odds of providing referrals to mental health professionals and to health educators.

Conclusion: This study helps characterize the current landscape of referral practices and management strategies of clinicians who care for pediatric patients with obesity.

OPEN ACCESS

Edited by:
Fatima Cody Stanford, Harvard Medical School, United States

Reviewed by:
Hellas Cena, University of Pavia, Italy
Allen F. Browne, Maine Medical Center, United States

****Correspondence:***
Omoye E. Imoisili
oimoisili@cdc.gov

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *06 September 2018*
Accepted: *12 November 2018*
Published: *12 December 2018*

Citation:
Imoisili OE, Goodman AB, Dooyema CA, Park S, Harrison M, Lundeen EA and Blanck H (2018) Referrals and Management Strategies for Pediatric Obesity—DocStyles Survey 2017. Front. Pediatr. 6:367. doi: 10.3389/fped.2018.00367

Our data provide insight into the clinician, clinical practice, and reported patient characteristics associated with childhood obesity referral types. Understanding referral patterns and management strategies may help improve care for children with obesity and their families.

Keywords: pediatric obesity, obesity management, weight management programs, clinician referrals, clinician characteristics

INTRODUCTION

Childhood obesity is a serious health problem associated with both physical and psychological consequences, including hypertension, hyperlipidemia, insulin resistance, asthma, weight stigma, and bullying, among others (1–6). Approximately 18.5% of children ages 2–19 in the United States have obesity (body mass index [BMI] kg/m^2 $\geq$95th percentile for age and sex) (7), and childhood obesity tracks into adulthood (8). Among children with obesity, reductions of BMI in childhood might decrease the risk of developing insulin resistance, dyslipidemia, and hypertension (9, 10), as well as have positive benefits for psychological well-being (11). To treat childhood obesity, coordinated action is needed in the places where children live, learn, and play. With 13.7 million U.S. children aged 2–19 already living with obesity (7), weight management services can help children achieve and maintain a healthy weight, and promote behavior change (12). A collective, multidisciplinary approach will likely require childhood obesity treatment and care management options delivered in community venues, clinics, and hospital-based settings, and involve different types of healthcare providers (13–16).

Clinical guidelines and recommendations exist to support childhood obesity prevention and management by healthcare providers, including the 2007 Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity (17), the 2017 Screening for Obesity in Children and Adolescents United States Preventive Services Task Force (USPSTF) Recommendation Statement (18), and the 2017 Endocrine Society Clinical Practice Guideline on Pediatric Obesity—Assessment, Treatment, and Prevention (19). Commonalities of these recommendations are that children be screened for obesity using BMI, and that children with obesity be referred to programs or services for the purpose of weight management. The Expert Committee recommendations promote staged prevention and treatment pathways, and the Endocrine Society also delineates clinical steps for management, whereas the USPSTF provides sufficient evidence to recommend children with obesity be referred to comprehensive behavioral interventions with moderate to high intensity, in order to promote a healthy weight status.

The implementation of these recommendations in practice likely vary, depending on factors, such as patient sociodemographics, intervention setting, payer type, and other key factors (13, 20–24). For example, referrals for pediatric weight management may include primary care providers, subspecialty providers, registered dietitians, physical or exercise therapists, health educators, behavioral counselors, mental health professionals, comprehensive, multidisciplinary pediatric weight management programs, and others. Such professionals are recognized as potential healthcare providers for children with obesity in the aforementioned recommendations. Children might also be referred to clinical subspecialists for management of comorbidities associated with obesity (25), such as those requiring management by endocrinologists or gastroenterologists due to comorbidities, such as type 2 diabetes, nonalcoholic fatty liver disease or gastroesophageal reflux disease (19, 26). Due to a lack of data beyond the local level, the current landscape of referral practices and management strategies for childhood obesity in the United States is not well understood. Exploring data that have more geographic diversity may be helpful in understanding the uptake of evidence-based practices regarding the management of childhood obesity across the nation. This paper aims to describe the management strategies and referral practices of clinicians who care for pediatric patients with obesity. We also explore clinician characteristics associated with these referrals.

METHODS

Design

This cross-sectional study used data from the 2017 *DocStyles* survey, a web-based panel survey of U.S. clinicians designed to further understand healthcare provider practices. *DocStyles* survey is administered by Porter Novelli Public Services, a public relations and social marketing firm.

Study Sample

Respondents were sampled from the SERMO Global Medical Panel—a global market research provider (27). From the SERMO panel, which included 51,000 primary care providers (PCPs, including internists), 12,700 Pediatricians, and 2,400 Nurse Practitioners, Porter Novelli set sample size quotas that included 1,000 primary care physicians (including family practitioners and internists), 250 pediatricians, 250 obstetrician/gynecologists, 250 nurse practitioners, 250 oncologists, 150 retail pharmacists, and 100 hospital pharmacists. When comparing physician respondents from *DocStyles* survey 2017 to physicians in the American Medical Association Physician Master File, survey respondents were more male (69.6 vs. 58.0%), slightly older (48.1 vs. 47.0 years), and practiced for a shorter duration (17.6 vs. 19.3 years). From June 8th to August 9th, 2017, responses were obtained (28). Panelists were verified via a double opt-in sign up process with telephone confirmation at their place of work. An honorarium of \$23–\$85 was paid to respondents for completing the survey, and was determined by the number of questions they were asked to complete.

Eligibility criteria for *DocStyles* survey 2017 included clinicians within the United States who have actively seen patients for at least 3 years in an individual, group, or hospital practice. There were 2,260 clinicians who completed the survey (**Figure 1**). For this particular analysis, questions were only asked of pediatricians, internists, family practitioners and nurse practitioners (n = 1,509). Furthermore, use of skip patterns narrowed the respondents to clinicians who reported caring for pediatric patients (age ≤17 years; n = 1,023). The final analytic sample consisted of 891 respondents, as 132 clinicians (12.9%) had missing data on referral to weight management programs for childhood obesity. These clinicians who were excluded from this study due to missing data did not differ by demographics, but differed by specialty [higher proportion of internists (27 vs. 13%) and nurse practitioners (27 vs. 15%)] and work setting [higher proportion of inpatient clinicians (23 vs. 5%)]. The CDC licensed the results of the *DocStyles* 2017 survey post-collection from Porter Novelli. Since personal identifiers were not included in the data files, IRB approval was not needed for this project because CDC was not engaged in human subjects research.

Outcome Measures

The primary outcomes for this analysis were clinician referrals to clinical specialists, behavioral specialists, and Weight Management Programs. The questions to clinicians were presented as follows: "The next few questions are about your referral practices for children with obesity (i.e., BMI ≥95th percentile). Among your patients aged 6–18 years with obesity, approximately what percentage do you refer to services or programs for the purpose of weight management?" Respondents provided a numeric value from 0 to 100. Subsequently, clinicians were asked: "What action(s) do you typically take for children with obesity (i.e., BMI ≥95th percentile) for the purpose of weight management?" Respondents could select all relevant options, which were not mutually exclusive. Response choices included: (1) Schedule a follow-up visit for obesity, or referral to (2) a subspecialty, such as endocrinology or gastroenterology; (3) a registered dietitian; (4) a behavioral/mental health

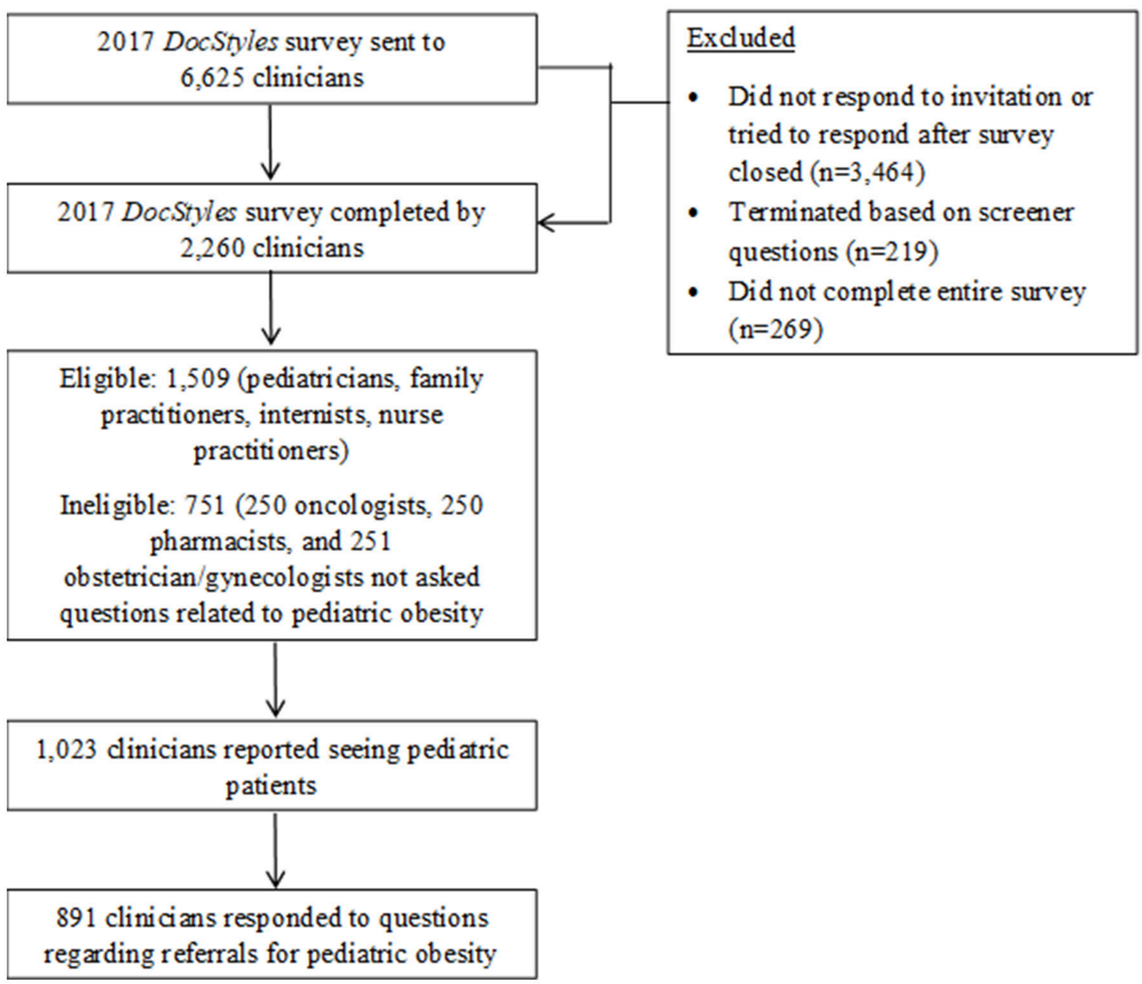

FIGURE 1 | Analytic sample flow chart for *DocStyles* survey, 2017.

profession; (5) a health educator/coach (6) a community-based weight management program/organization (e.g., YMCA, Weight Watchers); and (7) a clinic- or hospital-based weight management program/organization. Based on the response options, the main outcome variables for the analysis were the percentage of patients with obesity referred for services, and the types of referrals that clinicians typically made for children with obesity. Scheduling for a follow-up visit was considered a management strategy, while the other options were considered to be referrals.

Covariates

Covariates for these analyses were grouped into clinician, clinical practice, and reported patient characteristics. Clinician characteristics included clinician age (<45 or ≥45 years), gender (male and female), and race/ethnicity (non-Hispanic white, non-Hispanic Asian, and other). Age categories were determined by prior studies (29, 30) and respondent distribution. Clinical practice characteristics were comprised of practice location Census region (Northeast, South, Midwest, West), medical specialty (family practice, internal medicine, pediatrics, nurse practitioner), primary work setting (inpatient, individual outpatient, or group outpatient), teaching hospital privileges (yes or no), and number of well-child visits per week (<5, 5–14, or ≥15 visits, reported as a continuous variable, and categories were determined by distribution of the data). Clinicians reported on two characteristics of their patient population: income and weight status. They were asked to select the income category that best described the approximate household income of the majority of their patients. These responses were subsequently grouped into three categories based on distribution of the sample, and included low-income (<$50,000), middle-income ($50,000–<$100,000), and high-income (≥$100,000). Respondents also reported what percentage of their pediatric patients had obesity; these were categorized as <10, 10–<20, 20–<40, and ≥40% based on the data distribution.

Statistical Analysis

SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used to perform statistical analyses. Crude associations between reported referral and personal, clinical practice, and patient characteristics were assessed by chi-squared tests; the criterion for statistical significance was $p < 0.05$. A multivariable logistic regression model estimated the adjusted odds ratios (aOR) and 95% confidence intervals (CI) for characteristics associated with referral. All covariates (i.e., clinician, clinical practice, and reported patient characteristics) were included in one model after a diagnostic assessment did not reveal significant collinearity between variables.

RESULTS

Table 1 shows the clinician, clinical practice, and patient characteristics of the 891 clinicians in the analytic sample. The majority of respondent clinicians were white non-Hispanic (73%) and worked in a group outpatient setting (76%). Just over half of clinicians (54%) reported referring less than a quarter of their pediatric patients with obesity for the purposes of weight management (**Figure 2**). Additionally, 15% reported referring 25–<50% of their pediatric patients with obesity, and 17% referred 50–<75% of their pediatric patients. Only 15% referred ≥75% of their pediatric patients with obesity for weight management.

TABLE 1 | Characteristics of clinicians who see children, clinical practice, and patients, *DocStyles* survey 2017 ($N = 891$).

Clinicians characteristics	All respondents *n* (%)[a,b]
Total	891 (100)
AGE	
<45 years	357 (40)
≥45 years	534 (60)
GENDER	
Male	499 (56)
Female	392 (44)
RACE/ETHNICITY	
White, non-Hispanic	652 (73)
Asian, non-Hispanic	135 (15)
Other	104 (12)
CLINICAL PRACTICE CHARACTERISTICS	
Census region	
Northeast	196 (22)
South	319 (36)
Midwest	188 (21)
West	188 (21)
Specialty	
Family practitioner	420 (47)
Internist	113 (13)
Pediatrician	228 (26)
Nurse practitioner	130 (15)
Work setting	
Individual outpatient	170 (19)
Group outpatient	673 (76)
Inpatient	48 (5)
Teaching hospital privileges	
Yes	401 (45)
No	490 (55)
Number of well-child visits per week	
<5	190 (21)
5–14	324 (36)
≥15	377 (42)
CLINICIAN REPORTED PATIENT CHARACTERISTICS	
Patient income	
Low (<$50,000)	302 (34)
Middle ($50,000–<$100,000)	314 (35)
High (≥$100,000)	275 (31)
% Pediatric patients with obesity	
<10%	165 (19)
10–<20%	260 (29)
20–<40%	333 (37)
≥40%	133 (15)

[a]*Number and percentage indicates respondents who answered the question in the affirmative.* [b]*Due to rounding, the sum of percentages in each category may not exactly equal 100.*

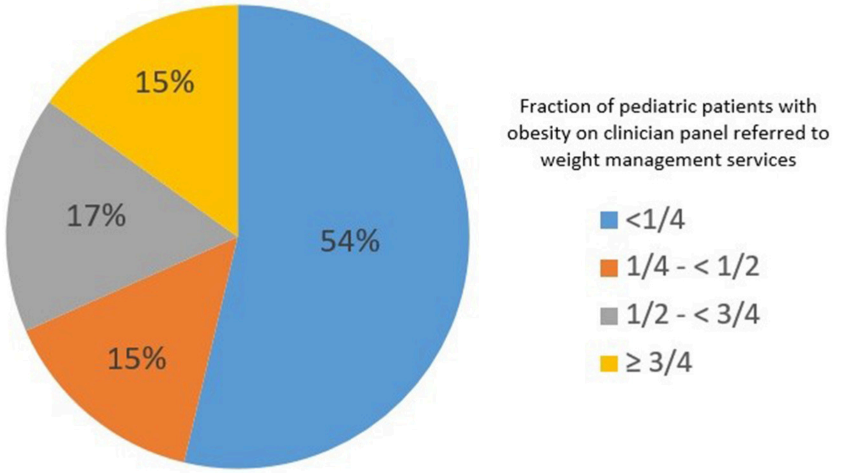

FIGURE 2 | Percentage of clinicians who refer pediatric patients with obesity for weight management services, *DocStyles* survey 2017 ($N = 891$).

Over two-thirds of clinicians (68%) scheduled pediatric patients for follow-up visits (**Table 2**). The most common clinical referral reported was to a registered dietitian (72%), followed by referral to a subspecialist (27%). The most common behavioral health referral was to a health educator/coach (26%) followed by behavioral/mental health professional (19%). Finally, approximately one-third of clinicians referred their pediatric patients with obesity to weight management programs, whether community-based (35%) or hospital/clinic-based (32%) (**Table 2**).

When we examined clinician characteristics, odds of clinical referrals to subspecialists were lower among clinicians ≥45 years of age (aOR = 0.7, 95% CI = 0.5–1.0) compared to clinicians <45 years (**Table 3**). Female clinicians had higher odds of referral to both community- and clinic/hospital-based weight management programs (aOR = 1.4, 95% CI = 1.0–2.0, and aOR = 1.5, 95% CI = 1.1–2.1, respectively).

Among the clinical practice characteristics, we found significant differences in referral practices by Census region and clinical subspecialty. Clinicians based in the West had higher adjusted odds of scheduling a follow-up visit vs. clinicians in the South (aOR = 1.8, 95% CI = 1.2–2.7). Odds of a clinical referral to a dietitian were higher in the Northeast and the Midwest vs. the South (aOR = 1.6, 95% CI = 1.0–2.4; aOR = 1.6, 95% CI = 1.1–2.5, respectively). Odds of referrals to a behavioral/mental health professional were higher in the Northeast compared to the South (aOR = 1.6; 95% CI = 1.0–2.6). Odds of referral to a hospital or clinic based weight management program were higher in in the Northeast and the Midwest vs. the South (aOR = 1.5, 95% CI = 1.0–2.2 and aOR = 1.6, 95% CI = 1.1–2.4, respectively). Clinical practice specialty was also associated with clinical referrals; family practitioners were less likely to refer to subspecialists compared to pediatricians (aOR = 0.5, 95% CI = 0.3–0.8). For behavioral referrals, all other specialties (family practitioners, internists, and nurse practitioners) had significantly higher odds of referrals to mental health professionals (aOR range: 2.4–3.5) or health educators (aOR range: 2.8–5.1) compared to pediatricians. Clinicians who primarily work in inpatient settings had higher odds of referral to health educators/coaches (aOR = 2.7, 95% CI = 1.4–5.3) compared to clinicians in group outpatient settings. Clinicians without teaching hospital privileges had lower odds of referring to a mental health professional (aOR = 0.7, 95% CI = 0.5–1.00) vs. clinicians with privileges. Finally, clinicians in practices that perform ≥5 well child visits per week had significantly higher odds of referral to subspecialists compared to those in practices that perform less than five per week (aOR: 1.7). Additionally, clinicians in practices that perform ≥15 well child visits per week had approximately twice the odds of a behavioral health referral (aOR range: 1.9–2.2) compared to those in practices that performed less than five per week.

Referral patterns also differed by clinician reported patient characteristics. When compared with clinicians serving high-income patient populations, clinicians serving low-income patient populations had lower odds of referral to a subspecialist (aOR = 0.6, 95% CI = 0.4–0.9). In addition, clinicians serving patients with middle-income populations had lower odds of scheduling a follow-up visit (aOR = 0.6; 95% CI = 0.5–0.9), but had higher odds of referral to a clinic/hospital-based weight management program (aOR = 1.9; 95% CI = 1.3–2.7). Odds of specific types of referrals did not differ based on the estimated percentage of children in the clinician's practice who had obesity.

DISCUSSION

Overall, about two-thirds of clinicians in this study reported scheduling patients for follow-up appointments as a management strategy for pediatric obesity. Approximately half of respondents reported referring less than one-quarter of their pediatric patients with obesity to services or programs

TABLE 2 | Characteristics of clinicians, clinical practice, and patients associated with referral practices, *DocStyles* survey 2017 ($N = 891$)[a].

	Clinical referral		Behavioral referral			Weight management program referral	
	Schedule follow-up visit, (%)	**Subspecialty, such as endocrinology or gastroenterology, (%)**	**Registered dietitian, (%)**	**Behavioral/ Mental health professional, (%)**	**Health educator/ Coach, (%)**	**Community-based weight management program, (%)**	**Clinic/Hospital based weight management program, (%)**
Total (*N* = 891)[b]	68	27	72	19	26	35	32
CLINICIANS CHARACTERISTICS							
Age							
<45 years (*n* = 357)	67	**31**	75	19	**30**	36	33
≥45 years (*n* = 534)	68	**24**	70	18	**23**	34	32
Gender							
Male (n=499)	66	25	70	19	27	**32**	**29**
Female (n=392)	70	30	75	18	24	**39**	**37**
Race/Ethnicity							
White, non-Hispanic (*n* = 652)	68	28	75	19	25	35	31
Asian, non-Hispanic (*n* = 135)	64	26	70	17	25	33	32
Other (*n* = 104)	70	22	65	17	33	39	39
CLINICAL PRACTICE CHARACTERISTICS							
Census region							
Northeast (*n* = 196)	**68**	**37**	**77**	24	25	31	**39**
South (*n* = 319)	**66**	**25**	**67**	16	29	35	**28**
Midwest (*n* = 188)	**62**	**22**	**77**	18	23	36	**37**
West (*n* = 188)	**76**	**24**	**72**	20	23	38	**28**
Specialty							
Family practitioner (*n* = 420)	68	**20**	68	19	**26**	32	**25**
Internist (*n* = 113)	64	**27**	72	24	**42**	40	**35**
Pediatrician (*n* = 250)	69	**38**	76	14	**15**	35	**44**
Nurse practitioner (*n* = 130)	66	**29**	78	22	**32**	40	**33**
Work setting							
Individual outpatient (*n* = 170)	67	22	69	17	**28**	38	28
Group outpatient (*n* = 673)	68	28	73	19	**23**	34	33
Inpatient (*n* = 48)	73	31	65	17	**52**	40	35
Teaching hospital privileges							
Yes (*n* = 401)	70	30	73	**22**	**29**	**40**	**41**
No (*n* = 490)	66	25	71	**16**	**23**	**30**	**25**
Number of well-child visits per week							
<5 (*n* = 190)	63	**18**	70	15	23	32	**28**
5–14 (*n* = 324)	69	**26**	70	19	29	32	**27**
≥15 (*n* = 377)	68	**33**	75	21	25	39	**39**
CLINICIAN REPORTED PATIENT CHARACTERISTICS							
Patient income							
Low (<$50,000) (*n* = 302)	**73**	**23**	74	18	26	35	**31**

(Continued)

TABLE 2 | Continued

	Clinical referral		Behavioral referral			Weight management program referral	
	Schedule follow-up visit, (%)	**Subspecialty, such as endocrinology or gastroenterology, (%)**	**Registered dietitian, (%)**	**Behavioral/ Mental health professional, (%)**	**Health educator/ Coach, (%)**	**Community-based weight management program, (%)**	**Clinic/Hospital based weight management program, (%)**
Middle ($50,000–<$100,000) (n=314)	**60**	**26**	72	19	27	37	**38**
High (≥$100,000) (*n* = 275)	**71**	**33**	70	20	24	32	**27**
% Pediatric patients with obesity							
<10%	71	24	70	21	**31**	38	33
10–<20%	65	29	76	17	**22**	32	32
20–<40%	66	29	73	19	**23**	33	35
≥40%	72	23	65	20	**33**	42	28

[a]Bold font indicates statistical significance based on chi-square test for report of referral to each option (selected or not selected), $P < 0.05$. [b]Number and percentage indicates respondents who answered the question in the affirmative.

for the purposes of weight management, and only 15% reported referring most (≥75%) of their pediatric patients with obesity.

The most common referral made among survey respondents was to registered dietitians, with almost three-quarters of clinicians reporting referral of children with obesity to this profession. Dietitians are specifically trained in nutrition and can be key members of multidisciplinary obesity management teams. A recent review found that for adults with type 2 diabetes, individual nutrition therapy conducted by dietitians resulted in better health outcomes, including a lower BMI, than care by other providers, such as physicians and nurses (31).

Approximately one-quarter of respondents reported referral to clinical subspecialists; similarly about one-quarter of surveyed clinicians also reported referral to health educators/coaches. However, we found that less than one in five reported referring pediatric patients with obesity to behavioral/mental health professionals. About one-third of clinicians referred pediatric patients with obesity to either a community-based or a clinic/hospital-based weight management programs. All of the aforementioned referral practices are potential referral options presented within the Expert Committee and USPSTF recommendations for childhood obesity. This study is the first to examine the frequency with which these referrals are made using data beyond one geographic location within the country. We also found that these referral practices differed based on clinician, clinical practice, and reported patient characteristics.

Clinician Characteristics

Older clinicians had lower odds of subspecialty referral compared to younger physicians in our study. A previous study of referral practices among primary care physicians found that years in practice, which likely correlates with physician age, was associated with lower subspecialist referral (32). Female clinicians in this study had higher odds of referral to both types of weight management programs. Women have been shown to be more likely to engage in preventive care, and more likely to make referrals to weight loss programs for adult patients with obesity to weight loss programs (33, 34). Our results are consistent with these findings, but demonstrated this association within a pediatric patient population with obesity.

Clinical Practice Characteristics

Respondents in the Northeast had higher odds of referrals to subspecialties, registered dietitians, behavioral/mental health professionals, and clinic/hospital-based weight management programs vs. those in the South. The Northeast region generally has a higher concentration of urban areas compared to other regions in the United States (35). Therefore, within this region resources for patients with obesity might be more attainable, with fewer geographic barriers, such as distance prohibiting access to weight management programs (36). Professionals, such as dietitians are more concentrated in the Northeast and Midwest (37). These factors could possibly contribute to the higher odds of referral to dietitians and clinic based weight management programs in the Midwest vs. the South.

Clinician specialty was also associated with some referrals, with all surveyed non-pediatric specialties having higher odds of behavioral referrals for childhood obesity, compared to pediatricians. Pediatricians are trained specifically to care for children and might have been taught about pediatric weight management while in training (38, 39). While self-efficacy for weight management holds value, evidence suggests non-traditional healthcare providers, such as health coaches (40) might be beneficial in pediatric weight management. In addition, inter-professional collaborations (i.e., between dietitians, exercise therapists, and others) are beneficial for childhood obesity management (17, 23). Family practitioners had lower odds of referral to clinical subspecialists, and to clinic/hospital-based weight management programs, compared to pediatricians. This is consistent with a prior study that also documented significant differences between the approaches of family practitioners and pediatricians in the treatment of children, with family physicians in that study having significantly lower odds of referral of

TABLE 3 | Adjusted Odds Ratios[a] of pediatric obesity referral practices by characteristics of clinicians, clinical practice, and patients, *DocStyles* survey 2017 (N = 891)[b].

	Clinical referral			Behavioral referral		Weight management program referral	
	Schedule follow-up visit, aOR (95% CI)[c]	**Subspecialty, such as endocrinology or gastroenterology, aOR (95% CI)**	**Registered dietitian, aOR (95% CI)**	**Behavioral/Mental health professional, aOR (95% CI)**	**Health educator/Coach, aOR (95% CI)**	**Community-based weight management program, aOR (95% CI)**	**Clinic/Hospital based weight management program, aOR (95% CI)**
CLINICIANS CHARACTERISTICS							
Age							
<45 years	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≥45 years	1.2 (0.8–1.6)	**0.7 (0.5–1.0)**	0.8 (0.6–1.1)	1.0 (0.7–1.5)	0.8 (0.6–1.1)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Gender							
Male	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Female	1.3 (0.9–1.8)	1.2 (0.9–1.7)	1.2 (0.8–1.6)	0.9 (0.6–1.4)	0.7 (0.5–1.1)	**1.4 (1.1–2.0)**	**1.5 (1.1–2.1)**
Race/Ethnicity							
White, non-Hispanic	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Asian, non-Hispanic	0.8 (0.6–1.3)	0.8 (0.5–1.2)	0.9 (0.6–1.3)	0.8 (0.5–1.3)	0.9 (0.6–1.4)	0.8 (0.5–1.3)	1.0 (0.7–1.6)
Other	1.0 (0.6–1.6)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.8 (0.5–1.5)	1.3 (0.8–2.1)	1.0 (0.7–1.6)	1.4 (0.9–2.2)
CLINICAL PRACTICE CHARACTERISTICS							
Census region							
Northeast	1.1 (0.7–1.6)	**1.5 (1.0–2.2)**	**1.6 (1.0–2.4)**	**1.6 (1.0–2.6)**	0.8 (0.5–1.2)	0.8 (0.5–1.1)	**1.5 (1.0–2.2)**
South	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Midwest	0.9 (0.6–1.3)	0.8 (0.5–1.3)	**1.6 (1.1–2.5)**	1.1 (0.6–1.7)	0.7 (0.4–1.1)	1.0 (0.7–1.5)	**1.6 (1.1–2.4)**
West	**1.8 (1.2–2.7)**	0.9 (0.6–1.3)	1.3 (0.9–1.9)	1.4 (0.8–2.2)	0.8 (0.5–1.2)	1.2 (0.8–1.8)	1.0 (0.7–1.5)
Specialty							
Family practitioner	1.2 (0.8–1.8)	**0.5 (0.3–0.8)**	0.7 (0.5–1.1)	**2.4 (1.4–4.0)**	**2.8 (1.7–4.5)**	1.2 (0.8–1.9)	**0.5 (0.3–0.8)**
Internist	0.9 (0.5–1.7)	0.8 (0.5–1.5)	1.0 (0.6–1.8)	**3.5 (1.8–6.8)**	**5.1 (2.7–9.4)**	1.7 (1.0–2.9)	0.8 (0.4–1.3)
Pediatrician	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Nurse practitioner	0.9 (0.5–1.5)	0.7 (0.4–1.3)	1.2 (0.6–2.1)	**3.0 (1.6–5.8)**	**4.2 (2.3–7.8)**	1.4 (0.8–2.4)	0.7 (0.4–1.2)
Work setting							
Individual outpatient	1.0 (0.7–1.5)	0.8 (0.5–1.3)	0.9 (0.6–1.4)	0.8 (0.5–1.3)	1.1 (0.7–1.7)	1.2 (0.8–1.8)	0.9 (0.6–1.4)
Group outpatient	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Inpatient	1.3 (0.7–2.6)	1.0 (0.5–2.0)	0.6 (0.3–1.2)	0.6 (0.3–1.5)	**2.7 (1.4–5.3)**	1.1 (0.6–2.0)	0.9 (0.5–1.7)
Teaching hospital privileges							
Yes	1.0	1.0	1.0	1.0	1.0	1.0	1.0
No	0.8 (0.6–1.1)	1.0 (0.7–1.4)	1.0 (0.7–1.4)	**0.7 (0.5–1.0)**	0.8 (0.5–1.1)	**0.6 (0.4–0.8)**	**0.5 (0.4–0.7)**
Number of well-child visits per week							
<5	1.0	1.0	1.0	1.0	1.0	1.0	1.0
5–14	1.3 (0.9–2.0)	**1.7 (1.0–2.6)**	1.0 (0.7–1.5)	1.3 (0.8–2.1)	1.4 (0.9–2.2)	1.0 (0.7–1.5)	0.9 (0.6–1.3)
≥15	1.3 (0.8–2.0)	**1.7 (1.0–2.9)**	1.2 (0.7–1.8)	**2.2 (1.3–3.7)**	**1.9 (1.2–3.1)**	1.5 (1.0–2.3)	1.1 (0.7–1.7)

(Continued)

TABLE 3 | Continued

	Clinical referral		Behavioral referral			Weight management program referral	
	Schedule follow-up visit, aOR (95% CI)[c]	**Subspecialty, such as endocrinology or gastroenterology, aOR (95% CI)**	**Registered dietitian, aOR (95% CI)**	**Behavioral/Mental health professional, aOR (95% CI)**	**Health educator/Coach, aOR (95% CI)**	**Community-based weight management program, aOR (95% CI)**	**Clinic/Hospital based weight management program, aOR (95% CI)**
CLINICIAN REPORTED PATIENT CHARACTERISTICS							
Patient income							
Low (<$50,000)	1.1 (0.8–1.6)	**0.6 (0.4–0.9)**	1.3 (0.9–1.9)	0.9 (0.6–1.4)	1.1 (0.8–1.7)	1.1 (0.80–1.63)	1.4 (0.9–2.00)
Middle ($50,000–≤$100,000)	**0.6 (0.5–0.9)**	0.8 (0.5–1.1)	1.1 (0.8–1.6)	0.9 (0.6–1.4)	1.2 (0.8–1.8)	1.3 (0.9–1.8)	**1.9 (1.3–2.7)**
High (≥$100,000)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
% Pediatric patients with obesity							
<10%	1.0	1.0	1.0	1.0	1.0	1.0	1.0
10–<20%	0.8 (0.5–1.2)	1.3 (0.8–2.0)	1.4 (0.9–2.1)	0.7 (0.4–1.2)	0.7 (0.4–1.1)	0.8 (0.5–1.2)	0.8 (0.5–1.3)
20–<40%	0.8 (0.5–1.2)	1.2 (0.8–1.9)	1.1 (0.7–1.7)	0.8 (0.5–1.4)	0.7 (0.5–1.1)	0.8 (0.5–1.2)	0.9 (0.6–1.4)
≥40%	1.0 (0.6–1.7)	0.9 (0.5–1.5)	0.7 (0.4–1.2)	0.9 (0.5–1.5)	1.0 (0.6–1.7)	1.0 (0.6–1.7)	0.7 (0.4–1.1)

[a]All provider personal, medical practice, and patient characteristics were included in one model for each referral option. [b]Bold font indicates statistical significance as 95% confidence interval does not include 1.0. [c]Adjusted odds ratio (95% confidence interval).

pediatric patients for further evaluation and management for weight related care (41).

Work setting and teaching hospital privileges were also associated with respondents' likelihood of behavioral referrals. Clinicians who practice inpatient had higher odds of referring to a health educator/coach in our study. These clinicians might be able to take advantage of inpatient health educators during patient admissions (42). Respondents without teaching hospital privileges had lower odds of referral to a behavioral/mental health professional and to clinic/hospital based weight management programs in the present study. It is possible that privileges with a teaching hospital could mean belonging to a referral network that facilitates patient access to such resources. For instance, a higher percentage of teaching hospitals offer psychiatric outpatient services compared to non-teaching hospitals (43).

In our study, the number of well-child visits per week per practice was associated with increased odds of referrals to clinical subspecialties and behavioral referrals. A greater number of well child visits per week might be indicative of a larger or more pediatric focused practice. In a study among primarily family practitioners, clinicians in solo or small group practice were less likely to make referrals compared to physicians in larger practices (32). Having larger patient volumes might mean less time per patient (44), and potentially more referrals.

Reported Patient Characteristics

In the present study, clinicians working with middle-income patients were less likely to schedule patients for a follow-up visit; however, they also had higher odds of referring their patients externally to clinic/hospital-based weight management programs. A previous study demonstrated that attending a pediatric weight management program after referral is associated with socioeconomic status and insurance status (45). However, data have not formally shown whether perceived likelihood of patient attendance affects clinician odds of referral. In addition, clinicians who reported caring for low-income patients had a lower odds of referrals to clinical subspecialists. It might be more difficult for patients with lower incomes to find subspecialists who will take their insurance, such as Medicaid (46–48).

Strengths and Limitations

This study is subject to several limitations. First, the *DocStyles* survey is a panel survey based on quota sampling, resulting in a sample that is not necessarily representative of the population, and thus the findings might not be generalizable to clinicians nationwide. In addition, survey respondents may differ compared to those who did not participate in the survey. However, this study uses a sample with more geographic diversity than previous samples rather than a limited local sample. Second, *DocStyles* data are based on the report of clinicians both about their personal practices and perceptions about their patient population; no objective measures were obtained. Thus, their responses are subject to reporting biases. Nevertheless, querying clinicians directly can provide insight into what influences their referral practices. Finally, the possibility exists that there are factors that confound or modify the association between clinician, clinical practice, or clinician reported patient characteristics and referral type that might not have been accounted for; for example, location in an urban or rural environment. Despite these limitations, this study adds valuable information to the literature by describing current practice and characteristics that may influence childhood obesity referral practices of clinicians in the United States.

CONCLUSION

In this study, clinicians caring for children with obesity referred patients to a wide range of providers and services for the purposes of weight management; although half of clinicians referred less than one-quarter of their pediatric patients with obesity for these interventions. Most respondents referred pediatric patients with obesity to dietitians, and the majority scheduled follow-up appointments, which is a recommended practice. Clinicians also referred to clinic-based weight management programs, clinical subspecialists, health educators, and behavioral/mental health professionals with varying frequencies, ranging from 19% for behavioral/mental health professionals to 72% for registered dieticians. Referrals were generally consistent with recommendations from the AAP or USPSTF to address the complex nature of childhood obesity management. Our findings contribute to understanding the current landscape of referral practices and management strategies of clinicians who care for pediatric patients with obesity. Our data also provide insight into the clinician, clinical practice, and reported patient characteristics associated with childhood obesity referral types. Understanding referral patterns and management strategies can help inform strategies to improve the uptake of current recommended care.

AUTHOR CONTRIBUTIONS

OI, AG, CD, SP, MH, EL, and HB wrote and contributed in the preparation of this manuscript. AG, CD, MH, and HB formulated research questions explored in this study, and contributed subject matter expertise. OI, SP, and EL engaged in statistical analysis of the survey data.

ACKNOWLEDGMENTS

We are appreciative for the contributions of Dr. Brook Belay toward the preparation of this manuscript.

REFERENCES

1. Akinbami LJ, Rossen LM, Fakhouri THI, Fryar CD. Asthma prevalence trends by weight status among US children aged 2–19 years, 1988–2014. *Pediatr Obes*. (2017) 13:393–6. doi: 10.1111/ijpo.12246
2. Bocca G, Ongering EC, Stolk RP, Sauer PJJ. Insulin resistance and cardiovascular risk factors in 3- to 5-year-old overweight or obese children. *Horm Res Paediatr*. (2013) 80:201–6. doi: 10.1159/000354662
3. Mazor-Aronovitch K, Lotan D, Modan-Moses D, Fradkin A, Pinhas-Hamiel O. Blood pressure in obese and overweight children and adolescents. *Isr Med Assoc J*. (2014) 16:157–61.
4. Pont SJ, Puhl R, Cook SR, Slusser W, Section on Obesity, Obesity Society. Stigma experienced by children and adolescents with obesity. *Pediatrics* (2017) 140:e20173034. doi: 10.1542/peds.2017-3034
5. Sikorski C, Luppa M, Luck T, Riedel-Heller SG. Weight stigma "gets under the skin"-evidence for an adapted psychological mediation framework: a systematic review. *Obesity (Silver Spring)* (2015) 23:266–76. doi: 10.1002/oby.20952
6. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med*. (2015) 373:1307–17. doi: 10.1056/NEJMoa1502821
7. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA* (2018) 319:1723–5. doi: 10.1001/jama.2018.3060
8. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev*. (2016) 17:95–107. doi: 10.1111/obr.12334
9. Kirk S, Zeller M, Claytor R, Santangelo M, Khoury PR, Daniels SR. The relationship of health outcomes to improvement in BMI in children and adolescents. *Obes Res*. (2005) 13:876–82. doi: 10.1038/oby.2005.101
10. O'Connor EA, Evans CV, Burda BU, Walsh ES, Eder M, Lozano P. Screening for obesity and intervention for weight management in children and adolescents: evidence report and systematic review for the US Preventive Services Task Force. *JAMA* (2017) 317:2427–44. doi: 10.1001/jama.2017.0332
11. Lloyd-Richardson EE, Jelalian E, Sato AF, Hart CN, Mehlenbeck R, Wing RR. Two-year follow-up of an adolescent behavioral weight control intervention. *Pediatrics* (2012) 130:e281–8. doi: 10.1542/peds.2011-3283
12. Wilfley DE, Staiano AE, Altman M, Lindros J, Lima A, Hassink SG, et al. Improving access and systems of care for evidence-based childhood obesity treatment: conference key findings and next steps. *Obesity (Silver Spring)* (2017) 25:16–29. doi: 10.1002/oby.21712
13. Brown CL, Perrin EM. Obesity prevention and treatment in primary care. *Acad Pediatr*. (2018) 18:736–45. doi: 10.1016/j.acap.2018.05.004
14. Katzmarzyk PT, Barlow S, Bouchard C, Catalano PM, Hsia DS, Inge TH, et al. An evolving scientific basis for the prevention and treatment of pediatric obesity. *Int J Obes (Lond)*. (2014) 38:887–905. doi: 10.1038/ijo.2014.49
15. Wang Y, Cai L, Wu Y, Wilson RF, Weston C, Fawole O, et al. What childhood obesity prevention programmes work? A systematic review and meta-analysis. *Obes Rev*. (2015) 16:547–65. doi: 10.1111/obr.12277
16. Wu Y, Lau BD, Bleich S, Cheskin L, Boult C, Segal JB, et al. AHRQ future research needs papers. In: *Future Research Needs for Childhood Obesity Prevention Programs: Identification of Future Research Needs From Comparative Effectiveness Review No. 115*. Rockville, MD: Agency for Healthcare Research and Quality (US) (2013).
17. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* (2007) 120 Suppl. 4:S164–92. doi: 10.1542/peds.2007-2329C
18. Grossman DC, Bibbins-Domingo K, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, et al. Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA* (2017) 317:2417–26. doi: 10.1001/jama.2017.6803
19. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. (2017) 102:709–57. doi: 10.1210/jc.2016-2573
20. Bhuyan SS, Chandak A, Smith P, Carlton EL, Duncan K, Gentry D. Integration of public health and primary care: a systematic review of the current literature in primary care physician mediated childhood obesity interventions. *Obes Res Clin Pract*. (2015) 9:539–52. doi: 10.1016/j.orcp.2015.07.005
21. Lederer AM, King MH, Sovinski D, Seo DC, Kim N. The relationship between school-level characteristics and implementation fidelity of a coordinated school health childhood obesity prevention intervention. *J Sch Health* (2015) 85:8–16. doi: 10.1111/josh.12221

22. Simpson LA, Cooper J. Paying for obesity: a changing landscape. *Pediatrics* (2009) 123 Suppl. 5:S301–7. doi: 10.1542/peds.2008-2780I
23. Rhee KE, Kessl S, Lindback S, Littman M, El-Kareh RE. Provider views on childhood obesity management in primary care settings: a mixed methods analysis. *BMC Health Serv Res*. (2018) 18:55. doi: 10.1186/s12913-018-2870-y
24. Rausch JC, Perito ER, Hametz P. Obesity prevention, screening, and treatment: practices of pediatric providers since the 2007 expert committee recommendations. *Clin Pediatr (Phila)*. (2011) 50:434–41. doi: 10.1177/0009922810394833
25. Estrada E, Eneli I, Hampl S, Mietus-Snyder M, Mirza N, Rhodes E, et al. Children's Hospital Association consensus statements for comorbidities of childhood obesity. *Child Obes*. (2014) 10:304–17. doi: 10.1089/chi.2013.0120
26. Huang JS, Barlow SE, Quiros-Tejeira RE, Scheimann A, Skelton J, Suskind D, et al. Childhood obesity for pediatric gastroenterologists. *J Pediatr Gastroenterol Nutr*. (2013) 56:99–109. doi: 10.1097/MPG.0b013e31826d3c62
27. SERMO. *What is SERMO?* (2018). Available online at: http://www.sermo.com/what-is-sermo/overview
28. Porter Novelli Public Services. *DocStyles 2017 Methodology*. Washington, DC: Deanne Weber (2017).
29. VanFrank BK, Park S, Foltz JL, McGuire LC, Harris DM. Physician characteristics associated with sugar-sweetened beverage counseling practices. *Am J Health Promot*. (2016) 32:1365–74. doi: 10.1177/0890117116680472
30. Quader ZS, Cogswell ME, Fang J, Coleman King SM, Merritt RK. Changes in primary healthcare providers' attitudes and counseling behaviors related to dietary sodium reduction, DocStyles 2010 and 2015. *PLoS ONE* (2017) 12:e0177693. doi: 10.1371/journal.pone.0177693
31. Moller G, Andersen HK, Snorgaard O. A systematic review and meta-analysis of nutrition therapy compared with dietary advice in patients with type 2 diabetes. *Am J Clin Nutr*. (2017) 106:1394–400. doi: 10.3945/ajcn.116.139626
32. Forrest CB, Nutting PA, von Schrader S, Rohde C, Starfield B. Primary care physician specialty referral decision making: patient, physician, and health care system determinants. *Med Decis Making* (2006) 26:76–85. doi: 10.1177/0272989X05284110
33. Henderson JT, Weisman CS. Physician gender effects on preventive screening and counseling: an analysis of male and female patients' health care experiences. *Med Care* (2001) 39:1281–92.
34. Dutton GR, Herman KG, Tan F, Goble M, Dancer-Brown M, Van Vessem N, et al. Patient and physician characteristics associated with the provision of weight loss counseling in primary care. *Obes Res Clin Pract*. (2014) 8:e123–30. doi: 10.1016/j.orcp.2012.12.004
35. Bureau USC. *Metropolitan and Micropolitan Areas of the United States and Puerto Rico*. (2009). Available online at: https://www2.census.gov/geo/maps/metroarea/us_wall/Dec_2009/cbsa_us_1209_large.gif
36. Ambler KA, Hagedorn DW, Ball GD. Referrals for pediatric weight management: the importance of proximity. *BMC Health Serv Res*. (2010) 10:302. doi: 10.1186/1472-6963-10-302
37. Bureau of Labor Statistics USDoL. *29-1031 Dietitians and Nutritionists. Occupational Employment and Wage* (2017). Available online at: https://www.bls.gov/oes/current/oes291031.htm
38. Jacobson D, Gance-Cleveland B. A systematic review of primary healthcare provider education and training using the Chronic Care Model for childhood obesity. *Obes Rev*. (2011) 12:e244–56. doi: 10.1111/j.1467-789X.2010.00789.x
39. Perrin EM, Vann JC, Lazorick S, Ammerman A, Teplin S, Flower K, et al. Bolstering confidence in obesity prevention and treatment counseling for resident and community pediatricians. *Patient Educ Couns*. (2008) 73:179–85. doi: 10.1016/j.pec.2008.07.025
40. Rice KG, Jumamil RB, Jabour SM, Cheng JK. Role of health coaches in pediatric weight management. *Clin Pediatr (Phila)*. (2017) 56:162–70. doi: 10.1177/0009922816645515
41. Huang TT, Borowski LA, Liu B, Galuska DA, Ballard-Barbash R, Yanovski SZ, et al. Pediatricians' and family physicians' weight-related care of children in the U.S. *Am J Prev Med*. (2011) 41:24–32. doi: 10.1016/j.amepre.2011.03.01
42. Bureau of Labor Statistics USDoL. *Health Educators and Community Health Workers. Occupational Outlook Handbook* (2016). Available online at: https://www.bls.gov/OOH/community-and-social-service/health-educators.htm#tab-3
43. Grover A, Slavin PL, Willson P. The economics of academic medical centers. *N Engl J Med*. (2014) 370:2360–2. doi: 10.1056/NEJMp1403609
44. Kikano GE, Zyzanski SJ, Gotler RS, Stange KC. High-volume practice: are there trade-offs? *Fam Pract Manag*. (2000) 7:63–4.
45. Shaffer LA, Brothers KB, Burkhead TA, Yeager R, Myers JA, Sweeney B. Factors associated with attendance after referral to a pediatric weight management program. *J Pediatr*. (2016) 172:35–9. doi: 10.1016/j.jpeds.2016.02.011
46. Cook NL, Hicks LS, O'Malley AJ, Keegan T, Guadagnoli E, Landon BE Access to specialty care and medical services in community health centers. *Health Aff (Millwood)* (2007) 26:1459–68. doi: 10.1377/hlthaff.26.5.1459
47. Forrest CB, Shadmi E, Nutting PA, Starfield B. Specialty referral completion among primary care patients: results from the ASPN Referral Study. *Ann Fam Med*. (2007) 5:361–7. doi: 10.1370/afm.703
48. Office USGA. *Most Physicians Serve Covered Children but Have Difficulty Referring Them for Specialty Care*. Medicaid and CHIP (2011). Available online at: https://www.gao.gov/products/GAO-11-624

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 12 April 2018
doi: 10.3389/fped.2018.00101

Check for updates

Shape-Up and Eat Right Families Pilot Program: Feasibility of a Weight Management Shared Medical Appointment Model in African-Americans With Obesity at an Urban Academic Medical Center

Gitanjali Srivastava[1], Kenya D. Palmer[1], Kathy A. Ireland[2], Ashley C. McCarthy[1], Kate E. Donovan[2], Aaron J. Manders[2], Juhee McDougal[3], Carine M. Lenders[2] and Caroline M. Apovian[1]*

[1] Nutrition and Weight Management Research Center, Boston Medical Center, Department of Medicine, Section of Endocrinology, Diabetes, Nutrition and Weight Management, Boston University School of Medicine, Boston, MA, United States, [2] Nutrition and Fitness for Life Program, Boston Medical Center, Department of Pediatrics, Boston University School of Medicine, Boston, MA, United States, [3] Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA, United States

OPEN ACCESS

Edited by:
Fatima Cody Stanford, Harvard Medical School, United States

Reviewed by:
Tiffany M. Powell-Wiley, National Institutes of Health (NIH), United States
Hellas Cena, University of Pavia, Italy

****Correspondence:***
Gitanjali Srivastava
gitanjali.srivastava@bmc.org

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *29 January 2018*
Accepted: *27 March 2018*
Published: *12 April 2018*

Citation:
Srivastava G, Palmer KD, Ireland KA, McCarthy AC, Donovan KE, Manders AJ, McDougal J, Lenders CM and Apovian CM (2018) Shape-Up and Eat Right Families Pilot Program: Feasibility of a Weight Management Shared Medical Appointment Model in African-Americans With Obesity at an Urban Academic Medical Center. Front. Pediatr. 6:101. doi: 10.3389/fped.2018.00101

Objectives: Disparities in obesity care exist among African-American children and adults. We sought to test the feasibility of a pilot program, a 1-year family-based intervention for African-American families with obesity [shape up and eat right (SUPER)], adopting the shared medical appointment model (SMA) at an urban safety net hospital.

Outcomes: Primary outcomes: (1) family attendance rate and (2) program satisfaction. Secondary outcomes: change in body mass index (BMI), eating behaviors, and sedentary activity.

Methods: Adult parents (BMI $\geq$ 25 kg/m^2) $\geq$18 years and their child(ren) (BMI $\geq$ 85th percentile) ages 6–12 years from adult or pediatric weight management clinics were recruited. One group visit per month (n = 12) consisting of a nutrition and exercise component was led by a nurse practitioner and registered dietitian. Height and weight were recorded during each visit. Participants were queried on program satisfaction, food logs and exercise journals, Food Stamp Program's Food Behavior, and the Expanded Food and Nutrition Education Program food checklists.

Results: Thirteen participants from lower socioeconomic zip codes consented [n = 5 mothers mean age 33 years, BMI of 47.4 kg/m^2 (31.4–73.6 kg/m^2); n = 8 children; mean age 9 years, BMI of 97.6th percentile (94–99th percentile); 60% enrolled in state Medicaid]. Average individual attendance was 23.4% (14–43%; n = 13); monthly session attendance rates declined from 100 to 40% by program completion; two families completed the program in entirety. Program was rated (n = 5 adults) very satisfactory (40%) and extremely satisfactory (60%). Pre-intervention, families rated their eating habits as fair and reported consuming sugar-sweetened beverages or sports drinks, more so than watching more than 1 h of television ($p < 0.002$) or video game/computer activity ($p < 0.006$) and consuming carbonated sodas ($p < 0.004$). Post-intervention, reducing salt intake was the only statistically significant variable ($p < 0.029$), while children watched fewer hours of television and spent less time playing video games (from average 2 to 3 h daily; $p < 0.03$).

Conclusion: Attendance was lower than expected though children seemed to decrease screen time and the program was rated satisfactory. Reported socioeconomic barriers precluded families from attending most sessions. Future reiterations of the intervention could be enhanced with community engagement strategies to increase participant retention.

Keywords: shape-up and eat right families, weight loss in ethnic minorities, shared medical appointments, family-based weight loss, disparities to obesity care, maternal-child health, childhood obesity

INTRODUCTION

Obesity causes significant cardiovascular disease, diabetes, hypertension, and overall morbidity and mortality in the United States (US) (1, 2). Over one-third of US adults are afflicted with obesity (35% men and 40% women) and specifically women, not men, had worsening disease severity and progression to class III [body mass index (BMI) ≥40 kg/m^2] between 2005 and 2014 (3). About 18 and 7.9% of children and adolescents have obesity and severe obesity (≥120% of 95th percentile for BMI; class II and class III obesity) respectively (4). There also has been a rise in obesity in adolescents between the ages of 16–19 years with 41.5% having obesity and 4.5% meeting criteria for class III obesity (>140% of 95th percentile for BMI); children ages 6–11 years have had similar increase in obesity prevalence to 37.3% with respective 12.8% meeting criteria for class II and III obesity (4). In particular, in the US, the epidemic is marked by racial and ethnic disparities: non-Hispanic Black (15.8%) adolescents have the highest prevalence of this disease than non-Hispanic Whites (13.1%), non-Hispanic other race or multi-race (10.9%), and Hispanic (15.2%) adolescents with obesity (5). A lower percentage of non-Hispanic Blacks (35%) seek weight loss treatments compared to their non-Hispanic White counterparts (39%) (6); non-Hispanic Blacks are also more likely to avoid care (OR 0.49, 95% CI 0.26–0.90) and less likely to initiate weight loss discussion with their providers than non-Hispanic Whites (7). Persistent barriers and disparities to care among racial/ethnic minorities exist likely due to a combinatory effect of social, economic, biological, and environmental factors affecting macro- and micro-environments (8) with US medical professionals not adept or trained at addressing the complexity of care and higher attrition rates for medical weight loss visits (9–12).

As a result, it becomes more essential to evaluate novel effective obesity-care delivery models among various populations. In regards to chronic diseases and obesity, shared medical appointments (SMAs) are innovative, patient-receptive, cost-effective methods of clinical practice (13–16) with a family-based approach particularily utilized for pediatric interventions, such as in childhood obesity (17, 18). SMAs are a redesign of chronic care models where groups of patients (8–20) are seen by a multidisciplinary team in 1 h in efforts to improve clinic throughput and efficiency and have shown improved cardiovascular benefit and quality improvement in diabetes management (19). These group-based patient visits address the gaps in knowledge, skills, and support necessary to maintain overall health and well-being, while increasing the time allocated to discuss lifestyle modification and healthy behaviors, especially in the context of a busy clinical practice where an individual visits may last only 15–20 min (13). Moreover, in an effort to increase accessibility to care and address disparities, SMAs have been adopted as novel methods to address those needs among healthcare systems (20). However, to date, SMAs have not been studied in challenging or culturally relevant populations, such as in African-Americans, where attrition rates are typically higher and patients often present with decreased literacy, non-adherence to recommendations, and transportation concerns, along with patient–physician weight bias, all of which present remarkable barriers to effective treatment for obesity (21–23). SMAs may provide burgeoning solutions to more effective care for these populations in the long-term through group engagement, where individuals may identify themselves with others of similar background and through use of family friendly tools to enhance motivational change. Furthermore, previous studies evaluating group medical visits have shown the shift in focus of the provider to that of an adjudicator advocating self-care norms based on medical knowledge in the context of the patient's lived experience and subsequently the patient disseminating these norms to others within the family unit (24). Medical group visits may have tangible benefits to bridging challenging social needs, complex chronic diseases, and improving patient–provider experiences (25). Additionally, SMAs are typically age-specific, targeting either adult or pediatric patients (but not both) with specific disease process or health goals, rather than being an all-inclusive design with common health targets. Thus, we sought to determine feasibility of a unique monthly parent–child-based weight loss intervention among African-American families utilizing a novel family centered SMA model at an adult and pediatric weight management center associated with an urban safety net academic hospital.

MATERIALS AND METHODS

Shape-up and eat right (SUPER) families was a pilot program to identify the feasibility of a family-based multidisciplinary group program for weight loss at Boston Medical Center (BMC) over a period of 1 year to foster healthy eating and exercise patterns for the entire family. The study was a collaboration between two weight management programs at BMC: a pediatric program, the nutrition and fitness for life (NFL) and an adult program, the nutrition and weight management center (NWMC). The primary outcomes were: (1) family attendance rate and (2) satisfaction with the program. Secondary outcomes included (1) change in BMI and (2) change in eating and sedentary behaviors.

Recruitment

The study was approved by the BMC/Boston University Medical Campus institution review board. It was supported by the Vela Foundation. Inclusion criteria were as follows: African-American parents ≥18 years from the NWMC with either overweight or obesity (BMI ≥ 25 kg/m^2) with one or more children aged 6–12 years with at least overweight status (BMI ≥ 85th percentile for weight and height based on the Centers for Disease Control (CDC)′s BMI Percentile Calculator for Child and Teen [http://nccd.cdc.gov/dnpabmi/]) or if the parent and/or guardian from the NWMC had a child currently being treated at the NFL program or if a child from NFL had a parent with overweight or obesity who may have not been part of NWMC. Exclusion criteria were as follows: (1) families not currently enrolled in either NFL or NWMC, (2) primary language other than English, (3) inability or not willing to provide informed consent/assent, (4) ethnicity other than African-American, and (5) non-overweight or obesity in adult or child. Informed consent was obtained from parents of children at the time of enrollment and children aged 6–12 years provided assent. Once consent was obtained, all contact information was updated. The initial contact was made in the respective clinic or telephone based. Demographic information querying zip code, race, ethnicity, level of education, primary source of income, employment status, insurance coverage, health of household members, and number residing in the household were collected. An abridged self-reported physical activity questionnaire modified from PAQ-C and PAQ-A (26) was also completed by telephone, assisted by the nurse practitioner, with the purpose of guiding exercise education and physical activity component of the group sessions. The participants were then notified of the first group visit by phone, email, and/or postal mail. The pilot program aimed to enroll at least six families (at least one adult parent/guardian and one child) based on allocated funding from the Vela Foundation. Because families were recruited directly from either NFL or NWMC and this was a feasibility study, there was no randomization. To protect the children participating in this study, children were not separated from the parents. All materials provided to the children were "child-friendly," while adult materials were written at a fifth grade reading level. All program visits occurred at BMC.

Monthly Group Visits (Visit #1–11)

There were 12 monthly 60–90 min sessions scheduled over a period of 1 year. A nurse practitioner with a Masters in Exercise Science, registered dietitian, and research coordinator were present at each group. A routine medical intake was completed by the nurse practitioner during the initial visit. Attendance was recorded at each visit. During monthly group visits, anthropometric measurements (height/weight) were taken for both adults and children. The Food Stamp Program's Food Behavior Checklist (FBC) (27), which measures basic dietary behaviors, including frequency of fruit, vegetables, juice and low-fat dairy consumption, food insecurity, shopping, and cooking techniques, was administered at the first and last group session to assess changes in dietary behavior. A second questionnaire, The Expanded Food and Nutrition Education Program (EFNEP) Food Checklist (28–31), which evaluates the way families plan and prepare food and assesses sedentary and screen-time behaviors in children was also administered during the first and last group session. Adult participants were encouraged to use a free pedometer application if they had a smartphone; all families were provided a pedometer. All participants were given a food journal and a log to record their daily steps as well as a physical activity goal-setting worksheet. Degree of satisfaction was assessed using a validated five-point satisfactory Likert scale (32) at the end of each group visit and the end of the program. A mid-point survey was collected at 6 months to determine if program adjustments were needed. Families were contacted *via* telephone, email, and postal mail between visits.

Group visits included topics for nutrition, exercise, and stress management. Sessions began with a 20–30 min of exercise training (body weight/calisthenics) including moderate cardiovascular exercise led by a nurse practitioner trained in exercise science. Physical activity and exercise education were adapted from the guidelines promoted by the American College of Sports Medicine (ACSM) and the CDC. Workouts included a dynamic warm up and a combination of calisthenics (burpees, alligator walks, kicks, jumps) and body weight exercises (push-ups, lunges, and plank exercises). Participants were monitored by clinical study staff for any exercise-related adverse events and were asked to report during and after exercise if they were experiencing any chest pain, dizziness, leg pain, calf pain, or hip pain. Families were expected to do these exercises on their own as a family for 2–3 times per week with written explanations of the workouts provided upon request. Families were also expected to perform moderate-to-vigorous cardiovascular exercise 2–3 times weekly to achieve the ACSM/CDC recommended minimal levels of physical activity weekly. Specific, measurable, attainable, relevant/realistic, time-based short-term and long-term goal worksheets were also provided to patients during each visit, along with pictures and description of potential exercises which could be conducted within the home without the need for access to a gym, to help improve dietary intake and physical activity.

The second part of each session was devoted to nutrition education and counseling led by the dietitian. This included the basics of healthy eating (macronutrient content and calories), options for navigating dietary changes with children, plus optional healthy cooking demonstrations biweekly located at the demonstration kitchen on campus. The nutrition curriculum utilized in this pilot study was adapted from myplate.gov "10 Tips Nutrition Education series" and developed by NFL's registered dietitians. Information was adapted and provided in an age appropriate format.

Attendance was calculated by totaling the number of group visits completed, divided by the number of group visits offered. Satisfaction was measured *via* survey using a 1–5 Likert scale (32). Weight status was measured by comparing the height and weight from baseline to the end of the program. SPSS program was used for descriptive statistical analysis of the data.

Final Visit (Visit #12)

The final SUPER-families visit concluded the study. During this visit, families completed a final EFNAP and FBC program satisfaction questionnaires; and final heights and weights were recorded. Participants were also asked to identify long-term family dietary, nutrition, and/or stress-related goals. FitBits® were distributed as a reward for completion of the program.

Retention

Families were sent at least three reminder phone calls from study staff and letters prior to each group visit. If a family missed a session, every effort was made to contact the family, identify the reason, and encourage participation in the next session.

RESULTS

Demographics

Though a total of initial six families consented to participation, one family canceled on start date. Thus, a total of five families [five adult parents (all mothers though fathers and grandparents/and or guardians were also invited)] and eight children consented to the program and were present at initiation of the intervention. Adult average age was 33 years with average BMI of 47.4 kg/m^2 (31.4–73.6 kg/m^2). Average age for the children was 9 years with average BMI of 97.6th percentile (94th–99th percentile). All participants were of African-American descent living in an urban metropolitan area in lower socioeconomic zip codes; 60% of participants were enrolled in Mass Health Medicaid program. The highest educational degree attained by any of the parents was a college degree ($n = 2$); one family's source of child support was food stamps. All of the families spoke English as their primary language.

Primary Outcomes: Attendance Rates and Program Satisfaction

Attendance was lower than expected. Three families completed some of the sessions and two families completed the entire 12-month program. Individual attendance ranged from 14 to 43% (average 23.4%; $n = 13$) with session attendance rates declining from 100 to 40% by the end of the program. Parents were queried about barriers to attendance; the perceived barriers reported by 60% of the families included time conflicts due to other family member activities, transportation, loss of employment/housing, moving, new birth, and lack of personal time. Satisfaction survey ($n = 5$ adults) showed that 40% of the parents were very satisfied and 60% were extremely satisfied with the monthly sessions.

Secondary Outcomes: Change in BMI, Eating, and Sedentary Behaviors

Change in BMI (**Figure 1**) was calculated for the families completing the study. Adult mothers had an average BMI decrease of −1.71 kg/m^2 (range: −10.0 to 3.26 kg/m^2) and the children experienced an average BMI decrease of −2.6 kg/m^2 (range: −3.8 to −1.4 kg/m^2). There were no statistically significant differences in these outcomes, however ($p > 0.05$). Changes in eating behaviors were assessed based on families completing both pre- and post-questionnaires, food journals, and written feedback at the end of the sessions.

Eating and Food Behaviors Questionnaires

Prior to the intervention, families reported drinking milk often, eating an average of at least one serving of fruit and vegetable per day, having an average of at least one serving of fish daily, and rating their eating habits as fair (average rating 3.1, 1 = poor; 10 = excellent); the differences in these reported behaviors post-intervention were not statistically significant. Upon initial visit, families were less likely to have meat or dairy sit out for more than 2 h ($p < 0.002$) or thaw frozen foods at room temperature ($p < 0.0005$; **Figure 2**). Comparing prices was the highest variable affecting eating behaviors among the families with an inclination toward choosing healthy foods for the family (**Figure 2**). Planning meals, shopping with a list, and reading food labels were less likely to occur among the families. Most of the families had children who ate within 2 h of waking up. Families reported consuming 2.4 servings daily of sugar-sweetened beverages or sports drinks, more so than watching more than 1 h of television ($p < 0.002$) or video game/computer activity ($p < 0.006$) and consuming carbonated sodas ($p < 0.004$). The consumption of carbonated sodas (EFNEP checklist provided images of carbonated sodas on the questionnaire) was low among all of the families [an answer of "1" (serving) was reported]. No statistically significant changes were noted among frequency of sugar-sweetened beverage or soda consumption (**Figure 3**).

Reducing table salt when preparing food post-intervention was statistically significant ($p < 0.029$; data for families pre- and post-survey completers; **Figure 3**). Results from the EFNEP Food Checklist also showed that children watched fewer hours of television and spent less time playing video games (from average 3 to 2 h daily; $p < 0.03$ for survey completers; **Figure 3**) and reported an increase in sports participation after the intervention. No statistically significant changes were noted among frequency of sugar-sweetened beverage or soda consumption based on questionnaire results (**Figure 3**).

Food Journals and Written Feedback

Though the questionnaires post-intervention did not show statistically significant changes associated with frequency of sugar-sweetened or carbonated beverage consumption, patient-reported changes in behavior based on food journals, and written feedback were favorable indicating a change to ingesting less fruit drinks, sports drinks, or punch and increasing servings of fruit from 1 to 2 per day. Families reported healthier food habits,

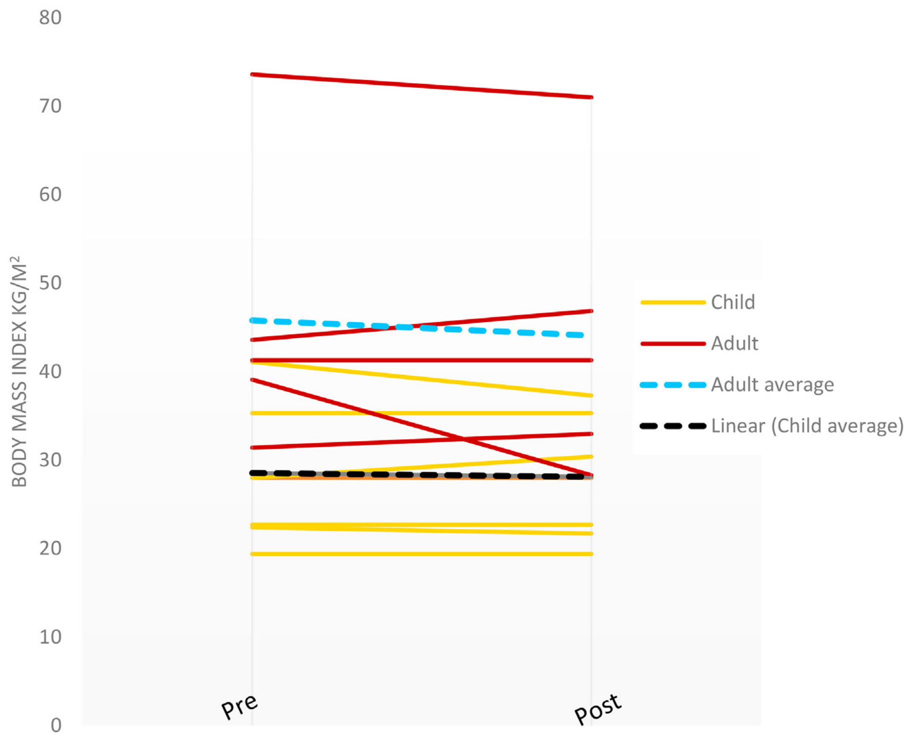

FIGURE 1 | Shape-up and eat right families body mass index changes pre- and post-intervention (last observation carried forward).

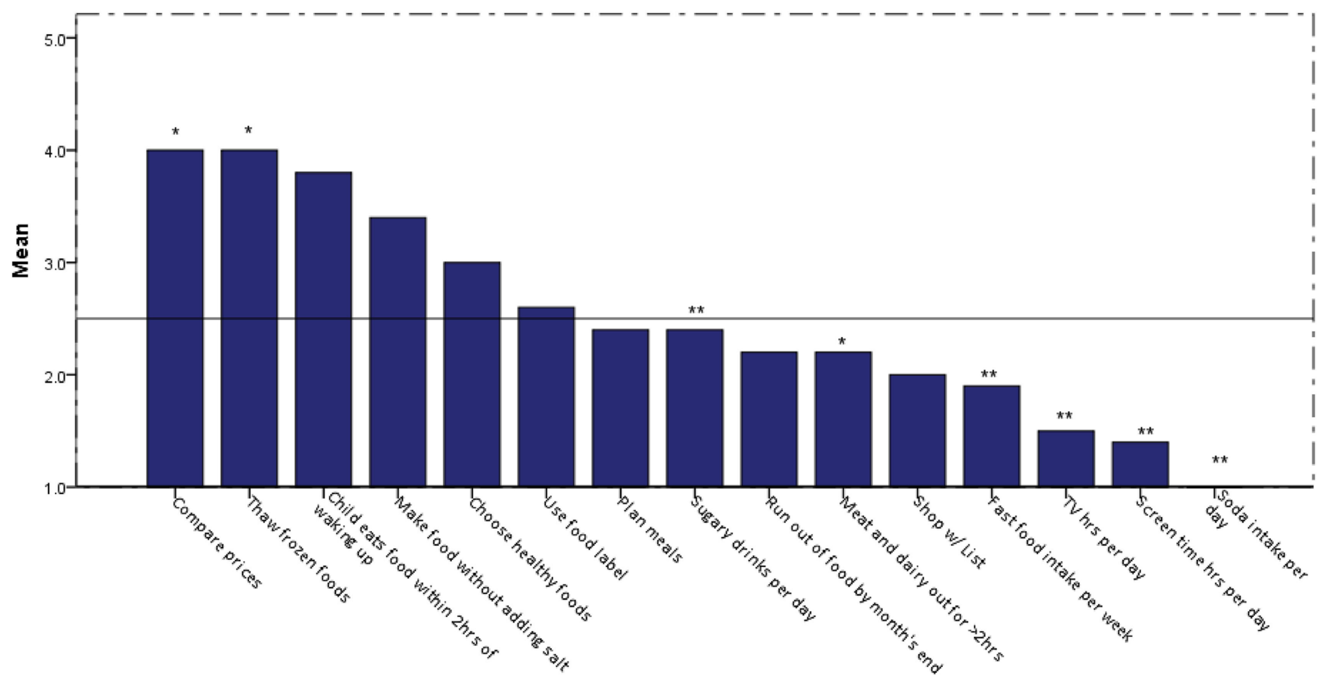

FIGURE 2 | Eating behaviors of shape-up and eat right-families prior to intervention. Legend: 1 = no, 2 = sometimes, 3 = often, 4 = very often, 5 = almost always; **Frequency on *Y*-axis corresponds to number variable; $^{*}p < 0.05$.

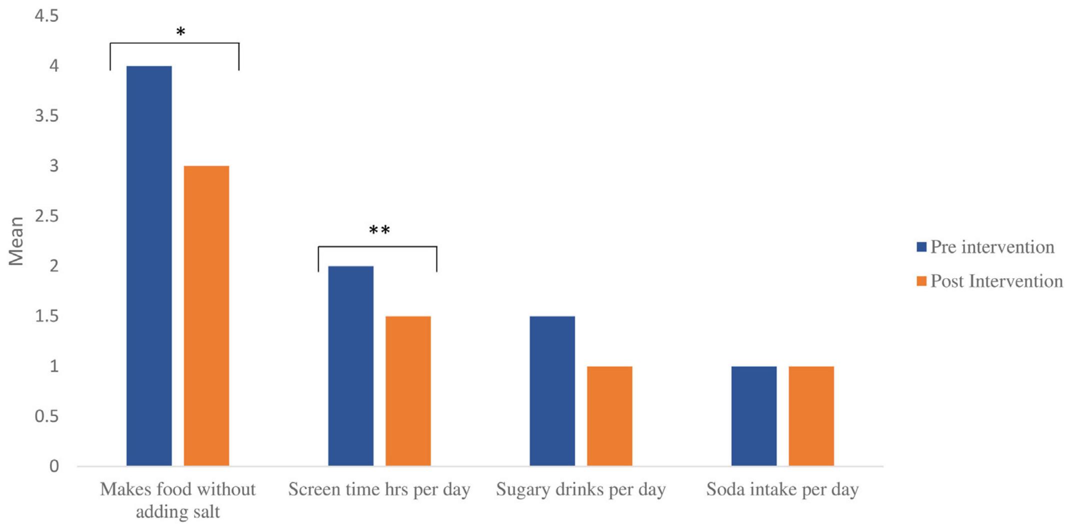

FIGURE 3 | Food and nutrition behaviors of shape-up and eat right families pre- and post-intervention (data for program completers). Legend: 1 = no, 2 = sometimes, 3 = often, 4 = very often, 5 = almost always; *p = 0.029, **p = 0.034; for sugary drinks and soda intake, value on Y-axis corresponds with numeric value per day.

including adding more fish to their diet, reading labels more often, and increased meal planning. Families planned to exercise more frequently together. Families also reported being very satisfied with the sessions and were very hopeful the program would continue in the future.

Physical Activity

Though pedometers were distributed to each family member with instructions to self-document step count on goal worksheets provided, participants did not record their step count and forgot to bring their pedometers during the visits. Thus, physical activity data was not quantifiable.

DISCUSSION

A parent–child group intervention for the treatment of overweight and obesity among African-American families had low attendance despite being deemed satisfactory by enrollees. The intervention was designed specifically taking disparities to care into account such as level of education (materials designed at fifth grade reading level), occurrence during evening hours to accommodate work/school schedules, and all-inclusive free visits, including accessibility to dietitians and medical providers on-site. A program fee was also not charged to any of the participants. Those who attended were likely quite motivated and thus rated the program as satisfactory. Parents were queried about barriers to attendance and reasons for this low affluence included several socioeconomic concerns; primary stability and sustainability of the family unit barred from attending medical group visits in the SUPER-families. The lack of participation and overall completion rate of this program reinforces current research noting and addressing significant barriers to care and health disparities among African-Americans (33–36).

In our study, the SMA model was within a traditional clinical academic urban hospital setting, rather than outsourced or integrated within a community or neighborhood. Barriers predominately at the socioeconomic and community level precluded attendance at the sessions and suggest that group-based interventions such as SUPER-families will likely be more successful in a community-based neighborhood setting with closer proximity and improved accessibility to care adopting the SMA model. However, probably more important than placement of these SMAs in community-based locations, is community engagement to determine strategies that might work in enhancing attendance. Though barriers to attendance were queried, parents were not queried on strategies to help overcome low attrition and attendance rates, which should be included in future reiterations of this intervention. Furthermore, though the urban inner-city academic hospital where the study took place serves a diverse racial/ethnic minority underserved population, efforts to engage the community in recruitment of community-based participatory research needs attention. A previous study from this institution has cited challenges in recruitment for pediatric obesity trials even with financial incentives (out of 179 eligible, only 4 attended the visits) (37). Recently, the Communication, Awareness, Relationships, and Empowerment (C.A.R.E.) model to engage at-risk African-American population in the Washington, DC area cultivated not only a visible presence at community events, but also through partnerships with churches, health organization, academic institutions, and governmental agencies, was able to successfully recruit and retain the study participants (38). Other strategies have included establishment of a community advisory board for at-risk populations in the metro area, which was able to conduct focus groups and pilot web-based and wearable technology through members representing churches in a cardiovascular health and needs assessment study (39). Community-based interventions have been shown to promote weight loss or positively influence diet and physical activity behavior in a culturally congruent manner, such as in churches or school-based programs, among African-Americans (40–43). For example, recently churches have been recognized as powerful outreaches for health services and interventions in an effort to address disparities among lower income, African-Americans families given the pastors' view on holistic health with integrated faith, such as their perspectives on obesity and infant mortality (44). Scalable, community-based weight loss programs with combination interventions, such as portable kiosks for assessments, email/text supports, and online-health coaches utilized in the Weigh and Win study of 40,038 adults, which combine outreach, effectiveness, and costs may help reduce disparities among African-Americans (45). Other studies have shown some benefit with incorporation of other resources such as tailored, interactive text-messages to enhance weight loss success among African-Americans with obesity (46). The use of a community-based participatory research approach to recruit African-Americans into pilot interventions and innovative health promotion programs has demonstrated success and feasibility along with scalability of the intervention as it applies to minority at-risk populations (47). Thus, though this current pilot SUPER-families SMA model was not successful in a hospital-based setting due to attrition and retention, programmatic elements could be better applied using the C.A.R.E. model for community engagement.

Though not statistically significant, it is noteworthy that the pilot study suggested an improvement of an average BMI change of −2.6 kg/m^2 in the children post-intervention. The study possibly suggests that this type of parent–child group-based intervention may potentially have long-term benefits for younger children with obesity. The education provided during the intervention did improve healthy living behaviors for all participants involved without determining overall effects on weight. Children may perhaps be more receptive to an intensive group-based education and weight loss intervention when paired with a parent/and or guardian. Moreover, the intervention improved sedentary time and decreased screen time behaviors for the children involved in the study. Of important consideration is that the rate of severe obesity has significantly increased in pre-school age children 2–5 years, since the 2013–2014 cycles (4). Because childhood obesity correlates closely with adolescent and adult obesity leading to worsening disease severity when older (48–51), and because children have a natural affinity toward their mothers, this SMA pilot intervention utilizing the mother–child relationship has a potential prospective of being adopted in pregnancy with a focus on prevention, rather than treatment. Early nutrition and growth in the initial years of life are important determinants of later body weight and metabolic health (52–54). Therefore, future SUPER-family models may consider preventive strategies targeting either pregnant African-American women or younger children ages 2–5 years, rather than 6–12 years old.

Furthermore, the pilot study, though a small number of enrolled participants, suggests an improvement in overall basic education around nutrition, eating, and sedentary behaviors with increased likelihood of implementation of these positively learned behaviors in the future, especially with regards to reducing salt intake and decreasing screen (video/computer) time. Reported screen time >3 h independent of physical activity has been associated with cardiometabolic risk factors and high BMIs in children (55, 56). Also noteworthy that these two behaviors (reduced salt intake and screen time) were simple, inexpensive, and could be implemented without difficulty and without much disruption to regular household duties, reinforcing that obesity interventions most likely need to be simplified in this specific population. Additionally, cost of food was of highest concern for the SUPER mothers though they preferred healthier foods. Recent studies have highlighted higher costs of healthier foods (57, 58), which could potentially be a challenging factor adversely affecting nutrition among African-American families. Research around understanding alternative healthier, affordable food patterns in this population to alleviate disparities to nutrition is recommended. Interestingly, differences in consumption of sugary beverages pre- and post-intervention in the study were not statistically significant though participants reported an average consumption of 2.4 drinks per day. A decrease in soda consumption could have led to cost savings, and the possibility of participant underreporting pre-intervention should be considered. Recent efforts discouraging sodas consumption from a public policy standpoint and overall public awareness (59–61) may have resulted in participant stigmata when answering the question relevant to beverage consumption. Because high fructose corn syrup found in sugary beverages has been well known to correlate with higher childhood adiposity and detrimental effects on metabolism (62, 63), more emphasis on avoidance of sugary beverages may be needed in future SUPER-families studies including clarifying the families' perception and understanding of these beverages given the negative statistical significance on the questionnaires compared to the food journal and written feedbacks.

Last, the study has several limitations. First, because the primary objective of the study was to estimate rate of participation, drop-out, or compliance, with a pre-determined number of minority families (n = 6) recruited based on funding allocated, data has limited interpretation due to small sample size, high attrition, and low retention rates, and cannot be generalizable to a whole population. A robust sample size is likely needed to determine overall effects of the study on primary and secondary outcomes. In addition, self-reported data on food journals, logs, and written feedback likely contain potential bias due to exaggeration and attribution. The families enrolled were already seeking treatment for weight loss prior to enrollment into the study and preselected without randomization. Thus any failure to lose weight may have been attributed to their perceived barriers to success and positive nutrition or physical activity behaviors exaggerated. Also, the study emphasized maternal–child pair, rather than father–child, or coparent–child relationship though fathers, grandparents, and/or legal guardians of the children were also invited to be part of the study. The latter relationships may yield different results. All adults in the study were mothers through self-selection and motherhood may reflect a greater role in child healthcare among this population. Though the study was done in African-Americans, the study cannot be generalized to other racial and/or ethnic minorities. Future improvements could also tailor culturally relevant exercises, rather than body weight and calisthenics conducted in the study.

CONCLUSION

In conclusion, although the study demonstrated an overall benefit in children more than adults in this particular population and was deemed satisfactory by enrollees, a family-based SMA intervention for weight loss in African-American families does not address barriers precluding high attrition rates for monthly nutrition and exercise visits, and would be more successful if applied in a field-based community setting. Despite acknowledging satisfaction and barriers half-way through the program, changes made were not enough to overcome barriers to care experienced by African-Americans in urban communities. Future research is needed to develop novel ways to deliver knowledge on nutrition and exercise, valued by families within a group program such as the one designed in this pilot study. New programs may include community-based locations, home visits, and web-based interventions to disseminate nutrition and physical activity education and tools in an effort to eliminate barriers to care and improve health outcomes as they relate to overweight and obesity within the African-American community. Moreover, because community engagement perpetuates scalability of the intervention, future re-design of the intervention might consider community-based advisory boards and partnerships for participant recruitment and retention.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of applicable federal, state, and local laws and regulations, and the relevant policies of the Human Research Protection Program, BMC, and Boston University with written informed consent from all adult subjects. All adult subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the BMC and Boston University Medical Campus Institutional Review Board. Written informed consent was obtained from parents of children at the time of enrollment and children ages 6–12 years provided assent.

AUTHOR CONTRIBUTIONS

KDP, KAI, ACM, AJM, CML, and CMA contributed equally to the planning of the study, conduct of the study, analysis of the data, and intellectual input in interpretation. KED contributed significantly in conduct of the study, analysis of the data, and intellectual input in interpretation. JM and GS contributed significantly in analysis and interpretation of the results. GS contributed significantly in intellectual content of manuscript. All authors are equally responsible for accuracy and originality of this work.

FUNDING

Funding for this study was provided by the Vela Foundation. We would like to thank the study participants for their time.

REFERENCES

1. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med* (1999) 341:427–34. doi:10.1056/NEJM199908053410607
2. Yu Y. The changing body mass-mortality association in the United States: evidence of sex-specific cohort trends from three national health and nutrition examination surveys. *Biodemography Soc Biol* (2016) 62:143–63. doi:10.1080/19485565.2015.1108835
3. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA* (2016) 315:2284–91. doi:10.1001/jama.2016.6458
4. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of obesity and severe obesity in US Children, 1999–2016. *Pediatrics* (2018) 141(3):e20173459. doi:10.1542/peds.2017-3459
5. An R. Racial/ethnic disparity in obesity among US youth, 1999–2013. *Int J Adolesc Med Health* (2015) 29(4):20150068. doi:10.1515/ijamh-2015-0068
6. Marquez B, Murillo R. Racial/ethnic differences in weight-loss strategies among US adults: national health and nutrition examination survey 2007–2012. *J Acad Nutr Diet* (2017) 117:923–8. doi:10.1016/j.jand.2017.01.025
7. Lewis KH, Gudzune KA, Fischer H, Yamamoto A, Young DR. Racial and ethnic minority patients report different weight-related care experiences than non-Hispanic whites. *Prev Med Rep* (2016) 4:296–302. doi:10.1016/j.pmedr.2016.06.015
8. Kershaw KN, Pender AE. Racial/ethnic residential segregation, obesity, and diabetes mellitus. *Curr Diab Rep* (2016) 16:108. doi:10.1007/s11892-016-0800-0
9. Spivack JG, Swietlik M, Alessandrini E, Faith MS. Primary care providers' knowledge, practices, and perceived barriers to the treatment and prevention of childhood obesity. *Obesity (Silver Spring)* (2010) 18:1341–7. doi:10.1038/oby.2009.410
10. Ruelaz AR, Diefenbach P, Simon B, Lanto A, Arterburn D, Shekelle PG. Perceived barriers to weight management in primary care – perspectives of patients and providers. *J Gen Intern Med* (2007) 22:518–22. doi:10.1007/s11606-007-0236-y
11. Bleich SN, Bandara S, Bennett WL, Cooper LA, Gudzune KA. U.S. health professionals' views on obesity care, training, and self-efficacy. *Am J Prev Med* (2015) 48:411–8. doi:10.1016/j.amepre.2014.11.002
12. Bleich SN, Pickett-Blakely O, Cooper LA. Physician practice patterns of obesity diagnosis and weight-related counseling. *Patient Educ Couns* (2011) 82:123–9. doi:10.1016/j.pec.2010.02.018
13. Delichatsios HK, Hauser ME, Burgess JD, Eisenberg DM. Shared medical appointments: a portal for nutrition and culinary education in primary care – a pilot feasibility project. *Glob Adv Health Med* (2015) 4:22–6. doi:10.7453/gahmj.2015.060
14. Trickett KH, Matiaco PM, Jones K, Howlett B, Early KB. Effectiveness of shared medical appointments targeting the triple aim among patients with overweight, obesity, or diabetes. *J Am Osteopath Assoc* (2016) 116:780–7. doi:10.7556/jaoa.2016.153
15. Guthrie GE, Bogue RJ. Impact of a shared medical appointment lifestyle intervention on weight and lipid parameters in individuals with type 2 diabetes: a clinical pilot. *J Am Coll Nutr* (2015) 34:300–9. doi:10.1080/07315724.2014.933454
16. Crowley MJ, Edelman D, Voils CI, Maciejewski ML, Coffman CJ, Jeffreys AS, et al. Jump starting shared medical appointments for diabetes with weight management: rationale and design of a randomized controlled trial. *Contemp Clin Trials* (2017) 58:1–12. doi:10.1016/j.cct.2017.04.004
17. Croker H, Viner RM, Nicholls D, Haroun D, Chadwick P, Edwards C, et al. Family-based behavioural treatment of childhood obesity in a UK National Health Service setting: randomized controlled trial. *Int J Obes* (2005) 36(2012):16–26. doi:10.1038/ijo.2011.182
18. Mead E, Brown T, Rees K, Azevedo LB, Whittaker V, Jones D, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *Cochrane Database Syst Rev* (2017) 6:Cd012651. doi:10.1002/14651858.CD012651

19. Kirsh S, Watts S, Pascuzzi K, O'Day ME, Davidson D, Strauss G, et al. Shared medical appointments based on the chronic care model: a quality improvement project to address the challenges of patients with diabetes with high cardiovascular risk. *Qual Saf Health Care* (2007) 16:349–53. doi:10.1136/qshc.2006.019158
20. Ramdas K, Darzi A. Adopting innovations in care delivery – the case of shared medical appointments. *N Engl J Med* (2017) 376:1105–7. doi:10.1056/NEJMp1612803
21. Kaplan-Lewis E, Percac-Lima S. No-show to primary care appointments: why patients do not come. *J Prim Care Community Health* (2013) 4:251–5. doi:10.1177/2150131913498513
22. Samuels RC, Ward VL, Melvin P, Macht-Greenberg M, Wenren LM, Yi J, et al. Missed appointments: factors contributing to high no-show rates in an urban pediatrics primary care clinic. *Clin Pediatr (Phila)* (2015) 54:976–82. doi:10.1177/0009922815570613
23. Kaplan LM, Golden A, Jinnett K, Kolotkin RL, Kyle TK, Look M, et al. Perceptions of barriers to effective obesity care: results from the national ACTION study. *Obesity (Silver Spring)* (2018) 26:61–9. doi:10.1002/oby.22054
24. Lavoie JG, Wong ST, Chongo M, Browne AJ, MacLeod ML, Ulrich C. Group medical visits can deliver on patient-centred care objectives: results from a qualitative study. *BMC Health Serv Res* (2013) 13:155. doi:10.1186/1472-6963-13-155
25. Wong ST, Browne A, Lavoie J, Macleod ML, Chongo M, Ulrich C. Incorporating group medical visits into primary healthcare: are there benefits? *Healthc Policy* (2015) 11:27–42.
26. Janz KF, Lutuchy EM, Wenthe P, Levy SM. Measuring activity in children and adolescents using self-report: PAQ-C and PAQ-A. *Med Sci Sports Exerc* (2008) 40:767–72. doi:10.1249/MSS.0b013e3181620ed1
27. US Department of Agriculture. *Food Behavior Checklist*. (2017). Available from: https://snaped.fns.usda.gov/materials/food-behavior-checklist (Accessed: June 15, 2017).
28. Townsend MS, Kaiser LL, Allen LH, Joy AB, Murphy SP. Selecting items for a food behavior checklist for a limited-resource audience. *J Nutr Educ Behav* (2003) 35:69–77. doi:10.1016/S1499-4046(06)60043-2
29. Banna JC, Townsend MS. Assessing factorial and convergent validity and reliability of a food behaviour checklist for Spanish-speaking participants in US Department of Agriculture nutrition education programmes. *Public Health Nutr* (2011) 14:1165–76. doi:10.1017/S1368980010003058
30. Banna JC, Vera Becerra LE, Kaiser LL, Townsend MS. Using qualitative methods to improve questionnaires for Spanish speakers: assessing face validity of a food behavior checklist. *J Am Diet Assoc* (2010) 110:80–90. doi:10.1016/j.jada.2009.10.002
31. Murphy SP, Kaiser LL, Townsend MS, Allen LH. Evaluation of validity of items for a food behavior checklist. *J Am Diet Assoc* (2001) 101:751–61. doi:10.1016/S0002-8223(01)00189-4
32. Likert R. *A Technique for the Measurement of Attitude*. (Vol. 22). New York: The Science Press (1932). 55 p.
33. Ford ME, Magwood G, Brown ET, Cannady K, Gregoski M, Knight KD, et al. Disparities in obesity, physical activity rates, and breast cancer survival. *Adv Cancer Res* (2017) 133:23–50. doi:10.1016/bs.acr.2016.08.002
34. Wong MS, Grande DT, Mitra N, Radhakrishnan A, Branas CC, Ward KR, et al. Racial differences in geographic access to medical care as measured by patient report and geographic information systems. *Med Care* (2017) 55(9):817–22. doi:10.1097/MLR.0000000000000774
35. Ray R, Sewell AA, Gilbert KL, Roberts JD. Missed opportunity? Leveraging mobile technology to reduce racial health disparities. *J Health Polit Policy Law* (2017) 42(5):901–24. doi:10.1215/03616878-3940477
36. Hines AL, Cooper LA, Shi L. Racial and ethnic differences in mental healthcare utilization consistent with potentially effective care: the role of patient preferences. *Gen Hosp Psychiatry* (2017) 46:14–9. doi:10.1016/j.genhosppsych.2017.02.002
37. Ireland KA, Manders AJ, Corkey BE, Lenders CM. Recruitment in a pediatric clinical research trial targeting underserved populations: efforts and challenges. *J Obes Weight Loss Ther* (2015) 5:262. doi:10.4172/2165-7904.1000262
38. Ceasar J, Peters-Lawrence MH, Mitchell V, Powell-Wiley TM. The communication, awareness, relationships and empowerment (C.A.R.E.) model: an effective tool for engaging urban communities in community-based participatory research. *Int J Environ Res Public Health* (2017) 14:E1422. doi:10.3390/ijerph14111422
39. Yingling LR, Brooks AT, Wallen GR, Peters-Lawrence M, McClurkin M, Cooper-McCann R, et al. Community engagement to optimize the use of web-based and wearable technology in a cardiovascular health and needs assessment study: a mixed methods approach. *JMIR Mhealth Uhealth* (2016) 4:e38. doi:10.2196/mhealth.4489
40. Barr-Anderson DJ, Singleton C, Cotwright CJ, Floyd MF, Affuso O. Outside-of-school time obesity prevention and treatment interventions in African American youth. *Obes Rev* (2014) 15(Suppl 4):26–45. doi:10.1111/obr.12204
41. Davis C, Dutton WB, Durant T, Annunziato RA, Marcotte D. Achieving cultural congruency in weight loss interventions: can a spirituality-based program attract and retain an inner-city community sample? *J Obes* (2014) 2014:641939. doi:10.1155/2014/641939
42. Yeary KH, Cornell CE, Turner J, Moore P, Bursac Z, Prewitt TE, et al. Feasibility of an evidence-based weight loss intervention for a faith-based, rural, African American population. *Prev Chronic Dis* (2011) 8:A146.
43. Kim KH, Linnan L, Campbell MK, Brooks C, Koenig HG, Wiesen C. The WORD (wholeness, oneness, righteousness, deliverance): a faith-based weight-loss program utilizing a community-based participatory research approach. *Health Educ Behav* (2008) 35:634–50. doi:10.1177/1090198106291985
44. Gross TT, Story CR, Harvey IS, Allsopp M, Whitt-Glover M. "As a community, we need to be more health conscious": pastors' perceptions on the health status of the black church and African-American communities. *J Racial Ethn Health Disparities* (2017) 1–10. doi:10.1007/s40615-017-0401-x
45. Estabrooks PA, Wilson KE, McGuire TJ, Harden SM, Ramalingam N, Schoepke L, et al. A quasi-experiment to assess the impact of a scalable, community-based weight loss program: combining reach, effectiveness, and cost. *J Gen Intern Med* (2017) 32:24–31. doi:10.1007/s11606-016-3971-0
46. Lin M, Mahmooth Z, Dedhia N, Frutchey R, Mercado CE, Epstein DH, et al. Tailored, interactive text messages for enhancing weight loss among African American adults: the TRIMM randomized controlled trial. *Am J Med* (2015) 128:896–904. doi:10.1016/j.amjmed.2015.03.013
47. Brewer LC, Jenkins S, Lackore K, Johnson J, Jones C, Cooper LA, et al. mHealth intervention promoting cardiovascular health among African-Americans: recruitment and baseline characteristics of a pilot study. *JMIR Res Protoc* (2018) 7:e31. doi:10.2196/resprot.8842
48. Evensen E, Wilsgaard T, Furberg AS, Skeie G. Tracking of overweight and obesity from early childhood to adolescence in a population-based cohort – the Tromso Study, fit futures. *BMC Pediatr* (2016) 16:64. doi:10.1186/s12887-016-0599-5
49. Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *J Pediatr* (2007) 150:12–7.e2. doi:10.1016/j.jpeds.2006.08.042
50. Biro FM, Wien M. Childhood obesity and adult morbidities. *Am J Clin Nutr* (2010) 91:1499S–505S. doi:10.3945/ajcn.2010.28701B
51. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-mass index in 2.3 million adolescents and cardiovascular death in adulthood. *N Engl J Med* (2016) 374:2430–40. doi:10.1056/NEJMoa1503840
52. Vieira SA, Magalhaes TC, Ribeiro AQ, Priore SE, Franceschini Sdo C, Sant'Ana LF. Influence of weight gain rate on early life nutritional status and body composition of children. *ScientificWorldJournal* (2014) 2014:616108. doi:10.1155/2014/616108
53. Rolland-Cachera MF, Maillot M, Deheeger M, Souberbielle JC, Peneau S, Hercberg S. Association of nutrition in early life with body fat and serum leptin at adult age. *Int J Obes (Lond)* (2013) 37:1116–22. doi:10.1038/ijo.2012.185
54. Zhang S, Rattanatray L, McMillen IC, Suter CM, Morrison JL. Periconceptional nutrition and the early programming of a life of obesity or adversity. *Prog Biophys Mol Biol* (2011) 106:307–14. doi:10.1016/j.pbiomolbio.2010.12.004
55. Norman GJ, Carlson JA, Patrick K, Kolodziejczyk JK, Godino JG, Huang J, et al. Sedentary behavior and cardiometabolic health associations in obese 11–13-year olds. *Child Obes* (2017) 13(5):425–32. doi:10.1089/chi.2017.0048
56. Kenney EL, Gortmaker SL. United States adolescents' television, computer, videogame, smartphone, and tablet use: associations with sugary drinks, sleep, physical activity, and obesity. *J Pediatr* (2017) 182:144–9. doi:10.1016/j.jpeds.2016.11.015
57. Darmon N, Drewnowski A. Contribution of food prices and diet cost to socioeconomic disparities in diet quality and health: a systematic review and analysis. *Nutr Rev* (2015) 73:643–60. doi:10.1093/nutrit/nuv027

58. Kern DM, Auchincloss AH, Robinson LF, Stehr MF, Pham-Kanter G. Healthy and unhealthy food prices across neighborhoods and their association with neighborhood socioeconomic status and proportion black/Hispanic. *J Urban Health* (2017) 94(4):494–505. doi:10.1007/s11524-017-0168-8
59. Min HM. Large-sized soda ban as an alternative to soda tax. *Cornell J Law Public Policy* (2013) 23:187–232.
60. Greathouse KL, Chriqui J, Moser RP, Agurs-Collins T, Perna FM. The association of soda sales tax and school nutrition laws: a concordance of policies. *Public Health Nutr* (2014) 17:2201–6. doi:10.1017/S1368980013003029
61. Babey SH, Jones M, Yu H, Goldstein H. Bubbling over: soda consumption and its link to obesity in California. *Policy Brief UCLA Cent Health Policy Res* (2009) PB2009-5:1–8.
62. Hu FB. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obes Rev* (2013) 14:606–19. doi:10.1111/obr.12040
63. Popkin BM. Sugary beverages represent a threat to global health. *Trends Endocrinol Metab* (2012) 23:591–3. doi:10.1016/j.tem.2012.07.003

Conflict of Interest Statement: KDP, KAI, ACM, KED, AJM, JM declare no competing interests. GS reports consultant fees from Johnson and Johnson. CML received support from New Balance Foundation and BNORC P30 DK40561. CMA reports personal fees from Nutrisystem, personal fees from Zafgen, personal fees from Sanofi-Aventis, grants and personal fees from Orexigen, personal fees from NovoNordisk, grants from Aspire Bariatrics, grants and personal fees from GI Dynamics, grants from Myos, grants and personal fees from Takeda, personal fees from Scientific Intake, grants and personal fees from Gelesis, other from Science-Smart LLC, personal fees from Merck, personal fees from Johnson and Johnson, grants from Dr. Robert C. and Veronica Atkins Foundation, grants from Coherence Lab, grants from Energesis, grants from PCORI, and grants from NIH outside the submitted work.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 10 January 2019
doi: 10.3389/fped.2018.00386

Understanding Family-Level Effects of Adult Chronic Disease Management Programs: Perceived Influences of Behavior Change on Adolescent Family Members' Health Behaviors Among Low-Income African Americans With Uncontrolled Hypertensions

Rachel L. J. Thornton[1,2,3,4*], *Tracy J. Yang*[5], *Patti L. Ephraim*[3,6], *L. Ebony Boulware*[7] *and Lisa A. Cooper*[2,3,4,6]

[1] Division of General Pediatrics and Adolescent Medicine, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, United States, [2] Johns Hopkins Center for Health Equity, Baltimore, MD, United States, [3] Department of Health, Behavior and Society at the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [4] Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD, United States, [5] New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, NY, United States, [6] Division of General Internal Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, United States, [7] Division of General Internal Medicine, Department of Medicine, Duke University School of Medicine, Durham, NC, United States

Background: Despite improvements in cardiovascular disease (CVD) prevention and treatment, low-income African Americans experience disparities in CVD-related morbidity and mortality. Childhood obesity disparities and poor diet and physical activity behaviors contribute to CVD disparities throughout the life course. Given the potential for intergenerational transmission of CVD risk, it is important to determine whether adult disease management interventions could be modified to achieve family-level benefits and improve primary prevention among high-risk youth.

Objective: To explore mechanisms by which African-American adults' (referred to as index patients) participation in a hypertension disease management trial influences adolescent family members' (referred to as adolescents) lifestyle behaviors.

Design/Methods: The study recruited index patients from the Achieving blood pressure Control Together (ACT) study who reported living with an adolescent ages 12–17 years old. Index patients and adolescents were recruited for in-depth interviews and were asked about any family-level changes to diet and physical activity behaviors during or after participation in the ACT study. If family-level changes were described, index patients and adolescents were asked whether role modeling, changes in the home food environment, meal preparation, and family functioning contributed to these changes. These mechanisms were hypothesize to be important based on existing research suggesting that parental involvement in childhood obesity interventions influences child

OPEN ACCESS

Edited by:
*Fatima Cody Stanford,
Harvard Medical School,
United States*

Reviewed by:
*Holly Lofton,
New York University, United States
Dawn Maree Aycock,
Georgia State University,
United States*

***Correspondence:**
*Rachel L. J. Thornton
rjohns21@jhmi.edu*

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *31 August 2018*
Accepted: *21 November 2018*
Published: *10 January 2019*

Citation:
Thornton RLJ, Yang TJ, Ephraim PL, Boulware LE and Cooper LA (2019) Understanding Family-Level Effects of Adult Chronic Disease Management Programs: Perceived Influences of Behavior Change on Adolescent Family Members' Health Behaviors Among Low-Income African Americans With Uncontrolled Hypertensions. Front. Pediatr. 6:386. doi: 10.3389/fped.2018.00386

and adolescent weight status. Thematic content analysis of transcribed interviews identified both a priori and emergent themes.

Results: Eleven index patients and their adolescents participated in in-depth interviews. Index patients and adolescents both described changes to the home food environment and meal preparation. Role modeling was salient to index patients, particularly regarding healthy eating behaviors. Changes in family functioning due to study participation were not endorsed by index patients or adolescents. Emergent themes included adolescent care-taking of index patients and varying perceptions by index patients of their influence on adolescents' health behaviors.

Conclusions: Our findings suggest that disease management interventions directed at high-risk adult populations may influence adolescent family members' health behaviors. We find support for the hypotheses that role modeling and changes to the home food environment are mechanisms by which family-level health behavior change occurs. Adolescents' roles as caretakers for index patients emerged as another potential mechanism. Future research should explore these mechanisms and ways to leverage disease management to support both adult and adolescent health behavior change.

Keywords: cardiovascular diseases, family health, hypertension, health promotion, disease management, health disparities

INTRODUCTION

Preventing and treating child and adolescent obesity is essential for reducing cardiovascular disease (CVD) risk over the life course. An estimated 17% of U.S. children and adolescents are obese (1–3). Despite recent improvements in available CVD prevention and treatment (4), low-income African Americans experience excess CVD-related morbidity and mortality (4, 5). Excess obesity risk among low-income African-American children and adolescents contributes to disparities in lifetime CVD risk (6, 7). Furthermore, racial/ethnic and socioeconomic disparities in childhood obesity (8, 9) have not improved over the past decade (10), and may even be worsening (11, 12).

Lifestyle modifications aimed at weight loss and promoting healthy diet and physical activity (PA) behaviors are important for primary and secondary prevention of CVD and related morbidity in adults (13, 14) and adolescents (15). Parent and family involvement is important for preventing child and adolescent obesity and decreasing CVD risk over the life course. Parent and family involvement may also improve disease management outcomes among adults (7, 13, 16, 17). Yet, the potential for adult disease management interventions to achieve intergenerational benefits via family-level effects has not been extensively studied and may represent a missed opportunity to address CVD-outcome disparities and optimize primordial and primary prevention among high-risk youth.

Our overall goal was to investigate mechanisms by which adult disease management interventions may positively influence adolescent health behaviors. We did this by exploring the extent to which adults with uncontrolled hypertension (index patients) and their adolescent family members (adolescents) perceive *spillover* effects of participation in a blood pressure control disease management comparative effectiveness trial on adolescents' diet and physical activity behaviors. *Spillover* is a well-developed concept in family psychology, describing the notion that participation in one domain (e.g., self-care) can affect participation in another domain (e.g., family) (18–20).

For example, a parent's role as a participant or index patient in a disease management intervention could produce *spillover* to the family domain and elicit behavior change among other family members, including children or adolescents. Qualitative research suggests that dietary behavior change among adults with diabetes can produce changes in children's diet (21) and sugar sweetened beverage intake (22). Other studies have found that weight loss and behavior change interventions targeting overweight parents can simultaneously produce improvements in diet and physical activity behaviors for their children (23–25).

Adolescence is a critical window for intervention, with elevated BMI in adolescence associated with increased risk of premature death and CVD in adulthood (26). Increases in BMI during transition from adolescence to adulthood have accelerated in recent decades, particularly for African-American females (6). Research suggests interventions to improve healthy diets among adolescents should target parental diet and the home food environment (27, 28). Given the important relationship of the home environment with adolescent obesity and CVD risk and the role of adult family members as agents of change (29), CVD risk reduction interventions solely targeting adults may represent missed opportunities to simultaneously address adolescent CVD and obesity risk.

This work highlights the importance of developing strategies for modifying adult-focused disease management interventions to achieve positive family-level effects (30). Yet, a review by Barr-Anderson and colleagues (31) examining family-focused

PA, diet, and obesity interventions in African-American girls found that, despite face validity to family engagement, there is a lack of clear evidence regarding how family engagement can best be used to achieve significant decreases in obesity risk. In this study, we investigate potential mechanisms by which adult patients' participation in a blood pressure control disease management intervention could produce *spillover* effects on the adolescent family members (adolescents) who live with them. We use guiding hypotheses grounded in existing research literature regarding mechanisms by which parental involvement has been shown to be an effective component of childhood obesity prevention and treatment interventions. Based on the existing literature, this qualitative study was developed with the guiding hypotheses that adult patients (index patients) would identify the following salient mechanisms for producing *spillover*: role modeling of healthy diet and physical activity behaviors, changes to the home food environment, changes in family meal preparation, and improvements in family functioning.

METHODS

Study Sample/Population

This study was approved by the Johns Hopkins Medical Institutions Institutional Review Board. Adult patients with uncontrolled hypertension who participated in the Achieving Blood Pressure Control Together Study (ACT Study) comparative effectiveness trial were recruited to participate in an in-depth interview following completion of a 12-months follow-up questionnaire (32). The ACT Study tested the relative effectiveness of social and behavioral interventions to improve BP control among an urban, low-income African-American population in Baltimore. The intervention components were tailored and combined using principles of community based participatory research with the goal of improving their effectiveness and sustainability in the specified patient population. All three intervention arms involved blood pressure self-monitoring training plus the use of community health workers. One arm also involved a brief patient and family activation intervention known as "Do My Part." This intervention was delivered to patients one-on-one in the clinical setting and could have also included an adult family member if he/she was accompanying the index patient to a medical visit but did not involve child or adolescent family members. Another arm also involved an 8-week-long problem-solving intervention delivered to index patients in groups.

Index patients who indicated willingness to be contacted for future research were re-contacted to participate in in-depth interviews that were conducted at their home or in a private conference room at the primary care clinic where index patients received primary care services. Index patients were eligible if they: (1) had completed the 12-months follow-up questionnaire after participating in one of the three arms of the ACT Study and (2) lived with at least one adolescent family member age 12–17 years old who was also willing to be interviewed. Adolescent respondents were eligible if they were 12–17 years old, self-identified as African American, and lived in a household with an index patient participating in an in-depth interview. Index patients and adolescents were recruited, and all interviews were conducted between September and November 2015. Informed consent was obtained by all index patients and primary caregivers of adolescents. Adolescents provided assent prior to study participation as well. Adult index patients were remunerated fifty dollars and adolescent family members forty dollars for their study participation. Interviews were audio recorded and were conducted one-on-one and separately for index patients and adolescent family members.

Measures

In-depth interview guides were developed for both index patient interviews and adolescent interviews. The interviews were conducted by trained staff. In-depth interviews focused on potential mechanisms by which ACT Study involvement might produce *spillover* effects on diet and PA behaviors among adolescents and whether family-level behavioral and environmental factors could mediate these effects. The major domains discussed included the general experience of ACT Study involvement, descriptions of the relationship between index patients and adolescent family members, role modeling of healthy diet and PA behaviors by index patients, and the influence of index patient participation in the ACT Study on family food environment, family meal preparation, and family functioning. The interviews were intended to explore the a priori hypotheses regarding mechanisms by which the ACT Study interventions were likely to produce spillover effects on adolescent family members' health behaviors.

Table 1 presents some of the questions included in the index patient and adolescent interview guides to provide examples of the types of questions asked and the content covered in these interviews. Of note, interviewers probed as appropriate based on index patients' and adolescents' responses to glean the richest and most complete picture possible of the relationship of index patients' participation in the ACT study and potential spillover effects on their adolescent family members' health behaviors. The goal was to engage index patients and adolescents in a dialogue around the topics outlined in the interview guide. The specific questions asked varied by interview and were responsive to topics discussed by the index patient and adolescent respondents. Interviews were audio-recorded using a digital recording device. They were subsequently transcribed verbatim. Transcripts were cleaned and verified by a study staff member prior to analysis.

Data Analysis

Verbatim transcripts from the audio-recorded in-depth interviews and typed field notes from team debriefs after interviews were reviewed prior to analysis. Interview transcripts were coded and then analyzed to identify key themes. Analysis included both deductive hypotheses drawn from the interview guides and inductive findings that emerged from the interviews. A trained member of the study team created code books for use in coding index patient and adolescent interview transcripts with *a priori* codes drawn from the in-depth interview guides and emergent codes based on initial analysis of interview transcripts. The codebook was refined using an iterative process and then applied to all transcripts. Two independent coders trained in

TABLE 1 | Example questions in ACT study index patient and adolescent interview guides.

Theme	Role modeling	Changes to the home food environment	Changes in meal preparation	Family functioning
Question	Sometimes we look to others for examples of how to make healthy choices about what we eat or how active we are. Who do you look to for examples about how to live a healthy lifestyle?	What kinds of foods are available in your home? Since you/your family member participated in the ACT Study, how has anything about the food available in your home changed?	What kinds of foods do you eat for meals like breakfast, lunch, and dinner? Since you/your family member participated in the ACT Study, how has anything about mealtime in your home changed?	Have you noticed any changes in the way members of your family get along with one another since you/your family member participated in the ACT Study? If so, what are these changes?

qualitative research methods read and coded index patient interview transcripts (KJ and TY). Codes were grouped into categories based on *a priori* and emergent themes. The study team used ATLAS.ti 7 Software to facilitate interview transcript coding and data management (33).

Disagreements in coding were discussed with the study PI (RT). The adjudication process was tracked for all transcripts. The index patient codebook underwent iterative revisions during coding to better capture data relevant to the study's research questions. Analytical coding reports for index patient interviews were generated and organized by theme and discussed between the study PI and the research team. One independent coder read and coded adolescent family member interview transcripts. A second study team member analyzed the coded adolescent transcripts to identify potential areas of convergence or divergence with index patient interviews. Memos were used to document the iterative process of codebook development and emergent themes.

Thematic analysis of the interviews explored the mechanisms through which the parent study may have produced *spillover* effects, including role modeling of healthy behaviors and changes to the home food environment and meal preparation. Analysis also explored the relationship of family functioning with the index patient's disease management and behavior change. Emergent themes were also developed through this process. The adolescent interviews were coded and analyzed to compare perspectives related to *a priori* and emergent themes with the index patients' interviews.

RESULTS

Twenty-six percent (41 of 159) of index patients enrolled in the ACT Study reported having children in the household ranging in age from 2 to 17 years old (mean = 10.6 years old). The number of children per household ranged from 1 to 5 (mean = 1.7). The mean age of index patients was 54 years old (range 34–75 years old). Sixteen index patients were in the CHW arm, 13 in CHW plus problem solving classes, and 12 in CHW plus Do My Part. Relationships between index patients and child or adolescent family members fell into eight relationship categories: grandmother-granddaughter, grandmother-grandson, grandfather-grandson, mother-daughter, mother-son, stepmother-stepdaughter, father-daughter, and father-son. Among those ACT Study index patients who agreed to be re-contacted for future research, there were 21 who reported living with at least one adolescent family member ages 12–17 years old. Thirteen of these index patients expressed interest in completing in-depth interviews. Ultimately, 11 index patients and 11 adolescents were consented and completed one-on-one in-depth interviews as part of this study.

These 11 ACT index patients consenting to an in-depth interview were similar in age to all ACT index patients living with child or adolescent family members; and the children and adolescents in their household were also of similar age to all children living with ACT index patients. The mean age of ACT Study index patients consenting to the sub-study was 54 years old (range 42–70 years old). Adolescents who participated in this sub-study were between the ages 12–17 years old (mean = 14.3 years old).

Consistent with *a priori* hypotheses, index patients and adolescents described role modeling (Theme 1), changes in the food environment (Theme 2), and changes in meal preparation (Theme 3) as areas where index patient's participation in the ACT Study produced *spillover* influences on adolescent behavior. Counter to a priori hypotheses, however, physical activity and changes to family functioning were not identified by index patient or adolescent interviews as salient mechanisms for *spillover*. Two emergent themes relating to *spillover* were also identified: perceptions of caregiver influence on adolescent family members' health behavior (Theme 4) and adolescent caretaking behaviors (Theme 5). The former (Theme 4) was frequently described in index patient interviews as related to *spillover* mechanisms, and the latter (Theme 5) emerged in the context of discussions regarding adolescents' recognition of index patients' health status, respectively.

Theme 1: Role Modeling

Role modeling was very salient to index patients' descriptions of how they thought their participation in disease management interventions produced *spillover* on adolescents' health behaviors. Most of the role modeling discussions focused on healthy eating behaviors and not physical activity. Index patients described serving as role models to adolescents but also to other friends and family members in the area of disease management. One index patient and father describes his own dietary changes and how he used his behavior change as motivation to also improve his daughter's diet:

"And sometimes we get off the wagon, go to McDonald's or something like that, yeah, sometimes. But not regular. She [adolescent family member] loves McDonald's. I'm trying to teach her eventually if you keep going, you're going to have high cholesterol. We try to avoid all of that fast food and if we do go, I get the wrap… I see they got the grilled chicken and stuff like that, and that's about it." 66 years-old father of daughter

This disease management role modeling also seems to provide another avenue for educating adolescents about chronic disease. Some index patients describe getting support from their adolescents to engage in disease management related behaviors. These index patients articulate a sense that engaging their adolescents in this process could help them avoid similar health challenges as adults:

"It's just m[e] and my daughter are the only two with high blood pressure, so he [adolescent] [is] on her about [taking] her meds, and I'm on her about [taking] her meds. And they talk to me, you take your medicine, you know, this that and the third. But we basically, you know, we concerned about each other health issues. So, we stick together with the health thing. . . ."—50 years-old grandmother of grandson

Thus, index patients made connections between being in the ACT study and influencing health behaviors within their families. They identified ways in which they served as a role model to encourage *spillover* of positive health behavior changes they made in response to participation in the disease management interventions that were part of the ACT study. Yet they also saw their condition as a warning of sorts to adolescent family members and hoped that they could encourage adolescents to make healthy choices so as to prevent or delay onset of illnesses, such as hypertension.

Theme 2: Changes to the Home Food Environment

Changing the home food environment is often discussed by index patients. Strategies for changing the home food environment described by index patients include avoiding certain foods, changing the environment around mealtimes, and making healthier choices when purchasing meals and snacks for consumption at home. One index patient and stepmother describes judiciously avoiding meats that she knows can negatively affect cardiovascular health:

"… But now, you know, I'm more in tuned to my health. I take my vitamins, you know. I exercise, you know. I watch what I eat. I don't eat no beef. I don't eat no pork. It's strictly like chicken, turkey and seafood, you know… "—46 years-old stepmother of stepdaughter

Another index patient and grandmother specifically describes efforts to change the dynamics in the household around mealtimes and how these have helped her to stick to eating foods that she knows are healthy but that she may find less palatable than the unhealthy foods that adversely affect her blood pressure control:

"… Everybody ate at a separate time, you know, everybody ate at their own time. And now that I'm retired and I'm home, uh, we were finding less time to eat together too, but then, uh, when I joined the ACT study, we just, we just sat down and ate together you know. We'd just sit down and eat together. Um, and, um, that way, um it's very distracting, as I said, from what you're eating, especially if it doesn't have the taste that you're used to. So, uh, we find it beneficial for both reasons, health reasons and then, uh, you know, just to sit down and have conversation or whatever."—72-years-old grandmother of granddaughter

Another index patient discussed the way that his increased awareness of health vs. unhealthy foods affects food purchases during shopping trips with his son:

"He [IFM] goes to the market with me sometimes. Well, the majority of the times, he [adolescent family member] did go to the market with me, because I need him to carry the bags. But he goes. He's getting better because he doesn't grab junk like he used to. He might grab chips and he might grab—he doesn't grab junk like he used to. He'll probably grab some Twizzlers and that's it, and some chips. He grabs granola bars now, and he's drinking a lot of water, so he's better with that. So, I just really—I noticed it but it didn't really dawn on me. But he's getting better with grocery shopping."—44 years-old father of son

As these examples demonstrate, some index patients discussed removing certain items from the home entirely or limiting purchases of certain foods, and others changed the environment around meal times in an effort to improve dietary behaviors of their whole household, thus facilitating *spillover*. Respondents describe these approaches as directed toward improving their own health but also as a means of creating a home environment that fosters healthier eating behaviors among their adolescents and other family members in the household.

Theme 3: Changes in Meal Preparation

Given the varied responsibilities of adolescents in the household, the issue of meal preparation was frequently discussed. Index patients describe different approaches to addressing needs for healthier meal preparation techniques for themselves as a means of supporting blood pressure control. Some families adopted a policy of making two separate meals, and others modified meal preparation techniques for the entire household. In several cases, adolescents were actively involved in cooking and meal preparation. As a result, they also learned about and implemented healthier meal preparation methods based on input from index patients:

"*They cut down on the, uh, the fried food. Most of the stuff we grill or bake. So, you know, it calls attention to what they eat too. . . .*

"But she, she [adolescent] does a lot of cooking, uh, for me. So, when she cooks, I come down and keep her company. While she cook, she may ask me, you know, so if I put this in there, will it do this, or will it do that? And you know, and I have to tell her, you know, the best,

and know how, um, what's right, and what's not right, what's good for me, and what's not. But she, she eats, uh, a lot of the times what I eat too."—72 years-old grandmother of granddaughter

As this example illustrates, through their involvement in cooking for index patients, adolescents gain insight into healthier cooking techniques, which has the potential of producing *spillover* effects on adolescents' dietary behaviors, particularly when they eat the same foods that they cook for index patients.

Emergent Themes

Theme 4: Varying Perception of Caregiver Influence on Adolescent Family Members

While there were many examples from index patient interviews describing their efforts to produce *spillover* effects of their behavior changes on adolescents, index patients expressed varying levels of confidence about their ability to influence adolescents. Index patients' attitudes about the extent to which their behavior changes influenced adolescents may have affected parental engagement and the likelihood of giving advice. As such, index patients expressed a wide range of opinions about their ability to influence adolescents' health behaviors. Some index patients were intentional about changing adolescents' behaviors and felt they exerted a lot of influence while others were tentative about changing adolescents' behaviors and skeptical of their ability to influence adolescents because they believe they would be ineffective.

In general index patients fell into three categories along a continuum with respect to parental influence: (1) strong influence (i.e., index patients describe intentional efforts to influence adolescents' health behaviors because they felt they were highly influential in adolescents' health behavior decisions), (2) moderate influence (i.e., index patients did not intentionally influence adolescents' health behaviors but did observe changes in adolescents' behaviors that they associated with their own behavior change), and (3) limited influence (i.e., index patients explicitly described that they were ineffectual in influencing adolescents' health behaviors and were unaware if their own health behavior changes had any influence on adolescents). Yet, we found relatively consistent references in adolescent interviews to the fact that adolescents paid attention to what index patients were doing and saying about health behaviors. And, in many cases, we found that the actions and recommendations of index patients influenced adolescents to either make changes, or contemplate health behavior change.

Table 2 presents the index patients' perception of their influence on adolescents' behaviors juxtaposed with exemplar quotes from adolescents, thus representing perspectives from both members of the dyad. These examples are used to demonstrate observed variation in the extent to which index patients perceive that adolescents internalized messages about health behavior change. Because of the contrast between index patient and adolescent perspectives for this emergent theme, **Table 2** includes paired quotes from index patient and adolescent interviews.

Theme 5: Adolescent Caretaking of the Parent

In addition to describing the ways in which their own attempts at health behavior change influenced adolescents; some index patients described adolescents as being in a caretaking role. Some index patients felt that this caretaking role was another way that disease management programs produced *spillover* effects on adolescents because they were familiar with the health behaviors that were required to manage high blood pressure and prevent adverse health outcomes related to hypertension (**Table 3**). While not specific to healthy dietary or physical activity behaviors, one index patient described her grandson's knowledge about the importance of medication adherence and blood pressure monitoring and his caretaking role in reminding her of the importance of these:

"First thing he [adolescent] will ask is did you take your medicine granny? I'm like yeah. I took my medicine. You take your pressure today. Yeah, I took my pressure. Was it normal? Was it high? Oh, it was okay. Then you know, he'll go get the blood pressure cuff. Then he'll turn it on. Then he'll read it. Oh, that was good. It's like such and such points lower than what it was yesterday. Now, you know, this is better than what this reading was all week, you know. He's a good boy and, you know, he's concerned about everybody's health, yeah, very much."—50-years-old grandmother of grandson

Implicit in many descriptions of adolescent caretaking behaviors is this notion that involvement in the ACT study not only made index patients more aware of the need to improve their health behaviors but it provided an avenue by which adolescent family members had a better understanding of the types of behaviors that would help keep their family members healthy and they wanted to be involved in supporting disease management.

Additional Findings

Two hypothesized *spillover* mechanisms were not corroborated by index patient or adolescent interviews: changes in physical activity, and changes in family functioning due to study participation. Family functioning in particular was not the primary focus areas of most disease management interventions included in the ACT study. Yet, while the issue of family functioning associated with the parental role was discussed explicitly by some, there were also implicit references to family challenges as a source of stress. And some index patients made a clear connection between family stress, blood pressure control, and health behaviors. As one father put it:

"*I'm stubborn, I've got to the point now I hollers a lot at her [adolescent]. Instead of talking to her, I'll holler and—because it seems that when I tell her to do something, she don't even do it. And then before I knew it… I'll be done blowed up and then that's run the pressure up a lot. And then I have to count to 10. And say hey, it's a child you're talking to, count to 10."—66-years-old father of daughter*

This recognition that role stress can affect blood pressure may suggest that there is untapped potential for family-engaged disease management interventions. Such interventions may provide support to index patients and family members to

TABLE 2 | Exemplar quotes: parental influence and teen behavior change.

Parental sense of influence	Parent exemplar quote	Corresponding adolescent family member quote
Strong	"I mean, I take my other kids, too, so they'll know also, but I mostly tell him [teen], you go, you get certain things. I also let him know what I'm looking for, he'll read the label, and everything on the box. If it doesn't say what I want, he doesn't bring it back to me, cause he knows that's not what I want" −43-years-old female (mother)	**I:** Who do you look for, or who do you look to for examples on how to be healthy? **F:** My father and my mother …. Like sometimes she'll [index participant] say I need to stop eating a lot of junk food and stuff, and like I can't have junk food every day, and I need to–even though I'm gaining weight, I need to stop doing that.−12-years-old male (son)
Moderate	"… she [adolescent family member] watch what I eat. She know that I don't eat no beef, or no pork…She know I don't do the salt at all. So she, she pays attention. I may not think she paying attention, but she is. She is."−46-years-old female (stepmother)	Because the way how she [index participant] eat is so healthy, like she eat weird healthy food, like, uh, asparagus and stuff like that. I'm like I wonder how that taste. Like she be, she make sure we eat a lot of healthy food, and make sure we drink a lot of water…"−16-years-old female (stepdaughter)
Limited	"so, in terms of [adolescent family member], he can fry it up. He can fry anything he want to fry. I tried to get him away from frying, but he he's got to fry his food. Got to fry those potatoes, and for chicken nuggets, I try to get him to put them in a pan, stick them in the oven, and heat them up that way, but he won't do it."—66-years-old male (grandfather)	He [index participant] likes to like enforce us eating healthier foods. Like he always tells me—us to eat healthy and say I should always eat fruit. He thinks I don't eat fruit but I do…. I just—like, he buys a lot of bananas and stuff. Like I like oranges and stuff like that, so like when he always buys bananas—like I'll eat a banana, but like not regularly. But like he'll say I don't eat any fruits or whatever because I don't eat the bananas…"−15-years-old male (grandson)

TABLE 3 | Exemplar quotes: adolescent caretaking behaviors.

"And when I set her down and explain to her '[adolescent family member],' I said, 'I'm sick.' 'No, daddy, you've got to do things. That's what's wrong. If I do everything, you'll just lay down and don't do nothing.' Like hey, I'm going to make you work. I said, 'No, you do your part and Daddy going to do his part."'—66-years-old male (father)
"[Other child in household] always concerned about my health, always concerned. How you feel? Um, you need some water. Um, um, you take your needle shot (laughter). I'm like yeah [other child in household]. Yes [other child]. Yes [other child]. You know, he, very concerned, and when I was going to the Saturday meetings, he was like you coming back. I'm yeah, I'm coming back, you know. And, 'cause he was just so worried that I was going to go in the hospital, you know. So it, it really helped. And he see how I eat now, you know. And I be telling him boy, I'm getting ready to, getting ready to put you on that diet with me. Sure is, 'cause he is, he done out grew all his clothes, new clothes that we just bought him he can't fit at all. I'm like yeah, you, getting ready to do some exercises and all that with me. And he be like okay (laughter). He, that's my boy. That's, he like my right hand man. I take him everywhere."−46-years-old female (stepmother)
"That's the main time when I see him [adolescent family member], when he needs something. But as far as that, he really doesn't bother me because he knows my condition, because he knows I'm probably upstairs, with oxygen. And he doesn't really bother because I'm on a lot of medication and stuff. So if he needs something, he comes upstairs, or if he wants something. But as far as that, he'll come to say hi."—*44-years-old (father)*

address role stress and family dynamics that produce physiologic and behavioral responses to stress that are counterproductive to achieving blood pressure control and maintaining healthy diet and physical activity behaviors. While interesting and provocative, however, this sentiment was not articulated as clearly as the themes described above.

DISCUSSION

We found that index patients see themselves as important role models of behavior change for adolescent family members. We also found support from index patients' reported perceptions that their participation in a disease management intervention may produce *spillover* effects on adolescents' dietary behaviors, particularly via role modeling, changes in the home food environment, and meal preparation. These changes were perceived to be associated with increasing knowledge and awareness of healthy eating behaviors among adolescents in addition to improving index patients' own awareness of healthy foods and meal preparation techniques. In contrast, we did not find evidence to suggest significant spillover effects on adolescents' physical activity behaviors. While, there were a few interviews in which physical activity was briefly discussed, in general much more of the discussion focused on dietary behaviors. While it is possible that this difference in spillover for dietary vs. physical activity behaviors reflects a difference in the extent to which these behaviors are susceptible to intergenerational spillover, more likely these differences reflect the fact that the ACT study placed significant emphasis on promoting dietary behavior change as a method for improving blood pressure control (e.g., via intervention messages intended to decrease index patients' consumption of sodium and fried foods).

Because this study relied entirely on data from interviews with index patients and adolescents, we are unable to corroborate index patients' and adolescents' perceptions with objective data related to adolescents' health. Ideally future research would measure adolescents' perceptions of spillover alongside use of objective measures to assess their health behaviors and their objective health status including anthropometric measurements, assessment of weight status, and potentially evaluation of blood pressure and other clinical indicators, such as blood glucose and cholesterol levels.

Beyond these hypothesized mechanisms for adult disease management program participation producing *spillover* effects on the behaviors of adolescent family members, many index patients described an explicit effort to encourage adolescents to adopt healthier lifestyle behaviors. We also found that, despite variation in index patients' perceptions of their influence over adolescents, most adolescents recalled the advice related to diet behaviors that index patients passed onto them after participating in disease management programs. Thus, this study provides evidence to suggest that adolescents are internalizing the new knowledge and behavior changes of their adult family members acquired via disease management program participation. Furthermore, some adolescents employ new skills and disease management techniques to support disease management and minimize negative health outcomes for their adult family members by taking on an active caretaking role, reminding index patients of what they should do to support their own health.

Findings from this research suggest that disease management interventions addressing health behaviors among high-risk populations have untapped potential to produce family-level influences on adolescent health behavior change. This research also suggests a need for more focus on ways to increase family engagement in disease management programs. We argue, in particular, that such family-engaged or family level intervention strategies could increase the influence of disease management interventions over the life course in addressing CVD disparities. It could also be important for reducing childhood obesity and long-term CVD risk among high-risk children and adolescents living with adults family members with chronic disease who may be particularly motivated to prevent intergenerational transfer of CVD risk via health behavior change.

For example, work by Grandes and colleagues suggests that the presence of comorbid conditions associated with obesity can affect adult patients' readiness for behavior change (34). Rhee and colleagues have also found the same regarding parents' receptiveness to addressing obesity in their child (35). Thus, developing family-level disease management programs and increasing family engagement in existing programs targeting high-risk populations may be particularly important as a strategy for engaging adults living with child family members because they are motivated to change their own behavior when they are confident they can also influence health behavior change in other family members, particularly children and adolescents.

This research is exploratory and, while it suggests avenues for further inquiry, these findings are hypothesis generating and should not be viewed as exhaustive in terms of the mechanisms by which *spillover* may operate in the context of disease management programs. Furthermore, given the qualitative methodology of this study, the findings cannot be used to generalize to a broader population of families. Because we did not collect objective measures of health behaviors or clinical indicators, these findings merit further exploration and verification via more rigorous research that links self-reported perceptions of spillover with health behavior data and clinical measures for both adult patients and adolescent family members.

Additionally, there are risks that some responses were influenced by social desirability bias since index patients were educated about healthy behaviors via participation in the ACT study. Similarly, adolescent family members may have been influenced by social desirability bias. There is also a risk that interviewers who conducted in-depth interviews inadvertently gave index patients and adolescents cues regarding the types of responses they were expecting. This could further compromise the validity of the study findings. Future research should involve more in-depth use of qualitative and quantitative methods, potentially over time during implementation of a family-level intervention so as to prospectively evaluate both perceptions of spillover and objective measures of health behavior change and clinical outcomes. Such a study is important for better understanding the timing of adolescents' perceived health behavior changes and the relationship between the changes and the family-level disease management intervention. Ideally such research would also corroborate reports of behavior change using clinical indicators to track changes in weight status and diet composition. Future research should also involve larger patient and family populations and pay special attention to evaluating the factors and circumstances that are associated with both the presence and the absence of spillover effects among some adolescents. In particular, research to better understand the circumstances that prevent spillover effects on adolescents would be important to understand in more detail as understanding conditions that prevent effective spillover effects could inform future intervention development efforts.

Despite these caveats, we believe these findings are intriguing and warrant further, rigorous investigation and that they provide evidence to support the hypothesis that adult disease management interventions may produce *spillover* effects on adolescent family members. Future research should not only rigorously evaluate *spillover* effects of existing disease management programs on child family members, but it should also involve development, testing, and implementation of family-focused disease management programs that explicitly target adult chronic disease management and primordial or primary prevention via health behavior change among child family members. While potential for social desirability bias is important to consider, Our findings were generally consistent with existing literature about parental influence on adolescents. Future interventions could bolster parental confidence in their influence on their adolescent family members and help empower parents to exert role modeling and influence their child's behavior.

AUTHOR CONTRIBUTIONS

RT made substantial contributions to all phases of the research including conception or design, acquisition of data, analysis and interpretation of data, and drafting and revising the manuscript. TY made substantial contributions to analysis or interpretation of data for the work and drafting the work or revising it critically for important intellectual content. PE made substantial contributions to the conception or design of the work, the acquisition and interpretation of data for the work and contributing to revising this manuscript for important intellectual content. LB made substantial contributions to the conception or design of the work; the acquisition, analysis, and interpretation of data and also involved in critically revising this manuscript for important intellectual content. LC made substantial contributions to the conception or design of the work; and to the acquisition, analysis, or interpretation of data for the work and also made significant contributions to critically revising this manuscript for important intellectual content.

FUNDING

This study was supported by grants from the Johns Hopkins Center for Health Equity (formerly the Johns Hopkins Center to Eliminate Cardiovascular Health Disparities) which was funded by the National Heart, Lung, and Blood Institute (Grant No. P50 HL105187) (Principal Investigator: LC). The ACT study PI (LB) was funded as part of the Johns Hopkins Center for Health Equity which was funded by the NHLBI (Grant No. P50 HL105187). The study principal investigator (RT) is supported by a career development award through the NHLBI (Grant No. K23 HL121250). TY was supported by funds through RT's K23 and the Johns Hopkins School of Medicine Predoctoral Research Program for Medical Students. No copyrighted materials were used in this study.

ACKNOWLEDGMENTS

We thank the research staff and analysts including, Katherine A. Johnson, Ph.D. (KJ) Jamie Perin, Ph.D.; LaPricia Lewis Boyer, and Wyatt Smith.

REFERENCES

1. Ogden C, Carroll M, Kit B, Flegal K. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *JAMA*. (2012) 307:483–90. doi: 10.1001/jama.2012.40
2. Lasserre AM, Chiolero A, Paccaud F, Bovet P. Worldwide trends in childhood obesity. *Swiss Med Wkly*. (2007) 137:157–8.
3. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA*. (2010) 303:242–9. doi: 10.1001/jama.2009.2012
4. Keppel K, Pearcy J, Heron M. Is there progress towards eliminating racial/ethnic disparities in the leading causes of death? *Public Health Rep*. (2010) 125:689–97. doi: 10.1177/003335491012500511
5. Go A, Mozaffarian D, Roger V, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. (2013) 127:e6–245. doi: 10.1161/CIR.0b013e31828124ad
6. Lee JM, Pilli S, Gebremariam A, Keirns CC, Davis MM, Vijan S, et al. Getting heavier, younger: trajectories of obesity over the life course. *Int J Obes (Lond)*. (2010) 34:614–23. doi: 10.1038/ijo.2009.235
7. Richardson L, Hussey J, Strutz K. Origins of disparities in cardiovascular disease: birth weight, body mass index, and young adult systolic blood pressure in the National Longitudinal Study of Adolescent Health. *Ann Epidemiol.* (2011) 21:598–607. doi: 10.1016/j.annepidem.2011.02.012
8. Miech RA, Kumanyika SK, Stettler N, Link BG, Phelan JC, Chang VW. Trends in the association of poverty with overweight among US adolescents, 1971–2004. *JAMA*. (2006) 295:2385–93. doi: 10.1001/jama.295.20.2385
9. Ali MK, Bullard KM, Beckles GL, Stevens MR, Barker L, Narayan KM, et al. Household income and cardiovascular disease risks in U.S. children and young adults: analyses from NHANES 1999–2008. *Diabetes Care* (2011) 34:1998–2004. doi: 10.2337/dc11-0792
10. Rossen L, Schoendorf K. Measuring health disparities: trends in racial-ethnic and socioeconomic disparities in obesity among 2- to 18-year old youth in the United States, 2001–2010. *Ann Epidemiol.* (2012) 22:698–704. doi: 10.1016/j.annepidem.2012.07.005
11. Olds T, Maher C, Zumin S, Péneau S, Lioret S, Castetbon K, et al. Evidence that the prevalence of childhood overweight is plateauing: data from nine countries. *Int J Pediatr Obes.* (2011) 6:342–60. doi: 10.3109/17477166.2011.605895
12. Robert Wood Johnson Foundation. *Declining Childhood Obesity Rates–Where Are We Seeing the Most Progress?* (2012). Available online at: www.rwjf.org/healthpolicy; http://www.rwjf.org/content/dam/farm/reports/issue_briefs/2012/rwjf401163
13. U.S. Preventive Services Task Force. *The Guide to Clinical Preventive Services 2010–2011* (2010). Available online at: http://www.ahrq.gov/clinic/pocketgd1011/pocketgd1011.pdf
14. Danaei G, Rimm E, Oza S, Kulkarni S, Murray C, Ezzati M. The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med*. (2010) 7:e1000248. doi: 10.1371/journal.pmed.1000248
15. Ho M, Garnett S, Baur L, Burrows T, Stewart L, Neve M, et al. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. *Pediatrics* (2012) 130:e1647–71. doi: 10.1542/peds.2012-1176
16. Hingle M, O'Connor T, Dave J, Baranowski T. Parental involvement in interventions to improve child dietary intake: a systematic review. *Prev Med*. (2010) 51:103–11. doi: 10.1016/j.ypmed.2010.04.014
17. Foltz JL, May AL, Belay B, Nihiser AJ, Dooyema CA, Blanck HM. Population-level intervention strategies and examples for obesity prevention in children. *Annu Rev Nutr*. (2012) 32:391–415. doi: 10.1146/annurev-nutr-071811-150646
18. Grzywacz JG, Almeida DM, McDonald DA. Work-family spillover and daily reports of work and family stress in the Adult Labor Force. *Fam Relat.* (2002) 51:28–36. doi: 10.1111/j.1741-3729.2002.00028.x
19. Sturge-Apple ML, Davies PT, Cicchetti D, Cummings EM. The role of mothers' and fathers' adrenocortical reactivity in spillover between interparental conflict and parenting practices. *J Fam Psychol*. (2009) 23:215–25. doi: 10.1037/a0014198
20. Williams KJ, Alliger GM. Role stressors, mood spillover, and perceptions of work-family conflict in employed parents. *Acad Manage J.* (1994) 37:837–68. doi: 10.2307/256602
21. Laroche H, Davis M, Forman J, Palmisano G, Reisinger HS, Tannas C, et al. Children's roles in parents' diabetes self-management. *Am J Prev Med*. (2009) 37(6 Suppl. 1):S251–61. doi: 10.1016/j.amepre.2009.08.003
22. Laroche H, Heisler M, Forman J, Anderson M, Davis M. When adults with diabetes attempt to drink less soda: resulting adult-child interactions and household changes. *J Natl Med Assoc.* (2008) 100:1004–11. doi: 10.1016/S0027-9684(15)31436-X
23. Klohe-Lehman D, Freeland-Graves J, Clarke K, Cai G, Voruganti VS, Milani TJ, et al. Low-income, overweight and obese mothers as agents of change to improve food choices, fat habits, and physical activity in their 1-to-3-year-old children. *J Am Coll Nutr*. (2007) 26:196–208. doi: 10.1080/07315724.2007.10719602
24. Lubans D, Morgan P, Collins C, Okely A, Burrows T, Callister R. Mediators of weight loss in the "Healthy Dads, Healthy Kids" pilot study for overweight fathers. *Int J Behav Nutr Phys Act*. (2012) 18:45. doi: 10.1186/1479-5868-9-45

25. Sato A, Jelalian E, Hart C, Lloyd-Richardson EE, Mehlenbeck RS, Neill M, et al. Associations between parent behavior and adolescent weight control. *J Pediatr Psychol*. (2011) 36:451–60. doi: 10.1093/jpepsy/jsq105
26. Ma J, Flanders W, Ward E, Jemal A. Body mass index in young adulthood and premature death: analyses of the U.S. National Health Interview Survey linked mortality files. *Am J Epidemiol.* (2011) 174:934–44. doi: 10.1093/aje/kwr169
27. Arcan C, Neumark-Sztainer D, Hannan P, van den Berg P, Story M, Larson N. Parental eating behaviours, home food environment and adolescent intakes of fruits, vegetables, and dairy foods: longitudinal findings from Project EAT. *Public Health Nutr.* (2007) 10:1257–65. doi: 10.1017/S1368980007687151
28. Hanson N, Neumark-Sztainer D, Eisenberg M, Story M, Wall M. Associations between parental report of the home food environment and adolescent intakes of fruits, vegetables and dairy foods. *Public Health Nutr.* (2005) 8:77–85. doi: 10.1079/PHN2004661
29. Golan M. Parents as agents of change in childhood obesity–from research to practice 65. *Int J Pediatr Obes.* (2006) 1:66–76. doi: 10.1080/17477160600644272
30. Laroche H, Davis M, Forman J, Palmisano G, Heisler M. What about the children? The experience of families involved in an adult-focused diabetes intervention. *Public Health Nutr.* (2007) 11:427–36. doi: 10.1017/S1368980007000791
31. Barr-Anderson D, Adams-Wynn A, DiSantis K, Kumanyika S. Family-focused physical activity, diet and obesity interventions in African-American girls: a systematic review. *Obes Rev*. (2013) 14:29–51. doi: 10.1111/j.1467-789X.2012.01043.x
32. Ephraim PL, Hill-Briggs F, Roter DL, Bone LR, Wolff JL, Lewis-Boyer L, et al. Improving urban African Americans' blood pressure control through multi-level interventions in the achieving blood pressure control together (ACT) study: a randomized clinical trial. *Contemp Clin Trials* (2014) 38:370–82. doi: 10.1016/j.cct.2014.06.009
33. Friese S. *ATLAS.ti 7: User Guide and Reference*. Berlin: Atlas.ti Scientific Software Development GmbH (2013).
34. Grandes G, Sanchez A, Torcal J, Sánchez-Pinilla RO, Lizarraga K, Serra J, et al. Targeting physical activity promotion in general practice: characteristics of inactive patients and willingness to change. *BMC Public Health* (2008) 8:172. doi: 10.1186/1471-2458-8-172
35. Rhee K, De Lago C, Arscott-Mills T, Mehta S, Davis R. Factors associated with parental readiness to make changes for overweight children. *Pediatrics* (2005) 116:e94–101. doi: 10.1542/peds.2004-2479

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 22 January 2019
doi: 10.3389/fped.2018.00433

Where Children Live: Examining Whether Neighborhood Crime and Poverty Is Associated With Overweight and Obesity Among Low-Income Preschool-Aged Primary Care Patients

Nakiya N. Showell*, Jacky M. Jennings, Katherine A. Johnson, Jamie Perin and Rachel L. J. Thornton

Division of General Pediatrics and Adolescent Medicine, Johns Hopkins School of Medicine, Baltimore, MD, United States

OPEN ACCESS

Edited by:
Fatima Cody Stanford,
Harvard Medical School,
United States

Reviewed by:
Tudor Lucian Pop,
Iuliu Haţieganu University of Medicine and Pharmacy, Romania
Corentin Babakissa,
Université de Sherbrooke, Canada

****Correspondence:***
Nakiya N. Showell
nshowel1@jhmi.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *01 November 2018*
Accepted: *27 December 2018*
Published: *22 January 2019*

Citation:
Showell NN, Jennings JM, Johnson KA, Perin J and Thornton RLJ (2019) Where Children Live: Examining Whether Neighborhood Crime and Poverty Is Associated With Overweight and Obesity Among Low-Income Preschool-Aged Primary Care Patients. Front. Pediatr. 6:433. doi: 10.3389/fped.2018.00433

Introduction: Low-income and racial/ethnic minority preschoolers (aged 2–5 years) are disproportionately affected by obesity and its associated health consequences. Individual-level factors (e.g., diet) *and* environmental factors (e.g., neighborhood conditions) contribute to these disparities. However, there is limited research examining the role of neighborhood factors on obesity risk specifically among high-risk preschoolers. The objectives of this study are to describe the geographic distribution of preschool patients receiving care at two primary care pediatrics clinics affiliated with an academic medical center, and explore whether exposure to neighborhood crime and poverty is associated with obesity risk among this population.

Methods: Cross-sectional multilevel study linking clinical administrative data on patient visits between 2007 and 2012 with data from the American Community Survey and the Baltimore City Police Department. Home addresses of 2–5 year-old patients were geocoded to their neighborhood (i.e., census block group) of residence. We used logistic regression to examine the cross-sectional relationship between obesity and overweight and neighborhood-level factors. All analyses were adjusted for age and gender, and stratified by race/ethnicity (Black, Hispanic, and White).

Results: The majority of preschool patients lived in moderate or high crime (84%) or high poverty (54%) neighborhoods. A significantly higher proportion of Black preschoolers lived in high poverty neighborhoods compared to White preschoolers (61% vs. 38%, $p < 0.001$). Among this clinic-based sample of preschoolers, living in high crime or high poverty neighborhoods was not associated with a clinically significant increased odds of overweight or obesity.

Conclusions: This study examines the association between neighborhood factors and obesity and overweight among a clinic-based population of low-income racial/ethnic minority preschoolers. The neighborhoods where preschoolers in this sample lived, on average had higher crime counts and poverty than the citywide average for Baltimore.

Our findings also suggest that Black preschoolers are exposed to higher levels of neighborhood poverty compared to Whites. While no meaningful association between these neighborhood factors and odds of obesity or overweight was found in this cross-sectional analysis, our findings suggest avenues for future studies informative to the development of clinic-based obesity management interventions aimed at effectively addressing neighborhood contributors to early childhood obesity disparities.

Keywords: obesity, neighborhood crime, neighborhood poverty, primary care pediatrics, intervention

INTRODUCTION

More than 20% of preschoolers (ages 2–5 years) are overweight or obese by the time of school entry (1). Obese preschoolers children are more likely to become obese adults and resultantly are at higher-risk for obesity-related health complications including hypertension, diabetes, and cardiovascular disease (2, 3). While national data suggests obesity rates may be declining among preschoolers, racial/ethnic and socioeconomic (SES) disparities in obesity prevalence in this age group are persistent (4); and threaten to curtail efforts to curb the childhood obesity epidemic.

The mechanisms responsible for producing and sustaining racial/ethnic- and SES-based obesity disparities are likely multifactorial and are hypothesized to include both individual risk factors (e.g., television viewing, increased intake of sugar-sweetened beverage intake) and neighborhood conditions including neighborhood SES, neighborhood safety, and neighborhood crime exposure (5–7).

Neighborhood SES and crime are postulated to influence obesity risk in part through their potential effects on physical activity. Though emerging, data exists supporting an association between these neighborhood conditions and physical activity among children. For instance, a recent systematic review of cohort studies demonstrated that living in unsafe neighborhoods was associated with a reduction in children's (aged ≤17 years) physical activity level (8). The majority of studies examined in the aforementioned review incorporated perceived neighborhood safety measures and a lesser number of studies utilized objective measures of crime (8). A prior review conducted by Davison and Lawson, demonstrated that objectively measured local crime rates were inversely associated with children's reported physical activity level (9). Notably, most studies, particularly those focused on preschoolers, have solely utilized subjective measures of neighborhood safety with significant heterogeneity or have examined these types of neighborhood environmental exposures over large geographic areas such as census tracts or counties (9–12).

Despite the potential importance of neighborhood factors such as SES and crime on childhood obesity risk, research examining the association between such factors and obesity risk itself is limited, particularly among low-income racial/ethnic minorities who experience disparities in obesity risk throughout the life course and are also more likely to reside in potentially obesogenic neighborhoods characterized by lower SES and higher levels of crime (6, 8, 13). Fewer studies still have explored the association of neighborhood SES and crime with obesity risk among *clinic-based* pediatric patient populations (14, 15). The findings of such studies can be particularly informative to the development of clinic-based obesity management interventions that integrate strategies responsive to the neighborhood social contexts in which patients live.

In this study, we used data from two urban hospital-affiliated pediatric primary care practices in Baltimore, Maryland to: (1) describe the geographic distribution of residence and neighborhood levels of crime and SES among preschool-aged patients and (2) determine the association of neighborhood levels of crime and SES with the prevalence of obesity and overweight among this clinic-based sample of preschoolers.

MATERIALS AND METHODS

Study Design

This study was a cross-sectional analysis of primary care patient data from preschoolers from October 1, 2007 to November 6, 2012. Patient data were extracted from electronic medical records and manual chart reviews and linked with neighborhood poverty data from the American Community Survey (16) and crime data from the Baltimore City Police Department (BCPD) (17). The Johns Hopkins School of Medicine Institutional Review Board approved this study protocol.

Setting and Participants

Patient data were from two urban, hospital-based pediatric primary care clinics (Clinic A and Clinic B) affiliated with a large academic medical center in Baltimore, Maryland. Clinic A serves a population that is 65% Hispanic, the majority of whom are children of Mexican and Central American immigrants to the U.S. Clinic B serves a patient population that is approximately 90% non-Hispanic Black. Both sites serve predominantly low-income populations; more than 80% of patients at each site receive health insurance through the state Medicaid program. Preschool-aged patients from both clinic sites were included in this study if they met the following criteria: (1) documented address within Baltimore City limits; (2) ≥1 clinic visit documented in data extraction period with a clear record of height, weight, gender, race/ethnicity and insurer; (3) race/ethnicity documented as White, Black or Hispanic; (4) valid address for geocoding; and (5) biologically valid height, weight and body mass index z-score.

Data Sources

Patient data were obtained for all study participants from the most recent preventive health visit in each calendar year. The clinic data included the following information from the most recently recorded visit date: date of birth, gender, residential address, zip code, insurance provider/guarantor, language preference, race/ethnicity, patient weight, and patient height.

Measures

The main outcome measure of overweight and obese was calculated using child age-and sex-specific body mass index (BMI) percentile. We used reported height and weight, and gender, date of birth, and date of visit to calculate the BMI percentile for each patient using standard methodology (18). We report results based on the Centers for Disease Control and Prevention growth chart cutoffs for underweight, normal weight, overweight, and obese. The calculated BMI percentiles were then standardized to produce a BMI z-score for each patient using the 2006 World Health Organization (WHO) Child Growth Standards for children under 60 months of age (19).

The two main neighborhood variables of interest were crime and neighborhood SES. Geographic information system (GIS) software (20) was used to characterize neighborhood crime and neighborhood SES of participants based on geocoded residential addresses. Participant neighborhoods were defined as the 2010 census block group (CBG) using ArcGIS software. Using BCPD data, we operationalized neighborhood crime as the average number of violent crimes (e.g., homicide, aggravated assault) per 1,000 residents in each CBG over the 5-calendar years from 2006 to 2010. Tertiles of neighborhood crime were calculated using the distribution of crime density across the 653 CBGs in the city as the reference. Low-crime neighborhoods had <48 crimes/mi2, moderate-crime neighborhoods had 48–103 crimes/mi2 and high-crime neighborhoods had >103 crimes/mi2. Because Baltimore generally has a high crime rate, and there are not nationally accepted thresholds for determining what constitutes high vs. low crime across all neighborhood contexts, we elected to assess crime as a continuous exposure as opposed to defining high vs. low crime neighborhoods based on the distribution of crime counts across Baltimore CBGs. Using data from the 5-year 2013 American Community Survey (aggregated data from 2008 to 2012) (16), we operationalized neighborhood SES as the percent of households living below the Federal Poverty Line within a CBG. This approach has been used in previous research and is thought to be a more accurate measure of neighborhood poverty level for children as compared to neighborhood median income because it takes into account the number of individuals per household (21). Poverty was dichotomized as high (≥20% of households living below the poverty line) and low (<20% of household living below the poverty line). Thus, the threshold for identifying high poverty or low SES neighborhoods was independent of the median poverty rate across Baltimore City and is based on accepted standard measures.

Data Analysis

Summary statistics were used to describe the study population by individual and neighborhood level factors overall and by race/ethnicity. We examined potential differences in individual child and neighborhood-level factors by race/ethnicity using Chi-square tests for categorical variables and ANOVA test for continuous variables. Logistic regression was used to evaluate the association between the odds of overweight or obesity and number of violent crimes and separately, neighborhood poverty per CBG. Resulting estimates of associations were calculated for the overall study sample and stratified by race/ethnicity. For neighborhood violent crimes, estimates are reflected as odds ratios for an increase of 10 violent crimes in each child's CBG. For neighborhood SES, estimates are reflected as odds ratios comparing patients living in CBGs with high poverty to patients living in CBGs with low poverty. Statistical significance was defined as an odds ratio that did not cross 1.0 and a p-value that was <0.05. All logistic models were adjusted for age and gender.

RESULTS

Data Extraction

The initial study population included 5,433 unique study participants and 10,975 unique clinic visits (**Figure 1**). Among these, 2,769 of visits were excluded because the listed residential address was outside the Baltimore City limits. Three hundred and eighty-two of visits with missing or unclear records for height, weight, gender, race/ethnicity, or insurer were also excluded as were children whose race/ethnicity was not listed as White, Black or Hispanic (n = 31 visits), children with missing/invalid addresses (n = 286 visits) or those where height, weight, or body mass index z-score deemed biologically implausible (n = 377 visits). The final study population included 3,684 study participants with 7,130 visits, representing 68 and 65% of initial total patients and total visits, respectively.

Patient Sample Characteristics and Geographic Distribution

Figure 2 demonstrates the geographic distribution of neighborhoods of residence for all patients receiving care at Clinic A and Clinic B who live within the Baltimore City limits. This figure demonstrates that the majority of the CBGs with the largest number of clinic patients fall within a1.5-mile buffer of each clinic location. This buffer size was chosen to capture the overlapping area between the two clinic sites. 54.5% (N = 2,148) of all patients lived in CBGs that are completely or partially inside the 1.5-mile buffer for the two clinics. The patient population for Clinic A is concentrated within 1.5 miles with 73.9% (N = 1,203 patients) residing within this catchment area while only 37.4% (N = 865 patients) of clinic B patients reside within 1.5 miles of the clinic. Together, the patients from these two clinics represent 29.1% of all children residing within the catchment area.

The median crime count for the neighborhoods where the study population lived was 75 crimes per CBG as compared to a median crime count of 64 crimes per CBG for Baltimore neighborhoods overall. And, 54% of preschoolers in the study

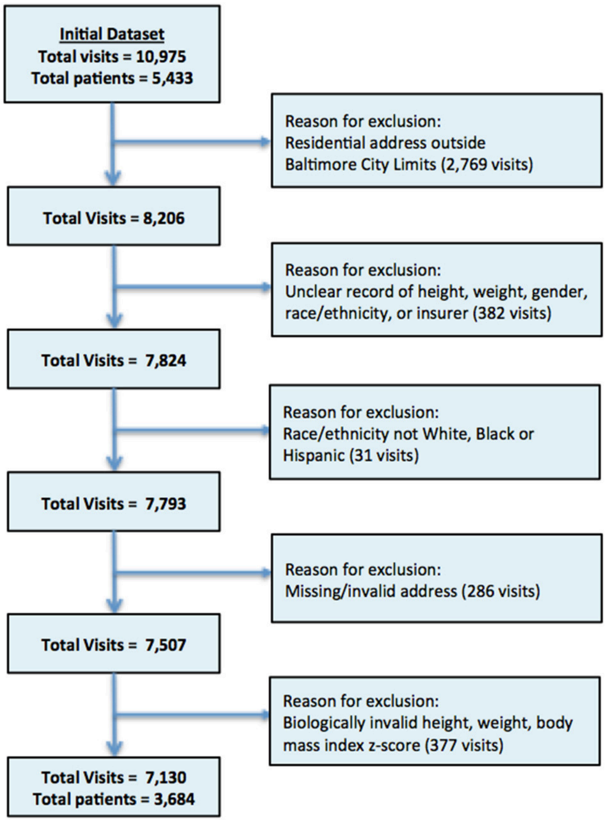

FIGURE 1 | Flow Chart patient data extraction process.

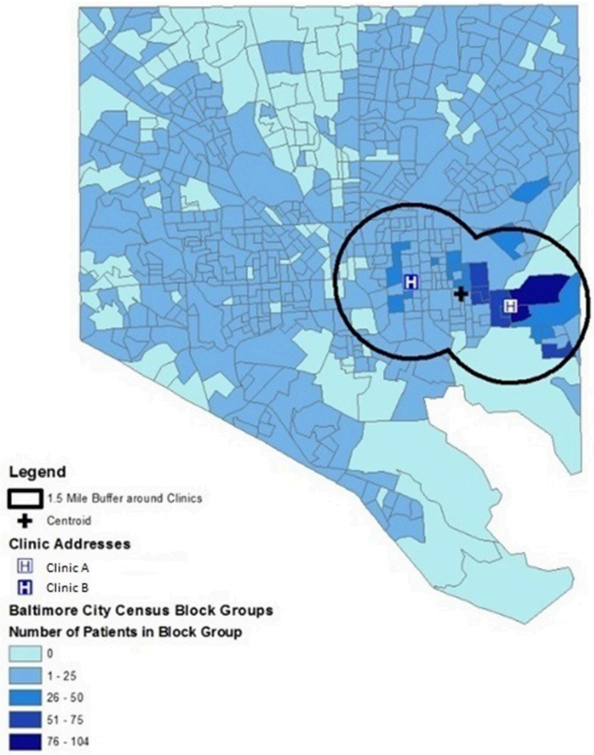

FIGURE 2 | Geographic distribution of neighborhoods of residence for patients residing within Baltimore City limits who received care at two urban, hospital-affiliated primary care clinics. Neighborhoods are depicted as census block groups, and 1.5-mile buffer around each clinic and point location of each clinic are shown.

population live in high poverty neighborhoods (≥20% of families living below the federal poverty line) compared to 40% of all Baltimore residents who live in high poverty neighborhoods.

Table 1 provides more detail regarding the demographic characteristics of all patients under study. On average White patients attending these clinics were younger (Whites: mean age 3.8 years vs. Hispanics: mean age 4.0 years, $p < 0.001$), more likely to have private insurance (Whites: 28% vs. Hispanics: 1%, $p < 0.001$), and less likely to be obese as compared to Hispanic patients (Whites: 14% vs. Hispanics: 23%, $p < 0.001$). Black patients were more likely to live in CBGs with high poverty compared to Whites (61 vs. 38%, $p < 0.001$). Similarly, Black and Hispanic patients were both more likely to reside in CBGs with a high number of violent crimes compared to Whites (Blacks: 42%; Hispanics: 44% vs. Whites: 34%, $p < 0.001$).

Neighborhood Violent Crime

Table 2 shows estimates of associations between overweight, obesity and number of violent crimes per CBG of patient residence. The odds of obesity or overweight for Hispanic and White preschoolers were not associated with living in a higher crime neighborhood (Hispanics: odds ratio−0.994, 95% CI: 0.974–1.013; Whites: odds ratio−1.008, 95% CI: 0.979–1.037). There was, however, a statistically significant association of the odds of obesity with crime among Black children such that adjusted odds of obesity was 0.978 for every increase of 10 violent crimes in a child's neighborhood (95% CI, 0.959 to 0.998, $p = 0.031$). This result was in the opposite direction of what was hypothesized and was only observed for Black preschoolers. A sensitivity analysis examining whether this association was the result of differences in the neighborhood crime exposure for preschoolers of different races demonstrated that these results were consistent for Black children even after four children living in extremely high crime neighborhoods were excluded (not shown), and when stratifying preschoolers by neighborhood poverty level (not shown).

Neighborhood Poverty

Table 3 displays estimates of associations between overweight, obesity and neighborhood SES operationalized as neighborhood poverty level dichotomized as high poverty (≥20% of households living below the federal poverty line) and low poverty (<20% of households living below the federal poverty line). Although neighborhood crime and poverty rates are closely related (Pearson correlation estimate 0.23, 95% CI 0.15–0.31, $p < 0.001$), poverty is not associated with obesity or overweight in unadjusted and adjusted analyses in this patient population, overall, and among any of the three racial/ethnic groups studied (**Table 3**).

TABLE 1 | Individual and neighborhood characteristics overall and by race/ethnicity among a primary care-based clinic sample of preschoolers, October 1, 2017–November 6, 2012, Baltimore City, Maryland.

	Overall	By race/ethnicity			*p**
		Black	Hispanic	White	
N	3,684	2,531	904	249	
CHILD FACTORS					
Age–mean years (SD)	4.2 (1.2)	4.3 (1.2)	4.0 (1.2)	3.8 (1.2)	<0.001
Source of insurance					<0.001
Public	3,365 (91%)	2,290 (90%)	895 (99%)	180 (72%)	
Private	319 (9%)	241 (10%)	9 (1%)	69 (28%)	
Weight status					<0.001
Below normal	130 (4%)	104 (4%)	15 (2%)	11 (4%)	
Normal	2,363 (64%)	1,677 (66%)	516 (57%)	170 (68%)	
Overweight	589 (16%)	394 (16%)	162 (18%)	33 (13%)	
Obese	602 (16%)	356 (14%)	211 (23%)	35 (14%)	
Gender					0.218
Male	1,858 (50%)	1,301 (51%)	436 (48%)	121 (49%)	
Female	1,826 (50%)	1,230 (49%)	468 (52%)	128 (51%)	
NEIGHBORHOOD FACTORS					
CBG more than 20% of HHs in poverty	1,992 (54%)	1,548 (61%)	350 (39%)	94 (38%)	<0.001
CBG number of violent crimes–mean (SD)	105.1 (73.0)	107.0 (71.9)	103.3 (69.8)	93.0 (91.6)	0.010
CBG crime tertile within Baltimore City					<0.001
High crime (>103)	1,542 (42%)	1,059 (42%)	399 (44%)	84 (34%)	
Moderate crime (48–103)	1,550 (42%)	1,112 (44%)	335 (37%)	103 (42%)	
Low crime (less than 48)	591 (16%)	360 (14%)	170 (19%)	61 (25%)	

**Significance for the association or difference anywhere between race/ethnicity group and given factor, determined by a Chi-square test for categorical factors or ANOVA test for continuous factors.*

TABLE 2 | Associations between obesity, overweight and overweight or obese and average number of violent crimes in each census block group of patient residence.

		Black patients			Hispanic patients			White patients		
		Est.	95% CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*
CDC-STANDARDIZED BMI PERCENTILE										
Obese vs. Normal weight	Bivariate	0.979	(0.961, 0.998)	**0.028**	0.985	(0.960, 1.010)	0.238	0.999	(0.962, 1.038)	0.962
	Adjusted*	0.978	(0.959, 0.998)	**0.031**	0.987	(0.962, 1.013)	0.330	1.007	(0.969, 1.046)	0.718
Overweight vs. Normal	Bivariate	0.998	(0.983, 1.013)	0.745	1.004	(0.980, 1.027)	0.761	1.013	(0.982, 1.044)	0.424
	Adjusted*	0.998	(0.982, 1.014)	0.790	1.003	(0.979, 1.027)	0.836	1.012	(0.981, 1.045)	0.446
Overweight OR Obese	Bivariate	0.990	(0.977, 1.002)	0.108	0.994	(0.974, 1.013)	0.522	1.008	(0.979, 1.037)	0.599
	Adjusted*	0.990	(0.976, 1.003)	0.134	0.995	(0.975, 1.015)	0.594	1.011	(0.982, 1.041)	0.469

*Associations are shown as odds ratios for an increase of 10 crimes. *Adjusted for age, gender and proportion of households living under the poverty line in each census block group.*

DISCUSSION

In this clinic-based population of 3,684 low-income, predominantly racial/ethnic minority preschoolers, we found that the majority of patients lived in neighborhoods with high levels of crime and poverty. Among this sample of children from predominantly high poverty neighborhoods we found no statistically significant association between neighborhood SES and child overweight or obesity. Furthermore, while we found a statistically significant association between neighborhood crime and obesity among Black preschoolers such that there was a statistically significantly *lower* odds of obesity for every 10 count increase in crimes, this is likely not a clinically significant association nor is it consistent across all racial/ethnic groups within the study sample.

Our findings are in contrast to some other studies that have found statistically significant associations between neighborhood SES and neighborhood crime and child obesity (11, 22–24). Potential explanations for the lack of associations observed in our study include unmeasured neighborhood-level exposures that may contribute to obesity risk such as the neighborhood food environment and proximity to parks or other recreational

TABLE 3 | Associations between obesity, overweight and overweight or obese and poverty per CBG of patient residence. Associations are shown as odds ratios comparing those in CBGs with 20% or more of households below poverty line (high poverty) vs. those with less than 20% (low poverty).

		Black patients			Hispanic patients			White patients		
		Est.	95% CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*
CDC-STANDARDIZED BMI										
Obese vs. Normal weight	Bivariate	0.896	(0.710, 1.131)	0.356	0.989	(0.711, 1.375)	0.947	1.604	(0.771, 3.336)	0.206
	Adjusted*	0.884	(0.700, 1.117)	0.302	0.970	(0.695, 1.354)	0.859	1.548	(0.740, 3.236)	0.246
Overweight vs. Normal	Bivariate	1.048	(0.836, 1.314)	0.686	1.113	(0.777, 1.596)	0.559	1.104	(0.514, 2.371)	0.800
	Adjusted*	1.039	(0.828, 1.304)	0.742	1.125	(0.784, 1.616)	0.522	1.089	(0.505, 2.348)	0.827
Overweight OR Obese	Bivariate	0.972	(0.815, 1.160)	0.754	1.041	(0.792, 1.369)	0.771	1.341	(0.758, 2.373)	0.314
	Adjusted*	0.963	(0.807, 1.149)	0.676	1.042	(0.791, 1.373)	0.768	1.314	(0.740, 2.332)	0.351

Adjusted for age and gender.

facilities. Additionally, we were unable to capture additional individual- or family-level contributors to obesity risk among children including *child* diet, sedentary and physical activity behaviors, and *parent* weight status or parent diet and physical activity behaviors. Our analysis further relies on violent crime reports obtained from the Baltimore City Police Department and does not take into account parental perceptions of neighborhood crime or safety.

Our study utilizes a convenience sample of a clinic-based populations serving predominantly low-income Black and Hispanic patients who received primary care, and hence may have limited generalizability to other populations. We found that these preschoolers live in higher crime neighborhoods and in lower SES neighborhoods on average than do residents in Baltimore, Maryland overall. Also, the preschoolers in our sample represent only 29% of all children living in the included CBGs and, thus, may not be representative of all children in the included neighborhoods.

Furthermore, though we assume that the number of violent crimes within a CBG is reflective of a child or family's experience of crime and is relatively stable over time. This may not hold true for all patients. Perceptions or fear of crime may represent a stronger driver of behavioral patterns than objective measures. Additionally, the cross-sectional design of our study may hinder our ability to detect true associations between neighborhood exposures and child overweight and obesity.

Despite these limitations, our study makes an important contribution to the existing literature on neighborhood context and child obesity risk. First, this is one of a few studies to describe the geographic distribution and neighborhood environmental exposures with respect to crime and SES for preschool-aged primary care patients. Secondly, the neighborhood exposures of interest are objectively measured and assessed on a granular scale since we use census block groups as the neighborhood geography of interest, which, in an urban context, is frequently synonymous with an area that is only a few square blocks in size. As such, we measure the neighborhood exposure in the immediate vicinity around a child's neighborhood of residence, which is strength of our methodological approach. We argue that measuring neighborhood exposures in a small geographic area is critically important for understanding the association of SES, crime and obesity risk among preschoolers because, in many cases, the environment immediately surrounding their home most closely reflects their lived experience (25, 26). Other strengths of this study include a robust sample size of over 3,600 participants and use of objectively measured height and weight data obtained from the electronic health record.

Our approach to understanding the catchment areas of the clinics in an attempt to further elucidate the potential impact of neighborhood SES and crime on the health of preschool-aged patients is underutilized in the existing literature. Instead of assuming a certain geographic radius around each clinic as the catchment area, this study describes the distribution of patients and demonstrates that a significant proportion of preschool aged patients from each clinic live within a 1.5-mile radius of each clinic. As such, this study can inform how other clinical practices characterize the patient population they serve using geography and neighborhood exposures to augment what is known about individual patients and families.

CONCLUSIONS

In summary, in this clinic-based sample of preschool-aged patients, we found that the majority of preschoolers lived in neighborhoods characterized by high or moderate crime and high poverty. Furthermore, Black preschoolers lived in higher poverty neighborhoods compared to Whites. While no clinically significant association was found between the odds of overweight or obesity and neighborhood poverty and crime among this sample, findings from this study have implications for future research centered on the development of interventions addressing child obesity disparities.

FUTURE IMPLICATIONS

Our findings suggest avenues for future research examining the relationship of neighborhood conditions and childhood obesity risk. In particular, future studies using data from clinical populations should include comprehensive data regarding sociodemographic characteristics of patients and families, intermediate behavioral indicators (child-and parent-level) such as diet and physical activity patterns, and other neighborhood-level exposures. Future research should incorporate both perceived *and* objective measures of neighborhood environments and examine associations between neighborhood exposures and growth trajectories over time. Building this body of work is a critical step in designing and implementing effective clinic- and community-based multi-level pediatric obesity management interventions that are responsive to neighborhood conditions where children and families live.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, name of committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board.

AUTHOR CONTRIBUTIONS

NS, JJ, KJ, and RT contributed to conception and design of this study. KJ and JP performed data analyses. NS revised the initial draft of the manuscript and revised all subsequent drafts. All authors critically revised the manuscript, read and approved the submitted version.

FUNDING

This study was supported by grants from the Johns Hopkins Center for Behavior and Health (Principal Investigator: Dr. RT), the National Heart, Lung, and Blood Institute (K23HL121250-01A1 to Dr. RT). Dr. NS is also supported by a Johns Hopkins University School of Medicine Clinician Scientist Award.

ACKNOWLEDGMENTS

The authors wish to thank Mr. Abhay Singh for his assistance with formatting of the included Figures.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA* (2012) 307:483–490. doi: 10.1001/jama.2012.40
2. Wang Y, Beydoun MA. The obesity epidemic in the United States–gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev.* (2007) 29:6–28. doi: 10.1093/epirev/mxm007
3. Centers for Disease Control and Prevention. *Adult Obesity and Consequences*. (2018). Available online at: https://www.cdc.gov/obesity/adult/causes.html (Accessed October 30, 2018).
4. Ogden CL, Carrol MD, Lawman HG, Fryar CD, Kruszon-Moran D, Flegal KM. Trends in obesity prevalence among children and adolescents in the united states, 1988-1994 through 2013-2014. *JAMA* (2016) 315:2292–9. doi: 10.1001/jama.2016.6361
5. Taveras EM, Gilman MW, Kleinman K, Rich-Edwards JW, Rifas-Schiman SL. Racial/ethnic differences in early-life risk factors for childhood obesity. *Pediatrics* (2010) 125:686–95. doi: 10.1542/peds.2009-2100
6. Kumanyika SK. Environmental influences on childhood obesity: ethnic and cultural influences in context. *Physiol Behav.* (2008) 94:61–70. doi: 10.1016/j.physbeh.2007.11.019
7. Institute of Medicine. *Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation*. Washington, DC: National Academies Press (2012). Available online at: http://iom.nationalacademies.org/Reports/2012/Accelerating-Progress-in-Obesity-Prevention.aspx (Accessed October 29, 2018).
8. An R, Yang Y, Hoschke A, Xue H, Wang Y. Influence of neighbourhood safety on childhood obesity: a systematic review and meta-analysis of longitudinal studies. *Obes Rev.* (2017) 18:1289–309. doi: 10.1111/obr.12585
9. Davison KK, Lawson CT. Do attributes in the physical environment influence children's physical activity? A review of the literature. *Int J Behav Nutr Phys Act.* (2006) 3:19. doi: 10.1186/1479-5868-3-19
10. Bruner C. ACE, place, race, and poverty: building hope for children. *Acad Pediatr*. (2017) 17:S123–9. doi: 10.1016/j.acap.2017.05.009
11. Kimbro RT, Denney JT. Neighborhood context and racial/ethnic differences in young children's obesity: structural barriers to interventions. *Soc Sci Med.* (2013) 95:97–105. doi: 10.1016/j.socscimed.2012.09.032
12. Lumeng JC, Appugliese D, Cabral HJ, Bradley RH, Zuckerman B. Neighborhood safety and overweight status in children. *Arch Pediatr Adolesc Med*. (2006) 160:25–31. doi: 10.1001/archpedi.160.1.25
13. Williams DR, Collins C. Racial residential segregation: a fundamental cause of racial disparities in health. *Public Health Rep.* (2001) 116:404–16. doi: 10.1016/S0033-3549(04)50068-7
14. Flechtner L, Cheng ER, Lopez G, Sharifi M, Taveras EM. Multilevel Correlates of Healthy BMI Maintenance and Return to a Healthy BMI among children in Massachusetts. *Child Obes*. (2017) 13:146–53. doi: 10.1089/chi.2016.0261
15. Sharifi M, Sequist TD, Rifas-Shiman SL, Melly SJ, Duncan DT, Horan CM, et al. The role of neighborhood characteristics and the built environment in understanding racial/ethnic disparities in childhood obesity. *Prev Med.* (2016) 91:103–9. doi: 10.1016/j.ypmed.2016.07.009
16. United States Census Bureau. *2013 American Community Survey (5-Year Estimates). Gener by Jason Lambden; using Am FactFinder*. (2018). Available at: http://factfinder2.census.gov (Accessed October 20, 2018).
17. Baltimore Police Department. *Baltimore Police Department Open Data*. Available online at: https://www.baltimorepolice.org/crime-stats/open-data (Accessed October 21, 2018).
18. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. *CDC Growth Charts: US Advance Data From Vital and Health Statistics; No. 314, National Center for Health Statistics, 2000*. (2018). Available online at: http://www.cdc.gov/growthcharts (Accessed October 24, 2018).
19. WHO Multicentre Growth Refernce Study Group. WHO child growth standards based on length/height, weight and age. *Acta Paediatr Suppl.* (2006) 450:76–85. doi: 10.1111/j.1651-2227.2006.tb02378.x
20. *ArcGIS 10.1*. Redlands CA: ESRI.
21. Krieger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Geocoding and monitoring of US socioeconomic inequalities in mortality and cancer incidence: does the choice of area-based measure and geographic level matter? The public health disparities geocoding project. *Am J Epidemiol.* (2002) 156:471–82. doi: 10.1093/aje/kwf068
22. Lovasi GS, Schwartz-Soicher O, Quinn JW, Berger DK, Neckerman KM, Jaslow R, et al. Neighborhood safety and green space as predictors of obesity among preschool children from low-income families in New York City. *Prev Med.* (2013) 57:189–93. doi: 10.1016/j.ypmed.2013.05.012

23. Salois MJ. The built environment and obesity among low-income preschool children. *Health Place*. (2012) 18:520–7. doi: 10.1016/j.healthplace.2012.02.002
24. Nau C, Schwartz BS, Bandeen-Roche K, Liu A, Pollak J, Hirsch A, et al. Community socioeconomic deprivation and obesity trajectories in children using electronic health records. *Obesity* (2015) 23:207–12. doi: 10.1002/oby.20903
25. Showell NN, Washington K, Johnson K, DeCamp LR, Bair-Merritt M, Thornton RL. Neighborhood and parental influences on diet and physical activity behaviors in young low-income pediatric patients. *Clin Pediatr*. (2017) 56:1235–43. doi: 10.1177/0009922816684599
26. Schaefer-McDaniel N. *Children Talk about Their New York City Neighborhoods - The Role of Subjective and Objective Neighborhood Evaluations in Understanding Child Health*. Saarbrucken: VDM Verlag Dr. Mueller E.K. (2007) .

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

BRIEF RESEARCH REPORT
published: 19 September 2018
doi: 10.3389/fped.2018.00251

Weight Loss Surgery Utilization in Patients Aged 14–25 With Severe Obesity Among Several Healthcare Institutions in the United States

Karen J. Campoverde Reyes[1,2], *Madhusmita Misra*[1,3], *Hang Lee*[4] and *Fatima Cody Stanford*[1,3,5]*

[1] Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [2] Liver Research Center, Beth Israel Deaconess Medical Center, Boston, MA, United States, [3] Pediatric Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [4] MGH Biostatistics Center, Massachusetts General Hospital, Boston, MA, United States, [5] MGH Weight Center, Massachusetts General Hospital, Boston, MA, United States

OPEN ACCESS

Edited by:
Andrew S. Day, University of Otago, New Zealand

Reviewed by:
Hellas Cena, University of Pavia, Italy
Sravan Kumar Reddy Matta, Children's National Health System, United States

***Correspondence:**
Fatima Cody Stanford
fstanford@mgh.harvard.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *12 July 2018*
Accepted: *28 August 2018*
Published: *19 September 2018*

Citation:
Campoverde Reyes KJ, Misra M, Lee H and Stanford FC (2018) Weight Loss Surgery Utilization in Patients Aged 14–25 With Severe Obesity Among Several Healthcare Institutions in the United States. Front. Pediatr. 6:251. doi: 10.3389/fped.2018.00251

Introduction: Obesity is associated with early co-morbidities and higher mortality. Even though weight loss surgery (WLS) in adolescents with severe obesity reliably achieves safe and lasting improvement in BMI and superior resolution of comorbid diseases, its utilization among young patients in the clinical practice stands unclear.

Objective: To show the prevalence of weight loss surgery utilization rates in adolescents and young adults among several healthcare institutions in the United States.

Method: WLS in 14–25 years old between 2000 and 2017 was obtained from Washington University, Morehouse Medical, University of Texas, Wake Forest Baptist Medical Center, Beth Israel Deaconess Medical Center, Boston Children's Hospital, Boston Medical Center, and Partners Healthcare using the Shared Health Research Information Network (SHRINE) and Research Patient Data Registry (RPDR) web-based query tools. ICD-9 codes were used for bariatric surgery.

Results: Among 2500635 individuals, 18008 (0.7%) had severe obesity. At Partners, 1879 patients had severe obesity, of which 404 (21.5%) underwent WLS, whereas at Washington University, 44 (2.5%) of 1788 the underwent WLS. 13 (2.3%) of the 575 at BIDMC, 43 (1.5%) of the 2969 at BMC, and 37 (0.4%) of 8908 at BCH underwent WLS ($p < 0.0001$ for all).

Discussion: Even though WLS has shown to be the most effective treatment to create sustainable changes in metabolic derangements for moderate to severe obesity and its comorbidities, it has been underutilized. Further studies need to be conducted to ensure WLS is utilized for those patients who would achieve the most benefit.

Keywords: obesity surgery, weight loss, adolescent, youth, bariatric surgery

INTRODUCTION

Obesity rates have reached pandemic levels in the United States with prevalence rates of 39.8% in adults and 18.5% in youth (1). Current reports in children and adolescents show a significant increase in severe obesity in children and an upward trend in many subgroups, including adolescents (2, 3).

Severe obesity is defined as a BMI ≥ 99th percentile for age and gender, equivalent to a BMI Z-score of +2.5, which is an adult BMI of 30 kg/m^2 (4). A high BMI for age, especially in those with severe obesity, is associated with early co-morbidities, such as type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), dyslipidemia, obstructive sleep apnea (OSA), hypertension (HTN), heart disease, and early mortality. About 4% of children in the US have a BMI ≥99th (5).

Obesity is the most significant threat to the health of younger generations due to its cumulative health impact (4). Current indications for WLS in adolescents include a BMI ≥35 kg/m^2 or ≥120% of the 95th percentile with clinically significant comorbid conditions such as OSA (apnea-hypopnea index (AHI) >5 events/h), type 2 diabetes, idiopathic intracranial hypertension, NASH, Blount's disease, slipped capital femoral epiphysis, gastroesophageal reflux disease or HTN; or BMI ≥40 kg/m^2 or ≥140% of the 95th percentile (6). In adolescents with severe obesity, WLS reliably achieves a safe and lasting improvement in BMI and resolution of comorbid diseases superior to other treatment modalities (7–11). Long term remission of comorbidities such as diabetes, dyslipidemia, HTN, NAFLD, and OSA have been reported in adolescents. WLS is recommended as a reasonably safe and effective approach in adolescents and young adults. (4, 9, 12–15). However, dietary supplementation and lifelong vitamin level monitoring are required since inadequate absorption of calcium, vitamin D, iron, vitamin B1, B6, B12, A, and folate has been reported in these patients (4, 6).

Ensuring a multidisciplinary team (MDT) optimizes preoperative selection and education, as well as postoperative outcomes (6, 16). Many academic institutions in the US do not offer this treatment modality. Even though WLS is the most effective treatment to date to create sustainable changes in metabolic derangements for those with moderate to severe obesity and its comorbidities, its utilization among young patients in the clinical practice remains unclear. Our hypothesis is that WLS in adolescents and young adults with severe obesity is highly underutilized, despite its benefits. In our study, we evaluate the prevalence of severe obesity and WLS utilization in individuals between 14 and 25-years-old among several academic healthcare institutions in the United States.

METHODS

The prevalence of obesity, severe obesity, and WLS utilization between 2000 and 2017 in patients between 14 and 25-years-old were obtained using the Scalable Collaborative Infrastructure for a Learning Health System (SCILHS) and the Research Patient Data Registry (RPDR) query web-based tools. The SCILHS covers more than 8 million patients across 10 health systems, enabling a national research network formed on an advanced information technology infrastructure (17). The RPDR is a centralized clinical data registry that gathers clinical information from various hospitals in the Partners Healthcare system (PHS), such as Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH), covering around 4 million patients.

Data on gender, age, race, and WLS utilization were available from 8 healthcare systems: Washington University in St. Louis, Morehouse Medical School, University of Texas-Houston, Wake Forest Baptist Medical Center, Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Boston Medical Center (BMC), and PHS. Individuals with obesity were identified utilizing ICD-9 code for obesity, BMI>30 kg/m^2, and BMI pediatric ≥ 95th percentile for age. Individuals with severe obesity were identified using the ICD-9 code for severe obesity, morbid obesity, and BMI ≥40. Data for WLS were also obtained using ICD-9 codes:: gastric restrictive procedure, gastric bypass for morbid obesity; short limb Roux-en-Y with small intestine reconstruction to limit absorption, laparoscopic surgical gastric restrictive procedure with gastric bypass, and Roux-en-Y gastroenterostomy. Statistical analyses involved a series of univariate analyses consisting of Fisher's exact test to evaluate the difference in WLS utilization rates between each healthcare institution and PHS. This study was approved by the Partners Healthcare Institutional Review Board. The study contained only de-identified information, and we have followed the principles in accordance with the Declaration of Helsinki.

RESULTS

Prevalence of Obesity

Our study collected information on 2,500,638 individuals 14–25 years old. As illustrated in **Table 1**, we ascertained demographics of the total population, of individuals with obesity and with severe obesity, by gender, race and academic institution. For the total population, gender distribution was overall even. Overall, Partners Healthcare had the highest percentage of individuals between 14-25 years old (38.8%), followed by BCH (22.3%). We found that 18008 (0.7%) patients had severe obesity, of whom 61% were female, 39% were male. By healthcare institution, BCH had the highest proportion of individuals with severe obesity.

Utilization of WLS

Only 3% of individuals with severe obesity underwent WLS. The gender distribution was 2:1 in favor of women, and utilization was higher in the White population (42.3%), followed by Unknown (24.4%), Other (15.5%), African American (6.5%), and Asian (0.7%). The distribution of WLS by healthcare institution was as follows: at PHS, 404 (21.5%) of 1879 patients with severe obesity underwent WLS. In contrast, 44 (2.5%) of 1788 at Washington University, 13 (2.3%) of the 575 at BIDMC, 43 (1.4%) of the 2969 at BMC, and 37 (0.4%) of 8908 individuals with severe obesity at BCH underwent WLS. As illustrated in **Figure 1**, we used Fisher's exact test to determine whether each of the other institutions differed from PHS in WLS utilization rates among those with severe obesity. There was a statistically

TABLE 1 | Demographics of individuals by gender, race and healthcare institution.

	Total Population (*n* = 2500638)	Individuals with obesity (*n* = 78867)	Individuals with severe obesity (*n* = 18008)
Female	1271087 (50.8%)	44802 (56.8%)	10967 (61.0%)
Male	1228202 (49.1%)	34059 (43.2%)	7031 (39.0%)
RACE			
White	1215940 (48.6%)	32344 (41.0%)	7279 (40.4%)
American Indian	4306 (0.2%)	129 (0.2%)	13 (0.1%)
Asian	75255 (3.0%)	2078 (2.6%)	210 (1.2%)
African American	283826 (11.4%)	17656 (22.4%)	4612 (25.6%)
Pacific Islander	674 (0.02%)	18 (0.02%)	0
Other	241630 (9.6%)	14810 (18.8%)	3107 (17.3%)
Unknown	679004 (27.2%)	11832 (15%)	2787 (15.5%)
HEALTHCARE INSTITUTIONS			
BIDMC	139000 (5.6%)	3157 (4.0%)	575 (3.2%)
Wake Forest	173500 (6.9%)	8750 (11.1%)	654 (3.6%)
U Texas	207884 (8.3%)	5239 (6.6%)	1115 (6.2%)
Boston Children's Hospital	558159(22.3%)	21347 (27.1%)	8908 (49.5%)
BMC	112505(4.5%)	8670 (11.0%)	2969 (16.5%)
Washington University	333338(13.3%)	6173 (7.8%)	1788 (9.9%)
Partners Healthcare System	970010(38.8%)	24944 (31.6%)	1879 (10.4%)
Morehouse	6242 (0.3%)	587 (0.7%)	120 (0.7%)

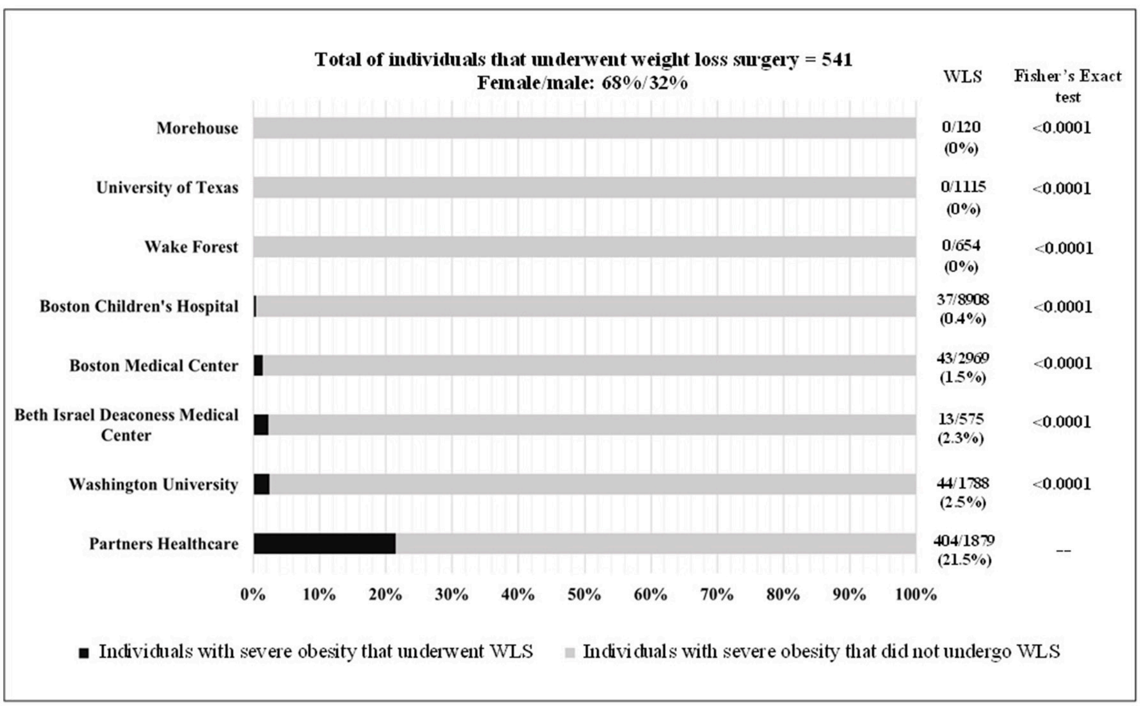

FIGURE 1 | Weight loss surgery utilization in patients 14-25 years old in several healthcare academic institutions in US.

significant difference in WLS utilization rates between each of the other healthcare institutions and PHS ($p < 0.0001$ for all).

DISCUSSION

Despite evidence that adolescent bariatric surgery is a safe, effective, and appropriate consideration when severe obesity in the adolescent patient does not respond to behavioral changes or medical interventions, our results demonstrate low utilization rates of WLS in adolescent and young adult patients with severe obesity in a nationwide sample of institutions. We compared WLS utilization rates in other academic health care institutions to that within the PHS (based on the obviously higher utilization of WLS in the latter). A vast difference was found among academic institutions, despite some being localized in the same city. Of the institutions evaluated, PHS has the longest history of providing care to patients in a tertiary multidisciplinary weight management program (which includes the availability of weight loss surgery), and this may have influenced its highest percentage of WLS utilization when compared to peer institutions. Patients with severe obesity can only undergo WLS after being carefully selected, and WLS can produce meaningful short term and long term weight loss, improvements in cardiometabolic risk factors, diabetes mellitus, and quality of life (12, 18). To our knowledge, all academic institutions included in our analyses utilize a multidisciplinary weight management program for their patient population.

Numerous factors are believed to impact WLS utilization. These include limited medical education about the physiology of obesity and its treatment, obesity bias with healthcare providers assuming it is the patient's deficient effort to achieve weight loss that results in severe obesity, limited decisional capacity and autonomy in adolescents, a limited ability to manage challenging lifestyle changes, lack of awareness that adolescents and young adults are eligible for WLS, inequities in access to healthcare resources, differences in socioeconomic status (SES), obstacles obtaining treatment authorization from insurance carriers, and limited studies on long-term outcomes (12, 18, 19). The adolescent years are a very vulnerable time of one's life and are characterized by a peak in psychological and social development. Severe obesity may leave a more significant metabolic imprint in adolescents than in adults, for which is imperative to consider WLS as an approach if applicable. In patients with severe obesity, the embracing of a new lifestyle after WLS potentially results in a more energetic, healthy, and sociable young individual, with a better self-esteem and a sense of self-empowerment, however these benefits must always outweigh the risks of micronutrient deficiencies and possibility of more abdominal procedures in the future (7.9%) (4, 12, 13, 20). Limitations of this research included not having access to insurance and SES. Further studies are required to elucidate the reasons of WLS underutilization in an adolescent and young adult population.

CONCLUSION

Management of severe obesity is a lifelong challenge and requires a multidisciplinary and individualized approach that includes a combination of lifestyle changes, behavioral therapy, nutrition education, medications, and possibly WLS. WLS is a safe and effective treatment for adolescents and young adults with severe obesity; however, it is widely underutilized. More tertiary multidisciplinary weight management centers are necessary to ensure the beneficial early intervention outcomes of WLS. Inadequate education and awareness, suboptimal support and inadequate tools and access to navigate the decision-making process regarding WLS might influence this outcome. These factors remain unclear and further measures are necessary to ensure that WLS is adequately utilized for those patients who would achieve the most benefit.

AUTHOR CONTRIBUTIONS

All authors have made substantial contribution to the paper. KC was responsible for acquisition of data, drafting the manuscript and interpreting the data. FS was responsible for responsible for the conception and design of the study and critical review of the paper. HL was responsible of data analyses and interpreting the data. FS and MM were responsible for revising the article critically and adding important intellectual content. All authors have read and approved the final version of the paper.

FUNDING

This work was supported by the Physician, Scientist Development Award (PSDA) granted by the Executive Committee on Research (ECOR) at MGH (FS), NIH NIDDK RO1 DK103946-01A1 (MM), and NIHP30 DK040561 (MM and FS).

REFERENCES

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015–2016. *NCHS Data Brief* (2017) 1–8.
2. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of obesity and severe obesity in US children, 1999–2016. *Pediatrics* (2018) 141:e20173459. doi: 10.1542/peds.2017-3459
3. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA* (2018) 319:1723–5. doi: 10.1001/jama.2018.3060
4. Durkin N, Ashish PD. What is the evidence for paediatric/adolescent bariatric surgery? *Curr Obes Rep*. (2017) 6:278–5. doi: 10.1007/s13679-017-0277-4
5. Freedman D, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children: bogalusa heart study. *J Pediat*. (2007) 150:12–7.e2. doi: 10.1016/j.jpeds.2006.08.042
6. Pratt JS, Browne A, Browne NT, Bruzoni M, Cohen M, Desai A, et al. ASMBS pediatric metabolic and bariatric surgery guidelines, 2018. *Surg Obes Relat Dis*. (2018) 14:882–901. doi: 10.1016/j.soard.2018.03.019.
7. Campos GM, Lanning DA. Bariatric surgery for nonalcoholic fatty liver disease in adolescents with severe obesity. *Surg Obes Relat Dis*. (2015) 449–450. doi: 10.1016/j.soard.2014.12.015

8. Nandagopal R, Brown RJ, Rother KI. Resolution of type 2 diabetes following bariatric surgery: implications for adults and adolescents. *Diab Technol Therapeut.* (2010) 12 671–7. doi: 10.1089/dia.2010.0037
9. Maffazioli GD, Stanford FC, Campoverde Reyes KJ, Stanley TL, Singhal V, Corey KE, et al. Comparing outcomes of two types of bariatric surgery in an adolescent obese population: roux-en-Y gastric bypass vs. Sleeve Gastrectomy. *Front Pediatr*. (2016) 4:78. doi: 10.3389/fped.2016.00078
10. Inge TH, Siegel RM, Xanthakos SA. Weight loss maintenance: a hard nut to crack. *JAMA Pediatr.* (2014) 168:796–7. doi: 10.1001/jamapediatrics.2014.672
11. Treadwell JR, Sun F, Schoelles K. Systematic review and meta-analysis of bariatric surgery for pediatric obesity. *Ann Surg.* (2008) 248:763–76. doi: 10.1097/SLA.0b013e31818702f4
12. Shoar S, Mahmoudzadeh H, Naderan M, Bagheri-Hariri S, Wong C, Parizi AS, et al. Long-term outcome of bariatric surgery in morbidly obese adolescents: a systematic review and meta-analysis of 950 patients with a minimum of 3 years follow-up. *Obes Surg.* (2017) 27:3110–7. doi: 10.1007/s11695-017-2738-y
13. Khidir N, El-Matbouly MA, Sargsyan D, Al-Kuwari M, Bashah M, Gagner M. Five-year outcomes of laparoscopic sleeve gastrectomy: a comparison between adults and adolescents. *Obes Surg.* (2018) 28:2040–5. doi: 10.1007/s11695-018-3139-6
14. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* (2009) 122:248–56. doi: 10.1016/j.amjmed.2008.09.041
15. Peterli R, Wölnerhanssen BK, Peters T, Vetter D, Kröll D, Borbély Y, et al. Effect of laparoscopic sleeve gastrectomy vs laparoscopic roux-en-y gastric bypass on weight loss in patients with morbid obesity the SM-BOSS randomized clinical trial. *JAMA* (2018) 319:255–65. doi: 10.1001/jama.2017.20897
16. Elahmedi MO, Alqahtani AR. evidence base for multidisciplinary care of pediatric/adolescent bariatric surgery patients. *Curr Obes Rep.* (2017) 6:266–77. doi: 10.1007/s13679-017-0278-3
17. Mandl KD, Weber GM, Natter M, Mandel J, Adams WG. Scalable collaborative infrastructure for a learning healthcare system (SCILHS): architecture. *J Am Med Informat Assoc.* (2014) 21:615–20. doi: 10.1136/amiajnl-2014-002727
18. Childerhose JE, Alsamawi A, Mehta T, Smith JE, Woolford S, Tarini BA. Adolescent bariatric surgery: a systematic review of recommendation documents. *Surg Obes Relat Dis.* (2017) 13:1768–79. doi: 10.1016/j.soard.2017.08.008
19. Inge TH, Boyce TW, Lee M, Kollar L, Jenkins TM, Brandt ML, et al. Access to care for adolescents seeking weight loss surgery. *Obesity* (2014) 22:2593–7. doi: 10.1002/oby.20898
20. Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, et al. weight loss and health status 3 years after bariatric surgery in adolescents. *N Eng J Med.* (2016) 374:113–23. doi: 10.1056/NEJMoa1506699

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

ORIGINAL RESEARCH
published: 19 February 2019
doi: 10.3389/fped.2019.00037

Comparison of Measured and Estimated Resting Energy Expenditure in Adolescents and Young Adults With Severe Obesity Before and 1 Year After Sleeve Gastrectomy

*Frances A. Rickard [1,2], Landy P. Torre Flores [2], Sonali Malhotra [3], Alexander T. Toth [2], Abeer Bader [4], Fatima Cody Stanford [2,4], Hang Lee [5], Miriam A. Bredella [6], Madhusmita Misra [2,3] and Vibha Singhal [2,3,4]**

[1] Melbourne School of Medicine, University of Melbourne, Melbourne, VIC, Australia, [2] Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [3] Pediatric Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [4] MGH Weight Center and Harvard Medical School, Boston, MA, United States, [5] Biostatistics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [6] Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States

OPEN ACCESS

Edited by:
*Valentino Cherubini,
Azienda Ospedaliero Universitaria
Ospedali Riuniti, Italy*

Reviewed by:
*Ronald Cohen,
University of Chicago, United States
Gianpaolo De Filippo,
Bicêtre Hospital, France*

***Correspondence:**
*Vibha Singhal
vsinghal1@mgh.harvard.edu*

Specialty section:
*This article was submitted to
Pediatric Endocrinology,
a section of the journal
Frontiers in Pediatrics*

Received: *03 December 2018*
Accepted: *29 January 2019*
Published: *19 February 2019*

Citation:
Rickard FA, Torre Flores LP, Malhotra S, Toth AT, Bader A, Stanford FC, Lee H, Bredella MA, Misra M and Singhal V (2019) Comparison of Measured and Estimated Resting Energy Expenditure in Adolescents and Young Adults With Severe Obesity Before and 1 Year After Sleeve Gastrectomy. Front. Pediatr. 7:37. doi: 10.3389/fped.2019.00037

Introduction: Resting energy expenditure (REE) is often evaluated in adults and adolescents with obesity to estimate caloric requirements when advising dietary changes. However, data are lacking regarding the accuracy of methods used to clinically assess REE in adolescents with severe obesity. Moreover, there are no data regarding the effects of sleeve gastrectomy (SG) on REE in adolescents. We evaluated the accuracy and error rate between estimated and measured REE in adolescents with severe obesity and changes in REE following (SG).

Materials and Methods: *Cross-sectional study* (CSS): 64 adolescents and young adults, 14–22 years old, with moderate to severe obesity were enrolled. We measured REE (mREE) by indirect calorimetry and estimated REE (eREE) using Derumeaux (Deru), Mifflin-St Jeor (MS), Harris Benedict (HB), and World Health Organization (WHO) equations. DXA was used to determine body composition. Bland Altman analysis evaluated agreement between eREE and mREE. *Longitudinal study*: 12 subjects had repeat indirect calorimetry and DXA 1 year after SG. Longitudinal analysis was used to assess changes in REE and body composition.

Results: *CSS*: Median BMI was 45.2 kg/m^2 and median age was 18.0 (16.3–19.9) years. mREE correlated strongly with eREE . Bland Altman analysis demonstrated that only a few points were beyond the 1.96 SD limit of disagreement. However, there was considerable overestimation of mREE by most equations. *Longitudinal Study*: In the subset that underwent SG, after 12-months, absolute REE decreased from 1709 (1567.7–2234) to 1580.5 (1326–1862.5) Calories ($p = 0.002$); however, the ratio of REE/Total Body Weight (TBW) increased from 13.5 ± 2.3 at baseline to 15.5 ± 2.2 at 1 year ($p = 0.043$). When evaluating parameters affecting % total weight loss, we found that it correlated positively with REE/TBW at 12 months ($R = 0.625$; $p = 0.03$) and negatively with % fat mass at 12 months ($R = -0.669$; $p = 0.024$).

Discussion: In adolescents with moderate-severe obesity, despite a correlation between mREE using indirect calorimetry and eREE using the Deru, MS, HB, and WHO equations, there is significant over-estimation of REE at the individual level, challenging their clinical utility. One year after SG, REE/TBW increased and strongly correlated with % total weight loss in adolescents.

Keywords: obesity, adolescents, resting energy expenditure, calorimetry, equation, sleeve gastrectomy

INTRODUCTION

Childhood and adolescent obesity is a growing public health concern. Currently, more than 20% of children in the United States have obesity, placing them at increased risk of obesity and its comorbidities as adults (1).

While obesity is a multifactorial disease, it is ultimately the result of a state of positive energy balance combined with a genetic predisposition for weight gain (2). To address energy imbalance, current recommendations for treating childhood obesity include family based lifestyle interventions with diet and exercise modifications (3). As part of this current strategy, energy requirements are often measured to guide the development of appropriate recommendations to achieve weight loss or maintenance. Indirect calorimetry is the current gold standard to measure resting energy expenditure (REE), but this technique is expensive and often difficult to access in clinical practice. Equations that estimate REE have been developed, however their accuracy in children with obesity is questionable, which makes it difficult to rely on these estimates in a clinical setting for this patient population (4).

Bariatric surgery is a useful treatment option for adolescents with severe obesity (5). When weight loss is achieved through diet and exercise, there is an associated decrease in REE (6, 7), which makes continued weight loss challenging. In adults, bariatric surgery results in decreases in absolute REE, but this decrease in REE is not evident when controlled for total body weight, suggesting that REE actually does not change (7). There are only a few studies in adults that have evaluated changes in REE after sleeve gastrectomy (SG), and results are conflicting (8, 9). To our knowledge, there are no studies that have assessed metabolic changes in adolescents after SG.

The primary objectives of this study are to (i) evaluate the accuracy of predictive equations used in clinics to estimate REE in adolescents with moderate to severe obesity, and (ii) to explore metabolic adaptations in adolescents and young adults with severe obesity 12 months following SG. We hypothesized that REE predictive equations would be inaccurate in adolescents with severe obesity, and that SG would lead to metabolic adaptations, causing a reduction in REE.

METHODS

This study was carried out in accordance with the Belmont principles and was approved by the Institutional Review Board of Partners Healthcare System. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Subjects $\geq$18 years of age, and parents of subjects $<$18 years of age provided written informed consent, and informed assent was obtained from subjects $<$18 years of age. Sixty-four adolescents and young adults, ranging from 14–22 years of age, with moderate to severe obesity, BMI > 35 kg/m^2 were enrolled. Exclusion criteria included untreated thyroid dysfunction, smoking $>$10 cigarettes/day, substance abuse disorder, pregnancy or breast feeding as these effect REE. Four of our participants were on medications for attention deficit hyperactivity disorder (ADHD)—three were on dextroamphetamine and one on methylphenidate. Although, considered stimulant drugs, literature suggests that these medications do not alter REE (10). We did not exclude adolescents on stimulant medications given the frequency of their use in the general population, as this would limit the generalizability of our results. No participant was on stimulant medications for weight loss.

MEASUREMENTS

Indirect calorimetry (MetCart) was used to measure fasting REE under thermal neutrality using VMAX Encore 29 metabolic cart (Viasys Healthcare, Carefusion; San Diego, CA). All measurements were conducted at the Clinical Research Center of our institution. Subjects fasted for at least 8 h before measurement and were instructed to refrain from heavy exercise, tobacco, and alcohol the night before. Subjects did not alter their usual food intake the day prior to the visit. They rested for 20 min before measurement. Dual energy x-ray absorptiometry (Hologic QDR 4500) was used to measure body composition, specifically total fat and lean mass. Activity levels were recorded using the Paffenberger questionnaire.

Four REE equations were used to compare measured vs. estimated REE. These included the Derumeaux, Harris Benedict, World Health Organization/Food and Agriculture Organization and Mifflin- St Jeor equations (**Table 1**). These equations were chosen because clinically they are the most commonly used equations, and/or because younger populations were included in their initial derivation. Twelve subjects underwent SG and had repeat indirect calorimetry and DXA measurements 12 months after surgery.

TABLE 1 | REE equations evaluated in adolescents with moderate-severe obesity.

Author	Sex	Age	Equations to estimate resting energy expenditure
Derumeaux-Burel et al. (11)	Male		$REE = 0.1096 \times FFM + 2.8862$
	Female		$REE = 0.1371 \times FFM - 0.1644 \times age + 3.3647$
Harris et al. (12)	Male		$REE = 66.473 + (13.752 \times W) + (5.003 \times H) - (6.755 \times age)$
	Female		$REE = 665.096 + (9.5634 \times W) + (1.849 \times H) - (4.6756 \times age)$
Mifflin et al. (13)	Male		$REE = (9.99 \times W) + (6.25 \times H) - (4.92 \times age) + 5$
	Female		$REE = (9.99 \times W) + (6.25 \times H) - (4.92 \times age) - 161$
WHO (14)	Male	>18	$R\,EE = 15.3 \times W + 679$
		<18	$EE = 17.5 \times W + 651$
	Female	>18	$REE = 15.3 \times W + 496$
		<18	$REE = 12.2 \times W + 746$

REE, resting energy expenditure; Deru, Derumeaux; WHO, World Health Origination; FFM, free fat mass; kg, W, weight, kg; H, height; cm, age in years.

STATISTICAL ANALYSIS

JMP Pro12 (SAS Institute, Cary, NC, USA) was used for data analysis. The variables were assessed for normality of distribution and descriptive analysis is presented accordingly. The percentage of subjects with accurate prediction of REE on an individual level was also calculated, where an accurate prediction was defined as the estimated REE being between 90 and 110% of the measured REE (based on previous studies and clinical impact) (15). If the eREE was <90% of mREE, this was defined as an under prediction, whereas if the eREE was >110% of the mREE this was considered an over prediction. The percentage of the maximum positive/maximum negative error refers to the maximum positive and negative individual value of eREE that was the furthest away from the mREE (over and under prediction, respectively). Correlation is simple linear correlation between eREE and mREE. Bland Altman plots were used to evaluate the agreement between four predictive equations and measured REE (16).

For the longitudinal component of the study, we used the paired samples *t*-test or the Wilcoxon signed rank test, depending on distribution, to test if there was a significant within- group change over 12 months. For correlational analysis, Pearson's or Spearman's correlation was used depending on data distribution.

TABLE 2 | Subject characteristics.

	***N* = 64**
Age, years	18.0 (16.3–19.9)
Sex	16 Male, 48 Female
RACE	
Caucasian (%)	48.4
African American (%)	21.9
More than one race (%)	12.5
American Indian (%)	3.1
Unknown (%)	12.5
ETHNICITY	
Hispanic (%)	40.6
Non-Hispanic (%)	59.4
Weight, kg	125.3 (111.9–144.9)
Height, cm	167.5 ± 7.7
BMI, kg/m^2	45.2 (40.4–49.0)
% Ideal BMI for age	209.6 (190.1–229.8)
% Fat Mass	49.8 (45.7–52.3)
% Lean Mass	48.8 (46.8–53.1)
Vigorous exercise, h/wk	3.8 (0.0–7.0)
Sleeping hours, h/wk	54.2 ± 11.8

Values are presented as median (IQR) or mean ± SD or as a % of total subjects. BMI, body mass index.

RESULTS

Subject Characteristics

The demographic and anthropometric characteristics of the 64 adolescents and young adults with moderate to severe obesity included in this study are displayed in **Table 2**. Almost half of our participants were Caucasians and 40% were Hispanic in ethnicity. The median hours of vigorous activity per week was 3.8 (0–7).

Accuracy of REE Predictive Equations

Table 3 shows the difference between measured REE using indirect calorimetry and predicted REE using the four representative predictive equations (**Table 1**). The percentage of accuracy, over prediction, bias, maximum positive and negative error are listed. The Mifflin equation had the lowest difference from the mREE with a mean difference of 303.6 kcal/day. The WHO equation was the furthest from the mREE, showing a mean difference 683.3 kcal/day. Over all, the Mifflin equation performed best in our subjects with the lowest bias (18.9%), and an accurate prediction of REE in 25% of subjects. The WHO equation performed the poorest showing the highest bias (39.3%) and giving an accurate prediction in only 3.1% of subjects. The maximum positive error was estimated using the WHO equation, where one subject was predicted to have an REE that was 87.4% higher than the measured value. More than a third of the time, all four equations over predicted REE.

Bland Altman plots, **Figure 1**, shows the distributions of differences against the means, obtained with the two different methods, and the limits of agreement. Most subjects were within

TABLE 3 | Comparison of measured REE and estimated REE in adolescents with moderate-severe obesity.

Predictive equations	Absolute difference (eREE -mREE) (Kcal/day)	Accurate prediction (%)	Under prediction (%)	Over prediction (%)	Bias (%)	Maximum negative error (%)	Maximum positive error (%)	Correlation with mREE*
Deru	480.7	14.1	1.6	84.4	27.9	−13.5	62.2	0.70
HB	435.3	9.4	1.6	89.1	25.6	−15.5	70.8	0.78
Mifflin	303.6	25	1.6	73.4	18.9	−15.7	48.8	0.80
WHO	683.3	3.1	0	96.9	39.3	NA	87.4	0.78

Accurate prediction: percentage of patients predicted by equation within 10% of measured value.
Under prediction: percentage of patients predicted by this equation <10% of measured value.
Over prediction: percentage of patients predicted by this equation> 10% of this measure value.
Bias: mean percentage error between predictive equation and measured value.
*EREE, estimated resting energy expenditure; MREE, measured resting energy expenditure; Deru, Derumeaux; HB, Harris Benedict; WHO, World Health Organization. *P-value for all correlation < 0.0001.*

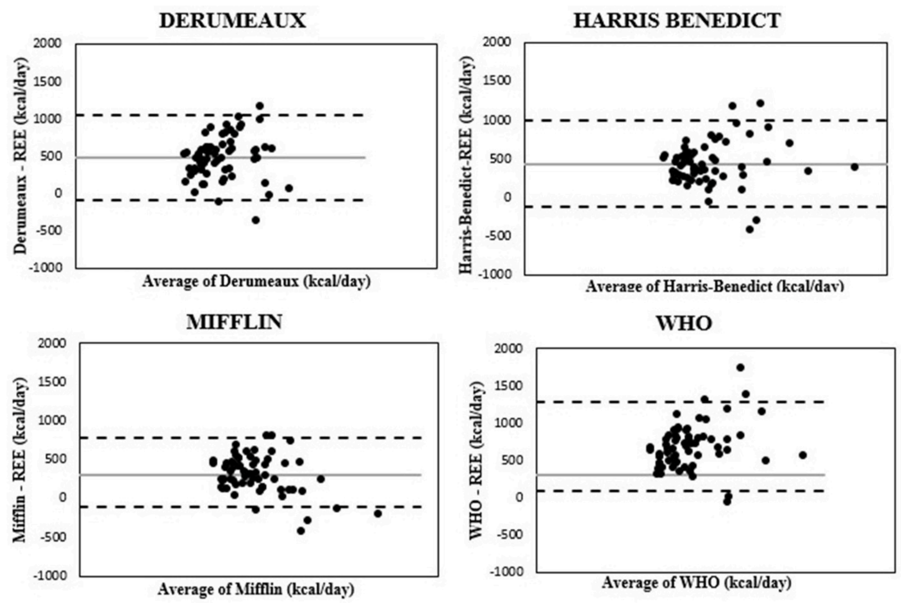

FIGURE 1 | Bland-Altman plots comparing absolute differences between measured and estimated REE and average of measured and estimated REE for the four equations. ——, Mean; - - - -, +/−1.96SD, •Subject.

the suggested limits of agreement across the four equations, and there was no evidence of dependency of the differences in the entire range of energy expenditure levels suggesting the lack of systematic error.

REE and Metabolic Changes After Sleeve Gastrectomy

Weight, body composition and metabolism changes from baseline to 12 months in adolescents and young adults undergoing SG ($N = 12$) are shown in **Table 4**. The group was composed of mostly white (9/12) females. About 42% were of Hispanic ethnicity. The mean age baseline was 18.8 ± 2.2. As expected, they had a decrease in weight, BMI, total and % fat mass and total lean mass. Although the group showed a decrease in absolute REE, REE was unchanged after controlling for lean mass. Further, REE/total body weight increased 12 months after SG.

Correlation of Weight Loss With Body Composition and REE After Sleeve Gastrectomy

In an effort to seek the factors that could affect weight loss, we evaluated the correlation between total percent weight loss and body composition and REE parameters at baseline (before surgery) and after surgery. There was no correlation between percent total weight loss and body composition and REE parameters at baseline. However, percent total weight loss was positively associated with REE/TBW at 12 months and negatively with fat mass and % fat mass at 12 months. This is shown in **Table 5**.

TABLE 4 | Anthropometric and metabolic changes 1 year after sleeve gastrectomy.

Characteristics	Pre-surgical	Post-surgical	*P*-value
Weight (kg)	143.5 ± 30.4	100.1 (90–115.5)	**0.0005**
Excess body weight (%)	53.2 ± 6.9	41.4 ± 13.7	**0.0005**
BMI (kg/m²)	50.1 ± 8.6	33.9 (31–53)	**0.034**
Fat mass (kg)	69.7 ± 13.1	44.9 ± 11.5	**0.001**
% Fat mass	50.4 ± 3.8	43.7 ± 6.1	**0.005**
Lean Mass (kg)	65.7 ± 9.6	55.3 ± 8.6	**0.001**
% Lean mass	47.8 ± 3.6	54.6 ± 5.6	**0.003**
REE (kcal/day)	1709 (1567.7–2234)	1580.5 (1326–1862.5)	**0.002**
REE/LBM (kcal/day/kg)	0.027 (0.025–0.028)	0.028 ± 0.002	0.577
REE/TBW (kcal/day/kg)	13.5 ± 2.3	15.5 ± 2.2	**0.043**

Values are presented as mean ± SD or as median (IQR). Excess body weight, weight – ideal body weight (50th for age). BMI, body mass index; REE, resting energy expenditure; LBM, lean body mass; TBW, total body weight. Bold values indicate p < 0.05.

TABLE 5 | Correlation of % total weight loss and body composition and measured REE before and after surgery.

	Pre-surgical		Post-surgical	
	r/Rho	*P*-value	r/Rho	*P*-value
PERCENT OF INITIAL WEIGHT LOST				
% Fat Mass	0.003	0.992	−0.669	**0.024**
Fat mass (kg)	0.271	0.490	−0.642	**0.033**
% Lean Mass	−0.105	0.759	0.576	0.064
Lean Mass (kg)	0.233	0.419	0.032	0.926
REE	−0.035	0.914	0.028	0.931
REE /LBM	−0.264	0.433	0.436	0.178
REE /TBW	−0.152	0.637	0.625	**0.03**

Linear Correlation- Spearman's test for non-parametric and Pearson for parametric distribution. BMI, body mass index; REE, resting energy expenditure; LBM, lean body mass; TBW, total body weight. Bold values indicate p < 0.05.

Correlation of Changes in Measured and Estimated REE Before and After Sleeve Gastrectomy

To evaluate if the routinely used equations can at least be used to track the changes in REE before and after surgery, we ran a correlation analysis on the changes in REE obtained with indirect calorimetry (mREE at 12 months—mREE at baseline = ΔmREE) with the changes in estimated REE obtained by each of the four equations (eREE at 12 months—eREE at baseline). We found that Δ mREE with Δ Mifflin eREE ($r = 0.48$; $p = 0.06$); Δ mREE with Δ Harris-Benedict eREE ($r = 0.41$; $p = 0.11$); Δ mREE with Δ WHO eREE ($r = 0.52$; $p = 0.04$) and Δ mREE with Δ Deru eREE ($r = 0.43$; $p = 0.10$).

DISCUSSION

Resting Energy Expenditure Equations in Adolescents and Young Adults With Severe Obesity

This study questions the utility of using predictive equations clinically to estimate REE in adolescents and young adults with moderate to severe obesity because of the high degree of variability in these predictions with a meaningful clinical error. Even the Mifflin equation, which provided the most reliable estimates, only accurately predicted REE in approximately one quarter of the subjects in our cohort. All four equations tended to overestimate REE with a high degree of bias (20–40%) above the measured REE. The Bland-Altman plots, which quantify the agreement between the two quantitative measures, showed reasonable agreement for all the equations tested (16). While these agreements are acceptable at the population level, the degree of discrepancy at the individual level limits the clinical utility of using the equations in guiding weight management treatment. The average calorie deficit recommended to achieve a weight loss of 1–2 pounds/week is about 500 kcal/day and most of these equations overestimated the individual calorie goal by that amount.

Previous scientific literature has also found that equations are inaccurate in predicting REE for adolescents with obesity (4, 11, 15, 17). However, our results seem to have even lower accuracy when compared to other studies. Even when looking at the same equation, for example, Derumeaux, our study found an accuracy prediction in 14.1% of subjects, compared to Marra et al. (4), who found accurate predictions in 43% of females and 48% of males. Lazzer et al. (15) also tested the Derumeaux equation, finding an accurate prediction in 22% of subjects. The results of our study, and in the context of these other similar studies, suggest that predictive REE equations should be used with caution in this age and weight group.

Similarly, other research has reported inaccuracies between measured and predicted REE in adults with obesity (18). Marra et al. evaluated 1851 adults with obesity to find that overall prediction accuracy was low. Testing 15 different equations, an average of 55% of subjects were found to have an accurate predicted REE. When compared with our results, the accuracy of REE prediction in adolescents with obesity is far lower, reaching a mean 12.9% between the four equations.

There are different reasons for the lack of accuracy of these equations and these should be considered before applying them to patients. For example, in our study, the Harris Benedict equation accurately predicted REE in 6.3% of subjects, overestimating REE in the majority (91.7% of subjects). Harris and Benedict developed this equation using data from normal-weight adults aged 20–70 in 1918, and the equation was not designed to predict REE in a younger population with excess weight. Though the Harris Benedict equation takes height, weight and age into account, other factors that contribute to REE such as fat free mass (11) and race (19) are not considered. In comparison, the Derumeaux equation includes fat free mass as a variable, but it was developed using data from children with obesity in a French population and does not take age into account for calculations in subjects. The ethnic diversity of our subjects may also contribute to the inaccuracy of this equation in predicting REE. Since REE can be affected by many factors at an individual level namely, lean mass, sleep, macronutrient composition of the previous meal and season of the year, it is extremely challenging to develop a precise equation at an individual level. Inaccuracy between measured REE and calculated REE has been reported in other studies of adolescents with obesity (4, 15, 17), and given these results we suggest using caution while using these equations to predict REE in adolescents with obesity unless validated in the specific population being assessed.

Energy Expenditure, Calorie Counting, and Weight Loss

In clinical practice, an assessment of energy requirements has been a key component to guiding dietary recommendations for weight loss. The Academy of Nutrition and Dietetics, Intervention of the treatment of overweight and obesity in adults (20) suggest that the Mifflin equation should be used to estimate metabolic rate in adults, followed by a dietary intervention to decrease consumption of energy. The National Institute of Health (NIH) suggests a deficit of 500–750 kcal/day is required for weight loss. It provides a website and body weight planner based on the research by Hall et al. (21), with targeted deficits to achieve desired weight loss based on REE predictions. Eat for Health (22) is an initiative by the Australian Government that contains a similar calorie calculator. The initiative, in line with the Australian Dietary Guidelines and health promotion, suggests *"any energy intake above the estimated requirement is likely to result in weight gain."* Furthermore, many gym and fitness programs use predictive equations to guide their programs. Equinox, a worldwide luxury fitness company uses REE equations in their initial consultations to help individuals achieve their specified fitness goals. Popular phone application "My Fitness Pal", was founded in 2005 and has over 19 million monthly users. It aims to helps its users achieve their weight goals by asking them to input height, weight, gender and amount of desired weight loss, using predictive equations to give a daily net calorie goal as well as a specific date that your weight goal should be achieved. Weight Watchers uses a very similar approach, allocating an individual a number of "points" to eat per day based on the Mifflin equation. Textbooks such as Handbook of Clinical Nutrition and Dietetics (23) include whole chapters on predictive equations and how to use them.

New forms of technology including hand held indirect calorimeters and arm bands are being tested as a cheaper and more accessible option to measure REE accurately for continued use in the clinical setting (24, 25). On a different note, recent research suggests that perhaps the quality of calories ingested and not the quantity should be the primary focus for weight loss (26). In a study by Gardner et al. adult subjects with overweight and obesity were placed on a healthy diet with either low fat or low carbohydrate content and received instructional sessions every 2 weeks on healthy eating over 12 months, educating patients to eat more vegetables and less processed foods without following a caloric target. Subjects in both groups lost an average of 5–6 kilograms at 12 months regardless of diet in the absence of any caloric targets (26).

In addition to the inaccuracy of REE calculations, the accuracy of food labels, which are often used to estimate the caloric content, needs to be considered. Furthermore, the amount of calories extracted from any one food may differ from person to person. Studies have shown that our individual microbiome can affect digestion and the energy required to break down different foods (27). Thus, there are many variables that may impact the accuracy of calorie counting, leading to very crude estimations even in the hands of an astute patient.

The mental health effects of recommending calorie counting in adolescents should also be considered. Adolescents with obesity are at increased risk of developing an eating disorder and are more likely to use maladaptive behaviors to control weight (e.g., use of laxatives or induced vomiting) when compared to normal weight peers (28, 29). Students who diet by severely restricting their energy intake are at much greater risk of developing an eating disorder compared to those who do not diet (30).

Thus, given these inaccuracies in estimation of REE, compounded by the fact that it is difficult to get an accurate estimate of caloric intake and doing so may not be beneficial to the overall well-being of adolescents with obesity, we should challenge the utility of this practice. Providers, government recommendations and the health and fitness industry should move away from inaccurate energy expenditure calculations, calorie goals, and weight targets, and instead focus on promoting healthy lifestyle habits.

Changes in Energy Expenditure After Bariatric Surgery

Bariatric surgery is an effective weight loss tool (31), which results in long term weight loss and improvement in metabolic outcomes across the age spectrum (32). There are many factors that affect weight loss and weight regain after surgery, and alteration in REE is postulated to be one of these factors. Sleeve gastrectomy is currently the most commonly used bariatric procedure. To our knowledge, this is the first study that evaluates changes in REE after SG in adolscents (33). Our results show that absolute REE decreases after SG, consistent with reductions in total lean mass. When comparing these changes to a historical cohort where adults with obesity lost weight by lifestyle intervention (The Biggest Loser), we found a smaller reduction in REE in our cohort who underwent SG. After 7 months, Knuth et al. found that participants of the Biggest Loser lost 35 ± 7.1% body weight, associated with a 617 kcal/day reduction in REE (7). Interestingly, our cohort who underwent SG, lost a similar percentage of body weight to the biggest loser participants, however had a far lesser decrease in REE after 12 months. The smaller reduction in energy expenditure after SG or a "blunting" of adaptive metabolic change may be an additional mechanism to explain how SG is more effective as a weight loss strategy than conventional diet/exercise weight loss over time.

Despite a reduction in absolute REE, REE controlled for total body weight increases after SG in adolescents. This is likely a reflection of the relatively greater decrease in metabolically inactive fat mass compared to metabolically active lean mass. We also found a very strong correlation between percent total weight loss and the ratio of REE/TBW, suggesting that this may be a significant factor that affects the degree of weight loss in adolescents after SG as seen in adults after gastric bypass (9). Further monitoring is needed to determine whether this contributes to weight loss maintenance and if it can be an early predictor of response to surgery.

Moreover, when we evaluated the changes in REE as obtained by indirect calorimetry before and after surgery with the changes estimated using the equations before and after surgery in our small cohort, we did not find a strong correlation. This suggests that the predictive equations are not reliable to even monitor the trend after sleeve gastrectomy. This finding further emphasizes the guarded use of these equations in a surgical setting as well.

Limitations of this study include the small sample size. Due to limited numbers, we were unable to assess the accuracy of predictive REE equations in specific ethnic groups. We were unable to compare metabolic changes in bariatric surgery with adolescents with those who lost a comparable amount of weight with diet and exercise alone, given the practical difficulty of losing 20–30% of body weight by lifestyle measures.

CONCLUSION

Treating obesity remains a challenge. Predictive REE equations in adolescents with moderate to severe obesity have a considerable margin of error and should be used with caution in the clinical setting. It is time to shift away from calorie counting based on predictive estimates, given that these estimations are imprecise and may also be detrimental to the mental health of adolescents. Instead, providers should focus on promoting a healthy lifestyle in the absence of caloric targets. SG, the most commonly used bariatric procedure in adolescents, is associated with increases in REE after controlling for total body weight, likely from the proportionally greater loss of metabolically inactive fat mass and maintenance of lean mass. These changes in REE also correlate with percent total weight loss 1-year post-surgery.

AUTHOR CONTRIBUTIONS

All authors have made substantial contribution to the paper. FR, LT, SM, AT, FS, and VS were responsible for acquisition of data and data analyses. FS, VS, and HL were responsible for interpreting the data. FR, LT, and VS were responsible for drafting the manuscript. VS was responsible for the conception and design of the study and critical review of the paper. AB, SM, FS, MB, MM, and VS were responsible for revising the article critically and adding important intellectual content. MB, MM, and VS were responsible for acquiring the funding that sponsored the study. All authors have read and approved the final version of the paper.

FUNDING

NIH grant P30 DK040561 (FS, MB, MM, VS), NIH L30 DK118710 (FS), NIH R01 31 DK103946 (MB, MM), K24DK109940 (MB), K24HD071843 (MM), K23DK110419 (VS), and 32 P30DK040561 (VS).

REFERENCES

1. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev*. (2008). 9:474–88. doi: 10.1111/j.1467-789X.2008.00475.x
2. Kumar S, Kelly AS. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. *Mayo Clin Proc*. (2017) 92:251–65. doi: 10.1016/j.mayocp.2016.09.017
3. Barlow SE, Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and overweight and obesity: summary report. *Pediatrics* (2007) 120 (Suppl. 4):S164–92. doi: 10.1542/peds.2007-2329C
4. Marra M, Montagnese C, Sammarco R, Amato V, Della Valle E, Franzese A, et al. Accuracy of predictive equations for estimating resting energy expenditure in obese adolescents. *J Pediatr*. (2015) 166:1390–6.e1. doi: 10.1016/j.jpeds.2015.03.013
5. Inge TH, Krebs NF, Garcia VF, Skelton JA, Guice KS, Strauss RS, et al. Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics* (2004) 114:217–23. doi: 10.1542/peds.114.1.217
6. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. *Int J Obes*. (2010) (34 Suppl. 1):S47–55. doi: 10.1038/ijo.2010.184
7. Knuth ND, Johannsen DL, Tamboli RA, Marks-Shulman PA, Huizenga R, Chen KY., et al. Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. *Obesity* (2014) 22:2563–9. doi: 10.1002/oby.20900
8. Bettini S, Bordigato E, Fabris R, Serra R, Dal Pra' C, Belligoli A. et al. Modifications of resting energy expenditure after sleeve gastrectomy. *Obes Surg*. (2018) 28:2481–6. doi: 10.1007/s11695-018-3190-3
9. Schneider J, Peterli R, Gass M, Slawik M, Peters T, Wölnerhanssen BK. Laparoscopic sleeve gastrectomy and Roux–en–Y gastric bypass lead to equal changes in body composition and energy metabolism 17 months postoperatively: a prospective randomized trial. *Surg Obes Relat Dis*. (2016) 12:563–70. doi: 10.1016/j.soard.2015.07.002
10. Butte NF, Treuth MS, Voigt RG, Llorente AM, Heird WC. Stimulant medications decrease energy expenditure and physical activity in children with attention–deficit/hyperactivity disorder. *J Pediatr*. (1999) 135(2 Pt. 1):203–7. doi: 10.1016/S0022-3476(99)70023-5
11. Derumeaux-Burel H, Meyer M, Morin L, Boirie Y. Prediction of resting energy expenditure in a large population of obese children. *Am J Clin Nutr*. (2004) 80:1544–50. doi: 10.1093/ajcn/80.6.1544
12. Harris JA, Benedict FG. A biometric study of human basal metabolism. *Proc Natl Acad Sci USA*. (1918) 4:370–3.
13. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr*. (1990) 51:241–7. doi: 10.1093/ajcn/51.2.241
14. WHO. *Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation.* World Health Organ Tech Rep Ser (1985). p. 1–206.
15. Lazzer S, Agosti F, De Col A, Mornati D, Sartorio A. Comparison of predictive equations for resting energy expenditure in severely obese Caucasian children and adolescents. *J Endocrinol Invest*. (2007) 30:313–7. doi: 10.1007/BF03346298
16. Bland JM, Altman DG. Measurement error and correlation coefficients. *BMJ* (1996) 313:41–2. doi: 10.1136/bmj.313.7048.41
17. Acar-Tek N, Ağagündüz D, Çelik B, Bozbulut R. Estimation of resting energy expenditure: validation of previous and new predictive equations in obese children and adolescents. *J Am Coll Nutr*. (2017) 36:470–80. doi: 10.1080/07315724.2017.1320952
18. Marra M, Cioffi I, Sammarco R, Montagnese C, Naccarato M, Amato V., et al. Prediction and evaluation of resting energy expenditure in a large group of obese outpatients. *Int J Obes*. (2017) 41:697–705. doi: 10.1038/ijo.2017.34
19. Morrison JA, Alfaro MP, Khoury P, Thornton BB, Daniels SR. Determinants of resting energy expenditure in young black girls and young white

girls. *J Pediatrics* (1996) 129:637–42. doi: 10.1016/S0022-3476(96)70142-7
20. Raynor HA, Champagne CM. Position of the academy of nutrition and dietetics: interventions for the treatment of overweight and obesity in adults. *J Acad Nutr Diet* (2016) 116:129–47. doi: 10.1016/j.jand.2015.10.031
21. Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL., et al. Quantification of the effect of energy imbalance on bodyweight. *Lancet* (2011) 378:826–37. doi: 10.1016/S0140-6736(11)60812-X
22. Eat For Health. Available online at: https://www.eatforhealth.gov.au (2019) (Accessed January 3, 2019).
23. Stewart R. *Handbook Of Clinical Nutrition And Dietetics*. Southport: Griffith University, School of Public Health (2009).
24. Nieman DC, Austin MD, Chilcote SM, Benezra L. Validation of a new handheld device for measuring resting metabolic rate and oxygen consumption in children. *Int J Sport Nutr Exer Metabol.* (2005) 15:186–94. doi: 10.1123/ijsnem.15.2.186
25. Predieri B, Bruzzi P, Lami F, Vellani G, Malavolti M, Battistini NC. et al. Accuracy of sensewear Pro2 armband to predict resting energy expenditure in childhood obesity. *Obesity* (2013) 21:2465–70. doi: 10.1002/oby.20427
26. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA., et al. Effect of low–fat vs low–carbohydrate diet on 12–month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *J Am Med Assoc*. (2018) 319:667–79. doi: 10.1001/jama.2018.0245
27. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I., et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr*. (2018) 57:1–24. doi: 10.1007/s00394-017-1445-8
28. Sim LA, Lebow J, Billings M. Eating disorders in adolescents with a history of obesity. *Pediatrics* (2013) 132:e1026–30. doi: 10.1542/peds.2012-3940
29. Field AE, Camargo CA, Taylor CB, Berkey CS, Frazier AL, Gillman MW, et al. Overweight, weight concerns, and bulimic behaviors among girls and boys. *J Am Acad Child Adolesc Psychiatry* (1999) 38:754–60.
30. Patton GC, Selzer R, Coffey C, Carlin JB, Wolfe R. Onset of adolescent eating disorders: population based cohort study over 3 years. *BMJ* (1999) 318:765–8. doi: 10.1136/bmj.318.7186.765
31. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K., et al. Bariatric surgery: a systematic review and meta–analysis. *J Am Med Assoc*. (2004) 292:1724–37. doi: 10.1001/jama.292.14.1724
32. Inge TH, Jenkins TM, Xanthakos SA, Dixon JB, Daniels SR, Zeller MH., et al. Long–term outcomes of bariatric surgery in adolescents with severe obesity (FABS−5+): a prospective follow–up analysis. *Lancet Diabetes Endocrinol*. (2017) 5:165–173. doi: 10.1016/S2213-8587(16)30315-1
33. Griggs CL, Perez NP, Goldstone RN, Keller CM, Chang DC, Stanford FC, et al. National trends in the use of metabolic and bariatric surgery among pediatric patients with severe obesity. *JAMA Pediatr*. (2018) 72:1191. doi: 10.1001/jamapediatrics.2018.3030

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

MINI REVIEW
published: 04 October 2018
doi: 10.3389/fped.2018.00271

New Insights Regarding Genetic Aspects of Childhood Obesity: A Minireview

Cristina Oana Mărginean[1], *Claudiu Mărginean*[2]* and *Lorena Elena Meliţ*[1]

[1] Department of Pediatrics, University of Medicine and Pharmacy Târgu Mureş, Târgu Mureş, Romania, [2] Department of Obstetrics and Gynecology, University of Medicine and Pharmacy Târgu Mureş, Târgu Mureş, Romania

Introduction: Childhood obesity is occurring at alarming rates in both developed and developing countries. "Obesogenic" environmental factors must be associated with variants of different risk alleles to determine polygenic or common obesity, and their impact depends on different developmental stages.The interaction between obesogenic environment and genetic susceptibility results in the so-called polygenic forms of obesity. In contrast, monogenic and syndromic obesity are not influenced by environmental events. Therefore, this review aimed to underline the roles of some of the most studied genes in the development of monogenic and polygenic obesity in children.

Results: Among the most common obesity related genes, we chose the fat mass and obesity-associated (FTO) gene, leptin gene and its receptor, tumor necrosis factor alpha (TNF-α), the melanocortin 4 receptor gene (MC4R), Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1), and others, such as peroxisome proliferator-activated receptor gamma (PPARG), angiotensin-converting enzyme (ACE), glutathione S-transferase (GST), and interleukin-6 (IL-6) genes. The roles of these genes are complex and interdependent, being linked to different cornerstones in obesity development, such as appetite behavior, control of food intake and energy balance, insulin signaling, lipid and glucose metabolism, metabolic disorders, adipocyte differentiation, and so on.

Conclusions: Genetic predisposition is mandatory, but not enough to trigger obesity.Dietary interventions and proper lifestyle changes can prevent obesity development in genetically predisposed children. Further studies are needed to identify the precise role of both genetic and obesogenic factors in the development of childhood obesity in order to design effective preventive methods.

Keywords: obesity, genetics, children, etiology, dietary interventions

Edited by:
Fatima Cody Stanford, Massachusetts General Hospital, Harvard Medical School, United States

Reviewed by:
Sonali Malhotra, Massachusetts General Hospital, Harvard Medical School, United States
Michael Freemark, Duke University Medical Center, United States

****Correspondence:***
Claudiu Mărginean
marginean.cluaudiu@gmail.com

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *21 March 2018*
Accepted: *10 September 2018*
Published: *04 October 2018*

Citation:
Mărginean CO, Mărginean C and Meliţ LE (2018) New Insights Regarding Genetic Aspects of Childhood Obesity: A Minireview. Front. Pediatr. 6:271. doi: 10.3389/fped.2018.00271

SUMMARY

Childhood obesity has become recently a global epidemic due to its high rates in both developed and developing countries. In Romania, a recent study found that one in four children is overweight or obese, and identified male gender, prepuberal age, and urban environment as risk factors for overweight. This major public health problem is a result of the interaction between environmental factors and individual genetic susceptibility. "Obesogenic" environmental factors must be associated with variants of different risk alleles to determine polygenic or common obesity, and their impact depends on different developmental stages.

INTRODUCTION

Recently, childhood obesity has become a global epidemic, occurring at high rates in both developed and developing countries (1). Most studies regarding this health burden were performed on adult populations, and only a few of them included children. In Romania, a recent study found that one in four children is overweight or obese and identified male sex, prepubertal age, and urban environment as risk factors for incidences of overweight (2). This major public health problem is a result of the interaction between environmental factors and individual genetic susceptibility. Heritability plays a key role in the development of childhood obesity, with a rate of determinism as high as 70%, and it was proven to be higher in children than adults (3, 4). Obesogenic environment is only a trigger, and not the leading-cause for excessive weight gain, a genetic susceptibility to fat gain being mandatory for an individual to become obese (5–7). Therefore, environmental factors just favor the phenotypic expression in individuals programmed to become obese (8). Moreover, the impact of obesogenic environment differs during different developmental stages. For example, Silvenstoinen et al. performed a systematic review on twins and adopted children and proved that environmental factors moderately influence BMI variation only up to the age of 13 years, their effect disappearing beyond this age (6). It is true BMI curve in children is therefore genetically programmed, but at the same time environmental circumstances are able to modify this curve (8). Another well-documented fact is that fetal and early postnatal environmental events, such as maternal nutritional status during pregnancy, maternal smoking, gestational diabetes, increased birth weight, rapid weight gain, or feeding practices, may also influence the development of obesity later in life (8–16). In addition, the expression of genetic risks predominates during infancy and early childhood leading to an earlier adiposity rebound and higher BMI in children that carry a genetic susceptibility (17–19).

Therefore, it is apparent that "obesogenic" environmental factors alone are not responsible for the development of obesity; they must be associated with variants of different risk alleles to determine polygenic or common obesity (20). Many studies focused on assessing the role of different genes in the determination of obesity and found that certain variants are associated with weight regulation and adipose tissue accumulation (21). Therefore, recent genome-wide association studies identified over 50 genetic loci that can be associated with obesity (22), resulting in polygenic forms of obesity. Polygenic' variants are defined as any of a group of alleles at different gene loci that express a combined effect on controlling the inheritance of a quantitative phenotype or which can modify the expression of a qualitative character. Therefore, certain traits can be the result of the simultaneous presence of DNA changes in multiple genes. In case of quantitative traits, it was proved that each allele owns a small effect and these effects can be additive or non-additive. It is generally assumed that many of these polygenic variants are involved in body weight regulation and in individuals who harbor multiple of these variants, obesity can occur. Thus, the hypothesis of polygenic obesity implies that every obese individual carries his own specific set of polygenic variants which are unlikely to be same in another subject with obesity (21).

On the other hand, there are also rare forms of obesity that lack the influence of environmental factors, the so-called recessive monogenic obesity; examples include mutations affecting the leptin gene or its receptor, proopiomelanocortin and pro-hormone convertase subtilisin/kesin type, all leading to a fast and dramatic weight gain (8). These forms present complete penetrance in comparison to the particular form of obesity related to MC4R, and probably MC3R as well; polymorphisms in these genes are associated with forms of obesity that are more severe than typical polygenic obesity but less severe than homozygous gene mutations (8). In contrast to these types of monogenic obesity, the syndromic ones usually occur after infancy, such as Prader-Willi syndrome, Bardet-Biedl syndrome, Albright's hereditary osteodystrophy, Alström syndrome, and WAGR (Wilms' tumor, aniridia, genitourinary anomalies, and retardation) syndrome. Apart from obesity, these syndromes involve dysmorphic features, cognitive impairment, and malformations of major organs (23).

This review summarizes information about the roles of genetic mutations and polymorphisms in the pathogenesis of polygenic obesity in childhood.

FAT MASS AND OBESITY-ASSOCIATED (FTO) GENE AND OBESITY

The FTO gene is located on chromosome 16, position 16q12.2, and comprises 9 exons. This gene is expressed in the hypothalamus, at the level of the arcuate nucleus, which is responsible for appetite behavior and fatty acid metabolism, among others (24, 25). Therefore, a recent cross-sectional study was performed on 406 Brazilian children and adolescents aged 7–17 years, among whom 34.5% were overweight or obese. The study proved a positive association between AA genotype of the rs9939609 FTO gene polymorphism and the risk of overweight/obesity (26). Similarly, Cecil et al. stated that the A allele is related to increased fat mass and body mass index (BMI) in Scottish children aged 4–10 years (27). In addition, a study performed on 289 subjects aged 6–19 years proved that the carriers of the AT or AA genotype more frequently expressed a tendency toward intake of food with higher fat content and a loss of food intake control (28). Similarly, a Chinese study performed on children and adolescents found that the AA genotype carriers expressed a preference for a meat-based diet in comparison with those carrying the TT genotype, who preferred a plant-based diet (29). Contradictory results were reported by de Araújo Pereira et al. who did not find any association between FTO gene polymorphisms and overweight or obesity risk in a study performed on 195

Abbreviations: ACE, angiotensin-converting enzyme; ENPP1, ectoenzyme nucleotide pyrophosphate phosphodiesterase 1; FTO, fat mass and obesity-associated gene, GST, glutathione S-transferase; IL, interleukin; MC4R, melanocortin 4 receptor gene; PC-1, plasma cell glycoprotein 1; PI, ponderal index; PPARG, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor alpha.

obese/overweight individuals with a mean age of 11 years (30). Another study that included 478 African-American children also failed in identifying any association between different FTO gene variants and BMI (31). Therefore, ethnicity might be an important variable regarding the role of FTO gene polymorphism in obesity development. A recent study performed on Polish young adults, which assessed multiple polymorphisms of the FTO gene (rs1121980, rs1421085, rs9930506, and rs9939609), found that this population expressed two disparate haplotypes of the FTO gene variants: TCGA risk haplotype and CTAT protective haplotype, the alleles provided in the previously mentioned order (20). Nevertheless, the genetic susceptibility for obesity can be influenced by dietary interventions in combination with exercise, as stated by Zou et al. in a study performed on obese children carrying the at-risk FTO rs9939609 genotype (32). The rs9939609 FTO gene polymorphism was associated with certain obesity complications, such as high blood pressure, percentage body fat and fat mass, plasma insulin levels, and insulin resistance (33). In contrast, anthropometrical neonatal parameters can influence the nutritional status further on in life. Therefore, a recent study emphasized that a lower PI [i.e., PI, an index computed as birth weight (kg) divided by birth length (m) cubed] suggests that an individual is more vulnerable to the negative effects of the A risk allele of FTO polymorphism on body fat mass (34). In contrast, it was also shown that mothers carrying the variant A allele of rs9939609 FTO polymorphism had newborns with a lower BMI (9). Further functional studies are needed to determine the precise role of the FTO gene in determining obesity and its complications.

LEPTIN AND OBESITY

Leptin is a hormone synthesized and secreted into the blood flow by white adipocytes and plays a key role in regulating control of food intake and energy balance. It was proven that, in obese individuals, there is an endogenous leptin resistance mechanism that limits these regulatory effects, explaining the correlation between serum leptin levels and body fat mass (35). This leptin resistance mechanism was related to the presence of the A allele variant of the FTO gene (36), partially explaining the associations of the FTO gene polymorphisms with increased dietary consumption (37) or a hyperphagic phenotype (27, 28). During pregnancy, leptin is synthesized by not only the adipose tissues of both the mother and fetus but also the placenta, and it was proven that the leptin levels in the umbilical cord are positively correlated with birth weight (38, 39). Leptin exerts its roles through the leptin receptor; therefore, the leptin receptor gene is considered a biological pathway related to obesity development (9). A recent study focused on the positive effect of neonatal and maternal leptin gene receptor rs1137101 polymorphism on birth weight and BMI (9). The congenital deficit of leptin results in morbid obesity, severe hyperphagia, hyperinsulinemia or type 2 diabetes mellitus, hypogonadotropic hypogonadism, hypofunction of T cells, and endocrine or metabolic dysfunctions (40, 41). However, mutations in the leptin gene are associated with T cells of normal function and moderate obesity (42). It is well-documented that serum leptin levels depend on age and sex and are correlated with body fat mass (42–44). A study performed on white children assessing 223, 492, and 1019 leptin receptor gene polymorphisms concluded that the most frequent combinations in children with obesity were AG/GG/GA, AG/GG/GG, and AA/GG/GA (10). The same study also underlined that anthropometrical parameters and leptin and adiponectin levels are correlated with the variant genotype of the leptin receptor 223 gene. Therefore, it is well documented that leptin gene receptor 223, 1019, 492, and 976 polymorphisms can modulate the nutritional status in both normal and overweight/obese children (10), but these effects also depend on environmental, nutritional, and social factors. Thus, it was proven that even from birth, weight is positively correlated with maternal fat mass, total body water, body metabolism rate, and metabolic age, whereas it is negatively correlated with maternal smoking status (11). Leptin and leptin gene receptor polymorphisms play a well-established role in childhood obesity.

TUMOR NECROSIS FACTOR ALPHA (TNF-α) AND OBESITY

TNF-α is a proinflammatory cytokine expressed as a cell surface transmembrane protein involved in the pathogenesis of multiple inflammatory disorders located on the chromosome 6, site p21.1–21.3. It is also proven to have a catabolic role in infection and cancer but can also be a mediator of cachexia with associated hyperlipidemia (45). Therefore, TNF-α is involved in lipid metabolism leading to hypertriglyceridemia as a result of decreasing lipoprotein lipase activity (46) and increasing the hepatic de novo synthesis of fatty acids (47). It is well known that in subjects with obesity, TNF-α expression is high and correlated with hyperinsulinemia (48). Furthermore, TNF-α was found to regulate leptin expression and secretion (49). A G/A substitution in the promoter region (G-308) of the TNF-α gene was identified (50). Thus, the G-308A polymorphism of this gene is associated with hypertension, leptin levels, and hypercholesterolemia, resulting in metabolic syndrome development (51). In contrast, studies on Caucasian (52) and Chinese (53) populations found correlations between TNF-α 308 G allele and obesity risk. Regarding the presence of different genotypes, Sobti et al. emphasized that the AA and GA genotypes of this gene are more frequently associated with obesity in men, whereas in women, the AG genotype was associated with a higher risk for obesity (54). Nonetheless, a study performed on Iranian subjects failed to prove any correlation between TNF-α 308 G>A gene polymorphism and obesity (55). Similarly, a study performed on Romanian children showed that the variant genotype of TNF-α 308 G>A gene polymorphism was found most frequently in normal weight children (12). Based on all previously mentioned studies, the role of TNF-α 308 G>A gene polymorphism is not clear, but obesity can indeed be considered an inflammatory status.

MELANOCORTIN 4 RECEPTOR (MC4R) AND OBESITY

The MC4R gene is located on chromosome 18q21.32 and, similar to the FTO gene, plays a regulatory role in food intake control and energy balance (56, 57). The common rs17782313 MC4R gene polymorphism was associated with obesity in both European adults and children showing a synergistic effect with FTO gene on obese phenotype (58–60). Rarely, mutations in MC4R gene leading to function loss can lead to monogenic forms of obesity (58), but MC4R-linked obesity is better defined as a particular form which stands between rare recessive monogenic obesity forms and common polygenic ones (8). The rs12970134 and rs17782313 polymorphisms of the MC4R gene were identified to be associated with child and adult obesity, respectively in both Asian and European populations (58, 61–65). A recent study underlined a strong effect of MC4R rs17782313 on body size and fat distribution, proving that the C/C genotype is associated with higher BMI (66). Another study that assessed the same polymorphism of MC4R gene highlighted a significant association with obesity in Mexican children (67). In addition, the authors also identified that both MC4R and FTO risk genotypes increase the metabolic risk in children with obesity (67). The same findings were also identified in Greek children and adolescents with obesity, but the study failed to show an association with the metabolic profile of these children (60). Another important recent discovery is that adiponectin may be involved in mediating the effect of MC4R gene on obesity, based on the findings of Wu et al. who reported that the rs17782313 MC4R gene polymorphism is associated with adiponectin in Chinese children (68). A study performed on newborns in Greece assessed both risk FTO and MC4R variants and concluded that approximately 80% of the Greek population are genetically predisposed to obesity development further on in life (69). According to the results of several studies, the individuals at high risk for obesity development may be homozygous for both FTO and MC4R genes or may be homozygous for one of the two genes and heterozygous for the other (70–72). In contrast, it has also been proven that the rs17782313 MC4R polymorphism has a key role in the eating behavior and control of the eating behavior. Therefore, a recent study performed on children with obesity showed that obese girls that carry the C allele of this genotype express lower satiety responsiveness and higher uncontrolled eating scores in comparison to noncarriers, whereas, in obese boys, the carriers of the same allele present a lower rewarding value of food compared with those who do not carry the C allele Similarly, other studies performed on both adults and children showed that the expression of MC4R and FTO genes can be modulated by lifestyle and physical activity (73, 74).

ECTOENZYME NUCLEOTIDE PYROPHOSPHATE PHOSPHODIESTERASE 1 (ENPP1) AND OBESITY

ENPP1 or plasma cell glycoprotein 1 (PC-1) is located on chromosome 6q23.2 and was identified to encode a protein that inhibits insulin signaling (75). The role of this gene in energy metabolism and fat tissue physiology has been widely assessed in the literature (76). K121Q polymorphism was associated with insulin resistance, type 2 diabetes mellitus, and obesity, but the results are contradictory (75, 77–81). In addition to this polymorphism, Bockenski et al. also identified the rs997509 ENPP1 gene polymorphism as a potential contributor to the development of type 2 diabetes mellitus among individuals with obesity (82). Similarly, a study performed on children with obesity underlined the potential role of K121Q ENPP1 polymorphism in not only early perturbations of glucose and insulin metabolism but also subsequent obesity development (83). A large study performed on 1,685 obese and normal-weight Mexican children found nominal associations between different gene polymorphisms, like those in ENPP1 rs7754561 and MC4R rs17782313, and obesity risk or BMI (84). Interestingly, the same authors identified a different pattern for the risk allele of ENPP1 rs7754561 in Mexican individuals showing a protective role in obesity development compared with that in European individuals where the same gene presented positive associations with obesity risk (84). It has also been proven that the overexpression of ENPP1 in human adipocyte cell lines leads to impaired adipocyte maturation (85). In addition to insulin resistance, the K121Q polymorphism was also proven to be associated with different obesity-related phenotypes such as percentage of body fat, fat mass, and plasma insulin levels (86).

OTHER GENES AND OBESITY

The peroxisome proliferator-activated receptor gamma (PPARG), located on chromosome 3p25.2, plays a role in regulating adipocyte differentiation and influences BMI and glucose metabolism (87). The rs1801282 Pro12Ala polymorphism of this gene has been associated with obesity risk, insulin resistance, type 2 diabetes mellitus, and cardiovascular events (88, 89). A recent study confirmed the association between PPARG and obesity in young adults (66). In addition, a study performed on mothers and their newborns emphasized that homozygous CC carriers of the PPARG genotype presented a higher risk for obesity than heterozygous newborns (13). Moreover, the same authors showed that mothers carrying the homozygous CC genotype of the same gene gave birth to newborns with increased risk for obesity (13).

Angiotensin-converting enzyme (ACE) located on chromosome 17q23.3 has also been shown to have a potential role in obesity development. The ACE rs4646994 has been associated with adiposity and metabolic disorders (90, 91). A potential functional correlation between the PPARG and ACE genes has been underlined based on the fact that PPARG controls the renin-angiotensin system through the transcriptional modulation of renin, angiotensinogen, ACE, and angiotensin II receptor 1 (92). Nevertheless, the results reported in the literature remain contradictory. Certain studies performed on children found that I/I carriers of the ACE gene are associated with higher BMI,[14] whereas others reported that the D/D genotype of the same gene is linked with increased values of the anthropometric parameters (91, 93). Moreover, other findings have failed to identify any association between ACE gene polymorphisms and body composition (66).

Another class of gene associated with a potential role in obesity development is the glutathione S-transferase (GST), which is involved in different intermediary chemical reactions with glutathione (94). It was proven that the null genotype of both the M1 and T1 alleles of the GST gene (GSTM1 and GSTT1) plays a major protective cellular role against xenobiotic toxic substances and oxidative stress (95, 96). Multiple studies focused on the correlations between these genotypes and neonatal birth weight (15, 97–102).

Interleukin (IL) 6 is a proinflammatory cytokine found to modulate the function of adipose tissue by regulating energy balance, presenting high levels in both obesity and cardiovascular diseases (103–106). Certain genetic studies proved that different polymorphisms of the IL-6 gene present a key role in transcriptional regulation and influence plasmatic cytokine levels, supporting the fact that this gene interacts with metabolic modulation, resulting in different metabolic conditions, such as obesity (107). The G alleles of both IL-6 174 and IL-6 572 genes were associated with obesity and type 2 diabetes mellitus (108). Similarly, in a study performed on Caucasian children, the IL-6572CC, IL-6 190 CC, and IL-6 174 CG genotypes were encountered more frequently in children with obesity, whereas the IL-6 174 CC genotype was found to be a protective factor for childhood obesity (16). Nevertheless, further studies are needed to fully understand the role of the genome in childhood obesity onset.

CONCLUSIONS

Even though recent genetic studies identified over 50 genetic loci, dietary interventions and proper lifestyle changes can prevent obesity development in genetically predisposed people. Therefore, screening programs could be useful in identifying high-risk children, who could benefit from proper prophylactic measures. Perhaps, further studies should also focus on developing targeted genetic therapies designed for children that carry the burden of obesity risk.

AUTHOR CONTRIBUTIONS

COM, CM, and LEM conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

The English proofreading was managed by *Editage* Language Editing Services (https://app.editage.com/orders/download-files/CRARG_4).

This research was partially supported by the Collective Research Grants of the University of Medicine and Pharmacy Tîrgu Mureş, Romania (*The role of mother's genetic determinism in child's obesity correlated with bioimpedance and anthropometric parameters* no.275/4/11.01.2017).

REFERENCES

1. Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. *Mol Psychiatry* (2014) 19:544–54. doi: 10.1038/mp.2013.54
2. Chirita-Emandi A, Barbu CG, Cinteza EE, Chesaru BI, Gafencu M, Mocanu V, et al. Overweight and underweight prevalence trends in children from Romania - pooled analysis of cross-sectional studies between 2006 and 2015. *Obes Facts* (2016) 9:206–20. doi: 10.1159/000444173
3. Herrera BM, Keildson S, Lindgren CM. Genetics and epigenetics of obesity. *Maturitas* (2011) 69:41–9. doi: 10.1016/j.maturitas.2011.02.018
4. Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. *Front Endocrinol*. (2012) 3:29. doi: 10.3389/fendo.2012.00029
5. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr*. (2008) 87:398–404. doi: 10.1093/ajcn/87.2.398
6. Silventoinen K, Rokholm B, Kaprio J, Sørensen TI. The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies. *Int J Obes*. (2010) 34:29–40. doi: 10.1038/ijo.2009.177
7. Bouchard C. Defining the genetic architecture of the predisposition to obesity: a challenging but not insurmountable task. *Am J Clin Nutr*. (2010) 91:5–6. doi: 10.3945/ajcn.2009.28933
8. Tounian P. Programming towards childhood obesity. *Ann Nutr Metab*. (2011) 58 (Suppl. 2):30–41. doi: 10.1159/000328038
9. Mărginean C, Mărginean CO, Iancu M, Melit LE, Tripon F, Bănescu C. The FTO rs9939609 and LEPR rs1137101 mothers-newborns gene polymorphisms and maternal fat mass index effects on anthropometric characteristics in newborns: a cross-sectional study on mothers-newborns gene polymorphisms-The FTO-LEPR Study (STROBE-compliant article). *Medicine* (2016) 95:e5551. doi: 10.1097/MD.0000000000005551
10. Mărginean CO, Mărginean C, Voidăzan S, Melit L, Crauciuc A, Duicu C, et al. Correlations between leptin gene polymorphisms 223 A/G, 1019 G/A, 492 G/C, 976 C/A, and anthropometrical and biochemical parameters in children with obesity: a prospective case-control study in a Romanian population-The Nutrichild Study. *Medicine* (2016) 95:e3115. doi: 10.1097/MD.0000000000003115
11. Mărginean C, Mărginean CO, Bănescu C, Melit L, Tripon F, Iancu M. Impact of demographic, genetic, and bioimpedance factors on gestational weight gain and birth weight in a Romanian population: a cross-sectional study in mothers and their newborns: the Monebo study (STROBE-compliant article). *Medicine* (2016) 95:e4098. doi: 10.1097/MD.0000000000004098
12. Mărginean C, Mărginean C, Iancu M, Moldovan V, Meliş L, Bănescu C. The impact of TNF-α 308G>A gene polymorphism in child's overweight risk coupled with the assessment of biochemical parameters – a cross-sectional single center experience. *Pediatr Neonatol*. (2018) 2018:1–9. doi: 10.1016/j.pedneo.2018.03.003
13. Mărginean C, Mărginean CO, Iancu M, Szabo B, Cucerea M, Melit LE, et al. The role of TGF-β1 869 T > C and PPAR γ2 34 C > G polymorphisms, fat mass, and anthropometric characteristics in predicting childhood obesity at birth: a cross-sectional study according the parental characteristics and newborn's risk for child obesity (the newborns obesity's risk) NOR study. *Medicine* (2016) 95:e4265. doi: 10.1097/MD.0000000000004265
14. Mărginean CO, Bănescu C, Duicu C, Voidăzan S, Mărginean C. Angiotensin-converting enzyme gene insertion/deletion polymorphism in nutritional disorders in children. *Eur J Nutr*. (2015) 54:1245–54. doi: 10.1007/s00394-014-0802-0
15. Mărginean C, Bănescu CV, Mărginean CO, Tripon F, Melit LE, Iancu M. Glutathione S-transferase (GSTM1, GSTT1) gene polymorphisms, maternal

gestational weight gain, bioimpedance factors and their relationship with birth weight: a cross-sectional study in Romanian mothers and their newborns. *Romanian J Morphol Embryol.* (2017) 58:1285–93.

16. Mărginean CO, Bănescu C, Duicu C, Pitea AM, Voidăzan S, Mărginean C. The role of IL-6 572 C/G, 190 C/T, and 174 G/C gene polymorphisms in children's obesity. *Eur J Pediatr*. (2014) 173:1285–96. doi: 10.1007/s00431-014-2315-5
17. Elks CE, Loos RJ, Sharp SJ, Langenberg C, Ring SM, Timpson NJ, et al. Genetic markers of adult obesity risk are associated with greater early infancy weight gain and growth. *PLoS Med*. (2010) 7:e1000284. doi: 10.1371/journal.pmed.1000284
18. Elks C, Loos R, Hardy R. Adult obesity susceptibility variants are associated with greater childhood weight gain and a faster tempo of growth: the 1946 British Birth Cohort Study. *Am J Clin Nutr*. (2012) 95:1150–56. doi: 10.3945/ajcn.111.027870
19. Belsky DW, Moffitt TE, Houts R, Bennett GG, Biddle AK, Blumenthal JA, et al. Polygenic risk, rapid childhood growth, and the development of obesity: evidence from a 4-decade longitudinal study. *Arch Pediatr Adolesc Med*. (2012) 166:515–21. doi: 10.1001/archpediatrics.2012.131
20. Kolačkov K, Łaczmanski Ł, Lwow F, Ramsey D, Zdrojowy-Wełna A, Tupikowska M, et al. The frequencies of haplotypes of FTO gene variants and their association with the distribution of sody fat in non-obese poles. *Adv Clin Exp Med*. (2016) 25:33–42. doi: 10.17219/acem/60645
21. Hinney A, Vogel CI, Hebebrand J. From monogenic to polygenic obesity: recent advances. *Eur Child Adolesc Psychiatry* (2010) 19:297–310. doi: 10.1007/s00787-010-0096-6
22. Loos RJ. Genetic determinants of common obesity and their value in prediction. *Best Pract Res Clin Endocrinol Metab*. (2012) 26:211–26. doi: 10.1016/j.beem.2011.11.003
23. Mason K, Page L, Balikclouglu P. Screening for hormonal, monogenic, and syndromic disorders in obese infants and children. *Pediatr Ann*. (2014) 43:e218–24. doi: 10.3928/00904481-20140825-08
24. Lima W, Glaner M, Taylor A. Fenótipo da gordura, fatores associados e o polimorfismo rs9939609 do gene FTO. *Rev Bras Cineantropometria Amp Desempenho Hum*. (2010) 12:164–72. doi: 10.5007/1980-0037.2010v12n2p164
25. Apalasamy YD, Ming MF, Rampal S, Bulgiba A, Mohamed Z. Genetic association of SNPs in the FTO gene and predisposition to obesity in Malaysian Malays. *Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol*. (2012) 45:1119–26. doi: 10.1590/S0100-879X2012007500134
26. Reuter CP, Burgos MS, Bernhard JC, Tornquist D, Klinger EI, Borges TS, et al. Association between overweight and obesity in schoolchildren with rs9939609 polymorphism (FTO) and family history for obesity. *J Pediatr*. (2016) 92:493–8. doi: 10.1016/j.jped.2015.11.005
27. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CNA. An obesity-associated FTO gene variant and increased energy intake in children. *N Engl J Med*. (2008) 359:2558–66. doi: 10.1056/NEJMoa0803839
28. Tanofsky-Kraff M, Han JC, Anandalingam K, Shomaker LB, Columbo KM, Wolkoff LE, et al. The FTO gene rs9939609 obesity-risk allele and loss of control over eating. *Am J Clin Nutr*. (2009) 90:1483–8. doi: 10.3945/ajcn.2009.28439
29. Yang M, Xu Y, Liang L, Fu J, Xiong F, Liu G, et al. The effects of genetic variation in FTO rs9939609 on obesity and dietary preferences in Chinese Han children and adolescents. *PloS ONE* (2014) 9:e104574. doi: 10.1371/journal.pone.0104574
30. Pereira P de A, Alvim-Soares AM, Sandrim VC, Moreira Lanna CM, Souza-Costa DC, de Almeida Belo V, et al. Lack of association between genetic polymorphism of FTO, AKT1 and AKTIP in childhood overweight and obesity. *J Pediatr*. (2016) 92:521–7. doi: 10.1016/j.jped.2015.12.007
31. Grant SF, Li M, Bradfield JP, Kim CE, Annaiah K, Santa E, et al. Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. *PloS ONE* (2008) 3:e1746. doi: 10.1371/journal.pone.0001746
32. Zou ZC, Mao LJ, Shi YY, Chen JH, Wang LS, Cai W. Effect of exercise combined with dietary intervention on obese children and adolescents associated with the FTO rs9939609 polymorphism. *Eur Rev Med Pharmacol Sci*. (2015) 19:4569–75.
33. Prakash J, Mittal B, Srivastava A, Awasthi S, Srivastava N. Association of FTO rs9939609 SNP with obesity and obesity- associated phenotypes in a North Indian population. *Oman Med J*. (2016) 31:99–106. doi: 10.5001/omj.2016.20
34. Labayen I, Ruiz JR, Ortega FB, Gottrand F, Huybrechts J, Dallongeville J, et al. Body size at birth modifies the effect of fat mass and obesity associated (FTO) rs9939609 polymorphism on adiposity in adolescents: the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. *Br J Nutr*. (2012) 107:1498–504. doi: 10.1017/S0007114511004600
35. Könner AC, Klöckener T, Brüning JC. Control of energy homeostasis by insulin and leptin: targeting the arcuate nucleus and beyond. *Physiol Behav*. (2009) 97:632–8. doi: 10.1016/j.physbeh.2009.03.027
36. Labayen I, Ruiz JR, Ortega FB, Dallongeville J, Jiménez-Pavón D, Castillo MJ, et al. Association between the FTO rs9939609 polymorphism and leptin in European adolescents: a possible link with energy balance control. The HELENA study. *Int J Obes*. (2011) 35:66–71. doi: 10.1038/ijo.2010.219
37. Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, et al. The FTO/obesity associated locus and dietary intake in children. *Am J Clin Nutr*. (2008) 88:971–8. doi: 10.1093/ajcn/88.4.971
38. Souren NY, Paulussen AD, Steyls A, Loos RJ, Stassen AP, Gielen M, et al. Common SNPs in LEP and LEPR associated with birth weight and type 2 diabetes-related metabolic risk factors in twins. *Int J Obes*. (2008) 32:1233–9. doi: 10.1038/ijo.2008.68
39. Hauguel-de Mouzon S, Lepercq J, Catalano P. The known and unknown of leptin in pregnancy. *Am J Obstet Gynecol*. (2006) 194:1537–45. doi: 10.1016/j.ajog.2005.06.064
40. Farooqi IS. Monogenic human obesity. *Front Horm Res*. (2008) 36:1–11. doi: 10.1159/0000115333
41. Mazen I, El-Gammal M, Abdel-Hamid M, Amr K. A novel homozygous missense mutation of the leptin gene (N103K) in an obese Egyptian patient. *Mol Genet Metab*. (2009) 97:305–8. doi: 10.1016/j.ymgme.2009.04.002
42. Fischer-Posovszky P, von Schnurbein J, Moepps B, Lahr G, Strauss G, Barth TF, et al. A new missense mutation in the leptin gene causes mild obesity and hypogonadism without affecting T cell responsiveness. *J Clin Endocrinol Metab*. (2010) 95:2836–40. doi: 10.1210/jc.2009-2466
43. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. *Ann Intern Med*. (2010) 152:93–100. doi: 10.7326/0003-4819-152-2-201001190-00008
44. Anubhuti, Arora S. Leptin and its metabolic interactions: an update. *Diabetes Obes Metab*. (2008) 10:973–93. doi: 10.1111/j.1463-1326.2008.00852.x
45. Beutler B, Cerami A. Cachectin (tumor necrosis factor): a macrophage hormone governing cellular metabolism and inflammatory response. *Endocr Rev*. (1988) 9:57–66. doi: 10.1210/edrv-9-1-57
46. Morin CL, Schlaepfer IR, Eckel RH. Tumor necrosis factor-alpha eliminates binding of NF-Y and an octamer-binding protein to the lipoprotein lipase promoter in 3T3-L1 adipocytes. *J Clin Invest*. (1995) 95:1684–9. doi: 10.1172/JCI117844
47. Feingold KR, Grunfeld C. Role of cytokines in inducing hyperlipidemia. *Diabetes* (1992) 41 (Suppl. 2):97–101. doi: 10.2337/diab.41.2.S97
48. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest*. (1995) 95:2409–15. doi: 10.1172/JCI117936
49. Trujillo ME, Lee MJ, Sullivan S, Feng J, Schneider SH, Greenberg AS, et al. Tumor necrosis factor alpha and glucocorticoid synergistically increase leptin production in human adipose tissue: role for p38 mitogen-activated protein kinase. *J Clin Endocrinol Metab*. (2006) 91:1484–90. doi: 10.1210/jc.2005-1901
50. Wilson AG, di Giovine FS, Blakemore AI, Duff GW. Single base polymorphism in the human tumour necrosis factor alpha (TNF alpha) gene detectable by NcoI restriction of PCR product. *Hum Mol Genet*. (1992) 1:353.
51. Gupta V, Gupta A, Jafar T, Gupta V, Agrawal S, Srivastava N, et al. Association of TNF-α promoter gene G-308A polymorphism with metabolic syndrome, insulin resistance, serum TNF-α and leptin levels in Indian adult women. *Cytokine* (2012) 57:32–6. doi: 10.1016/j.cyto.2011.04.012
52. Hoffstedt J, Eriksson P, Hellström L, Rössner S, Rydén M, Arner P. Excessive fat accumulation is associated with the TNF alpha-308 G/A promoter polymorphism in women but not in men. *Diabetologia* (2000) 43:117–20. doi: 10.1007/s001250050015

53. Lee SC, Pu YB, Thomas GN, Lee Zs, Tomlinson B, Cockram CS, et al. Tumor necrosis factor alpha gene G-308A polymorphism in the metabolic syndrome. *Metabolism* (2000) 49:1021–4. doi: 10.1053/meta.2000.7704
54. Sobti RC, Kler R, Sharma YP, Talwar KK, Singh N. Risk of obesity and type 2 diabetes with tumor necrosis factor-α 308G/A gene polymorphism in metabolic syndrome and coronary artery disease subjects. *Mol Cell Biochem*. (2012) 360:1–7. doi: 10.1007/s11010-011-0917-z
55. Hedayati M, Sharifi K, Rostami F, Daneshpour MS, Zarif Yeganeh M, Azizi F. Association between TNF-α promoter G-308A and G-238A polymorphisms and obesity. *Mol Biol Rep*. (2012) 39:825–9. doi: 10.1007/s11033-011-0804-4
56. Razquin C, Marti A, Martinez JA. Evidences on three relevant obesogenes: MC4R, FTO and PPARγ. Approaches for personalized nutrition. *Mol Nutr Food Res*. (2011) 55:136–49. doi: 10.1002/mnfr.201000445
57. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Held IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. (2009) 41:25–34. doi: 10.1038/ng.287
58. Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet*. (2008) 40:768–75. doi: 10.1038/ng.140
59. Xi B, Chandak GR, Shen Y, Wang Q, Zhou D. Association between common polymorphism near the MC4R gene and obesity risk: a systematic review and meta-analysis. *PloS ONE* (2012) 7:e45731. doi: 10.1371/journal.pone.0045731
60. Lazopoulou N, Gkioka E, Ntalla I, Pervanidou P, Magiakou AM, Roma-Giannikou E, et al. The combined effect of MC4R and FTO risk alleles on childhood obesity in Greece. *Horm Athens Greece* (2015) 14:126–133. doi: 10.14310/horm.2002.1524
61. Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froquest P, et al. Common genetic variation near MC4R is associated with waist circumference and insulin resistance. *Nat Genet*. (2008) 40:716–18. doi: 10.1038/ng.156
62. Zhao J, Bradfield JP, Li M, Wang K, Zhang H, Kim CE, et al. The role of obesity-associated loci identified in genome-wide association studies in the determination of pediatric BMI. Obesity (2009) 17:2254–7. doi: 10.1038/oby.2009.159
63. Scherag A, Jarick I, Grothe J, Biebermann H, Scherag S, Volckmar AL, et al. Investigation of a genome wide association signal for obesity: synthetic association and haplotype analyses at the melanocortin 4 receptor gene locus. *PloS ONE* (2010) 5:e13967. doi: 10.1371/journal.pone.0013967
64. Vogel CI, Boes T, Reinehr T, Roth CL, Scherag S, Scherag A, et al. Common variants near MC4R: exploring gender effects in overweight and obese children and adolescents participating in a lifestyle intervention. *Obes Facts* (2011) 4:67–75. doi: 10.1159/000324557
65. Dwivedi OP, Tabassum R, Chauhan G, Kaur I, Ghosh S, Marwaha RK, et al. Strong influence of variants near MC4R on adiposity in children and adults: a cross-sectional study in Indian population. *J Hum Genet*. (2013) 58:27–32. doi: 10.1038/jhg.2012.129
66. Bordoni L, Marchegiani F, Piangerelli M, Napolioni V, Gabbianelli R. Obesity-related genetic polymorphisms and adiposity indices in a young Italian population. *IUBMB Life* (2017) 69:98–105. doi: 10.1002/iub.1596
67. García-Solís P, Reyes-Bastidas M, Flores K, Garcia OP, Rosado JL, Mendez-Villa L, et al. Fat mass obesity-associated (FTO) (rs9939609) and melanocortin 4 receptor (MC4R) (rs17782313) SNP are positively associated with obesity and blood pressure in Mexican school-aged children. *Br J Nutr*. (2016) 116:1834–40. doi: 10.1017/S0007114516003779
68. Wu L, Gao L, Zhao X, Zhang M, Wu J, Mi J. Associations of two obesity-related single-nucleotide polymorphisms with adiponectin in Chinese children. *Int J Endocrinol*. (2017) 2017:6437542. doi: 10.1155/2017/6437542
69. Molou E, Schulpis KH, Birbilis C, Thodi G, Georgiou V, Dotsikas T, et al. Early screening of FTO and MC4R variants in newborns of Greek origin. *J Pediatr Endocrinol Metab*. (2015) 28:619–22. doi: 10.1515/jpem-2014-0320
70. Farajian P, Panagiotakos DB, Risvas G, Karasouli K, Bountziouka V, Voutzourakis N, et al. Socio-economic and demographic determinants of childhood obesity prevalence in Greece: the GRECO (Greek Childhood Obesity) study. *Public Health Nutr*. (2013) 16:240–7. doi: 10.1017/S1368980012002625
71. Walters RG, Jacquemont S, Valsesia A, de Smith AJ, Martinet D, Andersson J, et al. A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. *Nature* (2010) 463:671–5. doi: 10.1038/nature08727
72. Day FR, Loos RJ. Developments in obesity genetics in the era of genome-wide association studies. *J Nutr Nutr*. (2011) 4:222–38. doi: 10.1159/000332158
73. Xi B, Wang C, Wu L, Zhang M, Shen Y, Zhao X, et al. Influence of physical inactivity on associations between single nucleotide polymorphisms and genetic predisposition to childhood obesity. *Am J Epidemiol*. (2011) 173:1256–62. doi: 10.1093/aje/kwr008
74. Ortega-Azorín C, Sorlí JV, Asensio EM, Coltell O, Martinez-Conzalez MA, Salas-Salvado J, et al. Associations of the FTO rs9939609 and the MC4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the Mediterranean diet pattern is low. *Cardiovasc Diabetol*. (2012) 11:137. doi: 10.1186/1475-2840-11-137
75. Abate N, Carulli L, Cabo-Chan A, Chandalia M, Snell PG, Grundy SM. Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. *J Clin Endocrinol Metab*. (2003) 88:5927–34. doi: 10.1210/jc.2003-030453
76. Goldfine ID, Maddux BA, Youngren JF, Reaven G, Accili D, Trischitta V, et al. The role of membrane glycoprotein plasma cell antigen 1/ectonucleotide pyrophosphatase phosphodiesterase 1 in the pathogenesis of insulin resistance and related abnormalities. *Endocr Rev*. (2008) 29:62–75. doi: 10.1210/er.2007-0004
77. Abate N, Chandalia M, Satija P, Adams-Hust B, Grundy SM, Sandeep S, et al. ENPP1/PC-1 K121Q polymorphism and genetic susceptibility to type 2 diabetes. *Diabetes* (2005) 54:1207–13. doi: 10.2337/diabetes.54.4.1207
78. Gu HF, Almgren P, Lindholm E, Frittitta L, Pizzuti A, Trischitta V, et al. Association between the human glycoprotein PC-1 gene and elevated glucose and insulin levels in a paired-sibling analysis. *Diabetes* (2000) 49:1601–3. doi: 10.2337/diabetes.49.9.1601
79. Kubaszek A, Markkanen A, Eriksson JG, Forsen T, Osmond C, Barker DJ, et al. The association of the K121Q polymorphism of the plasma cell glycoprotein-1 gene with type 2 diabetes and hypertension depends on size at birth. *J Clin Endocrinol Metab*. (2004) 89:2044–7. doi: 10.1210/jc.2003-031350
80. Matsuoka N, Patki A, Tiwari HK, Allison DB, Johnson SB, Gregersen PK, et al. Association of K121Q polymorphism in ENPP1 (PC-1) with BMI in Caucasian and African-American adults. *Int J Obes*. (2006) 30:233–7. doi: 10.1038/sj.ijo.0803132
81. Meyre D, Bouatia-Naji N, Tounian A, Samson C, Lecoeur C, Vatin V, et al. Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. *Nat Genet*. (2005) 37:863–7. doi: 10.1038/ng1604
82. Bochenski J, Placha G, Wanic K, Malecki M, Sieradzki J, Warram JH, et al. New polymorphism of ENPP1 (PC-1) is associated with increased risk of type 2 diabetes among obese individuals. *Diabetes* (2006) 55:2626–30. doi: 10.2337/db06-0191
83. Böttcher Y, Körner A, Reinehr T, Enigk B, Kiess W, Stumvoll M, et al. ENPP1 variants and haplotypes predispose to early onset obesity and impaired glucose and insulin metabolism in German obese children. *J Clin Endocrinol Metab*. (2006) 91:4948–52. doi: 10.1210/jc.2006-0540
84. Mejía-Benítez A, Klünder-Klünder M, Yengo L, Mayre D, Aradillas C, Cruz E, et al. Analysis of the contribution of FTO, NPC1, ENPP1, NEGR1, GNPDA2 and MC4R genes to obesity in Mexican children. *BMC Med Genet*. (2013) 14:21. doi: 10.1186/1471-2350-14-21
85. Liang J, Fu M, Ciociola E, Chandalia M, Abate N. Role of ENPP1 on adipocyte maturation. *PloS ONE* (2007) 2:e882. doi: 10.1371/journal.pone.0000882
86. Prakash J, Mittal B, Awasthi S, Agarwal CG, Srivastava N. K121Q ENPP1/PC-1 gene polymorphism is associated with insulin resistance in a North Indian population. *J Genet*. (2013) 92:571–6. doi: 10.1007/s12041-013-0287-2
87. Tontonoz P, Hu E, Devine J, Beale EG, Spiegelman BM. PPAR gamma 2 regulates adipose expression of the phosphoenolpyruvate carboxykinase gene. *Mol Cell Biol*. (1995) 15:351–7. doi: 10.1128/MCB.15.1.351
88. Masud S, Ye S, SAS Group. Effect of the peroxisome proliferator activated receptor-gamma gene Pro12Ala variant on body mass index: a meta-analysis. *J Med Genet*. (2003) 40:773–80. doi: 10.1136/jmg.40.10.773
89. Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, et al. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala

PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun*. (1997) 241:270–4. doi: 10.1006/bbrc.1997.7798

90. Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, et al. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet*. (1992) 51:197–205.
91. Ponsonby AL, Blizzard L, Pezic A, Cochrane JA, Ellis JA, Morley R, et al. Adiposity gain during childhood, ACE I/D polymorphisms and metabolic outcomes. Obesity (2008) 16:2141–7. doi: 10.1038/oby.2008.302
92. Roszer T, Ricote M. PPARs in the renal regulation of systemic blood pressure. *PPAR Res*. (2010) 2010:698730. doi: 10.1155/2010/698730
93. Eisenmann JC, Sarzynski MA, Glenn K, Rothschild M, Heelan KA. ACE I/D genotype, adiposity, and blood pressure in children. *Cardiovasc Diabetol*. (2009) 8:14. doi: 10.1186/1475-2840-8-14
94. Hayes JD, Strange RC. Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology* (2000) 61:154–66. doi: 10.1159/000028396
95. Park EY, Hong YC, Lee KH, Im MW, Ha E, Kim YJ, et al. Maternal exposure to environmental tobacco smoke, GSTM1/T1 polymorphisms and oxidative stress. *Reprod Toxicol*. (2008) 26:197–202. doi: 10.1016/j.reprotox.2008.08.010
96. Dusinská M, Ficek A, Horská A, Petrovská H, Vallová B, Drlicková M, et al. Glutathione S-transferase polymorphisms influence the level of oxidative DNA damage and antioxidant protection in humans. *Mutat Res*. (2001) 482:47–55. doi: 10.1016/S0027-5107(01)00209-3
97. Suh YJ, Kim YJ, Park H, Park EA, Ha EH. Oxidative stress-related gene interactions with preterm delivery in Korean women. *Am J Obstet Gynecol*. (2008) 198:541.e1–7. doi: 10.1016/j.ajog.2007.11.013
98. Mustafa MD, Pathak R, Ahmed T, Ahmed RS, Tripathi AK, Guleria K, et al. Association of glutathione S-transferase M1 and T1 gene polymorphisms and oxidative stress markers in preterm labor. *Clin Biochem*. (2010) 43:1124–8. doi: 10.1016/j.clinbiochem.2010.06.018
99. Sata F, Yamada H, Kondo T, Gong Y, Tozaki S, Kobashi G, et al. Glutathione S-transferase M1 and T1 polymorphisms and the risk of recurrent pregnancy loss. *Mol Hum Reprod*. (2003) 9:165–9. doi: 10.1093/molehr/gag021
100. Wang X, Zuckerman B, Pearson C, Kaufman G, Chen C, Wang G, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA* (2002) 287:195–202. doi: 10.1001/jama.287.2.195
101. Hong YC, Lee KH, Son BK, Ha EH, Moon HS, Ha M. Effects of the GSTM1 and GSTT1 polymorphisms on the relationship between maternal exposure to environmental tobacco smoke and neonatal birth weight. *J Occup Environ Med*. (2003) 45:492–8. doi: 10.1097/01.jom.0000063627.37065.a1
102. Lee BE, Hong YC, Park H, Ha M, Koo BS, Chang N, et al. Interaction between GSTM1/GSTT1 polymorphism and blood mercury on birth weight. *Environ Health Perspect*. (2010) 118:437–43. doi: 10.1289/ehp.0900731
103. Black PH. The inflammatory response is an integral part of the stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain Behav Immun*. (2003) 17:350–64. doi: 10.1016/S0889-1591(03)00048-5
104. Henningsson S, Håkansson A, Westberg L, Baghaei F, Rosmond R, Holm G, et al. Interleukin-6 gene polymorphism−174G/C influences plasma lipid levels in women. *Obesity* (2006) 14:1868–73. doi: 10.1038/oby.2006.216
105. Kubaszek A, Pihlajamäki J, Punnonen K, Karhapää P, Vauhkonen I, Laakso M. The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes* (2003) 52:558–61. doi: 10.2337/diabetes.52.2.558
106. Stephens JW, Hurel SJ, Cooper JA, Acharya J, Miller GJ, Humphries SE. A common functional variant in the interleukin-6 gene is associated with increased body mass index in subjects with type 2 diabetes mellitus. *Mol Genet Metab*. (2004) 82:180–6. doi: 10.1016/j.ymgme.2004.04.001
107. Goyenechea E, Parra D, Martínez JA. Impact of interleukin 6−174G>C polymorphism on obesity-related metabolic disorders in people with excess in body weight. *Metabolism* (2007) 56:1643–8. doi: 10.1016/j.metabol.2007.07.005
108. Grallert H, Huth C, Kolz M, Meisinger C, Herder C, Strassburger K, et al. IL-6 promoter polymorphisms and quantitative traits related to the metabolic syndrome in KORA S4. *Exp Gerontol*. (2006) 41:737–45. doi: 10.1016/j.exger.2006.05.002

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer SM and handling editor declared their shared affiliation.

frontiers in Pediatrics

MINI REVIEW
published: 16 November 2018
doi: 10.3389/fped.2018.00345

Is There an Association of Vascular Disease and Atherosclerosis in Children and Adolescents With Obesity and Non-alcoholic Fatty Liver Disease?

*Sara Karjoo**

Department of Pediatrics, Johns Hopkins Medicine, All Children's Hospital, St. Petersburg, FL, United States

OPEN ACCESS

Edited by:
Fatima Cody Stanford, Massachusetts General Hospital, Harvard Medical School, United States

Reviewed by:
Dexter Canoy, University of Oxford, United Kingdom
Tudor Lucian Pop, Iuliu Haţieganu University of Medicine and Pharmacy, Romania

***Correspondence:**
Sara Karjoo
skarjoo1@jhmi.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *28 August 2018*
Accepted: *25 October 2018*
Published: *16 November 2018*

Citation:
Karjoo S (2018) Is There an Association of Vascular Disease and Atherosclerosis in Children and Adolescents With Obesity and Non-alcoholic Fatty Liver Disease? Front. Pediatr. 6:345. doi: 10.3389/fped.2018.00345

Carotid intima media thickness (cIMT) and brachial flow-mediated dilation (FMD) evaluated by ultrasound are non-invasive markers of atherosclerosis. Increased cIMT in adults has been correlated to early vascular damage. Several studies show similar correlations of elevated cIMT in children with obesity, hyperlipidemia, and metabolic syndrome. Additionally, several articles have correlated non-alcoholic fatty liver disease (NAFLD) with elevated cIMT, indicating early atherosclerosis. It is alarming that these vascular changes may be seen in children as young as 10 years of age. Children with NAFLD may also have an increased pulse wave velocity that correlates to increased arterial stiffness and increased left ventricular dimension, mass, and diastolic dysfunction. These articles are persuasive, indicating a correlation of Pediatric NAFLD and early vascular disease. However, study limitations include the use of elevated alanine aminotransferase (ALT) and echogenic changes on ultrasound that may have low accuracy to identify NAFLD. Ultrasound has low sensitivities and specificities for detection of NAFLD and therefore is not recommended for diagnosis. In comparison, studies that used liver biopsy or proton magnetic resonance spectroscopy to identify NAFLD did not find a correlation with elevated cIMT or reduction in FMD. Due to these conflicting findings, more studies looking at cIMT and FMD changes in children with NAFLD are needed with more accurate diagnostic methods for steatosis to identify if there truly is a correlation of increased liver steatosis to early atherosclerosis.

Keywords: pediatrics, non-alcoholic fatty liver disease, carotid intima media thickness, atherosclerosis, brachial flow mediated dilation

INTRODUCTION

The prevalence of obesity in the United States has increased in the past 4 years to 1 in 5 children (1). There has also been a considerable increase in the prevalence of obesity from 2015 to 2016 in children ages 2–5 years (1). Recent data shows increased rates of obesity in children of Hispanic and African American heritage as compared to other races (1). Obesity is a disease that effects the whole body. Non-alcoholic fatty liver disease (NAFLD) is just one finding in patients with obesity. As the rates of obesity increase, so does the prevalence of NAFLD (2). NAFLD is truly a histological diagnosis defined as steatosis >5% (3), and often is clinically asymptomatic. It occurs in higher frequency in individuals of Hispanic origin (especially from South America) and of Middle Eastern origin (4, 5). It also occurs with intermediate frequency in Whites, and less commonly in Blacks (4, 5). Those individuals of Hispanic heritage with fatty liver may have a higher rate of progression to fibrosis (5). In addition, it now well-known that children with the rs738409 C>G adiponutrin/patatin-like phospholipase domain-containing 3 (PNPLA3) polymorphism gene mutation have a higher risk of severe steatosis and progression to fibrosis (6). NAFLD can progress over time to a condition called nonalcoholic steatohepatitis (NASH), which has features of ballooning steatosis, fibrosis, and inflammation (4). There are concerns that NASH in young adults will become the leading cause of liver transplants in the future (7). In addition to liver damage, could the finding of NAFLD be correlated to early cardiac disease?

Historically, Berenson et al. published their post mortem autopsy findings of individuals ages 2–39 years, showing that aortic or coronary artery fatty streaks and fibrous plaques were strongly correlated to elevated body mass index (BMI), elevated blood pressure, and mixed hyperlipidemia (8). One non-invasive method to assess vascular changes is evaluation of carotid intima media thickness (cIMT) via carotid ultrasound. Increased cIMT in adults has been correlated to early vascular damage (9, 10). In addition, there are findings of coronary artery disease and altered ventricular function in adults with NAFLD (11–13). Adults with NAFLD were found to have coronary artery stenosis, higher coronary artery calcium, and all types of plaque (calcified and non-calcified) as compared to controls (14). Similarly, the authors of a systematic review and meta-analysis study showed increased left ventricular mass in adult patients with NAFLD as compared to controls (15). Clearly, there are many well-described associations of atherosclerosis and structural heart disease in adults who have NAFLD.

As discussed previously, there are racial difference with the prevalence of NAFLD. Similarly, there may be different prevalence and onset of cardiac disease in certain racial groups. In one recent adult study, the authors found that NAFLD was highest in patients who were of Hispanic heritage and lowest in Blacks and Chinese (16). Overall, the total prevalence of abdominal aortic calcification was highest in Whites, followed by Chinese, Blacks, and Hispanics (16). However, when evaluating the participants with NAFLD, the abdominal aortic calcification was highest in Hispanics, followed by Chinese, then Blacks, and finally Whites (16). The authors concluded that NAFLD did have an increased association with abdominal aortic calcification, and may affect different racial groups differently (16).

Such studies looking at the association of NAFLD and atherosclerosis with different racial groups has not been evaluated in children. This may be a possible topic for future Pediatric NAFLD research, looking at the differences and the onset of cardiac disease in various racial groups.

However, several pediatric articles have been published demonstrating the association of cIMT or brachial flow-mediated dilation (FMD) changes in children with NAFLD (17–34). In comparison, fewer and more recent articles have been published that do not show this association (35–37). The pediatric data currently published may have limitations and may not be generalizable to all children with NAFLD, due to the different onset and progression of heart disease in different racial groups. Overall, there likely is an association when taking into account the significant amount of published studies showing a link between NAFLD and vascular disease. However, better well-designed studies are needed with more accurate methods to identify NAFLD while taking into account racial onset and prevalence of hepatic steatosis. The articles published regarding the association of NAFLD with cIMT and FMD changes are reviewed in this article.

METHODS

The articles were identified with the help of an unbiased medical librarian at Johns Hopkins All Children's Hospital. Two independent searches 6 months apart was conducted. Embase and PubMed were used to identify articles that fit the criteria. The search was limited to ages 0–18 years, and key words of NAFLD, cIMT, FMD, hyperlipidemia, obesity, and atherosclerosis. Each term was used in combination to limit articles and each item was also searched independently. Articles that were relevant to this review were used. Articles were excluded if they did not have research subjects with NAFLD.

Studies Supporting Association of NAFLD With Elevated cIMT and Low FMD

Overall, there have been more articles in the literature in support of early vascular changes like elevated cIMT and low FMD in children with NAFLD and obesity (17–34). What is interesting is that these articles used either abdominal ultrasound alone or abdominal ultrasound and elevated liver enzymes (alanine aminotransferase in most studies >40 U/L) to identify steatosis and NAFLD (17–34, 38). One study also used magnetic resonance imaging (MRI) findings as well to identify patients with steatosis (19). In some papers, a grading system was used to identify the level of steatosis or changes on liver ultrasound (18, 21–23, 26, 28, 29, 33). Many of the papers either used BMI percentile (14, 17–19, 21–23, 25, 26, 28, 32, 38, 39) or a fixed BMI >28–30 kg/m^2 to define obesity (27, 29–31, 33). Echocardiography and carotid ultrasound were used to identify cIMT. FMD was evaluated via Doppler ultrasound imaging before and after an ischemic event caused by reduced blood flow from an inflated sphygmomanometer (19, 21, 37). All the papers excluded patients if they had systemic diseases or significant alcohol use.

There has been a series of articles by Pacifico et al. that have dominated the research in this area. In one of their studies, the authors found reduced FMD in obese children with NAFLD when exposed to ischemia (30). Children with NAFLD and obesity had elevated cIMT which was even higher if they had metabolic syndrome (30). In another study by the same group, the patients who had hepatic steatosis had higher mean and maximum cIMT measurements (23). They also found elevated cIMT was associated with elevated blood pressure, insulin resistance, NAFLD, and high triglyceride to high density lipoprotein cholesterol (TG/ HDL-c) ratio (12). The authors also demonstrated that after 12 month intervention of diet and exercise in children with NAFLD and obesity, the FMD improved but elevated cIMT did not regress (19). Failure of improvement of cIMT with lifestyle intervention is concerning, and further studies need to be done to see if this is a reproducible finding in children.

Other authors have also found similar correlations of elevated cIMT with NAFLD (18, 20–22, 25–28, 31, 33, 34), and have linked increased severity of steatosis to even higher cIMT values (18, 25), and lower FMD values (21). The inclusion of hepatic steatosis on ultrasound may improve the cIMT predictability of cardiac disease as compared to metabolic syndrome alone (28). A correlation of higher cIMT measurements was found with elevated aspartate aminotransferase to platelet ratio index (APRI), which is a marker for hepatic fibrosis (33).

Structural heart changes have also been reported such as increased thickening of the left ventricle, higher interventricular septal thickness in systole, increased left ventricular posterior wall thickness in diastole, increased left atrial and aortic diameters, higher left ventricular mass, and higher left ventricular mass index in children with NAFLD and obesity (22, 30, 31). The authors of one study looked at applanation tonometry to measure arterial stiffness via pulse wave velocity (29). They found that those patients who had NAFLD with other high risk metabolic abnormalities had greater pulse wave velocity as compared to those without metabolic complications (29).

In summary, there are many articles showing an association of early signs of structural heart disease and atherosclerosis in children with NAFLD. Perhaps practitioners need to be more concerned with the finding of NAFLD, as this may be a sign of early heart disease in children.

Studies Lacking Association of NAFLD With Elevated cIMT and Low FMD

What is interesting is that some newer articles do not support the association of elevated cIMT and low FMD in children who have NAFLD. What is unique about these articles is the use of either magnetic resonance spectroscopy or liver biopsy to define steatosis (35–37). When comparing degree of steatosis, inflammation, and fibrosis, there was no correlation with elevated right or left cIMT values (36). Steatosis and serum ALT was not correlated to elevated cIMT or arterial wall stiffness (35) either. The only predictor was BMI for abnormalities on cIMT (36). In addition, there was no association of hepatic fat fraction and FMD changes (37).

Diagnosis of Liver Steatosis, Fibrosis, and NAFLD

At this time, the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) clinical practice guideline for NAFLD in children recommends the use of serum ALT at the age of 10 years (40) for screening. Ultrasound has fallen out of favor for the screening and diagnosis of NAFLD due to the low sensitivities and specificities (40, 41). There are new radiologic techniques like magnetic resonance elastography with better sensitivities and specificities that are validated for the evaluation of hepatic steatosis and fibrosis (40, 42) in children. Magnetic resonance elastography also has ∼88% sensitivity and 85% specificity for detecting fibrosis (43). Ultimately, the gold standard for the evaluation of liver steatosis and fibrosis is histology of liver biopsy samples (3, 38, 44). Liver biopsy or magnetic resonance imaging are more accurate but also more expensive techniques for diagnosis (43). Liver biopsy is also invasive and can have complications of bleeding and damage to the gallbladder. There is also an added cost of anesthesia and 12–24 h hospital admission for observation post liver biopsy. To reduce the cost of diagnosis, non-invasive fibrosis scores, or serum biomarkers are under evaluation. In children, thus far, fibrosis scores that are typically used in adults are not accurate in predicting liver fibrosis (43). Equally, serum fibrosis biomarkers like caspase-cleaved cytokeratin 18 (CK18) show promise in recent research studies, but need further validation before it is recommended as part of clinical practice (43).

CONCLUSIONS

Overall, there are many studies correlating elevated BMI, hepatic steatosis, and metabolic syndrome with increased cIMT, lower FMD, possible increased arterial stiffness, and ventricular dysfunction in children. These articles predominantly used liver ultrasound with or without serum ALT to identify NAFLD. Some authors also used ultrasound grading of the echogenicity to correlate with severity of hepatic steatosis. Recently, ultrasound has fallen out of favor for screening for NAFLD due to the sensitivities and specificities of the test, and may not be an accurate way to identify hepatic steatosis. In comparison, the articles that define NAFLD with liver biopsy or proton magnetic resonance spectroscopy did not find this correlation to structural heart or vascular changes.

There is also a different prevalence of NAFLD in different racial groups. Perhaps the onset of cardiac disease, therefore, is different in different ethnic groups as well. One limitation of these studies is generalizability of the findings to all races and populations. Robust studies are needed which use more accurate diagnostic techniques for NAFLD, and take into consideration the differences of the disease frequency in different ethnic groups.

With the global health and economic impact of increased rates of obesity and therefore NAFLD in children, it is important for future research to identify if there is a correlation of hepatic steatosis to early atherosclerosis and at what age this occurs. The information from the future research would help create clinical programs for early diagnosis and intervention before significant vascular disease begins.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

ACKNOWLEDGMENTS

Want to give thanks to Pamela Williams, MS, MLS, AHIP, medical librarian at Johns Hopkins. All Children's Hospital for her help with the search for the articles.

REFERENCES

1. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of obesity and severe obesity in US Children, 1999–2016. *Pediatrics* (2018) 141:e20173459. doi: 10.1542/peds.2017-3459
2. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988–1994 to 2007–2010. *J Pediatr*. (2013) 162:496–500e1. doi: 10.1016/j.jpeds.2012.08.043
3. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Nonalcoholic steatohepatitis clinical research network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* (2005) 41:1313–21. doi: 10.1002/hep.20701
4. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the american association for the study of liver diseases. *Hepatology* (2018) 67:328–57. doi: 10.1002/hep.29367
5. Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. (2018) 16:198–210. doi: 10.1016/j.cgh.2017.09.041
6. Valenti L, Alisi A, Galmozzi E, Bartuli A, Del Menico B, Alterio A, et al. I148M patatin-like phospholipase domain-containing 3 gene variant and severity of pediatric nonalcoholic fatty liver disease. *Hepatology* (2010) 52:1274–80. doi: 10.1002/hep.23823
7. Doycheva I, Issa D, Watt KD, Lopez R, Rifai G, Alkhouri N. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in young adults in the United States. *J Clin Gastroenterol*. (2018) 52:339–46. doi: 10.1097/MCG.0000000000000925
8. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults, The Bogalusa Heart Study. *N Engl J Med*. (1998) 338:1650–6. doi: 10.1056/NEJM199806043382302
9. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study 1987–1999. *Am J Epidemiol*. (1997) 146:483–94. doi: 10.1093/oxfordjournals.aje.a009302
10. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: cardiovascular health study collaborative research group. *N Engl J Med*. (1999) 340:14–22.
11. Fotbolcu H, Yakar T, Duman D, Karaahmet T, Tigen K, Cevik C, et al. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. *Cardiol J*. (2010) 17:457–63.
12. Bonapace S, Perseghin G, Molon G, Canali G, Bertolini L, Zoppini G, et al. Nonalcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. *Diabetes Care* (2012) 35:389–95. doi: 10.2337/dc11-1820
13. Goland S, Shimoni S, Zornitzki T, Knobler H, Azoulai O, Lutaty G, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol*. (2006) 40:949–55. doi: 10.1097/01.mcg.0000225668.53673.e6
14. Lee SB, Park GM, Lee JY, Lee BU, Park JH, Kim BG, et al. Association between non-alcoholic fatty liver disease and subclinical coronary atherosclerosis: an observational cohort study. *J Hepatol*. (2018) 68:1018–24. doi: 10.1016/j.jhep.2017.12.012
15. Bonci E, Chiesa C, Versacci P, Anania C, Silvestri L, Pacifico L. Association of nonalcoholic fatty liver disease with subclinical cardiovascular changes: a systematic review and meta-analysis. *Biomed Res Int*. (2015) 2015:213737. doi: 10.1155/2015/213737
16. Remigio-Baker RA, Allison MA, Forbang NI, Loomba R, Anderson CAM, Budoff M, et al. Race/ethnic and sex disparities in the non-alcoholic fatty liver disease-abdominal aortic calcification association: the multi-ethnic study of atherosclerosis.*Atherosclerosis* (2017) 258:89–96. doi: 10.1016/j.atherosclerosis.2016.11.021
17. Pacifico L, Anania C, Martino F, Cantisani V, Pascone R, Marcantonio A, et al. Functional and morphological vascular changes in pediatric nonalcoholic fatty liver disease. *Hepatology* (2010) 52:1643–51. doi: 10.1002/hep.23890
18. Demircioglu F, Koçyigit A, Arslan N, Cakmakçi H, Hizli S, Sedat AT. Intima-media thickness of carotid artery and susceptibility to atherosclerosis in obese children with nonalcoholic fatty liver disease. *J Pediatr Gastroenterol Nutr*. (2008) 47:68–75. doi: 10.1097/MPG.0b013e31816232c9
19. Pacifico L, Arca M, Anania C, Cantisani V, Di Martino M, Chiesa C. Arterial function and structure after a 1-year lifestyle intervention in children with nonalcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis*. (2013) 23:1010–6. doi: 10.1016/j.numecd.2012.08.003
20. Madan SA, John F, Pyrsopoulos N, Pitchumoni CS. Nonalcoholic fatty liver disease and carotid artery atherosclerosis in children and adults: a meta-analysis. *Eur J Gastroenterol Hepatol*. (2015) 27:1237–48. doi: 10.1097/MEG.0000000000000429
21. Torun E, Aydin S, Gökçe S, Özgen IT, Donmez T, Cesur Y. Carotid intima-media thickness and flow-mediated dilation in obese children with non-alcoholic fatty liver disease. *Turk J Gastroenterol*. (2014) 25(Suppl. 1):92–8. doi: 10.5152/tjg.2014.5552
22. Alp H, Karaarslan S, Selver Eklioglu B, Atabek ME, Altin H, Baysal T. Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents. *Can J Cardiol*. (2013) 29:1118–25. doi: 10.1016/j.cjca.2012.07.846
23. Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, et al. Nonalcoholic fatty liver disease and carotid atherosclerosis in children. *Pediatr Res*. (2008) 63:423–7. doi: 10.1203/PDR.0b013e318165b8e7
24. Pacifico L, Chiesa C, Anania C, De Merulis A, Osborn JF, Romaggioli S, et al. Nonalcoholic fatty liver disease and the heart in children and adolescents. *World J Gastroenterol*. (2014) 20:9055–71. doi: 10.3748/wjg.v20.i27.9055
25. Hacihamdioglu B, Okutan V, Yozgat Y, Yildirim D, Kocaoglu M, Lenk MK, et al. Abdominal obesity is an independent risk factor for increased carotid intima- media thickness in obese children. *Turk J Pediatr*. (2011) 53:48–54.
26. Akin L, Kurtoglu S, Yikilmaz A, Kendirci M, Elmali F, Mazicioglu M. Fatty liver is a good indicator of subclinical atherosclerosis risk in obese children and adolescents regardless of liver enzyme elevation. *Acta Paediatr*. (2013) 102:e107–13. doi: 10.1111/apa.12099
27. Kelishadi R, Cook SR, Amra B, Adibi A. Factors associated with insulin resistance and non-alcoholic fatty liver disease among youths. *Atherosclerosis* (2009) 204:538–43. doi: 10.1016/j.atherosclerosis.2008.09.034
28. Rutigliano I, Vinci R, De Filippo G, Mancini M, Stoppino L, d'Apolito M, et al. Metabolic syndrome, hepatic steatosis, and cardiovascular risk in children. *Nutrition* (2017) 36:1–7. doi: 10.1016/j.nut.2016.10.017
29. Huang RC, Beilin LJ, Ayonrinde O, Mori TA, Olynyk JK, Burrows S, et al. Importance of cardiometabolic risk factors in the association between nonalcoholic fatty liver disease and arterial stiffness in adolescents. *Hepatology* (2013) 58:1306–14. doi: 10.1002/hep.26495
30. Sert A, Aypar E, Pirgon O, Yilmaz H, Odabas D, Tolu I. Left ventricular function by echocardiography, tissue Doppler imaging, and carotid intima-media thickness in obese adolescents with nonalcoholic fatty liver disease. *Am J Cardiol*. (2013) 112:436–43. doi: 10.1016/j.amjcard.2013.03.056
31. Sert A, Pirgon O, Aypar E, Yilmaz H, Odabas D. Relationship between left ventricular mass and carotid intima media thickness in obese adolescents with non-alcoholic fatty liver disease. *J Pediatr Endocrinol Metab*. (2012) 25:927–34. doi: 10.1515/jpem-2012-0187
32. Pacifico L, Bonci E, Andreoli G, Romaggioli S, Di Miscio R, Lombardo CV, et al. Association of serum triglyceride-to-HDL cholesterol ratio with carotid artery intima-media thickness, insulin resistance and nonalcoholic fatty liver disease in children and adolescents. *Nutr Metab Cardiovasc Dis*. (2014) 24:737–43. doi: 10.1016/j.numecd.2014.01.010
33. Sert A, Pirgon O, Aypar E, Yilmaz H, Dündar B. Relationship between aspartate aminotransferase-to-platelet ratio index and carotid intima-media thickness in obese adolescents with non-alcoholic fatty liver disease. *J Clin Res Pediatr Endocrinol*. (2013) 5:182–8. doi: 10.4274/Jcrpe.891
34. Caserta CA, Pendino GM, Amante A, Vacalebre C, Fiorillo MT, Surace P, et al. Cardiovascular risk factors, nonalcoholic fatty liver disease, and carotid artery intima-media thickness in an adolescent population in southern Italy. *Am J Epidemiol*. (2010) 171:1195–202. doi: 10.1093/aje/kwq073
35. Koot BG, de Groot E, van der Baan-Slootweg OH, Bohte AE, Nederveen AJ, Jansen PL, et al. Nonalcoholic fatty liver disease and cardiovascular risk in children with obesity. *Obesity*. (2015) 23:1239–43. doi: 10.1002/oby.21076

36. Manco M, Bedogni G, Monti L, Morino G, Natali G, Nobili V. Intima-media thickness and liver histology in obese children and adolescents with non-alcoholic fatty liver disease. *Atherosclerosis* (2010) 209:463–8. doi: 10.1016/j.atherosclerosis.2009.10.014
37. Weghuber D, Roden M, Franz C, Chmelik M, Torabia S, Nowotny P, et al. Vascular function in obese children with non-alcoholic fatty liver disease. *Int J Pediatr Obes*. (2011) 6:120–7. doi: 10.3109/17477161003792580
38. Fang J, Zhang JP, Luo CX, Yu XM, Lv LQ. Carotid Intima-media thickness in childhood and adolescent obesity relations to abdominal obesity, high triglyceride level and insulin resistance. *Int J Med Sci*. (2010) 18:278–83. doi: 10.7150/ijms.7.278
39. Caserta CA, Pendino GM, Alicante S, Amante A, Amato F, Fiorillo M, et al. MAREA Study Group: body mass index, cardiovascular risk factors, and carotid intima-media thickness in a pediatric population in southern Italy. *J Pediatr Gastroenterol Nutr*. (2010) 51:216–20. doi: 10.1097/MPG.0b013e3181d4c21d
40. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr*. (2017) 64:319–34. doi: 10.1097/MPG.0000000000001482
41. Awai HI, Newton KP, Sirlin CB, Behling C, Schwimmer JB. Evidence and recommendations for imaging liver fat in children, based on systematic review. *Clin Gastroenterol Hepatol*. (2014) 12:765–73. doi: 10.1016/j.cgh.2013.09.050
42. Schwimmer JB, Middleton MS, Behling C, Newton KP, Awai HI, Paiz MN, et al. Magnetic resonance imaging and liver histology as biomarkers of hepatic steatosis in children with nonalcoholic fatty liver disease. *Hepatology* (2015) 61:1887–95. doi: 10.1002/hep.27666
43. Alkhouri N. Putting it all together: Noninvasive diagnosis of fibrosis in nonalcoholic fatty liver disease in adults and children. *Clin Liver Dis*. (2017) 9:134–7. doi: 10.1002/cld.636
44. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. *World J Gastroenterol*. (2010) 16:5286–96. doi: 10.3748/wjg.v16.i42.5286

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

SYSTEMATIC REVIEW
published: 03 April 2019
doi: 10.3389/fped.2019.00123

Pediatric Obesity and Eating Disorders Symptoms: The Role of the Multidisciplinary Treatment. A Systematic Review

Rachele De Giuseppe[1], *Ilaria Di Napoli*[1†], *Debora Porri*[1*†] *and Hellas Cena*[1,2]

[1] Laboratory of Dietetics and Clinical Nutrition, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy, [2] Clinical Nutrition and Dietetics Service, Unit of Internal Medicine and Endocrinology, ICS Maugeri IRCCS, University of Pavia, Pavia, Italy

OPEN ACCESS

Edited by:
Fatima Cody Stanford,
Massachusetts General Hospital and Harvard Medical School,
United States

Reviewed by:
Emer Fitzpatrick,
King's College London,
United Kingdom
Marwan El Ghoch,
Beirut Arab University, Lebanon

***Correspondence:**
Debora Porri
debporri@gmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: 11 September 2018
Accepted: 12 March 2019
Published: 03 April 2019

Citation:
De Giuseppe R, Di Napoli I, Porri D and Cena H (2019) Pediatric Obesity and Eating Disorders Symptoms: The Role of the Multidisciplinary Treatment. A Systematic Review. Front. Pediatr. 7:123. doi: 10.3389/fped.2019.00123

The prevalence of obesity in children/adolescents has increased worldwide during the past 30 years, becoming a significant public health concern; prevention, and management of pediatric obesity onset is one of the most critical public health goals for both industrialized and developing countries. Pediatric obesity has been identified as a risk factor for various psychopathologies, including eating disorders (ED). Although it has been demonstrated that a comprehensive multidisciplinary treatment (MT), with small steps and practical approaches to lifestyle change, can be an effective treatment for children and adolescents with obesity, to the best of our knowledge, this is the first systematic review investigating the effect of MT on the development, progression or decrease of ED symptoms (EDS) in this target population. PubMed and Web of Science databases were searched (last search on 18 February 2019) according to a predetermined search strategy, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and Statement. Original studies published in English examining the effect of MT on pediatric overweight/obesity, paying particularly attention at the development of EDS, were eligible for inclusion. Seven hundred and forty-four records have been identified; nine articles with study quality ranging from weak to moderate have been included. MTs were heterogeneous in nature including length, number, frequency and type of sessions, parent-involvement and use of technology, besides several psychometric questionnaires were used to screen for EDS, since there are no standardized criteria. In 3 studies there was a significant decrease in external and emotional eating and in four studies a significant increase in restraint eating post MT. Two studies found a significant decrease of binge eating symptoms and other two studies showed an improvement of self-perception, weight, and shape concern. A statistical significant decrease in BMI, BMIz, BMISDS, and adjusted BMI was observed after all MTs, except one. A narrative summary of the evidences reported highlighted the positive impact of MT on the EDS. Moreover, since weight loss post MTs was not necessarily related to EDS, clinicians should also look for the presence of EDS and treat them accordingly.

Keywords: pediatric obesity, eating disorders, multidisciplinary treatment, obesity prevention, obesity management

INTRODUCTION

Pediatric obesity is one of the greatest health challenges of the Twenty-first century (1). Prevalence of overweight or obesity in infants and young children (0–5 years) has increased globally and rapidly over time from 32 million in 1990 to 41 million in 2016 (2). In the United States, more than 10% of infants or toddlers and more than 17% of children and teens are affected by obesity while in Europe (3), 19–49 and 18–43% respectively of boys and girls are affected by either overweight or obesity (4). If the current rates keep on rising, the number of infants and young children with overweight or obesity will reach 70 million by 2025 (2). In addition, evidence show that at least 25–50% of children and adolescents defined as having a healthy Body Mass Index (BMI)-for-age have excessive body fat and this may indicate a dangerous underestimation of "obesity" comorbidities risk (5–7). Indeed, childhood and adolescent obesity is associated with a number of negative health sequelae, including hypertension, hyperlipidemia, respiratory problems, endocrine consequences, orthopedic complications, which contribute to a significant decrease in quality of life and life expectancy (8).

Recently, the Childhood Obesity Task Force (COTF) of the European Association for the Study of Obesity (EASO) classified obesity as not just a health risk but as a chronic disease in children and adolescents, in order to develop tailored interventions and health policies to prevent and treat obesity at both public and individual level (1).

Furthermore, there is increasing evidence that childhood-onset obesity is not only a risk factor for metabolic complications in adulthood, but also associated with an increased risk of developing eating disorders (EDs) during adolescence (9–13).

Children with obesity or overweight experience psychosocial distress that significantly affects their quality of life and well-being, so mental health of these children has also gained the attention of researchers and clinicians (11, 14–16).

Additionally, pediatric obesity has been identified as a risk factor for psychopathology, that may manifest itself through eating disorder symptoms (EDS) like excessive shape and weight concerns, body image dissatisfaction, dieting, and other unhealthy weight control methods, or binge eating (17, 18), sneaking, hiding or hoarding food, eating in the absence of hunger and inhibition or embarrassment when eating in front of others (19).

ED symptoms do not always correspond in severity or specificity to full-syndrome ED (20); they encompass a broad array of dimensional maladaptive cognitions and behaviors relating to eating and weight, that are found across the range of full syndrome ED diagnoses as well as in subsyndromal variants (21). This is probably why they are continuously underdiagnosed by pediatric professionals, although they are more common than metabolic disorders in childhood and adolescence and are associated with high morbidity and mortality (20). Overweight adolescents have a 2 1/2 to 5 times higher risk of developing eating disorders than teens whose weight is in the healthy range (21, 22).

Prevention and management of obesity onset is one of the most critical public health goals, and childhood represents the ideal time for lifestyle intervention, throughout multidisciplinary treatment (MT), as lifestyle habits in youth are not yet ingrained (23, 24). In fact, evidences show that behavioral lifestyle interventions are effective for weight loss in most children and adolescents (25). Success in treatment of childhood obesity requires a multifaceted approach to nutrition patterns and physical activity, with particular attention paid to the family and other environmental factors that may significantly affect outcomes (26).

The 2016 WHO Commission on Ending Childhood Obesity report, recommended "family-based, multicomponent, lifestyle weight management services for children and young people who are obese" as part of the universal child and adolescent health care (2). There is no specific definition of "multidisciplinary treatment" (MT), but some authoritative sources [WHO (2); Endocrine Society (27)] underlined it should include some common components such as nutrition and physical activity, besides family counseling and psychosocial support.

The multidisciplinary approach should also include health professionals such as physicians, dieticians, health coaches, and psychologists or other mental health care providers able to offer behavioral counseling (28, 29). Working in teams allows for modification of assessment and treatment providing effective integral interventions in the management of childhood obesity.

Multidisciplinary treatments (MTs) have proven beneficial and effective in combating obesity reducing body mass index (BMI) as well as the risk of future comorbidities (30–32).

Treatment of overweight and obesity mainly aims at achieving weight loss and BMI reduction, fat mass decrease, risk factors for metabolic syndrome decline and increased health-related quality of life (33, 34). However, despite weight reduction is a common and legitimate outcome to pursue, psychosocial contributors to eating behaviors not be neglected (35–37).

Objectives

Since the effects of MT on eating behavior in children with overweight/obesity are largely unknown, in this systematic review, we attempted to address the question: is multidisciplinary treatment effective on eating disorder symptoms in children with obesity?

This systematic review has been conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines recommending to present a full electronic search strategy for at least 1 major database (38).

METHODS

Data and Search Strategy

Two electronic databases (PubMed and Web of Science) were searched from 2008 to 2019 using the following structured search strings: childhood obesity OR childhood overweight OR pediatric obesity OR pediatric overweight OR obesity in children OR overweight in children OR multidisciplinary treatment* OR multidisciplinary approach* OR multidisciplinary intervention* OR multidisciplinary program*, combined to eating behavior* OR binge eating OR sneaking food* OR hiding food*OR hoarding food* OR reward OR overeating.

Eligibility Criteria

All studies were assessed according to the following inclusion and exclusion criteria summarized below:

Participants

Eligible participants were children with overweight/obesity (as defined in the selected studies), age ranging from 6 to 18 years at the beginning of MT. Participants with pre-existing disease or organic cause for obesity and on medications that could affect weight were excluded.

Intervention

MT was defined as an approach covering lifestyle intervention on nutrition and healthy behavior dietary patterns and/or physical activity. According to this, we selected only studies that included MTs considering also EDS.

Assessment of EDS was obtained through a variety of different psychometric tests: DEBQ (Dutch Eating Behavior Questionnaire) (39), ChEDE (Child Eating Disorder Examination) (40), YEDE-Q (Youth Eating Disorder Examination Questionnaire) (41, 42), CEBQ (Children Eating Behavior Questionnaire) (43), TEFQ (Three-Factor Eating Questionnaire) (44), BES (Binge Eating Scale) (45), BITE (Bulimic Investigatory Test, Edinburgh) (46), EDI—II (Eating Disorder Inventory) (47), EES-C (Emotional Eating Scale for Children and Adolescents) (48), QWEP (Questionnaire on Weight and Eating Patterns) (49), EI (Eating Inventory) (50).

Comparison

Different study designs (i.e., randomized controlled-trials, case–control studies and pre–post uncontrolled studies with no comparison group) were included in this review.

Outcome

The outcome of this systematic review was to evaluate for the first time MT impact on EDS in children affected by overweight/obesity.

We also evaluated weight reduction and/or fluctuations, expressed as Body Mass Index (BMI), BMI z score (BMIz), BMI Standard Deviation Score (BMISDS) as a possible confounding factor.

Exclusion Criteria

The comprehensive search strategy inadvertently retrieved studies that were unrelated to the aim of this systematic review and were subsequently excluded. Narrative reviews, systematic reviews and case reports were excluded, as well as case series, descriptive studies, letters, comments, articles that did not correspond to the objective of this review or had no full-text accessible in English.

Selection Process

Titles and abstracts were screened by two authors (Di Napoli Ilaria, Porri Debora) for inclusion. Reference lists of primary articles and related reviews were checked to identify any other study appropriate for inclusion. Studies assessed as eligible, potentially eligible or unclear, were retrieved in full text whenever available. Any uncertainty concerning the inclusion of specific studies was resolved by discussing with a third author (De Giuseppe Rachele). Last search date 18/02/2019.

Data Extraction

Study's characteristics (e.g., multidisciplinary treatment, participants, aim, outcome of interest, and study design) were extracted into standardized tables. Data items extracted were used to investigate the effect of MT on EDS in children affected by overweight/obesity.

Data Synthesis

Due to the heterogeneity of study population characteristics and MTs features (such as length of the treatment, outcomes measured, and timing of assessment), we were not able to perform a meta-analysis. However, we conducted a narrative summary of the findings.

Quality Assessment and Risk of Bias

Study quality was assessed in duplicate using a designed appraisal tool, the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies, a useful tool for systematic reviews, which evaluates randomized and non-randomized intervention studies (51).

Individual component quality rankings, including the risk of bias measures are included in the **Supplementary Table 1**.

Component and overall quality ratings were scored as "strong," "moderate" or "weak" according to instructions accompanying the tool (52, 53).

RESULTS

Overview of Studies

A flowchart summarizing the study selection procedure is presented in **Figure 1**.

Electronic searches returned 1,160 records. Duplicates (n = 142) were firstly removed. Secondly, 194 studies were retained after screening the titles and abstract. Finally, 170 studies were further excluded after reading throughout full texts. Of the 184 excluded records, 17 referred on a wrong population, in 140 MT was not considered, in 10 was considered an intervention on parents and in 18 were not evaluated EDS post MT. Only 9 eligible studies met the inclusion criteria and were included in this review.

Data abstraction revealed 6 programs that had multiple publications either protocols, additional cohorts, further follow-up time-points or different outcome measures/other secondary analysis (see references in **Supplementary Table 1**). Hence, studies were grouped by program cohort for reporting and analysis. Disagreements were resolved via discussion.

Study Characteristics

Characteristics of selected studies are reported in **Table 1**. All studies have been published between 2008 and 2019.

Four studies were conducted in Europe (56, 57, 59, 61), two studies took place in US (55, 60) while one study was conducted in Canada (54), one study was conducted in Brazil (58), and one in Iran (62).

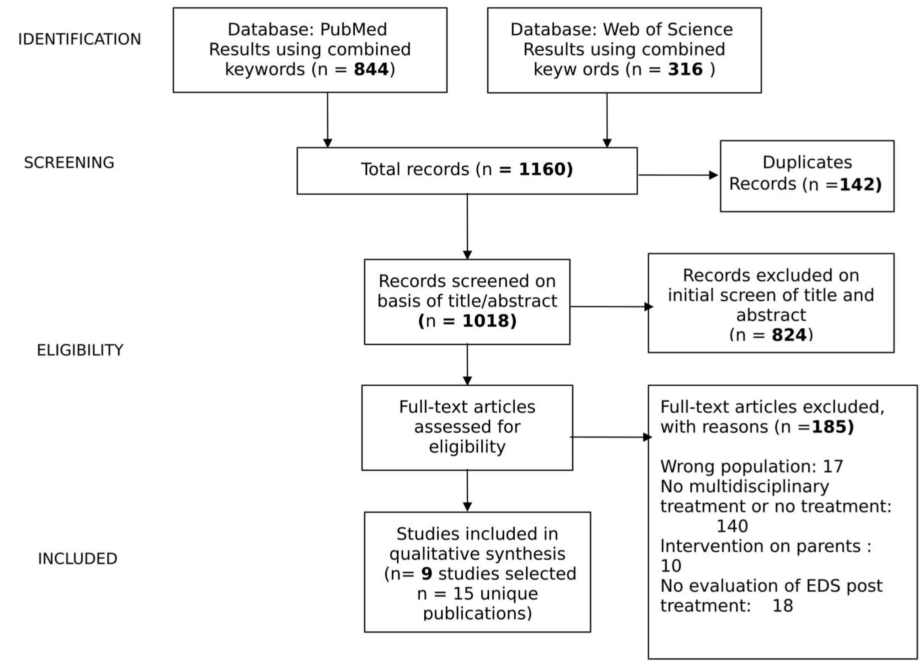

FIGURE 1 | Studies selection.

TABLE 1 | Characteristics of selected studies.

References	Study design	Quality score	Simple size	Age	Questionnaire
Cohen et al. (54)	Randomized Controlled Trial	moderate	78	6–8 year old	CEBQ(43)
Balantekin et al. (55)	Interrupted time series without comparison group	moderate	241	7–11 years old	ChEDE (40) YEDE-Q (41, 42)
Halberstadt et al. (56)	Interrupted time series without comparison group	weak	120	8–19 years old	DEBQ (39)
Adam et al. (57)	Interrupted time series without comparison group	weak	604	10 – 15 years old	TFEQ (44)
Raimunda Damaso et al. (58)	Interrupted time series without comparison group	moderate	97	15−19 years old.	BES (45) BITE (46)
De Niet et al. (59)	Randomized Controlled Trial	moderate	144	8–12 years old.	DEBQ (39)
Bishop-Gilyard et al. (60)	Randomized double blinded placebo–controlled trial	moderate	82	13–17 years old	QWEP (49) EI (50)
Goossens et al. (61)	Interrupted time series without comparison group	weak	108	10–17 years old	ChEDE (40)
Sarvestani et al. (62)	Non Randomized Controlled Trial	moderate	60	11-15 years old.	DEBQ (39)

The programs were evaluated as controlled trials ($n = 4$) (54, 59, 60, 62) both randomized ($n = 3$) (54, 59, 60) and non-randomized ($n = 1$) (62), and as interrupted time series without comparison group ($n = 5$) (55–58, 61).

Study quality was assessed to be weak for three studies (56, 57, 61); moderate for six (54, 55, 58–60, 62). Eight studies (54–57, 59–62) were rated as being weak for selection bias as they involved self-referrals from community advertisements and public service announcements, as is commonplace for community interventions, and thus participants were not randomly selected from the eligible population.

The sample size ranged from 60 to 504 children and adolescents while age of participants ranged from 7 to 18 years old.

In all studies, selected multidisciplinary treatment of pediatric obesity was provided. MTs were heterogeneous in nature, including length, number, frequency and type of sessions, parent-involvement and technology involvement.

Among selected studies, eight of them (54–57, 59–62) required either active and frequent participation of at least one parent/caregiver during MT or a "family-based intervention."

As regards the characteristics of the various MT approaches, all treatments (54–62) included either advice on healthy nutritional habits or advice on physical activity and healthy lifestyle.

Particularly, in one study (54), besides nutritional and lifestyle advice, both dietary treatment and structured physical activity were performed, while in other three studies (58, 61, 62) besides lifestyle advice, MT included the prescription of structured physical activity sessions, under the supervision of a skilled trainer.

Additionally, four studies (56, 57, 60, 61) combined an inpatient multidisciplinary program, ranging from 6 weeks to 10 months, with a strict control of children's daily dietary intake and lifestyle habits. De Niet et al. (59), evaluated the effect of Short Message Service (SMS) maintenance treatment (SMSMT) by means of smart devices.

Finally, only one study reported the use of medications (e.g., sibutramine) during MT (60).

Concerning psychological aspects in MT, all studies selected in this review (54–62) included support group therapy, with exception of Adam's (57) study for which we were not able to establish it since the protocol, described previously elsewhere, was written in German. Only Raimunda Damaso et al. (58) included also individual therapy in MT.

All MT approaches (54–62) included cognitive behavioral therapy (CBT), with parents' involvement promoting parent-child interaction patterns change toward a supporting relationship, instead of a parental controlling behavior, giving positive feedback and reinforcement. Three (56, 59, 61) of these nine studies analyzed also the psychosocial consequences of obesity and the relationships of children with their peers. Considering the duration of the various MT approaches, except one study (55) that did not state MT length, we reported different lengths of treatments ranging from 16 weeks (62) to 12 months (54, 56–60). As for follow ups three studies (56, 57, 61) reported follow ups ranging from 12 to 60 months post MT.

Outcome

The focus of this review was to evaluate MT outcome on ED symptoms in children affected by overweight/obesity (**Table 4**).

Different questionnaires have been used (**Table 2**) and administered at baseline, at the end of MT and during follow-up for ED symptoms screening in children and adolescents, since the lack of a standardized method.

MT features as sessions, length, follow-up, focus, prescriptions, target, and parental involvement are described in **Table 3** while the outcome of selected studies is reported in **Table 4**.

Additionally, we evaluated BMI fluctuations, expressed as BMI, BMIz, BMISD, or adjusted BMI, as a possible confounding factor, at end of treatment (MT) (54–62) and during follow-up period (56–58, 61) (**Table 4**).

Raimunda Damaso et al. (58) identified symptoms of binge eating and bulimia at baseline in 6% of their sample of adolescents with obesity, by means of BES and BITE questionnaires; at 12 months' follow up, the percentage of adolescents with binge eating symptoms had significantly decreased (2%) (**Table 4**).

Similarly, Bishop-Gilyard et al. (60) assessed symptoms of binge eating in adolescents affected by obesity by QWEP and EI questionnaires (**Table 2**), complemented by an interview to estimate the amount of food consumed during binging episodes and evaluate loss of control. The Authors (60) reported at baseline binge eating symptoms in 24% of participants with a significant decrease after 6 and 12-months' post MT, respectively 8 and 3%. Moreover, hunger and disinhibition significantly dropped, while cognitive restraint significantly increased over time (**Table 4**).

Concerning BMI reduction/fluctuation, the authors (60) also noticed that adolescents with obesity and binge eating episodes lost the same amount of weight as those without these episodes.

Besides binge eating, other eating disordered symptoms were identified by means of several others questionnaires as described in **Table 2**.

Choen et al. (54) conducted an RCT aimed at examining changes in EDS by means of CEBQ (**Table 2**) in children with overweight and obesity participating in a 12 months-MT protocol, based on a family-centered lifestyle intervention, according to Canadian dietary and physical activity guidelines. As shown in **Table 3**, the subjects were divided into three groups: control (Ctrl), standard (StnTx) and modified (ModTx) treatment. The StnTx and the ModTx attended 6 sessions plus a final of "prevention of relapse" session at the end the eighth month MT (**Table 3**) while the Ctrl group received the same session but at the end of 12 months of the study. CEBQ scores were then categorized as either Food Approach or Food Avoidance (**Table 2**), meaning for Food Approach food responsiveness, enjoyment of food, emotional overeating, and desire to drink scoring and for Food Avoidance slowness in eating, food fussiness, satiety responsiveness, and emotional under-eating scoring. Food Approach resulted significantly decreased only in the StnTx group and not in the ModTx group when compared to Ctrl group. Food Avoidance did not significantly change among groups (**Table 4**). Notably, this is the only study that used a parent-completed questionnaire (CEBQ).

Adam et al. (57) evaluated four parameters of EDS (disinhibition, cognitive control/restrained eating, flexible control, rigid control), by means of TFEQ questionnaire (**Table 2**) at baseline, at the end of MT and 24 and 48 months post treatment (MT). The Authors reported that cognitive control/restrained eating, flexible control, and disinhibition improved significantly at the end of MT as well as 24 and 48 months post MT, when compared to the baseline; rigid control improved but reached the significance only 24 and 48 months post MT (**Table 4**).

Goossens et al. (61) and Balantekin et al. (55) assessed different aspects such as restraint, eating, shape, weight concerns and loss of control (LC) overeating identified as objective binge eating (OBE) and subjective binge eating (SBE) on adolescents and children with overweight/obesity by using ChEDE, as described in **Table 2**. Balantekin et al. (55) used YEDE-Q (a version of ChEDE adapted for adolescent population) and EES-C to rate children desire to eat facing emotions; Goossens et al. (61) additionally used EDI-II (**Table 2**) aimed at assessing both eating

TABLE 2 | Description of questionnaires used in the different selected studies to assess ED symptoms.

References	Variables assessed	Questionnaires
Cohen et al. (54)	Items aimed at investigating: 1) Food Approach: food responsiveness, enjoyment of food, emotional overeating and desire to drink 2) Food Avoidance: headings slowness in eating, food fussiness, satiety responsiveness and emotional under eating.	CEBQ (43) Children Eating Behaviour Questionnaire
Balantekin et al. (55) Goossens et al. (61)	Items aimed at investigating four major areas of eating disorder psychopathology: restraint, eating, shape, and weight concerns.	ChEDE (40) Child Eating Disorder Examination
Balantekin et al. (55)	Adaption of ChEDE for adolescents.	YEDEQ (41, 42) Youth Eating Disorder Examination Questionnaire
Halberstadt et al. (56) De Niet et al. (59) Sarvestani et al. (62)	Items aimed at investigating: external eating, emotional eating and restrained eating.	DEBQ (39) Dutch Eating Behaviour Questionnaire
Adam et al. (57)	Items aimed at evaluating: disinhibition, cognitive control, flexible control and rigid control.	TFEQ(44) Three-Factor Eating Questionnaire
Raimunda Dâmaso et al. (58)	Items aimed at evaluating Bulimia symptoms.	BITE (46) Bulimic Investigatory Test, Edinburgh
Raimunda Damask et al. (58)	Items aimed at describing both behavioral manifestations and feeling/cognitions surrounding a binge episode and cognitive phenomena thought to be related to binge eating.	BES (45) Binge Eating Scale
Bishop-Gillard et al. (60)	Items aimed at measuring the ability to control food intake, loss of control over eating, and reported hunger	EI (50) Eating Inventory
Bishop-Gillard et al. (60)	Items aimed at measuring the BED diagnostic criteria.	QWEP(49) Questionnaire on Weight and Eating Patterns
Goossens et al. (61)	Items aimed at assessing both eating attitudes and related ego dysfunction characteristics. For the purpose of this study, nag eating attitudes (i.e., drive for thinness, bulimia, and body dissatisfaction) were evaluated	EDI-II (47) Eating Disorder Inventory

attitudes and related ego dysfunction characteristics (such as drive for thinness, bulimia, and body dissatisfaction).

Previous findings (63) hypothesized that EDS in youngsters with overweight, would remain stable or decrease over a certain period post MT. Similarly, Goossens et al. (61) investigated the stability of EDS in youngsters at 60 months post MT, reporting that some ED symptoms (like OBE, Restraint, Weight, and Shape Concerns) remained stable, while others decreased (like SBE, Eating Concern, Drive for Thinness, Bulimia, and Body Dissatisfaction) (**Table 4**).

Balantekin et al. (55) quantified each different aspect (restraint, eating, weight and shape concerns and loss control) investigated through ChEDE questionnaire (**Table 2**), identifying at baseline 4 different EDS patterns: (i) LOW (subjects with a very low probability to develop ED); (ii) SWC (subjects with a high probability to develop shape and weight concerns); (iii) OLOC (subjects at risk of loss of control eating); (iv) HIGH (subjects with a high probability to develop ED). The Authors (55) reported that after 16 MT sessions (**Table 4**), there was a significant decrease in weight concern from baseline to post treatment for the entire sample, with a significant time-by-group interaction. Compared with LOW children, HIGH, and SWC ones reported significantly greater reductions in weight concern; no differences were detected between children in LOW and OLOC and no significant change in shape concern from baseline to post treatment was observed for the entire sample. However, there was a significant time-by-group interaction; in fact, compared to LOW children, the HIGH, and SWC ones experienced a significantly greater reduction in shape concern. No significant change in the number of LOC eating episodes nor in the time-by-group interaction was found for the entire sample (**Table 4**). Interestingly, although the significant reduction in BMIz and weight concern after the MT in the whole study sample, Balantekin et al. (55) reported a lower decrease in BMIz in HIGH and SWC group when compared to LOW group. Moreover, shape and weight concern in HIGH group was not significantly related to BMIz reduction (55).

Finally, three studies (56, 59, 62) used DEBQ questionnaire (**Table 2**), in order to evaluate external, emotional and restrained eating in children and/or adolescent with overweight /obesity post MT.

Particularly, a RCT performed by de Niet et al. (59) and a non-RCT performed by Sarvestani et al. (62) reported a significant reduction in the emotional eating after 12 months and 6 months' MT, respectively (**Table 4**). Sarvestani et al. (62) also observed a significant increase in restraint eating (**Table 4**).

Similarly, Halberstadt et al. (56) in an interrupted time series with no control group study, noticed a significant increase of restraint eating in girls and, in agreement with others (62), a significant decrease in emotional eating but only in boys (**Table 4**).

TABLE 3 | Description of studies' multidisciplinary treatments.

References	Multidisciplinary treatment	Sessions	Length	Follow-up	Focus	Diet or physical activity prescribed by a specialist	Inpatient period	Parents involved
Cohen et al. (54)	Based on Canadian diet and physical activity guidelines. Children were randomized into 3 groups: – *Control* (Ctrl; no intervention) – *Standard treatment* (StnTx: 2 servings milk and alternatives/day (d), 3x/week. weight bearing physical activity) – *Modified treatment* (ModTx: 4 servings milk and alternatives/day; daily weight bearing physical activity). Ctrl received counseling after 12 months	StnTx and ModTx participated in 6 sessions, which were held at the end of each month for the first 5-months of the study, then a final "relapse prevention" session at the end of the 8th month. Ctrl group received the interventions after the end of the study.	12 months	NO	– Physical activity – Nutrition – Eating behavior – Parenting skills	YES (diet, structured physical activity)	NO	YES
Balantekin et al. (55)	Family-based behavioral weight loss treatment	16 session of family-based behavioral treatment.	Not specified	NO	– Nutrition, – Physical activity, – Eating behavior – Parenting skills	NO	NO	YES
Halberstadt et al. (56)	Combined multidisciplinary lifestyle intervention. Two months or 6 months period of inpatient treatment during weekdays requiring active and frequent participation of the parents/caregivers.	The MT had a period of inpatient treatment during weekdays of either 2 months and biweekly return visits of 2 days during the next 4 months or 6 months, followed by 6 monthly return visits of 2 days	12 months	12 months	– Nutrition, – Physical activity – Eating behavior – Parenting skills	NO	YES	YES
Adam et al. (57)	The DAK program, designed for one year with an initial multidisciplinary inpatient treatment followed by an outpatient family based treatment.	The details of MT was previously published elsewhere. The protocol was written in Germany (see **Supplementary Table 1**)	12 months	48 months	– Nutrition, – Physical activity – Eating behavior – Parenting skills	YES (diet and structured physical activity)	YES	YES
Raimunda Damaso et al. (58)	Multidisciplinary treatment with the supervision of an exercise physiologist	Once a week, the adolescents had classes on topics related to improved food consumption. Adolescents underwent therapy support group weekly Adolescents were involved in structured session of physical activity three times a week.	12 months	NO	– Physical activity – Nutrition – Eating behavior	YES (structured physical activity)	NO	NO
De Niet et al. (59)	SMS maintenance treatment (SMSMT) program After the first 3 months of treatment where children and parents were involved into educational session group, participants were randomly assigned to: – Intervention group, receiving SMSMT for 9 months, or to – Control group (no SMSMT)	1 intake session; 8 children sessions; 3 parent sessions; for 3 months.	12 months	NO	– Physical activity – Nutrition – Eating behavior – Technology involvement – Parenting skills	NO	NO	YES

(Continued)

TABLE 3 | Continued

References	Multidisciplinary treatment	Sessions	Length	Follow-up	Focus	Diet or physical activity prescribed by a specialist	Inpatient period	Parents involved
Bishop-Gilyard et al. (60)	Participants attending at a family based behavioral weight loss program were randomly assigned to: – Intervention group (sibutramine 15 mg/d) or to – Control group received placebo.	The treatment was structured into 2 phases. Phase 1: Both intervention and control group attended a behavioral counseling for 4 months followed by bi-weekly visits for an additional 2 months. Parents were instructed in methods of supporting their children. Phase 2: After the initial 6 months all participant received sibutramine for 6 months.	12 months	NO	– Physical activity – Nutrition – Eating behavior – Parenting skills	YES (diet)	NO	YES
Goossens et al. (61)	Inpatient non-diet healthy lifestyle program.	Each child received 4 hours of individual guided exercises. All children had facilities to take part in exercise programs for at least 14 hours per week. All children received a 12-week cognitive behavioral treatment.	10 months	60 moths	– Physical activity – Nutrition – Eating behavior – Parenting skills	YES (structured physical activity)	YES	YES
Sarvestani et al. (62)	Participants were randomized into: – Intervention group receiving lifestyle counseling and structured sessions of physical activity – Control group attended only three sessions of the same treatment.	Four-hour structured sessions of physical activity were held weekly for 16 weeks; each session involved 2 hours of behavior modification or dietary instruction and 2 hours of yoga therapy.	4 months	NO	– Physical activity – Nutrition – Eating behavior – Parenting skills	YES (structured physical activity)	NO	YES

TABLE 4 | Outcome of selected studies.

References	Outcome
Cohen et al. (54)	StnTx: - Food Approach ↓** - Food Avoidance not significantly change - BMIz ↓* ModTx: - Food Approach ↓ - Food Avoidance not significantly change - BMIz ↓ Ctrl: - Food Approach ↔ - Food Avoidance not significantly change - BMIz ↔ *
Balantekin et al. (55)	Entire sample: - Weight concern ↓** - Shape concern no significant change - LOC no significant change - BMIz↓*** HIGH and SWC (compared with LOW): - Weight concern ↓*** - Shape concern ↓***
Halberstadt et al. (56)	Girls: - Restraint eating ↑** - External eating↓ Boys: - Emotional eating ↓* - External eating ↓** Entire sample: BMISDS ↓***
Adam et al. (57)	- Cognitive control/Restrained eating ↑*** - Flexible control ↑*** - Disinhibition ↓*** - Rigid control ↓(at 24 months and at 48 months)*** - BMISDS ↓***
Raimunda Damaso et al. (58)	- Percentage of adolescents with binge eating symptoms ↓*** - BMI ↓***
De Niet et al. (59)	- Emotional eating ↓* - External eating ↓* - BMISDS ↓***
Bishop-Gilyard et al. (60)	- Percentage of adolescents with binge eating symptoms ↓** - Hunger ↓*** - Disinhibition ↓*** - Cognitive restraint ↑*** - BMI ↓
Goossens et al. (61)	- OBE ↔ - Restraint ↔ - Weight concern ↔ - Shape concern ↔ - SBE ↓ - Eating Concern ↓** - Drive for Thinness ↓** - Bulimia ↓** - Body Dissatisfaction ↓** - adjusted BMI ↓***
Sarvestani et al. (62)	- Emotional eating ↓* - Restraint eating ↑* - External eating ↓* - BMI ↓*

*SBE, subjective binge eating episodes; OBE, objective binge eating episodes; LOC, loss of control; HIGH, high probability to develop ED pathology group; SWC, shape and weight concern group; LOW, Low probability to develop ED pathology group; BMIz, BMI z score; BMISDS, BMI Standard Deviation Score; ↓ decrease; ↔ remain stable; ↑ increased. *p ≤ 0.05; **p ≤ 0.01; *** p ≤ 0.001.*

The authors (56) also reported a significant reduction of BMI and BMISDS post MT that was maintained during follow-up. However, a slight increase in BMI and BMISDS occurred after 12 months, showing that weight re-gain influenced significantly the increase of restraint and external eating post MT, only in girls.

Concerning external eating, all studies (56, 59, 62) reported a significant decrease after MT (**Table 4**).

DISCUSSION

Multidisciplinary treatment for children/adolescents with overweight and obesity should focus on diet and healthy eating habits, physical activity, and family coping strategies (64, 65).

Assessment and treatment of childhood obesity and associated medical conditions, including psychological consequences, should be ensured.

It is well known that psychological distress and risk for eating disorders in pediatric population with a history of obesity are frequent (19); however classifying eating disorders in youth is challenging (66).

During childhood, eating disorders often present with atypical or sub-threshold criteria. This is particularly true for Binge Eating, one of the most common ED symptom associated with childhood obesity (19). Despite binge eating symptoms in children with obesity are common, the diagnosis of binge eating disorder (BED) in youth is rare (67–69); compulsive eating and stereotypical disordered eating behaviors such as hiding food, eating in secret, purging, exercising excessively, can be frequently observed (20).

Previous research showed an association between pediatric obesity and EDS, such as dietary restraint, self-dieting, and body image dissatisfaction (70). Moreover, results confirmed by Boutelle et al. (71) suggested that external eating, satiety sensitivity, eating in the absence of hunger, loss of control eating, and emotional eating were related to adiposity and excessive weight gain in children.

Assessment and management of EDS caused by or consequent to excessive weight gain are not always contemplated with due caution; however, pediatric obesity should be considered a significant risk factor for the development of eating disorders during adolescence and childhood (17).

Although multidisciplinary treatments are well supported by the literature in their effectiveness to reduce BMI and risk of future co-morbidities (30–32), to the best of our knowledge the effect of MT on the development, progression or reduction of EDS in children/adolescents with overweight/obesity has never been evaluated.

In our systematic review, the first aim was to evaluate the effectiveness of MT on EDS in children with obesity.

Concerning MT efficacy on dietary restraint, results (56, 57, 60, 62) presented are conflict.

Adam et al. (57) found a significant decrease of dietary restraint after MT; they also reported a significant reduction of flexible control, a typical behavior characterized by a graduated "more or less" approach to eating and weight control, which is considered a permanent behavior (57).

These effects were also maintained during the whole follow-up period (57) and can reflect a success of MT since dietary restraint is often considered a determinant of overeating and a precursor of EDS (72). In fact, as previously demonstrated by Stice et al. (73) in a 60 months prospective study on 496 adolescent girls, children and adolescents with higher dietary restraint scores appeared to have an increased risk of developing obesity later on.

On the contrary, other findings (56, 60, 62) described in our systematic review, reported that children or adolescents with obesity, especially girls (56) showed a significant increase in dietary restraint after MT.

However, in the light of what has been described above, it is also important to note that while dietary restraint is often conceptualized as maladaptive for individuals with ED, in the context of obesity, a moderate degree of dietary restraint may be beneficial in facilitating weight loss, improving physical health and maintaining weight control after treatment (74).

It should be noted that dietary restraint scales measure the intention to eat less rather than the real energy intake restriction (75); although some people may develop an intention to restrict their food intake, this intention is not always translated into action (73, 75). Planning, maintenance self-efficacy and action control are suggested to be important variables that may explain the gap between intention and behavior; subjects showing higher food restriction intention are more vulnerable to future eating disorders and weight gain (76).

Similarly, self-dieting is common among adolescents but it is not always a harmless behavior (17, 77). In fact, if self-dieting is not supervised or controlled, may lead to negative emotions that increase the risk of binge eating and use of inappropriate compensatory behaviors (17, 78).

Additionally, binge eating is a cognitive and behavioral process that is particularly important in the context of obesity (74), as recently demonstrated by a meta-analysis (79) binge eating symptoms are prevalent in more than one quarter of children and adolescents with overweight and obesity (19, 79).

Goossens and Bishop-Gilyard (60, 61) found a significant decrease in binge eating symptoms in adolescents post MT, confirming the importance of a structured MT rather than self-made -diets. They also distinguished between OBE, with the onset of LC over eating a larger amount of food that other people would not do, and SBE, with the onset of LC over eating a subjective large amount of food, that other people would not quantify as unambiguously large (61). The authors (61) reported a decrease of SBE after MT while OBE did not change (**Table 4**). This may occur since SBE seems quite common in youngsters, and its association with obesity and psychological impairment has already been demonstrated (80) while OBE is more common in adults (80).

Moreover, children and adolescents with obesity can develop body dissatisfaction which is linked to unhealthy weight control behaviors, binge eating, and lower physical activity levels (81); in addition, children and adolescents with obesity or overweight may experience weight stigma that exacerbates weight gain and creates additional barriers to healthy behavioral changes (82).

However, concern for body image, which is central to adolescents' overall sense of self-esteem, can play a dual role according to personal and environmental interactions (83, 84). In fact, it may exert negative or positive feedback, respectively, pushing toward dieting and triggering overeating or acting as a motivational driver toward healthier eating and lifestyle behaviors (83, 84). Studies reported in our systematic review (55, 61) assessed concern for body image throughout different questionnaires, investigating self-perceptions, weight, and shape concern. Only Balantekin et al. (55) and Goossens et al. (61) showed an improvement of self-perception, weight and shape concern, post MT.

Among the EDS, emotional and external eating can be considered behaviors related to overeating. Emotional eating means eating in response to emotional states, such as hunger, fear or anxiety, while external eating identifies eating in response to environmental food stimuli, such as sight and smell of food, regardless of hunger, and satiety stimuli (85).

Moreover, disinhibition leads to increase food intake and overeating if exposed to emotional stimuli (57).

Studies described in our systematic review (56, 57, 59, 62) showed that MT had a positive impact on external eating, disinhibition of control and emotional eating. Many authors (56, 57, 59, 62) concluded by agreeing that MT could influence eating behavior and that children/adolescents with overweight/obesity undergoing MT learned to react to emotional stress and external stimuli.

In this systematic review, we also investigated the weight and/or BMI reduction/fluctuation, as possible confounding factor.

A statistically significant decrease in BMI was observed in all MT approaches (54–62) except for Bishop-Gilyard et al. (60) where the decrease did not reach the significance.

Some authors (55, 56, 60) also analyzed the relation between EDS, such as weight and shape concern (55), binge eating episodes (60), dietary restraint, and external eating (56) and BMI reduction and/or fluctuation post MT.

Balantekin et al. (55) reported that BMIz was not strictly related to weight and shape concern improvement. In fact, although the authors (55) described a significant reduction in BMIz and weight concern post MT in the whole study sample. They reported a lower reduction in BMIz in subjects with a high probability to develop ED and in subjects with a greater likelihood of developing weight and shape concerns, when compared to subjects with a low risk of ED. Moreover, shape and weight concern in subjects with at high risk of ED was not significantly related to BMIz reduction (55).

Bishop-Gilyard et al. (60) revealed that adolescents with obesity and binge eating episodes lost the same amount of weight as those without binge.

Halberstadt et al. (56) described a BMI re-gain impact on EDS, showing that weight re-gain affected the increase of restraint and external eating post MT, only in girls.

Therefore, given the small numbers of the studies mentioned above (55, 56, 60), we could only hypothesize that weight status and EDS improvement after MT were independent factors.

Notably, all selected studies (54–62) provided MT approaches including CBT and eight of them (54–61) considered either active and frequent participation of the parents/caregivers during MT or "family-centered" approaches.

Multiple organizations, including the American Dietetic Association, the American Academy of Pediatricians, and the National Academy of Medicine, support family-based treatments, encouraging healthy nutrition and parent education/modeling (86, 87). Nowadays, supporting parents to improve their skills regarding healthy child growth is considered an important public health goal (65, 88). In fact, it is well known (89) that parents impact child's behaviors throughout home environmental influence. For instance, parenting practices and lifestyle such as eating pattern, provision of nutritious food, physical activity reinforcement, and counteracting sedentary behaviors could influence children eating behavior. On the other hand, family-based interventions are an effective method, positively impacting pediatric obesity treatment outcome and improving the probability for children and adolescents to be adherent and successful once engaged in a weight loss program (90, 91).

Strength and Limitations

The strength of this systematic review includes the development of a comprehensive search strategy applied, for the first time, on the effect of MT on the development and/or progress of EDS in children with overweight/obesity.

The assessment of risk of BIAS reported that the quality of the included studies was variable. Weak studies were included in this review and study quality was generally limited by participants selection (see **Table S1**, column "selection bias"). In fact, participants were no more likely to be representative of the target population, according to the tool that was used in this systematic review (51–53); in the selected studies, participants are often referred from a clinic or self-recruited via fliers, newspapers, television, radio, referrals from schools and community providers.

Another limit is that MTs were largely heterogeneous in length, period of discharge of patient, frequency and intensity of sessions, parents' involvement. Finally, quite a number of behavioral and psychosocial variables were assessed, by means of different validated questionnaires.

CONCLUSIONS

Evidence showed that comprehensive MTs for children and adolescents with obesity reduce BMI and risk of future co-morbidities.

Although obesity and ED have traditionally been conceptualized as separate conditions, EDS in the pediatric population, with a history of obesity, are not unusual. Overweight and obesity in childhood and adolescence significantly increase the risk for ED development.

Results from this systematic review highlighted, for the first time, the positive short- and long-term impact of MTs on ED symptoms, which are not always associated to BMI reduction in children. Therefore, awareness amongst clinicians who treat children and adolescents with overweight and obesity should be raised so that EDS could be identified and treated accordingly.

AUTHOR CONTRIBUTIONS

RD, ID, and DP designed the search strategy. ID and DP screened studies for inclusion. RD resolved any uncertainty concerning the inclusion of specific studies. All authors analyzed results and drafted the manuscript. HC approved the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2019.00123/full#supplementary-material

REFERENCES

1. Farpour-Lambert NJ, Baker JL, Hassapidou M, Holm JC, Nowicka P, O'Malley G, et al. Childhood obesity is a chronic disease demanding specific health care–a position statement from the Childhood Obesity Task Force (COTF) of the European Association for the Study of Obesity (EASO). *Obes Facts*. (2015) 8:342–9. doi: 10.1159/000441483
2. WHO. *Commission on Ending Childhood Obesity*. Report of the Commission on Ending Childhood Obesity. Geneva: World Health Organization (2016).
3. Wijnhoven TM, van Raaij JM, Spinelli A, Starc G, Hassapidou M, Spiroski I, et al. WHO European Childhood Obesity Surveillance Initiative: body mass index and level of overweight among 6-9-year-old children from school year 2007/2008 to school year 2009/2010. *BMC Public Health.* (2014) 14:806. doi: 10.1186/1471-2458-14-806
4. Ogden C, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. *JAMA.* (2016) 315:2292–9. doi: 10.1001/jama.2016.6361
5. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk—a review of the literature. *Eur J Clin Nutr*. (2010) 64:16–22. doi: 10.1038/ejcn.2009.68
6. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet*. (2016) 387:1377–96. doi: 10.1016/S0140-6736(16)30054-X
7. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet*. (2017) 390:2627–42. doi: 10.1016/S0140-6736(17)32129-3
8. Rendón-Macías ME, Rosas-Vargas H, Villasís-Keever MÁ, Pérez-García C. Children's perception on obesity and quality of life: a Mexican survey. *BMC Pediatr*. (2014) 14:131. doi: 10.1186/1471-2431-14-131
9. Micali N, Solmi F, Horton NJ, Crosby RD, Eddy KT, Calzo JP, et al. Adolescent eating disorders predict psychiatric, high-risk behaviors and weight outcomes in young adulthood. *J Am Acad Child Adolesc Psychiatry.* (2015) 54:652–9. doi: 10.1016/j.jaac.2015.05.009

10. Rancourt D, McCullough MB Overlap in eating disorders and obesity in adolescence. *Curr Diab Rep*. (2015) 15:78. doi: 10.1007/s11892-015-0645-y
11. Sahoo K, Sahoo B, Choudhury AK, Sofi NY, Kumar R, Bhadoria AS. Childhood obesity: causes and consequences. *J Family Med Prim Care*. (2015) 4:187–92. doi: 10.4103/2249-4863.154628
12. Sim LA, Lebow J, Billings M. Eating disorders in adolescents with a history of obesity. *Pediatrics*. (2013) 132:e1026–30. doi: 10.1542/peds.2012-3940
13. Villarejo C, Fernández-Aranda F, Jiménez-Murcia S, Peñas-Lledó E, Granero R, Penelo E, et al. Lifetime obesity in patients with eating disorders: increasing prevalence, clinical and personality correlates. *Eur Eat Disorders Rev*. (2012) 20:250–4. doi: 10.1002/erv.2166
14. Sagar R, Gupta T. Psychological aspects of obesity in children and adolescents. *Indian J Pediatr*. (2018) 85:554–9. doi: 10.1007/s12098-017-2539-2
15. Nieman P, Leblanc CM, Canadian Paediatric Society, Healthy Active Living and Sports Medicine Committee. Psychosocial aspects of child and adolescent obesity. *Paediatr Child Health*. (2012) 17:205–6. doi: 10.1093/pch/17.4.205
16. Rankin J, Matthews L, Cobley S, Han A, Sanders R, Wiltshire HD, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolesc Health Med Ther*. (2016) 7:125–46. doi: 10.2147/AHMT.S101631
17. Cena H, Stanford FC, Ochner L, Fonte ML, Biino G, De Giuseppe R, et al. Association of a history of childhood-onset obesity and dieting with eating disorders. *Eat Disord*. (2017) 25:216-29. doi: 10.1080/10640266.2017.1279905
18. Goldschmidt AB, Tanofsky-Kraff M, Goossens L, Eddy KT, Ringham R, Yanovski SZ, et al. Subtyping children and adolescents with loss of control eating by negative affect and dietary restraint. *Behav Res Ther*. (2008) 46:777–87. doi: 10.1016/j.brat.2008.03.004
19. Fiechtner L, Fonte ML, Castro I, Gerber M, Horan C, Sharifi M, et al. Determinants of binge eating symptoms in children with overweight/obesity. *Child Obes*. (2018) 14:510–7. doi: 10.1089/chi.2017.0311
20. Campbell K, Peebles R. Eating disorders in children and adolescents: state of the art review. *Pediatrics*. (2014) 34:582–92. doi: 10.1542/peds.2014-0194
21. Evans EH, Adamson AJ, Basterfield L, Le Couteur A, Reilly JK, Reilly JJ, et al. Risk factors for eating disorder symptoms at 12 years of age: a 6-year longitudinal cohort study. *Appetite*. (2016) 108:12–20. doi: 10.1016/j.appet.2016.09.005
22. Veses AM, Martínez-Gómez D, Gómez-Martínez S, Vicente-Rodriguez G, Castillo R, Ortega FB, et al. AFINOS study groups. physical fitness, overweight and the risk of eating disorders in adolescents. The AVENA and AFINOS studies. *Pediatr Obes*. (2014) 9:1–9. doi: 10.1111/j.2047-6310.2012.00138.x
23. WHO. *Population-Based Approaches to Childhood Obesity Prevention*. Geneva: World Health Organization (2012).
24. Pandita A, Sharma D, Pandita D, Pawar S, Tariq M, Kaul A. Childhood obesity: prevention is better than cure. *Diabetes Metab Syndr Obes*. (2016) 9:83–9. doi: 10.2147/DMSO.S90783
25. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. *Cochrane Database Syst Rev*. (2009) CD001872. doi: 10.1002/14651858.CD001872
26. Ross MM, Kolbash S, Cohen GM, Skelton JA. Multidisciplinary treatment of pediatric obesity: nutrition evaluation and management. *Nutr Clin Pract*. (2010) 25:327–34. doi: 10.1177/0884533610373771
27. Styne DM, Arslanian SA, Connor EL, Sadaf Farooqi I, Murad MH, Silverstein JH, et al. Pediatric obesity—assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. (2017) 102:709–57 doi: 10.1210/jc.2017-00561
28. Spear BA, Barlow SE, Ervin C, Ludwig DS, Saelens BE, Schetzina KE, et al. Recommendations for treatment of child and adolescent overweight and obesity. *Pediatrics*. (2007) 120(Suppl. 4):S254–88. doi: 10.1542/peds.2007-2329F
29. Kelly KP, Kirschenbaum DS. Immersion treatment of childhood and adolescent obesity: the first review of a promising intervention. *Obes Rev*. (2011) 12:37–49. doi: 10.1111/j.1467-789X.2009.00710.x
30. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. (2007) 120:S164–92. doi: 10.1542/peds.2007-2329C
31. Mameli C, Krakauer JC, Krakauer NY, Bosetti A, Ferrari CM, Schneider L, et al. Effects of a multidisciplinary weight loss intervention in overweight and obese children and adolescents: 11 years of experience. *PLoS ONE*. (2017) 12:e0181095. doi: 10.1371/journal.pone.0181095.
32. Moores CJ, Bell LK, Miller J, Damarell RA, Matwiejczyk L, Miller MD. A systematic review of community-based interventions for the treatment of adolescents with overweight and obesity. *Obes Rev*. (2017) 19:698–715. doi: 10.1111/obr.12660
33. Bianchini JA, da Silva DF, Nardo CC, Carolino ID, Hernandes F, Nardo N Jr. Multidisciplinary therapy reduces risk factors for metabolic syndrome in obese adolescents. *Eur J Pediatr*. (2013) 172:215–21. doi: 10.1007/s00431-012-1865-7.
34. Carriere C, Cabaussel C, Bader C, Barberger-Gateau P, Thibault BH. Multidisciplinary care management has a positive effect on paediatric obesity and social and individual factors are associated with better outcomes *Acta Pædiatr*. (2016) 105:e536–42. doi: 10.1111/apa.13560
35. Coles N, Birken C, Hamilton J. Emerging treatments for severe obesity in children and adolescents. *BMJ*. (2016) 354:i4116. doi: 10.1136/bmj.i4116
36. EUFIC. *Childhood Obesity Review*. European Food Information Council (2017).
37. Reinehr T. Lifestyle intervention in childhood obesity: changes and challenges. *Nat Rev Endocrinol*. (2013) 9:607–14. doi: 10.1038/nrendo.2013.149
38. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and metanalyses: the PRISMA statement. *PLoS Med*. (2009) 6:e1000097. doi: 10.1136/bmj.b2535
39. Van Strien T, Frijters JER, Bergers GPA, Defares PB. The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional and external eating behavior. *Int J Eat Disord*. (1986) 5:295–315. doi: 10.1002/1098-108X(198602)5:2<295::AID-EAT2260050209>3.0.CO;2-T
40. Bryant-Waugh RJ, Cooper PJ, Taylor CL, Lask BD. The use of the eating disorder examination with children: a pilot study. *Int J Eat Disord*. (1996) 19:391–7. doi: 10.1002/(SICI)1098-108X(199605)19:4<391::AID-EAT6>3.0.CO;2-G
41. Goldschmidt AB, Doyle AC, Wilfley DE. Assessment of binge eating in overweight youth using a questionnaire version of the child eating disorder examination with instructions. *Int J Eat Disord*. (2007) 40:460–7. doi: 10.1002/eat.20387
42. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? *Int J Eat Disord*. (1994) 16:363–70. doi: 10.1002/1098-108X(199412)16:4<363::AID-EAT2260160405>3.0.CO;2-%23
43. Guthrie CA, Sanderson S, Rapoport L. Development of the childrens' eating behaviour questionnaire. *J Child Psychol Psychiatr*. (2001) 42:963–70. doi: 10.1111/1469-7610.00792
44. Pudel V, Westenhoefer J. Fragebogen zum Eßverhalten. Göttingen: Hogrefe. *Verlag für Psychologie* (1989).
45. Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among 340 obese persons. *Addict Behav*. (1982) 7:47–55. doi: 10.1016/0306-4603(82)90024-7
46. Henderson M, Freeman CP. A self-rating scale for bulimia. The 'BITE'. *Br J Psychiatry*. (1987) 150:18–24. doi: 10.1192/bjp.150.1.18
47. Garner D. *EDI-2: Eating Disorder Inventory-II. Professional Manual*. Odessa, FL: Psychological Assessment Resources (1991).
48. Tanofsky-Kraff M, Theim KR, Yanovski SZ, et al. Validation of the emotional eating scale adapted for use in children and adolescents (EES-C). *Int J Eat Disord*. (2007) 40:232–40. doi: 10.1002/eat.20362
49. Spitzer RL, Devlin M, Walsh BT, Hasin D, Wing R, Marcus M, et al. Binge eating disorder: a multisite field trial of the diagnostic criteria. *Int J Eat Disord*. (1992) 11:191–203. doi: 10.1002/1098-108X(199204)11:3<191::AID-EAT2260110302>3.0.CO;2-S

50. Stunkard AJ, Messick S. *Eating Inventory Manual.* San Antonio, TX: Psychological Corporation (1988).
51. Thomas BH, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs*. (2004) 1:176–84. doi: 10.1111/j.1524-475X.2004.04006.x
52. Effective Public Health Practice Project. *Quality Assessment Tool For Quantitative Studies*. Hamilton: Effective Public Health Practice Project. (1998).
53. Effective Public Health Practice Project. *Dictionary for the Effective Public Health Practice Project Quality Assessment Tool For Quantitative Studies.* (Accessed October, 2008).(Corresponding article of interest: Thomas, B.H., Ciliska, D., Dobbins, M., and Micucci, S. (2004). A process for systematically reviewing the literature: Providing the research evidence for public health nursing interventions. Worldviews on Evidence-Based Nursing, 1(3), 176-184).
54. Cohen TR, Hazell TJ, Vanstone CA, Rodd C, Weiler HA. Changes in eating behavior and plasma leptin in children with obesity participating in a family-centered lifestyle intervention. *Appetite.* (2018) 125:81–9. doi: 10.1016/j.appet.2018.01.017
55. Balantekin KN, Hayes JF, Sheinbein DH, Kolko RP, Stein RI, Saelens BE, et al. Patterns of eating disorder pathology are associated with weight change in family-based behavioral obesity treatment. *Obesity (Silver Spring).* (2017) 25:2115–22. doi: 10.1002/oby.22028
56. Halberstadt J, van Strien T, de Vet E, Eekhout I, Braet C, Jacob C, et al. The association of eating styles with weight change after an intensive combined lifestyle intervention for children and adolescents with severe obesity. *Appetite*. (2016) 99:82–90. doi: 10.1016/j.appet.2015.12.032
57. Adam S, Westenhoefer J, Rudolphi B, Kraaibeek HK. Three- and five-year follow-up of a combined inpatient-outpatient treatment of obese children and adolescents. *Int J Pediatr.* (2013) 2013:856743. doi: 10.1155/2013/856743
58. Raimunda Dâmaso A, de Piano A, da Silveira Campos RM, Corgosinho FC, Siegfried W, Caranti DA, et al. Multidisciplinary approach to the treatment of obese adolescents: effects on cardiovascular risk factors, inflammatory profile, and neuroendocrine regulation of energy balance. *Int J Endocrinol*. (2013) 2013:541032. doi: 10.1155/2013/541032
59. De Niet J, Timman R, Bauer S, van den Akke E, Buijks H, de Klerk C, et al. Effect of a short message service maintenance treatment on body mass index and psychological well-being in overweight and obese children: a randomized controlled trial. *Pediatr Obes.* (2012) 7:205–19. doi: 10.1111/j.2047-6310.2012.00048.x
60. Bishop-Gilyard CT, Berkowitz RI, Wadden TA, Gehrman CA, Cronquist JL, Moore RH. Weight reduction in obese adolescents with and without binge eating. *Obesity (Silver Spring).* (2011) 19:982–7. doi: 10.1038/oby.2010.249
61. Goossens L, Braet C, Verbeken S, Veerle Decaluwe MA, Bosmans G. Long-term outcome of pediatric eating pathology and predictors for the onset of loss of control over eating following weight-loss treatment. *Int J Eat Disord.* (2011) 44:397–405. doi: 10.1002/eat.20848
62. Sarvestani RS, Jamalfard MH, Kargar M, Kaveh MH, Tabatabaee HR. Effect of dietary behaviour modification on anthropometric indices and eating behaviour in obese adolescent girls. *J Adv Nurs*. (2009) 65:1670–5. doi: 10.1111/j.1365-2648.2009.05029.x
63. Braet C. Patient characteristics as predictors of weight loss after an obesity treatment for children. *Obesity*. (2006) 14:148–55. doi: 10.1038/oby.2006.18
64. NICE. *Weight Management: Lifestyle Services for Overweight or Obese Children and Young People*. Nice (2013). Available online at: https://www.nice.org.uk/guidance/ph47
65. NICE. *Obesity in Children and Young People: Prevention and Lifestyle Weight Management Programmes*. Nice (2015). Available online at: https://www.nice.org.uk/guidance/qs94
66. Goldschmidt AB, Crosby RD, Cao L, Moessner M, Forbush KT, Accurso EC, et al. Network analysis of pediatric eating disorder symptoms in a treatment-seeking, transdiagnostic sample. *J Abnorm Psychol*. (2018) 127:251–64. doi: 10.1037/abn0000327
67. Lewer M, Bauer A, Hartmann AS, Vocks S. Different facets of body image disturbance in binge eating disorder: a review. *Nutrients*. (2017) 9:E1294. doi: 10.3390/nu9121294
68. Glasofer DR, Tanofsky-Kraff M, Eddy KT, Yanovsky SZ, Theim KR, Mirch MC, et al. Binge eating in overweight treatment-seeking adolescents. *J Pediatr Psychol*. (2007) 32:95–105. doi: 10.1093/jpepsy/jsl012
69. Levine MD, Ringham RM, Kalarchian MA, Wisniewski L, Marcus M.D. Overeating among seriously overweight children seeking treatment: results of the children's eating disorder examination. *Int J Eat Disord.* (2006) 39:135–40. doi: 10.1002/eat.20218
70. Vander Wal JS, Thelen MH. Eating and body image concerns among obese and average-weight children. *Addict Behav*. (2000) 25:775–8. doi: 10.1016/S0306-4603(00)00061-7
71. Boutelle KN, Peterson CB, Crosby RB, Rydell SA, Zucker N, Harnack L. Overeating phenotypes in overweight and obese children. *Appetite*. (2014) 76:95–100. doi: 10.1016/j.appet.2014.01.076
72. Jansen A, Nederkoorn C, van Baak L, Keirse C, Guerrieri R, Havermans R. High-restrained eaters only overeat when they are also impulsive. *Behav Res Ther*. (2009) 47:105e110. doi: 10.1016/j.brat.2008.10.016
73. Stice E, Presnell K, Shaw H, Rohde P. Psychological and behavioral risk factors for obesity onset in adolescent girls: a prospective study. *J Consult Clin Psychol*. (2005) 73:195–202. doi: 10.1037/0022-006X.73.2.195
74. Smith KE, Mason TB, Crosbya RD, Engela SG, Crowd SJ, Wonderlicha SA, et al State and trait positive and negative affectivity in relation to restraint intention and binge eating among adults with obesity. *Appetite*. (2018) 120:327–34. doi: 10.1016/j.appet.2017.09.020
75. Stice E, Sysko R, Roberto CA, Allison S. Are dietary restraint scales valid measures of dietary restriction? Additional objective behavioral and biological data suggest not. *Appetite*. (2010) 54:331–9. doi: 10.1016/j.appet.2009.12.009
76. Larsen JK, van Strien T, Eisinga R, Herman CP, Engels RC. Dietary restraint: intention vs behaviour restrict food intake. *Appetite*. (2007) 49:100–8 doi: 10.1016/j.appet.2006.12.005
77. Neumark-Sztainer D, Wall M, Story M, Standish A. Dieting and unhealthy weight control behaviors during adolescence: Associations with 10-year changes in body mass index. *J Adolesc Health*. (2012) 50:80–6. doi: 10.1016/j.jadohealth.2011.05.010
78. Neumark-Sztainer D, Wall M, Larson NI, Eisenberg ME, Loth K. Dieting and disordered eating behaviors from adolescence to young adulthood: findings from a 10-year longitudinal study. *J Am Diet Assoc*. (2011) 111:1004–11. doi: 10.1016/j.jada.2011.04.012
79. He J, Cai Z, Fan X Prevalence of binge and loss of control eating among children and adolescents with overweight and obesity: an exploratory meta-analysis. *Int J Eat Disord*. (2017) 50:91–103. doi: 10.1002/eat.22661
80. Tanofsky-Kraff M, Marcus M, Yanovski S, Yanovski J. Loss of control eating disorder in children age 12 years and younger: proposed research criteria. *Eat Behav*. (2008) 9:360–5. doi: 10.1016/j.eatbeh.2008.03.002
81. Calzo JP, Sonneville KR, Haines J, Blood EA, Field AE, Austin SB. The development of association among body mass index, body dissatisfaction, and weight and shape concern in adolescent boys and girls. *J Adolesc Health*. (2012) 51:517–23. doi: 10.1016/j.jadohealth.2012.02.021
82. Pont SJ, Puhl R, Cook SR, Slusser W. Stigma experienced by children and adolescents with obesity. *Pediatrics*. (2017) 140:e20173034. doi: 10.1542/peds.2017-3034
83. Heinberg Joel LJ, Thompson K, Matzon JL. Body image dissatisfaction as a motivator for healthy lifestyle change: is some distress beneficial? In: Striegel-Moore RH, Smolak L, editors. *Eating Disorders: Innovative Directions in Research and Practice*. Washington, DC: American Psychological Association (2001), 215–232. doi: 10.1037/10403-011
84. Haines J, Neumark-Sztainer D. Prevention of obesity and eating disorders: a consideration of shared risk factors. *Health Educ Res*. (2006) 21:770–82. doi: 10.1093/her/cyl094
85. Cebolla A, Barrada JR, van Strien T, Oliver E, Baños R. Validation of the Dutch Eating Behavior Questionnaire (DEBQ) in a sample of Spanish women. *Appetite*. (2014) 73:58–64. doi: 10.1016/j.appet.2013.10.014

86. Daniels SR, Hassink SG, Committee On Nutrition. The role of the pediatrician in primary prevention of obesity. *Pediatrics.* (2015) 136:e275–92. doi: 10.1542/peds.2015-1558
87. Dietz WH, Belay B, Bradley D, Kahan S, Muth ND, Sanchez E, et al. *A Model Framework that Integrates Community and Clinical Systems for the Prevention and Management of Obesity and Other Chronic Diseases.* Washington, DC: National Academy of Medicine (2017).
88. Armstrong-Heimsoth A, Johnson M, McCulley A, Basinger M, Maki K. Davison A consumer health literacy program empowering parents to find quality health information online. *J Consum Health Internet*. (2017) 21:111–24. doi: 10.1080/15398285.2017.1308191
89. Ash T, Agaronov A, Young T, Aftosmes-Tobio A, Davison KK. Family-based childhood obesity prevention interventions: a systematic review and quantitative content analysis. *Int J Behav Nutr Phys Act*. (2017) 14:113. doi: 10.1186/s12966-017-0571-2
90. Gentile N, Kaufman TK, Maxson J, Klein DM, Merten S, Price M, et al The effectiveness of a family-centered childhood obesity intervention at the YMCA: a pilot study. *J Community Med Health Educ.* (2018) 8:591. doi: 10.4172/2161-0711.1000591
91. Brotman LM, Dawson-McClure S, Huang KY, Theise R, Kamboukos D, Wang J, et al. Early childhood family intervention and long-term obesity prevention among high-risk minority youth. *Pediatrics.* (2012) 129:e621–8. doi: 10.1542/peds.2011-1568

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

REVIEW
published: 23 January 2019
doi: 10.3389/fped.2018.00431

Check for updates

Pediatric Obesity Algorithm: A Practical Approach to Obesity Diagnosis and Management

Suzanne E. Cuda[1]* *and Marisa Censani*[2]

[1] *Department of Pediatrics, Baylor College of Medicine, Children's Hospital of San Antonio, San Antonio, TX, United States,*
[2] *Division of Pediatric Endocrinology, Department of Pediatrics, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, United States*

Childhood obesity is a growing global health problem. Despite the highest rates of childhood obesity in the United States and other developed countries over the last 30 years, there is still no clear treatment strategy. Practitioners often do not know where to turn to find guidance on managing the nearly one third of their population who present for medical care either with obesity that coexists with other medical problems or because of obesity. The Pediatric Obesity Algorithm is an evidence based roadmap for the diagnosis and management of children with obesity. In this article, we summarize topics from the Pediatric Obesity Algorithm pertaining to pediatric obesity diagnosis, evaluation, and management including assessment, differential diagnosis, review of systems, diagnostic work up, physical exam, age specific management, comorbidities, use of medications and surgery, and medication associated weight gain. Identifying and treating children with obesity as early as possible is important, as is identifying comorbid conditions. Earlier and more comprehensive management through resources such as the Pediatric Obesity Algorithm serve to help guide health care practitioners with a practical and evidence based approach to the diagnosis and management of children with obesity, and provide families with the tools needed for a healthy future.

Keywords: children, obesity, algorithm, adolescents, comorbidities

OPEN ACCESS

Edited by:
Angela K. Fitch,
Harvard Medical School,
United States

Reviewed by:
Kanakadurga Singer,
University of Michigan, United States
Marco Marigliano,
Integrated University Hospital Verona,
Italy

***Correspondence:**
Suzanne E. Cuda
Suzanne.cuda@bcm.edu

Specialty section:
This article was submitted to
Pediatric Endocrinology,
a section of the journal
Frontiers in Pediatrics

Received: *28 August 2018*
Accepted: *24 December 2018*
Published: *23 January 2019*

Citation:
Cuda SE and Censani M (2019)
Pediatric Obesity Algorithm: A
Practical Approach to Obesity
Diagnosis and Management.
Front. Pediatr. 6:431.
doi: 10.3389/fped.2018.00431

BACKGROUND

Childhood obesity is a growing global health problem. Despite a continual rise in the rate of childhood obesity in the United States and other developed countries over the last 30 years, there is still no clear treatment strategy. A great deal of the research effort into solving the problem of childhood obesity is directed toward prevention. There are few evidence based studies specifically addressing the treatment of childhood obesity, thus the management and treatment of the child with obesity is left to the practitioner to use clinical judgment and persuasion to modify the family's dietary and lifestyle habits (1–3).

Often, societal barriers pose roadblocks to early diagnosis and referral for treatment. Parents frequently do not recognize the problem until it is advanced and practitioners are neither adequately trained nor have the clinical support they need to provide the ongoing chronic care needed to manage a child with obesity. Pediatric weight management clinics are spread across the country leaving large swathes of areas where referral to these clinics is not reasonable. Bariatric surgery, while being done more frequently in adolescents, is still reserved for adolescents with severe obesity, and is best accomplished in a center with expertise.

Newer medications have come onto the market for the treatment of adults with obesity, but none of these newer medications are currently FDA approved for use in children with obesity. Endoscopic procedures are also in clinical trials, but adults are the target group. In the meantime, rates of severe obesity continue to increase, especially in minority and low income children (3).

Practitioners often do not know where to turn to find guidance on managing the nearly one third of their population who present for medical care either with obesity that coexists with other medical problems or because of obesity. The Pediatric Obesity Algorithm (4) is an evidence based roadmap for the diagnosis and management of children with obesity. These age specific recommendations are meant to be used by practicing clinicians managing children with obesity. The topics addressed range from assessment to the diagnosis and treatment approach of obesity comorbidities. The Pediatric Obesity Algorithm was created by a collaboration of clinicians from the Obesity Medicine Association who reviewed and summarized the literature and is intended for use by health care providers in clinical practice, research, and education. This manuscript is based on the initial version of the Pediatric Obesity Algorithm, sponsored by the Obesity Medical Association and launched in September 2016 (4).

INITIAL ASSESSMENT

Epigenetics is a term used to describe processes that result in heritable regulation of gene expression without a change in the base sequence of DNA sequence. Epigenetics is thought to play a large role in the precipitous rise in obesity over the past 30 years. Children are at increased risk for obesity if their parents have obesity: there is a 30% chance of obesity if one parent has obesity and a 90% chance if both parents have obesity. Obesity in childhood is associated with a maternal preconception BMI (body mass index) $\geq$30 kg/m^2, excessive gestational weight gain, and gestational diabetes mellitus (5–7). Infants who are small for gestational age due to tobacco abuse or insufficient maternal weight gain are also at risk for obesity and metabolic disease in childhood. Other exposures that can result in obesogenic epigenetic changes include but not are limited to: toxins, nutrition, medications, antibiotics, infection, and exogenous hormones (8–10).

Weight assessment of a child with obesity is accomplished by considering both the age of the child and the severity of the obesity. For infants up to the age of 2, BMI is not assessed. Instead, the infants' weight percentile is compared to length percentile. There are two options for the use of growth charts in infants up to the age of 2 years: Center for Disease Control (CDC) charts which are based on a cohort of mostly Caucasian American infants who were mostly bottle fed or WHO charts which are based on infants from multiple areas of the planet with diverse racial and ethnic backgrounds who were mostly breastfed. An infant whose weight for length percentile is increasing, or "jumping" percentile lines needs closer monitoring than one who is maintaining growth along the same percentile.

Body mass index charts are used for children between the ages of 2–20 years. These CDC charts were developed in 2000 and are color coded by BMI percentile:<5th percentile (red), 5th−85th percentile (green), 85th−95th percentile (yellow), and >95th percentile (red). The chart extends to a BMI of 35 kg/m^2. These charts were developed using five cross sectional nationally representative health surveys taken between the years of 1963–1994 (11). An additional BMI chart has been developed for children aged 2–20 years with severe obesity (12). On this chart, percentile lines are included for BMI measurements between 110 and 190% of the CDC 95th percentile. Both of these BMI charts display a "J" shaped curve with the BMI of young children decreasing normally between the ages of 2 and 6 years and then steadily increasing between the ages of 6–20 years. This decrease or dip and subsequent rise in the BMI curve is referred to as adiposity rebound. If a child's BMI either has no decrease or prematurely rises between the ages of 2 and 6 years, the child is at risk or has obesity. This phenomenon is called early adiposity rebound.

In June 2012 the American Medical Association declared obesity a disease. Children, like adults, suffer from the manifestations of obesity on most aspects of their physical and psychological health. Adiposopathy is a term used to describe endocrine and immune responses to increased adipose tissue while fat mass disease describes the physical response to increased adipose tissue (13, 14). A careful history that includes family history, prenatal, birth and postnatal care, followed by any medical complications in childhood and medications used both for the management of comorbid conditions and the management of obesity should be obtained.

In addition, psychological issues arise as a result of obesity and affect quality of life (**Figure 1**). The quality of life of children with obesity may be poor. They are at increased risk for isolation from peers, they are subject to bullying, they are at increased risk for anxiety and depression, and they are at increased risk for eating disorders, especially binge eating disorder, night eating disorder, and bulimia (15–17).

Social history includes not only a dietary recall, but also a history of breast or bottle feeding, the timing of introduction of complementary foods and parenting style. In addition, an assessment of the child's activity level including access to safe areas to exercise and support for a high level of activity is important. Finally, the clinician needs to assess sedentary time and non-academic screen time.

The differential diagnosis of children with obesity starts with an assessment of linear growth. Linear growth proceeds in children until fusion of growth plates. Children with obesity due to nutritional, also referred to as endogenous, obesity have consistent or accelerated growth. These children are at risk for early development of secondary sexual characteristics and may have bone age development that exceeds their chronological age by more than 2 standard deviations. In contrast, a child with obesity who has an underlying endocrinopathy will typically have decreased linear growth. It is in the children with a deceleration in growth

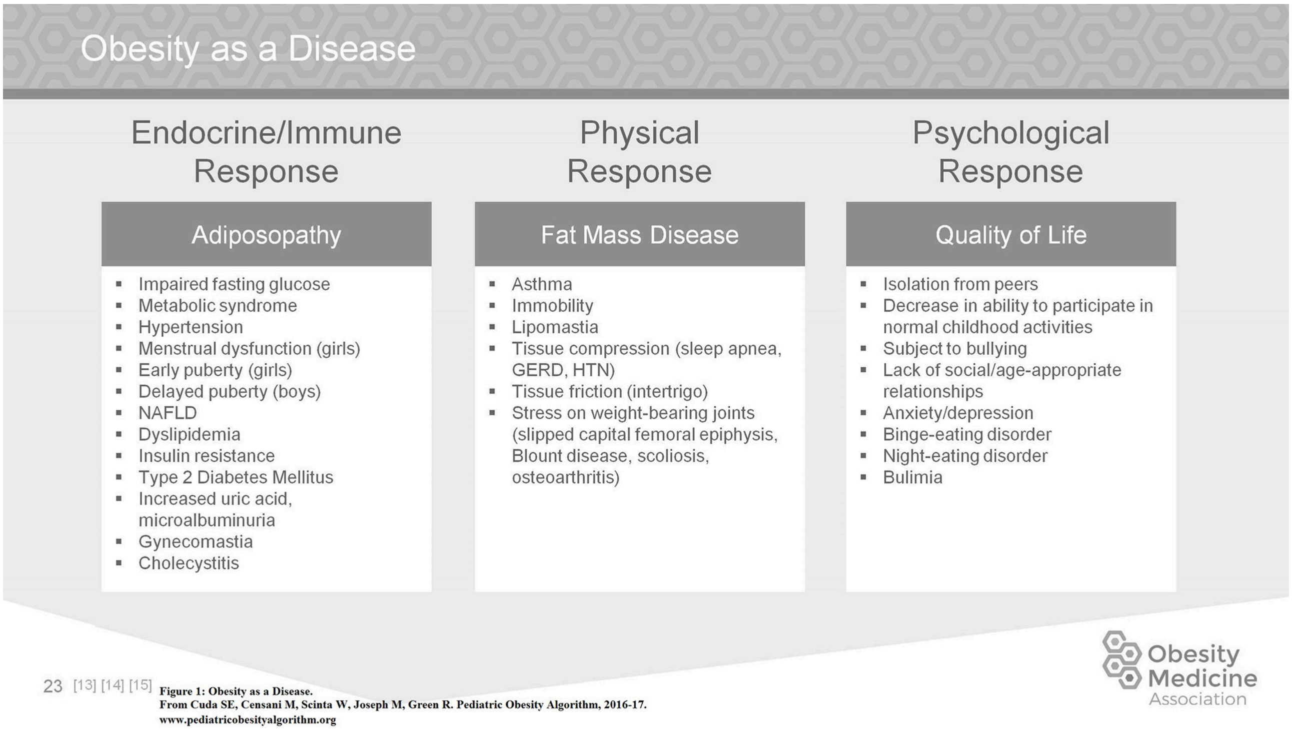

FIGURE 1 | Obesity as a disease.

that testing for thyroid hormones is indicated. If there is clinical suspicion of Cushing's syndrome, a dexamethasone suppression test or 24 h urinary free cortisol level is indicated (1, 2, 14).

Genetic causes of obesity should be considered in children with severe obesity before the age of 5 years. These young children may present with developmental delay, short stature, dysmorphic facies, or hyperphagia. Screening involves DNA methylation studies, exome sequencing and karyotyping looking for known syndromes: Prader Willi, Bardet-Biedl, Fragile X, Algrights Hereditary Osteodystrophy, Alstrom, Congenital Leptin deficiency, POMC deficiency, MC4R deficiency, and Cohen syndrome. However, many other genetic causes of obesity not associated with known syndromes no doubt contribute as well (18–20).

Children with special needs are at increased risk of developing obesity (21). Some of these children are at increased risk due to associated difficulties with movement or coordination. Developmentally delayed or special needs children can present with decreased or normal growth. Presentation is highly variable and the practitioner should take a careful family history and consider a referral to a geneticist.

Clinical evaluation of the child with obesity includes a focused review of systems. **Figure 2** lists the more commonly presenting signs or symptoms and their related comorbidities (22).

The diagnostic work up of a child with obesity is driven by a careful history of prenatal factors, family history, feeding history, sleep duration and issues, exercise, family and cultural expectations, screen time, location and timing of meals, bullying or social isolation, motivation and ability to make modifications of the family, and finally financial constraints. Appropriate labs and studies are considered according to the age, BMI percentile, and presence of risk factors as summarized in **Figure 3** (1–3, 23, 24).

Children with obesity presenting with deceleration of growth, symptoms of hypo or hyper thyroidism or other endocrinopathies, symptoms of diabetes, sustained hypertension, hirsutism, a family history of early cardiovascular disease, snoring, and/or daytime sleepiness will need additional workup. In addition, there are many other complications of obesity that require further investigation, some of which are discussed in the section on comorbidities.

APPROACH TO PHYSICAL EXAM

The physical exam is both important and challenging in children with obesity. While increased adiposity is usually apparent, children may go to considerable effort to conceal problems, for example removal of excess hair. Children with obesity commonly present wearing more clothing than called for by climatic conditions and may be wearing spandex or other restraining garments under their loose outerwear. The practitioner should take particular care to preserve the child or adolescent with obesity's need to cover up while still examining the patient. Instead of asking the child or adolescent to fully unclothe, the practitioner can examine the patient sequentially, taking care to

Focused Review of Systems

Symptoms	Related Co-morbidity
Nervousness, school avoidance, social inhibitions	Depression, anxiety, bullying
Fatigue, muscle aches	Vitamin D deficiency
Polyuria, polydipsia, fatigue, nocturia	Type 2 Diabetes (T2DM)
Headaches, facial numbness	Pseudotumor cerebri
Skin pigmenting, skin tags	Insulin resistance (IR)
Daytime somnolence, loud snoring, witnessed apnea	Obstructive sleep apnea (OSA)
Abdominal pain, indigestion	Gastroesophageal reflux disease (GERD), gall bladder disease, constipation
Hip or knee pain	Slipped capital femoral epiphysis (SCFE), early osteoarthritis
In-toeing, leg bowing, mild knee pain	Blount's disease
Hirsutism, acne, irregular menses	Polycystic Ovarian Syndrome (PCOS)

Obesity Medicine Association

27 [103] Figure 2: Focused Review of Systems.
From Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric Obesity Algorithm, 2016-17.
www.pediatricobesityalgorithm.org

FIGURE 2 | Focused review of systems.

Diagnostic Work-up: Labs and Studies

Infancy (0-24 months)	Toddler (Ages 2-4 years)	Early Childhood (Ages 5-9 years)	Puberty (Ages 10-14 years)	Adolescent (Ages 15-18 years)
Weight > Length	BMI $\geq 95^{th}$ percentile or $\geq 85^{th}$ percentile with two or more risk factors (24-48 months)	BMI $\geq 95^{th}$ percentile or $\geq 85^{th}$ percentile with two or more risk factors	BMI $\geq 95^{th}$ percentile or $\geq 85^{th}$ percentile with two or more risk factors	BMI $\geq 95^{th}$ percentile or $\geq 85^{th}$ percentile with two or more risk factors
	▪ Fasting blood glucose and/or HgA1c ▪ Fasting lipid panel/Non-fasting if fasting not feasible ▪ ALT, AST, consider GGT ▪ Consider 25 OH Vitamin D			
		▪ Consider sleep study ▪ Consider liver ultrasound ▪ Consider uric acid ▪ Consider fasting serum insulin		
			▪ Consider urine microalbumin/creatinine ratio ▪ Consider C-peptide, hs-CRP	

Obesity Medicine Association

31 [20] [21] Figure 3: Diagnostic work up: Labs and Studies.
From Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric Obesity Algorithm, 2016-17.
www.pediatricobesityalgorithm.org

FIGURE 3 | Diagnostic work up: labs and studies.

reclothe the body parts that are exposed before moving on to the next body part. A thorough discussion of all of the physical findings that can be associated with obesity does not follow, however we highlight a few areas that should be assessed in every child.

Acanthosis nigricans is a cutaneous marker associated with hyperinsulinemia which is frequently perceived by the parents or the child as being due to dirt or eczema, not melanin. An explanation of the cause can be reassuring to the child and the parent and provide opportunity for education of the physiology of glucose metabolism and underlying process of insulin resistance.

Pubertal or tanner staging helps the clinician determine growth potential as well as address the issue of premature thelarche in females or gynecomastia in males. These findings are exacerbated by excess adiposity. Pubertal status also informs laboratory results as some normal values change as puberty progresses.

The clinician should be aware of the skeletal problems that occur in children with obesity. Young children with the bowed tibias of Blount's disease are usually ambulatory and may be "early walkers" and unaware of any problem. A radiologic diagnosis is necessary. Slipped capital femoral epiphysis can present as knee or hip pain or without pain resulting in the diagnosis being missed. Prompt assessment and referral to an orthopedic surgeon if the diagnosis is made is necessary. Scoliosis is harder to detect due to adiposity despite occurring in children with obesity at as great or greater a frequency than in normal weight children (25–27). The practitioner should have a high index of suspicion for physical abnormalities and should carefully examine the child. Children with obesity are frequently poorly evaluated by the medical community until symptoms become severe.

A careful examination of the entire body for intertrigo, especially if this complaint is inhibiting the child's activity level should be performed. A sensitive examination of the status of excess hair in females should occur. Other findings from the review of systems may determine the examination: for example a history of snoring should prompt a thorough exam of the tonsillar pillars as well as neck circumference.

MANAGEMENT OF OBESITY

In considering how to modify the food intake of a child with obesity, there is no universally accepted approach. An understanding of appropriate intake for a normal weight child is necessary as a starting point. For easy reference, the algorithm breaks down intake guidelines for age groups between infancy and adulthood (**Figure 4**).

Managing a child with obesity is age dependent. In the first 6 months of life, exclusive breast feeding is the nutrition of choice. Complementary foods should ideally be delayed until 6 months of age. Increased BMI in childhood and adolescence is associated with early introduction of complementary foods. Infants with obesity should not be given any sugar sweetened beverages, nor any fast food or desserts. Infants already struggling to maintain their weight should have age appropriate amounts of formula, and should not be given juice in their bottles. Infants should not be watching TV or any screen of any kind for the first two years of life. Normal infants may need to sleep up to 18 h a day, and should sleep at least 12 h a day. Infants should be allowed to be as active as possible, either on the floor or in a playpen and the parents should be encouraged to have as much direct interaction with them as possible (**Figure 5**).

A toddler (age 2–4 years) with obesity should have three meals plus 1–2 snacks every day. They should not be offered sugar sweetened beverages, nor any fast food. Portion sizes should be age appropriate and they should be praised for trying new foods. Parents should model the eating behavior they want their child to have. Toddlers should have a routine sleep pattern. Snoring in this age group is frequently associated with tonsillar hypertrophy. If the tonsils cause significant obstruction, removal may be indicated.

Up to the age of 2 years, no screen time is recommended. Between the ages of 2 and 4, screen time should be kept to a minimum. Obesity is directly correlated with screen time in this age group. The family should adopt good meal hygiene to include meals at the table, no media while eating, no food rewards, no over controlling behaviors toward consumption of meals, and family based meals.

Obesogenic medications may be a factor for the young child with obesity (aged 5–9 years). The use of second generation antipsychotics should be minimized and asthma should be managed with controller medications instead of systemic steroids if clinically possible. Children at this age may also develop hypertension as a complication of their obesity, however etiologies other than obesity must be considered.

Parents are strong role models for children at this age and involvement of the family in the care of the child with obesity is highly recommended. Total non-academic screen time should be kept to a minimum. Replacement of screen time with moderately vigorous physical activity is associated with a decrease in obesity. Sleep is still very important with children in this age group needing between 11 and 14 h of sleep, preferably all at once and not achieved by napping during the day due to deficits at night.

Children with obesity in the 5–9 age group should be consuming 3 meals per day plus 1–2 nutritious snacks. Food groups should include 3 servings of protein per day, 1–2 servings of dairy per day, and 4–5 servings of non-starchy vegetables per day. They should not be consuming any sugar sweetened beverages, nor any fast food. Portion sizes should be age appropriate and children should be praised for trying new foods (**Figure 6**).

Children 5–9 years of age start to be involved in organized sports as well as continuing to need active play. Activity should be daily, as vigorous as possible, but fun. Sixty minutes or more per day of moderate to vigorous physical activity is recommended. Children ages 5–9 with obesity should be encouraged to exercise as often and as vigorously as normal weight children. Limitations due to adiposity are rare in this age group.

As children with obesity go through puberty and adolescence, management evolves. Many of the same recommendations as

General Intake Guidelines (Normal Weight): 5-18 Years

	5-9 years	10-14 years	15-18 years
Milk and Milk Products	2.5-3 cup/day	3 cups/day	3 cups/day
Serving: 1 cup of milk or cheese, 1.5 oz of natural cheese, 1/3 cup shredded cheese; encourage low-fat dairy sources			
Meat and Other Protein Foods	4-5 oz/day	5 oz/day	5-6 oz/day
Serving: (1 oz equivalent) = 1 oz beef, poultry, fish, ¼ cup cooked beans, 1 egg, 1 tbsp peanut butter, ½ oz of nuts			
Breads, Cereal, and Starches	5-6 oz/day	5-6 oz/day	6-7 oz/day
Fruits	1.5 cups/day	1.5 cups/day	1.5-2 cups
Serving: 1 cup of fruit or ½ cup dried fruit			
Vegetables (non-starchy vegetables to include sources of vitamin C and A: broccoli, bell pepper, tomatoes, spinach, green beans, squash)	1.5-2 cups/day	2-3 cups/day	3+ cups/day
Serving: (1 cup equivalent) = 1 cup of raw or cooked vegetables; 2 cups of raw leafy green greens			
Fats and Oil	4-5 tsp/day	5 tsp/day	5-6 tsp//day
Miscellaneous (desserts, sweets, soft drinks, candy, jams, jelly)	None	None	None

Obesity Medicine Association

40 [26] [27] **Figure 4: General Intake Guidelines (Normal Weight): 5-18 years.**
From Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric Obesity Algorithm, 2016-17.
www.pediatricobesityalgorithm.org

FIGURE 4 | General intake guidelines (normal weight): 5–18 years.

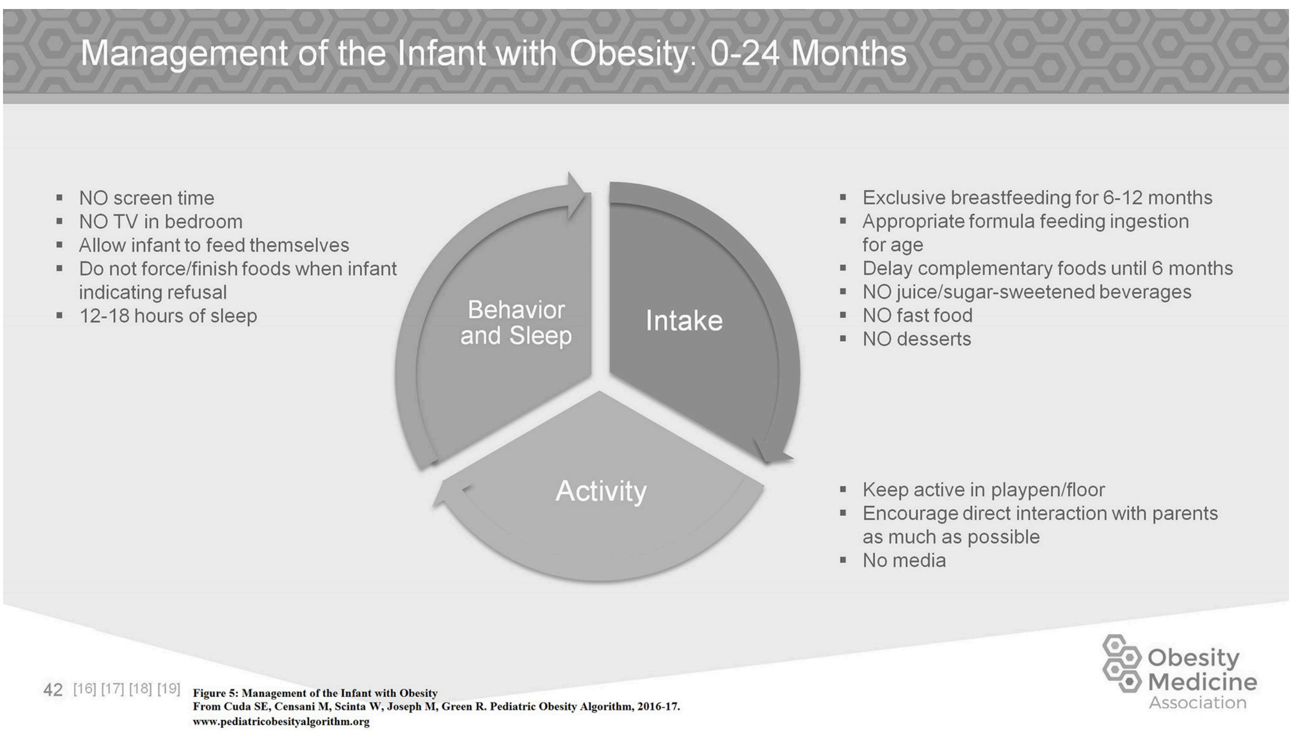

FIGURE 5 | Management of the infant with obesity.

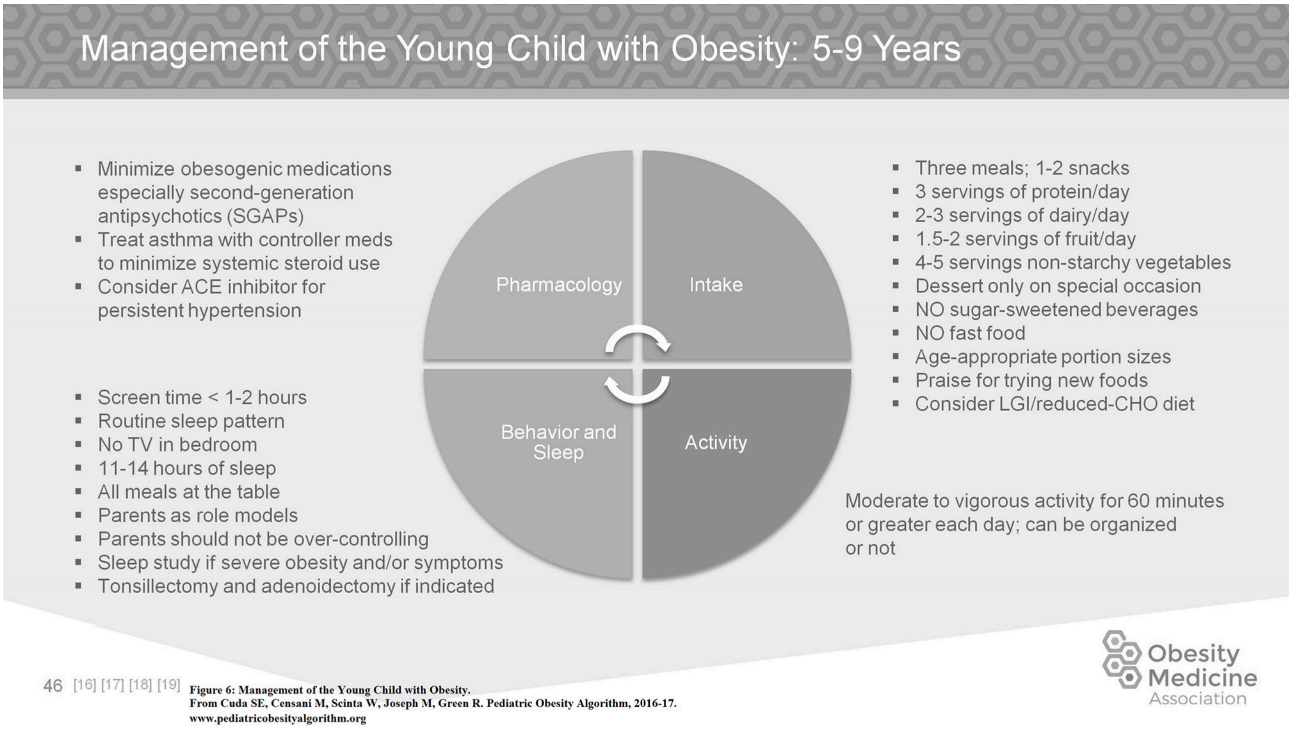

FIGURE 6 | Management of the young child with obesity.

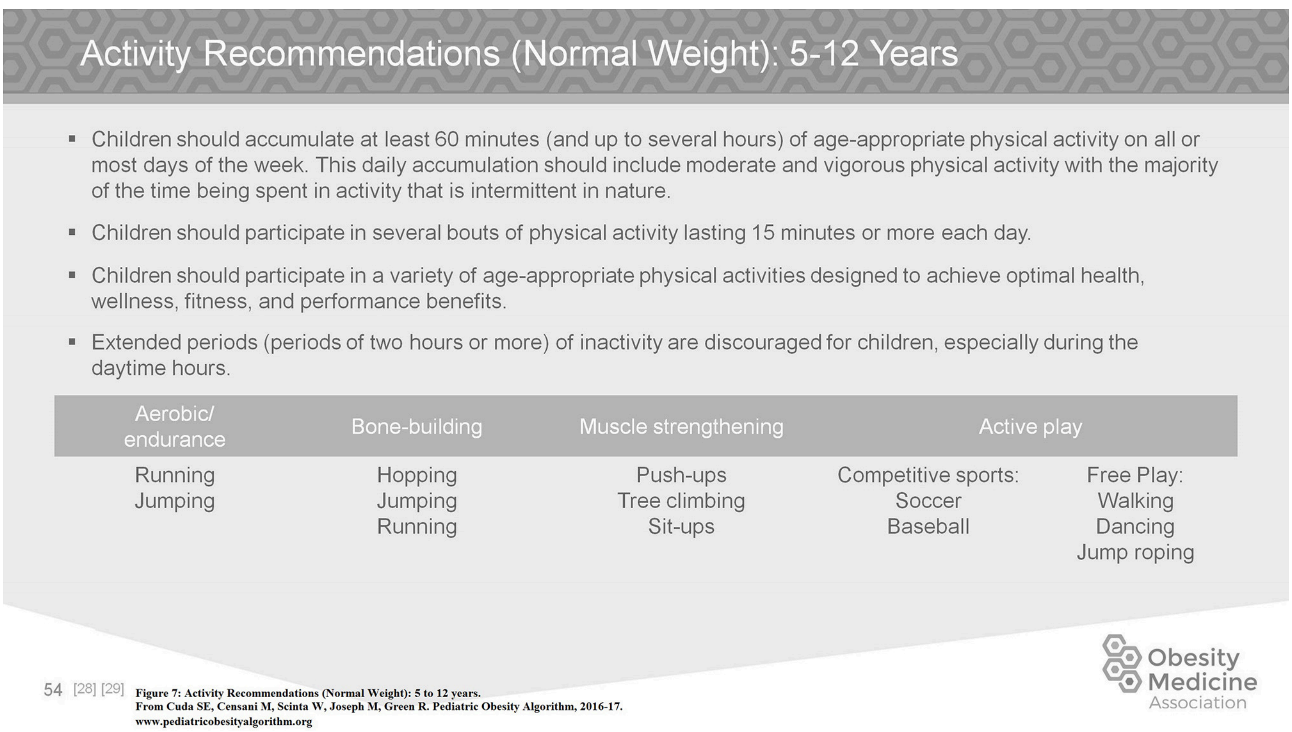

FIGURE 7 | Activity recommendations (normal weight): 5 to 12 years.

made in younger children are still valid, although must be adapted to the older child. In particular, meals should continue to be consumed at 3 a day and can include 1–2 snacks. Older children and adolescents with obesity frequently skip meals leading to overindulgence at the next meal or eating the majority of their intake starting in the afternoons and into evenings. Techniques for dealing with the almost constant exposure to non-nutritious foods should be discussed with the older child and adolescent since they are increasingly consuming food outside of the family home and school.

Older children and adolescents with obesity are able to track their exercise and meal intake using newer technologies which allow them to share their progress and compare themselves to their peer groups. In the age of the smart phone, children in this age group are rarely without their devices. These devices function as convenient activity trackers (28). After puberty, adolescents become less active in general. However, for the adolescent with obesity it is important to develop a regular exercise routine of 60–90 min of moderate to vigorous activity per day (**Figure 7**). This increased activity will preserve or increase cardiorespiratory fitness which mediates the development of Type II diabetes mellitus and/or the metabolic syndrome (29–31). A gradual increase in activity in those who are starting from relative inactivity is suggested.

Duration and quality of sleep should be addressed. Adolescents in particular may reverse their sleep wake cycles by staying up late at night, usually on social media or video games, and then sleep until midday or later. Correction of the sleep wake cycle is necessary to allow for a normal pattern of eating, especially eating with other family members. Electronic devices should be removed from bedrooms to allow uninterrupted sleep. Inadequate sleep contributes to hunger. Adolescents frequently need up to 10 h or more of sleep per night (32, 33).

OBESITY COMORBIDITIES

Comorbidity management complicates the treatment of children with obesity. Although children with obesity can present with all the same disease processes seen in normal weight children, certain disease processes occur secondary to obesity. The significance of these disease processes cannot be understated as they progress through adulthood and are associated with premature morbidity.

Hypertension occurs with an increased incidence in children with obesity as compared to normal weight children. The diagnosis of hypertension must be based on three separate measurements at least 1 week apart. Guidelines for diagnosis of hypertension in children now differ between children less than or greater than the age of 13. After the age of 13, a systolic blood pressure of 120–129 mm Hg and a diastolic pressure <80 mm Hg is considered elevated, while pressure of 130–139 mm Hg over 80–89 mm Hg are Stage I hypertension, and >140/90 mm Hg is Stage II hypertension. For children <13, diagnosis should be made by referring to normative date based on age, sex, and height. A diagnosis of stage II hypertension in a child or adolescent with obesity should include as assessment of end organ damage. Diagnostic studies may include a renal Doppler ultrasound, ECHO, serum uric acid, urine protein, and BUN/creatinine levels. Treatment should include a trial diet and lifestyle modifications prior to use of medication. A low sodium (<1,500 mg/day) or DASH (Dietary Approaches to Stop Hypertension) diet is usually recommended. Pharmacotherapy is used if the blood pressure is persistently elevated over 3 separate measurements and does not respond to lifestyle intervention. The primary treatment for obesity associated hypertension is weight loss (34–37).

Dyslipidemia is commonly found in children with obesity. Typically, the dyslipidemia of obesity is a high triglyceride level and low high density lipoprotein (HDL) level. This pattern usually quickly responds to dietary modification. The clinician should be aware that children with obesity can present with any dyslipidemia that occurs in normal weight children. If the pattern of dyslipidemia is different than an elevated triglyceride level and/or low HDL level, work up and treatment is detailed in the National Heart, Lung, and Blood Institute guidelines. On initial presentation, a child with obesity who consumes a large amount of sugar sweetened beverages can present with a triglyceride level between 150 and 400 mg/dl. Removing the refined carbohydrates from the child's diet will usually have a profound effect on the triglyceride level. If there is no response, further evaluation is needed (38, 39).

Sleep Disorders in children with obesity can have varied presentations including apnea associated with snoring or disrupted sleeping, daytime sleepiness, hyperactivity, depression, audible pauses in breathing, new onset nocturnal enuresis, irritability, and learning difficulties. The clinician's index of suspicion must be high as sleep disorders can also occur in the absence of symptoms. Referral for sleep studies or possible removal of tonsils and/or adenoids is based on clinical evaluation (40–42).

Impairment in glucose metabolism is important to screen for in children with obesity. Impaired fasting glucose is defined as a fasting plasma glucose of ≥100 mg/dl but <126 mg/dl on repeat measurements. Impaired glucose tolerance is defined as a 2 h plasma glucose on oral glucose tolerance test (OGTT) of ≥140 mg/dl but <200 mg/dl. Type 2 diabetes mellitus is the endpoint of metabolic decompensation that may evolve over months to years. In insulin resistance, the body produces insulin but muscle, fat, and liver do not respond properly to insulin and thus cannot easily absorb glucose from the bloodstream, with progression from insulin resistance to prediabetes with impaired glucose tolerance and impaired fasting glucose over time (39). Clinical findings of insulin resistance on physical exam include acanthosis nigricans, skin tags, and hyperpigmentation in axillae, umbilicus, groin, and popliteal fossae. Insulin resistance is also associated with polycystic ovarian syndrome. Treatment is weight loss through aggressive diet and lifestyle intervention including modified carbohydrate diets and low glycemic index food choices (43–47). Metformin is an insulin sensitizer that is FDA approved in children ≥10 years of age for the treatment of type 2 diabetes mellitus. Metformin decreases hepatic glucose production, decreases glucose intestinal absorption, and improves insulin sensitivity through increasing peripheral glucose use and uptake (48, 49).

Excessive weight gain can be associated with menstrual irregularity. Irregular menses is defined in adolescence as <21

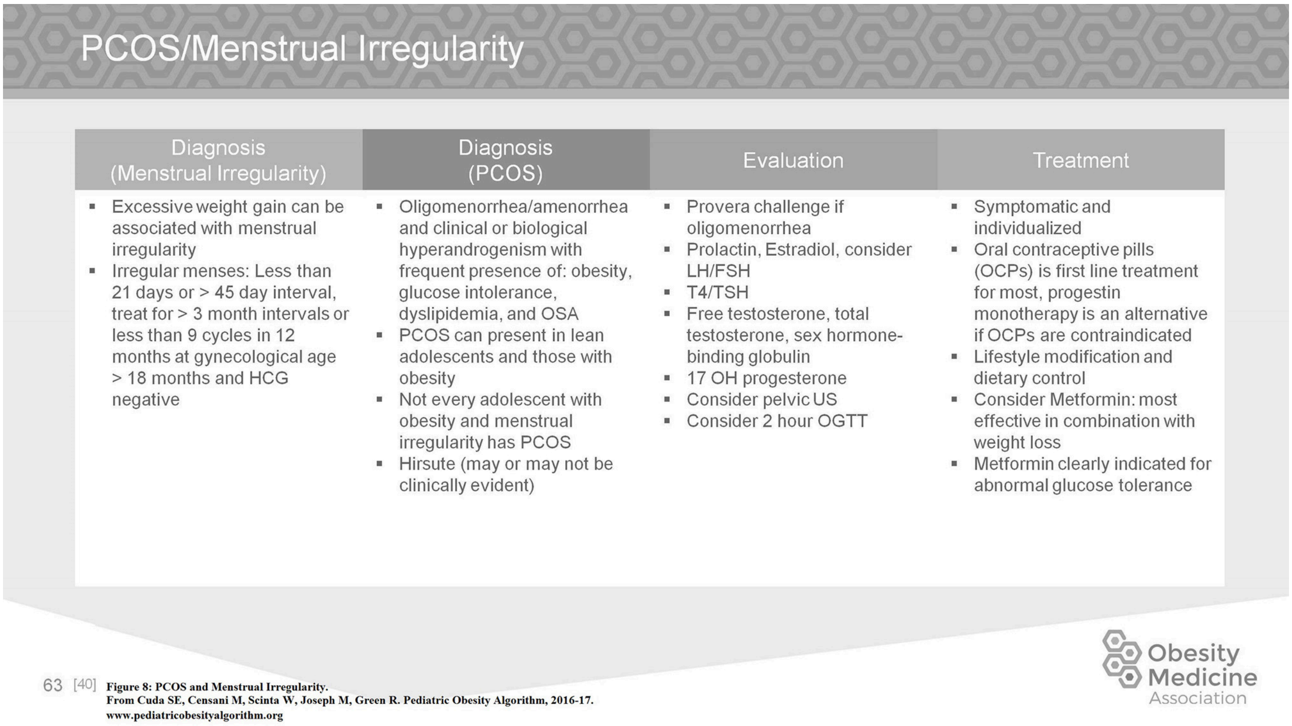

FIGURE 8 | PCOS and menstrual irregularity.

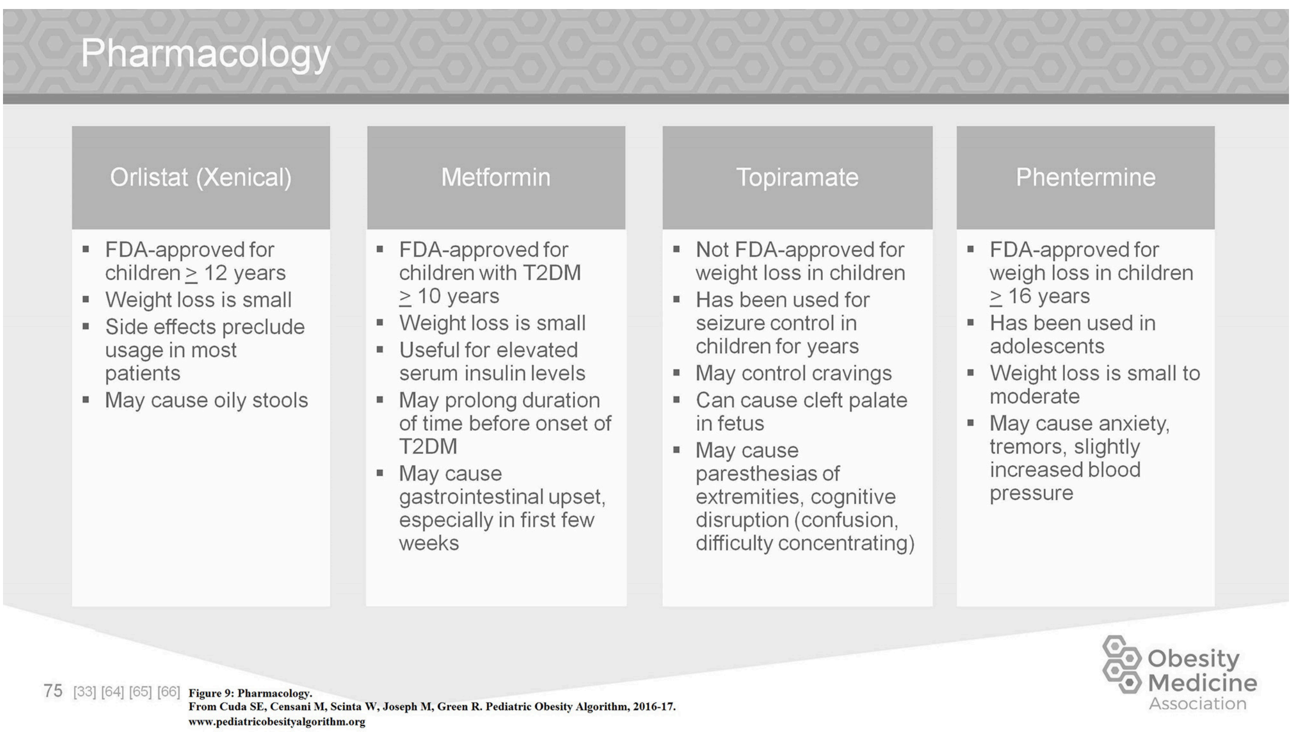

FIGURE 9 | Pharmacology.

Review of Medications: ADHD, Anti-seizure, Migraine, Diabetes and Other Medications

	Significant Weight Gain		Small to Neutral Weight Gain		Weight Loss (neutral to mild)
ADHD			Guanfacine		Atomoxetine Lisdexamfetamine Amphetamine Methylphenidate
Anti-Seizure	Valproate Vigabatrin	Pregabalin Gabapentin	Carbamazepine Oxocarbazepine	Lamotrigine Levetoracetam Phenytoin	Topiramate Zonisamide Felbamate
Migraine	Amitriptyline Divalproex Flunarizine	Gabapentin Metoprolol Propranolol	Timolol Levetiracetam		Zonisamide Topiramate
Diabetic Medications	Insulin and analogs				GLP-1 Receptor Agonists Metformin
Other Medications	Glucocorticoids Gleevac Depo Provera		Benzodiazepines Statins Antihistamines (Cyproheptadine) Carvedilol Oral Contraceptive Pills		

Obesity Medicine Association

77 [65] [67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87]

Figure 10: Medication Effects on Weight Status.
From Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric Obesity Algorithm, 2016-17. www.pediatricobesityalgorithm.org

FIGURE 10 | Medication effects on weight status.

Review of Medications: Psychiatric Medications

	Significant Weight Gain		Small to Neutral Weight Gain	Weight Loss
Antipsychotics	Clozapine Olanzapine Chlorpromazine Quetiapine Risperidone		Aripiprazole Haloperidol Ziprasidone	
Special considerations: "Youth may be particularly sensitive to weight gain, especially with olanzapine, as well as extrapyramidal side effects and metabolic changes." Many of the medications listed here have only been well-studied in adults.				
Antidepressants	Paroxetine* Amitriptyline Olanzapine Citalopram Nortriptyline Doxepin	Lithium Desipramine Imipramine Duloxetine Escitalopram	Venlafaxine Fluvoxamine Sertraline Trazodone Fluoxetine	Bupropion*
Mood Stabilizers	Valproate Lithium Gabapentin			Topiramate
Anxiolytics			Lorazepam Diazepam Oxazepam	

Obesity Medicine Association

78 [65] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [*Black box warning]

Figure 11: Review of Medications: Psychiatric Medications
From Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric Obesity Algorithm, 2016-17. www.pediatricobesityalgorithm.org

FIGURE 11 | Review of medications: psychiatric medications.

days or >45 day intervals or <9 cycles in 12 months at gynecological age >18 months, and cycles <3 days or >7 days duration. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting young women seen with oligomenorrhea or amenorrhea and clinical or biological hyperandrogenism with frequent presence of obesity, glucose intolerance, dyslipidemia, and obstructive sleep apnea. PCOS can present in lean adolescents as well as adolescents with obesity. In the evaluation of irregular menstrual cycles, hormonal evaluation is indicated including free testosterone, total testosterone, early morning 17 OH progesterone to rule out late onset congenital adrenal hyperplasia, DHEA-S, sex hormone binding globulin, thyroid function tests, and prolactin as well as consideration for pelvic ultrasound and a 2 h OGTT. Treatment is symptomatic and individualized. Oral contraceptive pills (OCPs) are first line treatment for most adolescent patients to help to regulate menstrual cycles and to lower the level of testosterone to improve acne and hirsutism. Progestin monotherapy is an alternative if OCPs are contraindicated. Treatment includes lifestyle modification and dietary control with studies finding metformin therapy when indicated to be effective in combination with weight loss (50, 51). Additional treatments such as antiandrogen therapy may be considered but are outside the scope of the Algorithm. An example of the approach to diagnosis, evaluation, and management of obesity comorbidities in the Pediatric Obesity Algorithm is found in **Figure 8** pertaining to PCOS.

Vitamin D is a fat soluble vitamin essential for skeletal health in growing children. It plays an important role for bone health through the absorption of calcium from small intestine, and is available in diet and through synthesis from sunlight. Vitamin D deficiency has been defined by the Institute of Medicine and Endocrine Society clinical practice guidelines as a serum 25-hydroxyvitamin D [25(OH)D] <20 ng/mL. Current recommendations for children aged 1–18 years include treatment with 2,000 IU daily of vitamin D2 or vitamin D3 for at least 6 weeks or 50,000 IU of vitamin D2 or D3 once a week for at least 6 weeks to achieve a blood level of 25(OH)D above the deficient range, followed by maintenance therapy of 600–1,000 IU daily. There should be special considerations for at risk patient populations including children with obesity, malabsorptive syndromes, or on medications affecting vitamin D metabolism such as anticonvulsants, glucocorticoids, antifungals, and antiretrovirals. Lower levels of vitamin D in obesity have been linked to decreased sun exposure and reduced dietary intake, in addition to decreased vitamin D bioavailability secondary to storage of fat soluble vitamin D in adipose tissue. These children may require 2 to 3 times the dose of vitamin D to achieve the same serum 25(OH)D levels as children without these conditions (52–56).

MEDICATIONS AND SURGICAL APPROACH

Bariatric surgery is reserved as treatment for severe obesity in adolescents. The number of surgeries performed is increasing each year. Surgical options include gastric sleeve resection, Roux-en-y gastric bypass, and laparoscopic adjustable gastric banding under the treatment of an experienced surgical center. Current adolescent bariatric recommendations include BMI >35 kg/m2 with moderate to severe comorbidities or BMI >40 kg/m2 and skeletal and sexual maturity (generally age 14 for girls and 15 for boys). Participation in a weight loss program with a multidisciplinary team involving pediatric surgery, nutrition, psychology, and pediatric specialists is recommended. Females are counseled on increased fertility and all adolescents give informed consent. Significant psychiatric disease is considered an exclusion criteria. There are limited data outcomes; however, one 3 year outcome study found mean percent weight loss of 27%, normalized blood pressure in 74%, normalized lipid levels in 66%, and over 50% of patients with T2DM in remission (57–61).

The use of weight loss medications in children with obesity is limited. Although there are several new medications on the market for adults, none have been FDA approved for children. Of the approved medications, orlistat can produce a small amount of weight loss but is associated with oily stools, a side effect not tolerated by many children. Topiramate is used in children as an antiepileptic medication but is not FDA approved in children for weight loss. Although the mechanism is unclear, it can help control cravings. However, topiramate must be used with caution due to side effects of paresthesias of the extremities, and cognitive disruption, especially at higher doses. In addition, it can cause cleft palate in the fetus, making it more complicated to use in an adolescent female. Phentermine is approved in children >16 years of age for weight loss. The associated weight loss is small to moderate (62–68). Phentermine may cause anxiety, tremors, and slightly increased blood pressure (**Figure 9**).

Medication associated weight gain is a significant management issue. The use of second generation antipsychotics, most of which are associated with weight gain, has increased markedly over the past decade. Many other commonly used medications in children include but are not limited to antidepressants, anxiolytics, mood stabilizers, antiseizure medications, migraine medications, antihypertensives, diabetic medications, glucocorticoids, and progestins. On assessing a child with obesity on medications, the clinician must first work within the pathology of the underlying problem. If possible, a substitution for a less obesogenic medication may aid in controlling weight gain. Metformin is frequently used to offset weight gain secondary to psychiatric medication. Controversy concerning the efficacy of the use of Metformin for this purpose exists (69, 70). **Figures 10**, **11** summarize commonly used medications for children and their effects on weight.

CONCLUSION

Obesity is a chronic disease which when originating in childhood can lead to medical and psychological complications and premature comorbidity and mortality. An increasing amount of children with obesity presenting for treatment have BMIs well above the 95th percentile and the increased amount of children with severe obesity concerns most clinicians. Identifying and classifying these children as early as possible is important, as is identifying comorbid conditions. Frequently the management of a child with obesity is not just to decrease their BMI but to minimize their disease state and change their development of further complications. A slowing of weight gain or lack of continued acceleration of weight gain can delay the onset of T2DM and early cardiovascular disease. In fact, addressing comorbid conditions such as obstructive sleep apnea, behavioral disorders, polycystic ovarian syndrome may be a necessary precursor to successful weight management. Clearly more needs to be done in our attempt to stop and eventually reverse this epidemic. Medical management of children with obesity is conservative based not only on the lack of evidence based studies but also on societal mores and cultural sensitivities. However, the epidemic of childhood obesity is permeating most other medical problems and it is increasingly clear that our current approach to managing obesity in children is not aggressive enough. Earlier and more comprehensive management through resources such as the Pediatric Obesity Algorithm serve to help guide health care practitioners with an evidence based roadmap for the diagnosis and management of children with obesity, and provide families with the tools needed for a healthy future.

AUTHOR CONTRIBUTIONS

SC and MC contributed to the research, writing and editing of the manuscript, approved the final version, and agreed to be accountable for the content of this work.

ACKNOWLEDGMENTS

We would like to extend our gratitude to the Pediatric Obesity Algorithm co-authors: Roger Green MD, FAAP, Madeline Joseph MD, FACEP, FAAP, Wendy Scinta MD, MS, in addition to the executive board and support staff of the Obesity Medicine Association without whose assistance the algorithm could not have been produced.

REFERENCES

1. Barlow SE. Expert Committee Recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: a summary report. *Pediatrics* (2007) 120(Suppl. 4):S164–92. doi: 10.1542/peds.2007-2329C
2. Krebs NF, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. *Pediatrics* (2007) 120(Suppl. 4):S193–228. doi: 10.1542/peds.2007-2329D
3. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity—assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* (2017) 102:709–57. doi: 10.1210/jc.2017-00561
4. Cuda SE, Censani M, Joseph M, Green R, Scinta W. Pediatric Obesity Algorithm. (2016-17). Available online at: www.Pediatricobesityalgorithm.org
5. Skelton JA, Cook SR, Auinger P, Klein JD, Barlow SE. Prevalence and trends of severe obesity among US children and adolescents. *Acad Pediatr.* (2009) 9:322–9. doi: 10.1016/j.acap.2009.04.005
6. Shearer GE, Whaley SE, Miller SH, House BT, Held T, Davis JN. Association of gestational diabetes and breast feeding on obesity prevalence in predominately Hispanic low income youth. *Pediatr Obes.* (2015) 10:165–71. doi: 10.1111/ijpo.247
7. Dugas C, Perron J, Kearney M, Mercier R, Tchernof A, Marc I, et al. Postnatal prevention of childhood obesity in offspring prenatally exposed to gestational diabetes mellitus: where are we now? *Obes Facts* (2017) 10:396–406. doi: 10.1159/000477407
8. Pettersen-Dahl A, Marzakanova G, Sandvik L, Laine K. Maternal body mass index as a predictor for delivery method. *Acta Obstet Gynecol Scand.* (2018) 97:212–8. doi: 10.1111/aogs.13265
9. Principi N, Esposita S. Antibiotic administration and the development of obesity in children. *Int J Antimicrobial Agents* (2016) 46:171–7. doi: 10.1016/j.ijantimicag.2015.12.017
10. Plagemann A, Harder T, Franke K, Kohlhoff R. Long term impact of neonatal breast feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care* (2002) 25:16–22. doi: 10.2337/diacare.25.1.16
11. Kuczmarski RJ, Ogen CL, Guo SS, Grummer-Strawn LM, Flegal KM, MeiZ, et al. CDC Growth charts for the United States: methods and development. National Center for Health Statistics. *Vital Health Stat.* (2000) 11:1–190. Available online at: http://www.cdc.gov/growthcharts
12. Gulati AK, Kaplan DW, Daniels SR. Clinical tracking of severely obese children: a new growth chart. *Pediatrics* (2012) 130:1–5. doi: 10.1542/peds.2012-0596
13. Bays HE, Gonzalez-Campov JM, Henry RR, Bergaman DA, Ketabchi AE, Schorr AB, et al. Is adiposopathy (sic fat) an endocrine disease? *Int J Clin Pract.* (2008) 62 1474–83. doi: 10.1111/j.1742-1241.2008.01848.x
14. Bays HE. "Sic fat," metabolic disease, and atherosclerosis. *Am J Med.* (2009) 122:S26–37. doi: 10.1016/j.amjmed.2008.10.015
15. McCuen-Wurst C, Ruggieri M, Allison KC. Disordered eating and obesity: associations between binge-eating disorder, night-eating syndrome, and weight-related comorbidities. *Ann N Y Acad Sci.* (2018) 1411:96–105. doi: 10.1111/nyas.13467
16. Hail L, Le Grange D. Bulimia nervosa in adolescents: prevalence and treatment challenges. *Adolesc Health Med Ther.* (2018) 9:11–6. doi: 10.2147/AHMT.S135326
17. Howell MJ, Schenck CH, Crow SJ. A review of nighttime eating disorders. *Sleep Med Rev.* (2009) 13:23–34. doi: 10.1016/j.smrv.2008.07.005
18. Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. *Adv Pediatr.* (2016) 63:47–77. doi: 10.1016/j.yapd.2016.04.005
19. Jones KL, Jones MC, Campo M. *Smith's Recognizable Patterns of Human Malformation, 7th ed.* Saunders: Philadelphia (2014).
20. Farooqi S, O'Rahilly S. Genetics of obesity in humans. *Endocr Rev.* (2006) 27:710–8. doi: 10.1210/er.2006-0040
21. Abeysekara P, Turchi R, O'Neil M. Obesity and children with special healthcare needs: special considerations for a special population. *Curr Opin Pediatr* (2014) 26:508–15. doi: 10.1097/MOP.0000000000000124
22. Stovitz SD, Pardee PE, Vazquez G, Duval S, Schimmer JB. Musculoskeletal pain in obese children and adolescents. *Acta Paediatr.* (2008) 97:489–93. doi: 10.1111/j.1651-2227.2008.00724.x
23. Agirbasli M, Tanrikulu A, Acar Sevim B, Azizy M, Bekirogly N. Total cholesterol-to-high-density lipoprotein cholesterol ratio predicts high sensitivity C-reactive protein levels in Turkish children. *J Clin Lipidol.* (2015) 9:195–200. doi: 10.1016/j.jacl.2014.12.010
24. Sakuno T, Tomita LM, Tomita CM, Giuliano IC, Ibagy A, Perin NM, et al. Sonographic evaluation of visceral and subcutaneous fat in obese children. *Radiol Bras.* (2014) 47:149–53. doi: 10.1590/0100-3984.2013.1828

25. Novais EN, Millis MB. Slipped capital femoral epiphysis: prevalence, pathogenesis, and natural history. *Clin Orthop Relat Res*. (2012) 470:3432–8. doi: 10.1007/s11999-012-2452-y
26. Falciglia F, Aulisa AG, Giordano M, Boldrini R, Guzzanti V. Slipped capital femoral epiphysis: an ultrastructural study before and after osteosynthesis. *Acta Orthop*. (2010) 81:331–6. doi: 10.3109/17453674.2010.483987
27. Gilbert SR, Savage AJ, Whitesell R, Conklin MJ, Fineberg NS. BMI and magnitude of scoliosis at presentation to a specialty clinic. *Pediatrics* (2015):135:e1417-24. doi: 10.1542/peds.2014-2000
28. Wilson M, Ramsay S, Young KJ. Engaging overweight adolescents in a health and fitness program using wearable activity trackers. *J Pediatr Health Care* (2017) 31:e25-e34. doi: 10.1016/j.pedhc.2017.03.001
29. *Active Start: A Statement of Physical Activity Guidelines for Children from Birth to Age 5. 2nd Edition*. Shape America - Society of Health and Physical Educators. Available online at: https://www.shapeamerica.org/standards/guidelines/activestart.aspx
30. American Academy of Pediatrics. Active healthy living: prevention of childhood obesity through increased physical activity. *Pediatrics* (2006) 117:1834–42. doi: 10.1542/peds.2006-0472
31. Meyer AA, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Card*. (2006) 48:1865–70. doi: 10.1016/j.jacc.2006.07.035
32. Primary reference. A Clinical Guide to Pediatric Sleep by Robert Hilt, MD, Jodi Mindell and Judith Owens
33. National Sleep Foundation: https://sleepfoundation.org/sleep-topics/sleep-hygiene
34. Ahern D, Dixon E. Pediatric hypertension: a growing problem. *Hypertension* (2015) 42:143–50. doi: 10.1016/j.pop.2014.09.003
35. Faulkner, B. Recent clinical and translational advances in pediatric hypertension. *Hypertension* (2015) 65:926–31. doi: 10.1161/HYPERTENSIONAHA.114.03586
36. Faulkner B. Monitoring and management of hypertension with obesity in adolescents. *Integ Blood Pressure Control*. (2017) 10:33–9. doi: 10.2147/IBPC.S125094
37. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guidelines for screening and management of high blood pressure in children and adolescents. *Pediatrics* (2017) 140:e20171904. doi: 10.1542/peds.2017-1904
38. Cook S, Kavey RE. Dyslipidemia and pediatric obesity. *Pediatr Clin North Am*. (2011) 58:1363–73. doi: 10.1016/j.pcl.2011.09.003
39. *National Heart, Lung, and Blood Institute, US Department of Health and Human Service, National Institutes of Health*. Expert Panel on Integrated Guidelines for Cardiovascular health and Risk Reduction in Children and Adolescents, Summary Report (2012).
40. Kotagal S, Pianosi P. Sleep disorders in children and adolescents: clinical review. *Br Med J*. (2006) 332:828–32. doi: 10.1136/bmj.332.7545.828
41. Sateia MJ. International classification of sleep disorders-3rd edition: highlights and modifications. Contemporary reviews in sleep medicine. *Chest* (2014) 146: 1387–94. doi: 10.1378/chest.14-0970
42. Gileles-Hillel A, Kheirandish-Gozal L, Gozal D. Biological plausibility linking sleep apnoea and metabolic dysfuntion. *Nat Rev Endocrinol*. (2016) 12:290–8. doi: 10.1038/nrendo.2016.22
43. Brook CGD, Brown RS. *Handbook of Clinical Pediatric Endocrinology 2008 1st Ed*. Malden MA: Blackwell Pub (2008).
44. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care* (2005) 28:902–9. doi: 10.2337/diacare.28.4.902
45. Haemer MA, Grow HM, Fernandez C, Lukasiewica GJ, Rhodes ET, Shaffer LA, et al. Addressing prediabetes in childhood obesity treatment programs: support from research and current practice. *Child Obes*. (2014) 10:292–303. doi: 10.1089/chi.2013.0158
46. >Elder DA, Hornung LN, Herbers PM, Prigeon R, WooJG, D'Allessio DA. Rapid deterioration of insulin secretion in obese adolescents preceding the onset of type 2 diabetes. *J Pediatr*. (2015) 166:672–8. doi: 10.1016/j.jpeds.2014.11.029
47. American Diabetes Association. Standards of medical care in diabetes-2014. *Diabetes Care* (2014) 37(Suppl. 1):S14–80. doi: 10.2337/dc14-S014
48. Gong L, Goswami S, Giacomini K.M. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics* (2012) 22:820–7. doi: 10.1097/FPC.0b013e3283559b22
49. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med*. (1995) 333:541–9. doi: 10.1056/NEJM199508313330902
50. Ibáñez L, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, et al. An international consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. *Horm Res Paediatr*. (2017) 13:307–31. doi: 10.1159/000479371
51. Rosenfield RL. The diagnosis of polycystic ovary syndrome in adolescents. *Pediatrics* (2015) 136:1154–65. doi: 10.1542/peds.2015-1430
52. Society for Adolescent Health and Medicine. Recommended vitamin D intake and management of low vitamin D status in adolescents: a position statement of the society for adolescent health and medicine. *J Adolesc Health* (2013) 52:801–3. doi: 10.1016/j.jadohealth.2013.03.022
53. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. (2011) 96:1911–30. doi: 10.1210/jc.2011-0385
54. Golden NH, Abrams SA. Committee on nutrition. Optimizing bone health in children and adolescents. *Pediatrics* (2014) 143:e1229–43. doi: 10.1542/peds.2014-2173
55. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* (2008) 122:398–417. doi: 10.1542/peds.2007-1894
56. Smotkin-Tangorra M, Purushothaman A, Gupta A, Nejati G, Anhalt H, Ten S. Prevalence of vitamin D insufficiency in obese children and adolescents. *J Pediatr Endocrinol Metab*. (2007) 7:817–23. doi: 10.1515/JPEM.2007.20.7.817
57. Black JA, White B, Viner RM, Simmons RK. Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis. *Obes Rev*. (2013) 14:634–44. doi: 10.1111/obr.12037
58. Paulus GF, de Vaan LE, Verdam FJ, Bouvy ND, Ambergen TA, van Heurn LW. Bariatric surgery in morbidly obese adolescents: a systematic review and meta-analysis. *Obes Surg*. (2015) 25:860–78. doi: 10.1007/s11695-015-1581-2
59. Vilallonga R, Himpens J, van de Vrande S. Long-term (7 Years) follow-up of Roux-en-Y gastric bypass on obese adolescent patients (<18 Years). *Obesity Facts* (2016) 9:91–100. doi: 10.1159/000442758
60. Inge TH, Courcoulas, AP, Jenkin TM, Michalsky MP, Helmrath MA, Brandt ML. Weight loss and health status 3 years after bariatric surgery in adolescents. *NEJM* (2016) 374:113–23. doi: 10.1056/NEJMoa1506699
61. Theodorous AN, Schwartzberg DM, Sathyaprasad CB. The hunger games: a systematic review of pediatric bariatric surgery. *J Pharm Nut Sci*. (2015) 5:1–15. doi: 10.6000/1927-5951.2015.05.02.7
62. Boland CL, Harris JB, Harris KB. Pharmacological management of obesity in pediatric patients. *Ann Pharmacother*. (2015) 49:220–32. doi: 10.1177/1060028014557859
63. Fox CK, Marlatt KL, Rudser KD, Kelly AS. Topiramate for weight reduction in adolescents with severe obesity. *Clin Pediatr*. (2015) 54:19–24. doi: 10.1177/0009922814542481
64. Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. *Int J Obes*. (2013) 37:1–15. doi: 10.1038/ijo.2012.144

65. Domecq JP, Prutsky G, Wang Z, Elraiyah T, Brito JP, Mauck K, et al. Drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. (2015) 100:363–70. doi: 10.1210/jc.2014-3421
66. Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. *Handb Exp Pharmacol*. (2012) 209:433–66. doi: 10.1007/978-3-642-24716-3_20
67. Taylor FR. Weight change associated with the use of migraine-preventive medications. *Clin Ther*. (2008) 30:1069–80. doi: 10.1016/j.clinthera.2008.06.005
68. Gallo M, Lopez L. Combination contraceptives: effects on weight. *Cochrane Database Syst Rev*. (2014) 1:CD003987.
69. Kaplowitz P. Is there a role for metformin in the treatment of childhood obesity? *Pediatrics* (2017) 140:1. doi: 10.1542/peds.2017-1205
70. McDonagh MS, Selph S, Ozpinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr*. (2014) 168:178–84. doi: 10.1001/jamapediatrics.2013.4200

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

CASE REPORT
published: 19 June 2018
doi: 10.3389/fped.2018.00166

Check for updates

Growth Failure and Excessive Weight Gain in a 10 Year Old Male With Obesity: Approach to Diagnosis, Management, and Treatment of Acquired Hypothyroidism

*Tiffany Schumaker and Marisa Censani**

Division of Pediatric Endocrinology, Department of Pediatrics, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, United States

We report the case of a 10 year old male with severe obesity who presented with a 2 year history of significant growth failure and excessive weight gain that was subsequently diagnosed with serum negative Hashimoto's thyroiditis and acquired hypothyroidism. Initial investigations revealed a markedly elevated thyroid stimulating hormone (TSH) concentration >100 uIU/mL and an undetectable free thyroxine with total thyroxine 0.56 ug/dL. Thyroid antibodies were negative, however ultrasound findings were consistent with Hashimoto's thyroiditis. After treatment with levothyroxine supplementation, he had significant weight loss and marked improvement in his growth velocity. This case emphasizes the need to recognize excessive weight gain and growth failure as an initial presentation of Hashimoto's thyroiditis and highlights management and approach to treatment. Diagnosis and treatment is vital as prolonged undiagnosed hypothyroidism can result in incomplete catch up growth and compromised final adult height.

Keywords: weight gain, obesity, hypothyroidism, Hashimoto's thyroiditis, growth

OPEN ACCESS

Edited by:
Angela K. Fitch, University of Cincinnati College of Medicine, United States

Reviewed by:
Allen F. Browne, Independent Researcher, Falmouth, ME, United States
Tudor Lucian Pop, Iuliu Haţieganu University of Medicine and Pharmacy, Romania

***Correspondence:**
Marisa Censani
mac9232@med.cornell.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *12 March 2018*
Accepted: *17 May 2018*
Published: *19 June 2018*

Citation:
Schumaker T and Censani M (2018) Growth Failure and Excessive Weight Gain in a 10 Year Old Male With Obesity: Approach to Diagnosis, Management, and Treatment of Acquired Hypothyroidism. Front. Pediatr. 6:166. doi: 10.3389/fped.2018.00166

BACKGROUND

Hypothyroidism is the most common disorder of thyroid function in children. Primary hypothyroidism is characterized by high serum thyroid stimulating hormone (TSH) and low serum free thyroxine (T4) concentrations. Autoimmune, or Hashimoto's, thyroiditis is the most common cause of acquired thyroid disease in children and adolescents in the western world. Although autoimmune thyroiditis, is usually characterized by positive serum anti-thyroperoxidase (TPO) antibodies and/or positive thyroglobulin antibodies, about 5% of patients have no measurable thyroid antibodies (1). Hypothyroidism can be associated with fatigue, constipation, dry skin, cold intolerance, coarse, and brittle hair; however, growth delay may present for years before other symptoms occur. Although change in school performance is uncommon at diagnosis and more often declines, it may actually improve in patients with long standing hypothyroidism, and can delay diagnosis secondary to decreased distractibility and improved concentration. Given the long term effects of prolonged undiagnosed hypothyroidism resulting in incomplete catch up growth and compromised final adult height, this case emphasizes the importance of recognizing the combination of excessive weight gain and growth failure, even in the absence of additional symptoms, as an initial presentation of acquired hypothyroidism in a child.

CASE PRESENTATION

A 10 year old male was referred to endocrinology clinic for evaluation of obesity, rapid weight gain, and growth deceleration. His mother noted he was previously one of the tallest children in his class, but now was one of the shortest. Review of previous growth charts revealed growth at the 90th percentile for height at 8 years of age with decrease to the 75th percentile at 9 years, and the 50th percentile by 10 years. His weight was consistently at the 95th percentile, but he had gained 5.5 kg (12 lbs) in the past year with weight now at the 97th percentile and body mass index (BMI) 27.5 kg/m2 at the 99th percentile, meeting criteria for extreme obesity.

His mother noted he had been markedly hyperactive as a child and that this behavior had decreased over the past 1–2 years with great improvement in his grades over the past year. His medical history was unremarkable and he did not take medication. Review of systems was unremarkable and he denied fatigue, muscle weakness, constipation, or cold intolerance. He had a good energy level and there were no recent changes in appetite or concentration. He had occasional dry skin. Family history was remarkable for maternal grandmother and mother with hypothyroidism. His midparental target height was 176.5 cm (69.5 inches) at the 50th percentile for height.

On physical examination, the patient measured 134.9 cm (26th percentile) and weighed 50.2 kg (97th percentile) with BMI 27.5 kg/m2 (99th percentile). He had a normal blood pressure 104/55 mm Hg and heart rate of 84 bpm. The patient was well appearing without dysmorphic features and had a normal affect. He had cherubic facies and fundi appeared normal. His thyroid was palpable and smooth with right and left lobe each measuring 4 cm with no lymphadenopathy. His chest, heart, and abdomen were normal. He had Tanner stage 1 genital development with 3 cc testes and no pubic hair. Skin examination was negative for rash, acanthosis, or striae.

FINAL DIAGNOSIS

Laboratory evaluation revealed a markedly elevated TSH (thyroid stimulating hormone) concentration >100 uIU/mL (0.5–4.3 uIU/mL), an undetectable free T4 (thyroxine) < 0.25 ng/dL (0.9–1.4 ng/dL), and total T4 0.56 ug/dL (5.6–14.9 ug/dL) with negative thyroid peroxidase and antithyroglobulin antibodies. A thyroid ultrasound showed an enlarged heterogeneous thyroid consistent with autoimmune thyroiditis.

CLINICAL COURSE

The patient was started on levothyroxine 50 mcg (1 mcg/kg) daily with dose titrated over the next several months (**Table 1**). Normalization of thyroid levels was achieved on levothyroxine 100 mcg daily with TSH 0.55 uIU/mL, free T4 1.6 ng/dL, and total T4 9.6 ug/dL at 7 months post initiation of levothyroxine supplementation. His growth parameters dramatically improved on treatment (**Figure 1**). His weight decreased from 50.2 kg (97th percentile) to 43.4 kg (86th percentile) with 6.8 kg (15 lb) weight loss, and BMI decreased from 27.5 kg/m2 (99th percentile) to 22 kg/m2 (93rd percentile). By 7 months post initiation of treatment, his height increased from 134.9 cm (26th percentile) to 140.5 cm (42nd percentile) with 5.6 cm (2.2 inches) of growth in 7 months, giving an annualized growth velocity of 9.7 cm (3.8 inches) per year.

TABLE 1 | Thyroid function tests at presentation and months post levothyroxine initiation.

	Range	Presentation	1 month	3 months	5 months	7 months
TSH (uIU/mL)	0.5–4.3	>100	65.45	10.86	4.42	1.82
Free T4 (ng/dL)	0.9–1.4	0.25	0.68	1.1	1.4	1.03
Total T4 (ug/dL)	5.6–14.9	0.56	5.69	7.1	11.2	9.34
TPO-Ab (IU/mL)	0.0–9.0	4.61				
Tg-Ab (IU/mL)	0.0–4.0	1.51				

TSH, Thyroid stimulating hormone; Free T4, free thyroxine; Total T4, total thyroxine; TPO-Ab, Antithyroid peroxidase antibodies; Tg-Ab, Anti-thyroglobulin antibodies.

DISCUSSION

This case highlights that pediatric patients presenting with excessive weight gain and a declining growth velocity with crossing of height percentiles should be evaluated for hypothyroidism, even in the absence of other associated features of hypothyroidism including constipation, declining school performance, or cold intolerance. Acquired hypothyroidism can be related to thyroid disease (primary hypothyroidism) or hypothalamic-pituitary disease (central hypothyroidism). However, most childhood cases of hypothyroidism are primary and are caused by chronic autoimmune thyroiditis. It usually presents in adolescence and has a female predilection, affecting females three to five times more commonly than males (1). Other rare causes of acquired hypothyroidism include excess iodine ingestion, anti-thyroid drugs and thyroid injury secondary to external radiation, thyroidectomy or infiltrative diseases. Iodine deficiency also remains an important cause of acquired hypothyroidism worldwide.

Autoimmune hypothyroidism is characterized by antibodies against thyroglobulin and thyroperoxidase (TPO) and by lymphocytic infiltration of the thyroid gland, which can result in thyromegaly (2). It has been documented that although around 90% of patients have positive anti-TPO antibodies and 50% have positive thyroglobulin antibodies, about 5% of patients with a diagnosis of Hashimoto's thyroiditis based on clinical grounds or by appearance on ultrasound have no measurable thyroid antibodies. In cases of seronegative autoimmune thyroiditis, thyroid ultrasound examination is considered the cornerstone for diagnosis as well as for differentiating this chronic inflammatory condition from other forms of non-autoimmune hypothyroidism of genetic origin (3).

In has been reported in adult literature that patients with Hashimoto's thyroiditis and negative thyroid antibodies have a milder form of the disease; however, pediatric literature regarding

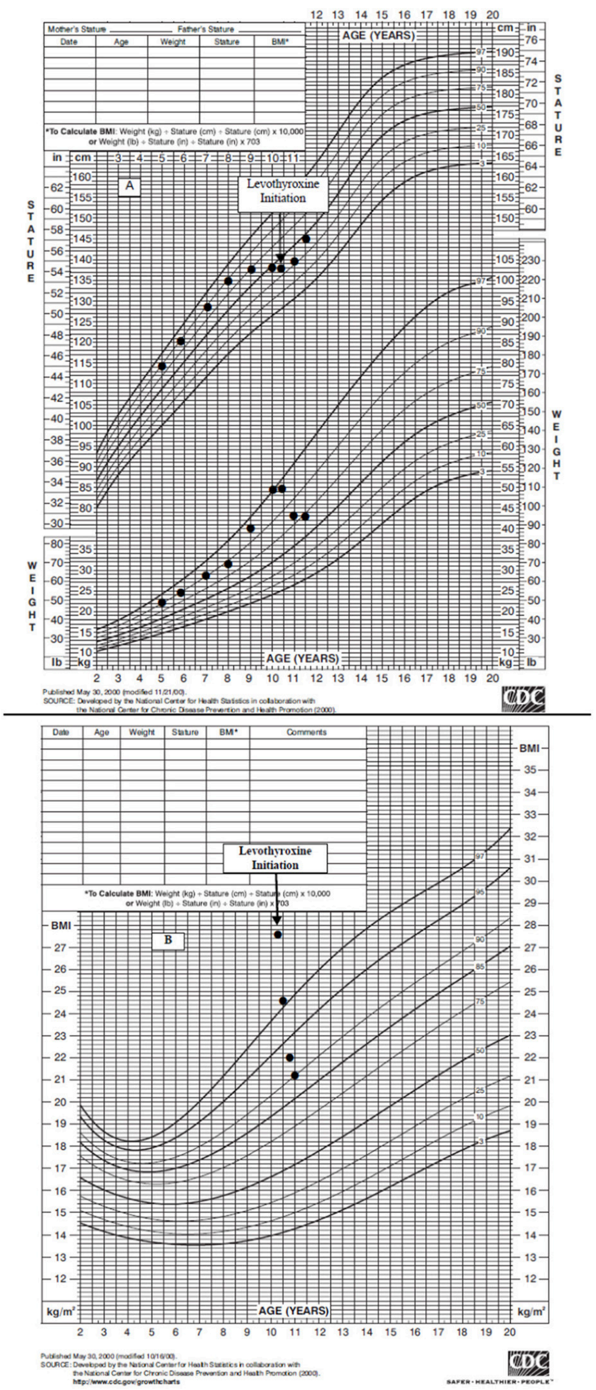

FIGURE 1 | (A) Boys Stature-for-age and Weight-for-age Curve. Linear Growth Curve reveals a crossing of percentiles from the 90th to the 25th percentile prior to levothyroxine initiation. Weight curve shows excessive weight gain and subsequent weight loss after levothyroxine initiation. **(B)** Body mass index-for-age Curve. BMI shows a significant decline from severe obesity to overweight status after levothyroxine initiation.

the clinical course of seronegative thyroiditis is sparse (3). Our patient presented with significant effects on growth parameters. Hashimoto's disease may be associated with a euthyroid state, hypothyroidism or transient hyperthyroidism. Patients with anti-TPO antibodies are at risk for developing hypothyroidism, however, it is known that some individuals with large goiters and high antibody levels can remain euthyroid for many years (4).

Among children who develop thyroid autoimmunity, a significant number go on to develop hypothyroidism, with one recent study showing that of the children with positive thyroid antibodies, about 20% began treatment with levothyroxine within 3 years after diagnosis. A concurrent diagnosis of celiac disease, an elevated baseline TSH and higher antithyroid antibody titers have been associated with an increased risk of progression to hypothyroidism (5).

CLINICAL PRESENTATION AND NATURAL HISTORY

The most common presentation of thyroiditis is thyroid gland enlargement, followed by clinical symptoms of hypothyroidism and then those found incidentally as part of routine screening or a work up for an unrelated condition (1, 6). The most common clinical manifestation of hypothyroidism in children is actually declining growth velocity, which can also be accompanied by increased and sometimes excessive weight gain. The growth delay is usually insidious in onset, and may be present for a few years before other symptoms occur (1). Children that present with severe growth failure usually have very low T4 values, often <2 ug/dL and an extremely elevated TSH, often >250 uIU/mL. Unfortunately, prolonged juvenile acquired hypothyroidism that is undiagnosed can result in incomplete catch up growth and the severity of the height deficit is proportionate to the duration of the hypothyroidism (7).

The signs and symptoms of hypothyroidism in children are often elusive and depend on severity and duration. Hypothyroidism can be associated with fatigue, constipation, dry skin, cold intolerance, coarse and brittle hair, and myxedema. However, these symptoms may escape detection and may only be discovered retrospectively. Change in school performance is uncommon at diagnosis and was documented in only 3.3% of children in one study (8). Although performance more often declines, it may actually improve in patients with long standing hypothyroidism and can delay diagnosis. This is thought to be secondary to decreased distractibility and improved concentration.

Of note, it is important to differentiate that in individuals with obesity, a slightly elevated TSH level in the setting of a normal T4 are physiologic and reflect the body's attempt to increase metabolism and do not necessitate treatment. With weight loss, TSH levels often normalize in these patients with obesity (9).

TREATMENT AND PROGNOSIS

The treatment of choice for acquired hypothyroidism is daily oral thyroxine. Recommendations for dosing are not standardized as there is variation in the effect of thyroxine replacement in different individuals. The initiation of treatment and subsequent monitoring typically requires the assistance of the pediatric endocrinologist. A low starting dose of 0.25–0.5 mcg/kg/day has been recommended to avoid potential acceleration of skeletal age advancement disproportionate to height gains (2). Once TSH concentrations normalize and catch up growth is complete, thyroid function tests can be monitored throughout puberty 2–3 times yearly (10).

In most patients, hypothyroidism will be permanent. However, there may be periods of remission with thyroid function fluctuation and therefore it may be appropriate to trial patients off thyroxine for 6–8 weeks after the completion of growth and puberty to determine if hypothyroidism is permanent (10). Those that had elevated TSH values while on thyroxine replacement do not need a trial of thyroxine withdrawal.

CONCLUSION

Given that prolonged undiagnosed hypothyroidism can result in incomplete catch up growth and a compromised final adult height, thyroid function tests should be strongly considered in the initial evaluation of a child with growth deceleration and weight gain. Our patient's decreasing height percentile and increasing weight, on review of his pediatrician's growth charts, were the major clues to his underlying diagnosis. His improved behavior was subsequently attributed to suppression of his ADHD symptoms due to his severe hypothyroidism and highlights the importance of recognizing change in academic performance as another sign of thyroid dysfunction. In contrast to adult literature with a milder disease state documented in serum negative autoimmune thyroiditis, our patient had severe overt hypothyroidism and significantly affected growth parameters, suggesting a more severe presentation in the pediatric population. Regardless of etiology, it is imperative to recognize growth failure as the possible initial presentation of acquired hypothyroidism in pediatric patients, even in the absence of commonly described symptoms. Laboratory assessment and early intervention can ultimately prevent the development of symptomatology and the loss of final adult height.

ETHICS STATEMENT

Written informed consent was obtained from the patient's parent prior to presenting the case.

AUTHOR CONTRIBUTIONS

TS and MC have directly cared for the patient. TS and MC contributed to the research, writing, and editing of the manuscript, approved the final version, and agreed to be accountable for the content of this work.

REFERENCES

1. de Vries L, Bulvik S, Phillip M. Chronic autoimmune thyroiditis in children and adolescents: at presentation and during long-term follow-up. *Arch Dis Child.* (2009) 94:33–7. doi: 10.1136/adc.2007
2. Sperling M. *Pediatric Endocrinology*. 4th ed. Philadelphia, PA: Elsevier/Saunders (2014).
3. Rotondi M, de Martinis L, Coperchini F, Pignatti P, Pirali B, Ghilotti S, et al. Serum negative autoimmune thyroiditis displays a milder clinical picture compared with classic Hashimoto's thyroiditis. *Eur J Endocrinol.* (2014) 171:31–6. doi: 10.1530/EJE-14-0147
4. Rapoport, B. Pathophysiology of Hashimoto's thyroiditis and hypothyroidism. *Annu Rev Med.* (1991) 42:91–6.
5. Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, et al. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. *Clin Endocrinol.* (2012) 76:394–8. doi: 10.1111/j.1365-2265.2011.04251.x
6. Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S, et al. The natural history of euthyroid Hashimoto's thyroiditis in children. *J Pediatr.* (2006) 149:827–32. doi: 10.1016/j.jpeds.2006.08.045
7. Rivkees SA, Bode HH, Crawford JD. Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. *N Engl J Med.* (1988) 318:599–602.
8. DeBoer MD, LaFranchi S. Differential presentation for children with autoimmune thyroiditis discovered because of symptom development or screening. *J Pediatr Endocrinol Metab.* (2008) 21:753–61. doi: 10.1515/JPEM.2008.21.8.753
9. Reinehr T. Thyroid function in the nutritionally obese child and adolescent. *Curr Opin Pediatr.* (2011) 23:415–20. doi: 10.1097/MOP.0b013e328344c393
10. Cappa M, Bizzarri C, Crea, F. Autoimmune thyroid diseases in children. *J Thyroid Res.* (2010) 2011:675703. doi: 10.4061/2011/675703

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

CASE REPORT
published: 27 November 2018
doi: 10.3389/fped.2018.00361

Check for updates

The Potential Role of Combination Pharmacotherapy to Improve Outcomes of Pediatric Obesity: A Case Report and Discussion

Claudia K. Fox and Aaron S. Kelly*

Department of Pediatrics, Center for Pediatric Obesity Medicine, University of Minnesota, Minneapolis, MN, United States

There is a gap in treatment modalities for pediatric patients with obesity for whom lifestyle modification therapy, on the one hand, may be insufficient to meaningfully reduce BMI, and bariatric surgery, which on the other hand, may not be indicated, available or desired. Although pharmacotherapy may help fill this treatment void, there is a paucity of FDA-approved medications indicated for pediatric obesity and further, most are single agents with only modest mean treatment effects. In contrast, combination pharmacotherapy, such as phentermine/topiramate, appears to offer greater weight loss efficacy in adults and may prove to be superior to monotherapy for pediatric patients as well. This case report describes the clinical management of severe obesity in a 10 year old girl with lifestyle modification therapy and subsequent addition of first topiramate and later phentermine. Using the case as a platform, the current state of pharmacotherapy for pediatric obesity will be described thereby highlighting the limited efficacy of single agents. Additionally, the biological rationale for combination pharmacotherapy, including potential mechanisms which may account for the poor response to single agents, will be discussed.

Keywords: pharmacotherapy, obesity, pediatric, medication, topiramate, phentermine

OPEN ACCESS

Edited by:
Fatima Cody Stanford, Massachusetts General Hospital, Harvard Medical School, United States

Reviewed by:
Baruch Yerushalmi, Ben-Gurion University of the Negev, Israel
Vrinda Bhardwaj, Children's Hospital of Los Angeles, United States

****Correspondence:***
Claudia K. Fox
lusc0001@umn.edu

Specialty section:
This article was submitted to Pediatric Gastroenterology, Hepatology and Nutrition, a section of the journal Frontiers in Pediatrics

Received: *01 September 2018*
Accepted: *06 November 2018*
Published: *27 November 2018*

Citation:
Fox CK and Kelly AS (2018) The Potential Role of Combination Pharmacotherapy to Improve Outcomes of Pediatric Obesity: A Case Report and Discussion. Front. Pediatr. 6:361. doi: 10.3389/fped.2018.00361

BACKGROUND

Lifestyle modification therapy (LSMT), which consists of dietary and physical activity counseling supported by behavioral strategies, is the cornerstone of obesity treatment. However, multiple studies indicate that for youth, particularly adolescents, with severe obesity, LSMT is often insufficient for achieving clinically significant and durable BMI reduction (1–4). Some data suggest that fewer than 2% of youth with severe obesity are able to achieve and *maintain* clinically-meaningful reduction in BMI.[1]

The challenge of weight loss maintenance stems from both behavioral and physiological responses to the reduced energy stores and negative energy balance. While long-term adherence to behavior changes tends to wane with time, the drive behind the waning effect is primarily physiological in nature. As fat stores decrease, fasting leptin and insulin decrease, thereby conveying a message of energy depletion to the hypothalamus resulting in increased hunger sensation. Additionally, cross talk between the hypothalamus and "non-homeostatic" hedonic and cognitive brain regions leads to a heightened sense of food palatability. Concurrently, total energy expenditure decreases due to decreased body mass and enhanced metabolic efficiency (5, 6) This process is termed "metabolic adaptation" and the net result is weight regain.

Obesity pharmacotherapy may address some of the physiological adaptations and counter-regulatory mechanisms that contribute to weight regain primarily via their effect on appetite and hunger. In this case report, we describe the use of medications, specifically topiramate and phentermine, for weight regain after success with LSMT in a 10 year old girl with severe obesity.

CASE PRESENTATION

A 10 year old white girl with severe (class 3: BMI ≥140% of the 95th percentile for age and sex) obesity and otherwise normal development presented to the Pediatric Weight Management Clinic with her mother. The mother reported that the patient had been at the 75th percentile for height and weight for most of the patient's life but she experienced a "20 to 30 pound" weight gain over the past year. The mother further explained that this recent weight gain coincided with treatment of seasonal allergies with montelukast and she wondered if this may have been the cause of the weight increase. The patient had no prior weight loss attempts.

The patient was born full term, weighing 3.18 kg. The mother's pregnancy was uncomplicated, as was the patient's newborn course. Aside from seasonal allergies, the patient was healthy. She had no history of hospitalizations, surgeries, or mental health concerns. She was not taking any medications.

The patient was eating regularly-spaced meals consisting primarily of highly processed foods and simple carbohydrates (e.g., pastries for breakfast, potatoes with cheese for dinner). The family was eating fast food three times per week on average. The patient endorsed having a big appetite and feeling hungry all the time. She was eating while watching TV and when bored. She denied binge eating, loss of control eating, emotional eating, sneaking/hiding food, or eating during the night. Her physical activity was limited to gym class at school three times per week.

The patient was living with her mother and her mother's partner. The patient's parents divorced when she was very young and the mother's partner had been living with them since the patient was a toddler. The patient saw her biological father rarely. She had no siblings. She was attending fourth grade and enjoyed reading and writing. The mother and her partner worked full-time and the patient was cared for by a baby sitter after school a few times per week. They had no food insecurity. The family history was notable for obesity in both biological parents and type 2 diabetes in the maternal grandmother.

The patient's review of systems was negative. She reached menarche several months prior to presentation. On physical examination, her weight was 70.31 kg (155 lbs.), height was 142 cm (4'8"), and BMI was 34 kg/m^2 (145% of the 95th percentile). Her blood pressure was 105/65 mmHg and pulse was 74 beats per minute. Her physical examination was normal. The results of her fasting labs were: total cholesterol 176 mg/dL (normal: <170 mg/dL), HDL-c 49 mg/dL (>45 mg/dL), LDL-c 96 mg/dL (<110 mg/dL), triglycerides 157 mg/dL (<90 mg/dL), ALT 27 (<50 U/L), AST 29 (<50 U/L), glucose 98 mg/dL (70-99 mg/dL), and HbA1c 5.5% (0-5.6%). Her Pediatric Symptom Checklist (routinely obtained in the Pediatric Weight Management Clinic) score was 8 (> 28 is considered abnormal).

The patient and family were started on a program of lifestyle modification therapy and responded particularly well with decreasing fast food consumption and liquid calories. Further, the patient started bringing her lunch to school instead of eating the school fare and was able to keep a food log almost daily. The patient's physical activity, however, continued to be limited. Over the course of 5 months, the patient's BMI decreased 5 units (15%), from 34 kg/m^2 to 29 kg/m^2 (145% of the 95th percentile to 125% of the 95th percentile).

At the end of the 5 month period, coinciding with the end of the school year and beginning of summer vacation, the patient's sleep/wake cycle became irregular. Because she did not like the hot weather, she chose to stay inside all day. Her mother left prepared meals for the patient to encourage healthy eating while mom was at work. Despite this, the patient's BMI began to trend upward from 29 kg/m^2 to 31 kg/m^2 over the summer months. Upon school resuming in the fall, the patient's sleep/wake cycle normalized and eating behaviors and patterns improved, returning to those of the previous school year. The patient's BMI stabilized for a few months but then increased further. The patient expressed frustration because she believed that she was eating well, which was indeed reflected in her daily food logs. She continued to attend monthly visits with the Pediatric Weight Management Clinic dietician, psychologist, and pediatrician with specialized training in obesity medicine. Yet, the patient's BMI continued to increase such that by 2 years after her initial appointment, the patient's BMI returned to baseline (135% of the 95th percentile) (see **Figure 1**).

Suspecting that metabolic adaptation was causing the patient's weight rebound, adjunct pharmacotherapy was recommended. Orlistat was considered but not started because of concern about gastrointestinal side effects and lack of insurance coverage. Metformin may have been another reasonable option but the patient's fasting glucose and HbA1c were in the normal range and she did not have acanthosis nigricans on physical examination which would have suggested insulin resistance. She was ultimately started on topiramate 75 mg daily in addition to ongoing LSMT. She and her mother were cautioned that although topiramate is not FDA-approved for the indication of obesity (in children or adults), multiple studies have demonstrated clinically-meaningful weight loss efficacy in adults. Additionally, it was explained that the side effect profile in children is well established stemming from its use for epilepsy treatment.

After 4 months of treatment with topiramate, the patient's BMI trajectory plateaued yet was not decreasing as was desired. Recognizing that the combination of topiramate and phentermine is the most effective weight loss medication currently available for adult obesity, phentermine 15 mg daily was added to the topiramate 75 mg daily. The patient and mother were informed that phentermine is FDA-approved only for individuals older than 16 years and for "short-term use." With combination treatment for ∼22 months, the patient experienced good BMI reduction, from 34.1 to 25.7 kg/m^2. Her blood pressure and heart rate were monitored regularly and though her blood pressure did not increase, her heart rate

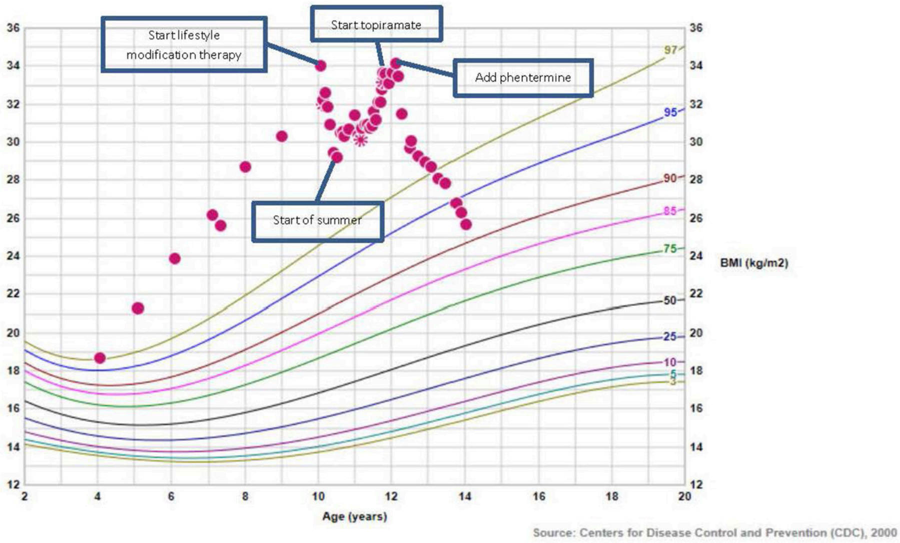

FIGURE 1 | BMI growth chart of patient.

increased slightly from 60 to 70 s, in line with the mechanisms of action of phentermine (stimulant-like effects). Later, the patient reported that she was experiencing some "memory" issues but noted no change in her academic performance. Although it seemed unusual for this type of symptom to emerge 10 months after starting topiramate, the topiramate dose was decreased from 75 to 50 mg daily and the memory issues resolved. Written informed consent was obtained from the parent of the patient for the publication of this case report.

DISCUSSION

Although the patient in the case presentation was able to impressively reduce her BMI via LSMT by nearly 15% over the course of 5 months, she was unable to maintain her BMI reduction despite her efforts in sustaining the dietary and physical activity behaviors that allowed her to reduce her BMI initially. This is not unexpected and highlights the effect of metabolic adaptation and the need for obesity pharmacotherapy to help sustain weight loss in many patients.

In the pediatric population there are only two FDA-approved medications indicated for obesity: orlistat and phentermine. Orlistat, a lipase inhibitor (which does not necessarily address physiological adaptations to weight loss), is FDA-approved for patients ≥12 years of age. In the largest study examining the effect of orlistat on BMI change in youth, 539 adolescents with obesity were randomized to either LSMT plus orlistat (120 mg three times daily) or placebo for 1 year. At the end of the study, BMI decreased 0.55 kg/m^2 in the orlistat group and increased 0.31 kg/m^2 in the placebo group. This translates into a treatment effect of ∼3% decrease in BMI from baseline. Further, there were no clinically significant changes in blood pressure, fasting lipids, insulin, or glucose tolerance. Mild to moderate gastrointestinal adverse events (most commonly fatty/oily stool) occurred in 9%-50% of the orlistat group compared to 1–13% of the placebo group (7).

Phentermine, a sympathomimetic (norepinephrine reuptake inhibitor), was approved by the FDA in 1959 for individuals >16 years of age for "short term use" and is currently the most widely prescribed medication for the treatment of obesity in adults (8). Although there are no randomized, controlled studies of this medication in adolescents that are more than 1-month in duration, a retrospective chart review of adolescents with severe obesity treated in a pediatric weight management clinic reported the six-month outcomes of phentermine plus LSMT on BMI. In this study, 25 adolescents with severe obesity treated with LSMT plus phentermine (most commonly 15 mg daily) were compared to 274 age- and BMI-matched adolescents treated with LSMT alone. At six months, the LSMT plus phentermine group decreased their BMI by 1.6 kg/m^2 [95% CI (−2.8 kg/m^2, −0.4 kg/m^2); $p = 0.011$] more than the LSMT alone group, translating into a treatment effect of 4% [(−7.1%, −1.0%); $p = 0.009$] decrease in BMI. There were no significant differences in blood pressure between groups, though heart rate was higher (but not statistically significant) in the phentermine group (9). These findings of no increase in blood pressure with phentermine are consistent with what has been found in adults. In adults, phentermine is not associated with increase in heart rate either (10). Further, phentermine abuse, psychological dependence, and withdrawal do not occur in adult patients treated with phentermine for obesity, even after years of treatment (11).

Among the other medications that have been studied for the indication of obesity in the pediatric population, metformin, exenatide, and topiramate have the most data. Metformin is FDA approved for type 2 diabetes in children ≥ 10 years of age and has modestly favorable weight loss properties. A meta-analysis of 14 randomized clinical trials examining metformin for pediatric obesity demonstrated an overall effect size of−1.16 kg/m^2 (12). Total cholesterol, but not other lipid outcomes or blood pressure, decreased slightly more with metformin compared with the control groups. Gastrointestinal adverse events were reported in 26% of the metformin group and 13% of the control group.

Exenatide, a glucagon-like peptide-1 receptor agonist, belongs to the class of incretins that also includes liraglutide which is FDA approved for adult obesity. In adolescents, two pilot placebo-controlled studies examined the effect of exenatide on BMI. In the first, 12 adolescents were randomized to exenatide 5 mcg twice daily or placebo for 3 months. The exenatide group decreased their BMI by 0.9 kg/m^2 and the control group increased their BMI by 0.84 kg/m^2. The treatment effect was −4.92% [(−8.61, −1.23); $p = 0.009$] BMI reduction (13). In the second, 26 adolescents were randomized and exenatide elicited a 2.7% [(−5.02,−0.37); $p = 0.03$] BMI reduction at 3 months. There were no significant changes in blood pressure, heart rate, lipids, or glucose. Nausea was the most common adverse event reported in 62% of the exenatide group and 31% of the placebo group (14).

Finally, topiramate, an antiepileptic agent that is FDA approved for seizures in children ≥ 2 years of age, has been extensively studied for the treatment of adult obesity (15). For youth, a retrospective chart review of 28 adolescents treated with LSMT plus topiramate (most commonly 75 mg daily) in a pediatric weight management clinic demonstrated a 4.9% [(−7.1, −2.8), $p < 0.001$] BMI reduction at 6 months (16). In a double blind pilot study, 30 adolescents with severe obesity completed four weeks of meal replacement therapy followed by randomization to 24 weeks of either topiramate 75 mg daily or placebo. There was a modest reduction in BMI (∼2%) that was not statistically significant between the topiramate group and the placebo group. The most common side effect was paresthesia and there were no adverse changes in cognitive function measured by highly sensitive instruments (17).

The outcomes of studies examining single medications, in contrast to combination medications, for the treatment of obesity in both adults and children demonstrate only modest effects of 3–5% weight or BMI reduction. This is true of the patient in the case. In fact, the patient in the case only experienced a suspension in her BMI increase, and not a BMI decrease, with topiramate monotherapy. It was not until phentermine was added to the topiramate that her BMI decreased significantly.

Combination pharmacotherapy may have advantages over monotherapy for several reasons. One is that there are redundant processes involved in the control of body weight. By employing medications with different mechanisms of action, the ability to effect more than one of these processes is enhanced thereby increasing the opportunity for a greater impact on adiposity. Second, employing more than one medication at a time allows for the possibility of using lower therapeutic doses of each of the medications which may mitigate side effects. This is particularly relevant to the pediatric population given the long duration of treatment. For example, the weight loss effects of topiramate is dose dependent but neurocognitive side effects, such as cognitive dulling and fatigue, tend to emerge above doses of 100 mg daily (15). This may limit its utility as a monotherapy. By combining a moderate dose of topiramate (i.e., <100 mg) with another weight loss medication that has a different side effect profile, such as phentermine, maximum weight loss effect may be achieved with limited adverse effects. Indeed, the combination of phentermine plus topiramate is the most effective weight loss medication currently FDA-approved for adult obesity.

CONCLUSION

Severe pediatric obesity is a serious and chronic disease. For many patients, LSMT is insufficient for achieving clinically significant and durable BMI reduction because LSMT does not address the biological underpinnings of this disease. Pharmacotherapy may hold promise as a safe and effective adjunct tool for the management of severe obesity in the pediatric population, yet more clinical trials are needed. Further, as in adults, combination medications, in contrast to monotherapy, may prove to be more advantageous.

ETHICS STATEMENT

Patient's guardian gave written consent for case report to be published.

AUTHOR CONTRIBUTIONS

CF and AK contributed to the conception of this case study. CF wrote the initial draft. Both contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Danielsson P, Kowalski J, Ekblom O, Marcus C. Response of severely obese children and adolescents to behavioral treatment. *Arch Pediatr Adol Med.* (2012) 166:1103–8. doi: 10.1001/2013.jamapediatrics.319
2. Knop C, Singer V, Uysal Y, Schaefer A, Wolters B, Reinehr T. Extremely obese children respond better than extremely obese adolescents to lifestyle interventions. *Pediatr Obesity* (2015) 10:7–14. doi: 10.1111/j.2047-6310.2013.00212.x
3. Johnston CA, Tyler C, Palcic JL, Stansberry SA, Gallagher MR, Foreyt JP. Smaller weight changes in standardized body mass index in response to treatment as weight classification increases. *J. Pediatr.* (2011) 158:624–7. doi: 10.1016/j.jpeds.2010.09.049
4. Kalarchian MA, Levine MD, Arslanian SA, Ewing LJ, Houck PR, Cheng Y, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. *Pediatrics.* (2009) 124:1060–8. doi: 10.1542/peds.2008-3727
5. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. *Am J Physiol Regul Integr Comp Physiol.* (2011) 301:R581–600. doi: 10.1152/ajpregu.00755.2010
6. MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: innovative research to improve maintenance of weight loss. *Obesity* (2015) 23:7–15. doi: 10.1002/oby.20967
7. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* (2005) 293:2873–83. doi: 10.1001/jama.293.23.2873

8. Hendricks EJ, Rothman RB, Greenway FL. How physician obesity specialists use drugs to treat obesity. *Obesity* (2009) 17:1730–5. doi: 10.1038/oby.2009.69
9. Ryder JR, Kaizer A, Rudser KD, Gross A, Kelly AS, Fox CK. Effect of phentermine on weight reduction in a pediatric weight management clinic. *Int J Obes*. (2017) 41:90–3. doi: 10.1038/ijo.2016.185
10. Hendricks EJ, Greenway FL, Westman EC, Gupta AK. Blood pressure and heart rate effects, weight loss and maintenance during long-term phentermine pharmacotherapy for obesity. *Obesity* (2011) 19:2351–60. doi: 10.1038/oby.2011.94
11. Hendricks EJ, Srisurapanont M, Schmidt SL, Haggard M, Souter S, Mitchell CL, et al. Addiction potential of phentermine prescribed during long-term treatment of obesity. *Int J Obes*. (2014) 38:292–8. doi: 10.1038/ijo.2013.74
12. McDonagh MS, Selph S, Ozpinar A, Foley C. Systematic review of the benefits and risks of metformin in treating obesity in children aged 18 years and younger. *JAMA Pediatr*. (2014) 168:178–84. doi: 10.1001/jamapediatrics.2013.4200
13. Kelly AS, Metzig AM, Rudser KD, Fitch AK, Fox CK, Nathan BM, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. *Obesity* (2012) 20:364–70. doi: 10.1038/oby.2011.337
14. Kelly AS, Rudser KD, Nathan BM, Fox CK, Metzig AM, Coombes BJ, et al. The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. *JAMA Pediatr*. (2013) 167:355–60. doi: 10.1001/jamapediatrics.2013.1045
15. Kramer CK, Leitao CB, Pinto LC, Canani LH, Azevedo MJ, Gross JL. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. *Obes Rev*. (2011) 12:e338–47. doi: 10.1111/j.1467-789X.2010.00846.x
16. Fox CK, Marlatt KL, Rudser KD, Kelly AS. Topiramate for weight reduction in adolescents with severe obesity. *Clin Pediatr*. (2015) 51:19–24. doi: 10.1177/0009922814542481
17. Fox CK, Kaizer AM, Rudser KD, Nathan BM, Gross AC, Sunni M, et al. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: a pilot randomized controlled trial. *Obesity* (2016) 24:2553–61. doi: 10.1002/oby.21633

Conflict of Interest Statement: CF receives research support from Novo Nordisk. AK serves as a consultant for Novo Nordisk, Orexigen, and Vivus.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership