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Socioeconomic Disparities in Childhood Obesity Risk: Association With an Oxytocin Receptor Polymorphism

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IMPORTANCE Pediatricians are paying increased attention to the effects of socioeconomic status (SES) on children's health. Low SES is a robust predictor of obesity across the life course and may interact with genes affecting metabolism to influence obesity risk. Recent animal literature and burgeoning human research suggest that the hormone oxytocin (OT) may be important for metabolic regulation. To date, this association has not been examined in children.

OBJECTIVES To examine whether an OT receptor polymorphism (rs53576) interacts with SES, potentially exacerbating and buffering the effects of stress, to predict anthropometry during childhood, and based on differential neurobiological susceptibility theory, to test whether carriers of the *A* allele of the *OXTR* gene, compared with *GG* genotyped individuals, would be most sensitive to the effects of SES on anthropometry for better or for worse.

DESIGN, SETTING, AND PARTICIPANTS In this observational study, families were recruited from public school classrooms and enrolled in the Peers and Wellness Study (PAWS), which examined the effects of social status on health. Families were assessed during children's kindergarten year (fall semester of 2003, 2004, and 2005) and again during middle childhood (2009-2011) for a follow-up assessment that included anthropometric measures and DNA collection. The dates of the analysis were January 2015 to June 2016.

EXPOSURES Socioeconomic disparities.

MAIN OUTCOMES AND MEASURES Child body mass index *z* score (BMIz) and triceps skinfold thickness. Family SES was collected through questionnaires mailed to homes. Body measurements and DNA were collected in homes by trained research assistants.

RESULTS From the original community sample of 338 typically developing children, participants were 186 socioeconomically and racially/ethnically diverse children (mean age, 10.3 years; age range, 9.4-11.3 years; 93 females [50%]) who had sufficient data at the follow-up assessment for inclusion in this study. Among 97 *A* allele carriers, a 1-SD increase in SES was associated with a decrease in BMIz of 0.28 (95% CI, −0.47 to −0.09) and a decrease in skinfold thickness of 0.95 (95% CI, −1.77 to −0.12) mm, such that they exhibited the highest BMIz and skinfold thickness in contexts of low SES but exhibited the lowest BMIz and skinfold thickness in contexts of high SES. Socioeconomic status was unrelated to BMIz (95% CI, −0.21 to 0.26) or skinfold thickness (95% CI, −0.42 to 1.45) for 89 *GG* genotyped children.

CONCLUSIONS AND RELEVANCE These findings advance etiologic understanding of childhood obesity, highlighting complex effects of SES on child health and adding to growing evidence that OT relates to human obesity risk. The results also support differential neurobiological susceptibility theory, suggesting that the *A* allele renders individuals more sensitive to both positive and negative health effects of socioecological context.

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Supplemental content

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Childhood obesity, an epidemic affecting almost 1 in 5 children in the United States,[1] is associated with poorer physical, social, and psychological health in childhood and adulthood.[1-3] Separate bodies of research have examined environmental and genetic determinants of childhood obesity, yet these investigations have rarely considered how gene × environment interactions occurring early in development may confer obesity risk. We examined the contribution of genetic and environmental factors, and their interaction, to the prediction of child anthropometry and body composition as indicators of obesity risk.

Recently, the American Academy of Pediatrics has emphasized the role of poverty, and the effect of socioeconomic status (SES) more generally, on children's health.[4] In particular, low SES is a robust predictor of body mass index (BMI), adiposity, and obesity risk across the life course. These associations may operate through various mechanisms, including lower birth weight, lack of access to health care, and limited availability of healthful foods and places to exercise.[5] Low SES is associated with greater exposure to environmental stressors, such as noise, crowding, air pollution, toxins, violence, and long-term stress.[6,7] Given documented effects of stress on weight,[8] such stressors may also contribute to socioeconomic disparities in childhood obesity,[9] yet there is also substantial variation in obesity risk within social classes.

Although increasing attention is devoted to discovering genes that specifically confer risk for obesity, genes explain only a limited amount of the variance in obesity.[10] In light of the robust effects of social environment on adiposity, examining genes that confer differential susceptibility is likely to further elucidate the variability underlying social disparities in obesity. Evidence is growing in support of differential neurobiological susceptibility (DNS) theories,[11-14] which posit that genetic and physiological variability predisposes some individuals to increased susceptibility to both positive and negative environments, whereas other individuals are less sensitive to external influences. Accumulating evidence suggests that *OXTR* (OMIM 167055), the receptor gene for the hormone oxytocin (OT), acts as an important modifier of environmental experience for a range of health outcomes and that it confers DNS to social environmental effects.[15] A known *OXTR* polymorphism (rs53576) involves a single-nucleotide, guanine to adenine switch.[16] Although the neurophysiological consequence of the *A* allelic and *G* allelic variations remains largely undetermined, preliminary research suggests structural and functional differences. Research has identified the *A* allele of the *OXTR* gene as the "risk" allele, such that individuals carrying 1 (*AG*) or 2 (*AA*) copies have increased sensitivity to short-term stress, poorer social skills, and negative mental health outcomes compared with their counterparts with the *GG* genotype.[17,18] Mechanistically, the *A* allele is associated with less efficacious OT binding.[19]

Although OT is best known for facilitating and maintaining affiliative behaviors and promoting antistress physiological responses,[20] the importance of peripheral and central OT processes in regulating metabolic homeostasis, appetite, energy expenditure, and body weight is becoming well established.[21-23] Both central and peripheral administration of OT has been shown to reduce overall food intake, increase energy expenditure, and cause weight loss in rats.[24] Oxytocin is also implicated in reward-based eating behavior that can promote obesity, with OT knockout mice demonstrating preference for sweets and carbohydrates.[22,25] Recent experimental findings also suggest that OT feeding behavior associations may be shaped by social context.[26] Furthermore, mice with OT or OT receptor deficiencies have been shown to develop late-onset obesity, despite normal food intake,[27] suggesting a direct effect of OT activity and receptor binding on body composition independent of food or exercise. Research in humans suggests similar associations. Individuals with Prader-Willi syndrome, a chromosomal abnormality associated with gross obesity and insatiable hunger, have 42% fewer OT neurons[28] and thus have less OT produced and less OT binding at receptor sites. Lower serum OT levels in humans also have been found in association with uncomplicated obesity and type 2 diabetes.[29] Even among nonoverweight humans, OT administration can influence appetite, intake of palatable foods, and metabolic regulation.[30] In light of several findings, including established associations between SES and body mass,[5] evidence for the *OXTR* polymorphism both exacerbating and buffering the effects of stress,[31] the role of OT in regulating appetite and metabolism,[21-23] and accumulating evidence supporting DNS theories, we hypothesized that the *OXTR* polymorphism would confer differential susceptibility to socioeconomic risk for childhood obesity. Specifically, we proposed that children who were carriers of the "sensitivity" allele of the *OXTR* polymorphism (*AA* or *AG* genotype) would demonstrate stronger associations between SES and the anthropometric outcomes of BMI *z* score (BMIz) and skinfold thickness compared with *GG* individuals.

Key Points

Question Does a genotype related to regulation of a hormone system known to influence metabolic processing and stress reactivity interact with early environment to predict child obesity risk?

Findings In this cohort study, children who were carriers of the *A* allele of the *OXTR* gene had greater body mass index and adiposity when reared in early life environments of low socioeconomic status (SES) but had the lowest body mass index and adiposity when reared in environments of high SES. Socioeconomic status was not associated with obesity risk for children with the *GG* genotype.

Meaning These findings suggest that genetic predispositions can affect health outcomes for better or for worse depending on early rearing environment.

Methods

Study Design and Population

Participants were originally recruited in 3 waves from 29 kindergarten classrooms within 6 public schools selected to represent various sociodemographic characteristics in the San Francisco Bay, California, area during the fall seasons of 2003, 2004, and

Table 1. Demographic Characteristics of the Sample by Genotype and Tests of Differences[a]

Characteristic	*GG* (n = 89)	*AG* (n = 82)[b]	*AA* (n = 15)[b]	*P* Value
Sex, No. (%)				
Male	41 (46.1)	45 (54.9)	7 (46.7)	.55
Female	48 (53.9)	37 (45.1)	8 (53.3)	
Age, mean (SD), y	5.32 (0.31)	5.35 (0.29)	5.39 (0.39)	
Race/ethnicity, No. (%)				
White	42 (47.2)	49 (59.8)	10 (66.7)	.14
Racial/ethnic minority	47 (52.8)	33 (37.8)	5 (33.3)	

[a] Group differences were investigated within each variable, with no statistically significant differences found ($P > .05$ for all).

[b] Because of the lack of differences and small sample size of children with *AA* genotype, and consistent with existing literature, *AA* and *AG* genotypes were combined for analyses and referred to as *A* allele carriers.

2005. At that time, they were enrolled in the Peers and Wellness Study (PAWS), a larger longitudinal study (n = 338) of social dominance, biological responses to adversity, and mental and physical health.[32] Parents' written informed consent and children's assent were obtained, and schools and families were given a modest payment for participation. Follow-up home visits were conducted with limited resources between 2009 and 2011 (PAWS Follow-up and PAWS-Genetics) to collect data on pubertal development, growth, and genetics. This study was approved by the institutional review boards of the University of California at Berkeley and San Francisco campuses. The dates of the analysis were January 2015 to June 2016.

Socioeconomic Status

During their child's kindergarten year (fall semester of 2003, 2004, and 2005) and again during middle childhood (2009-2011), caregivers provided demographic information via questionnaires mailed to homes, including items assessing total household income and level of parental education. Socioeconomic status was calculated using a composite of standardized total income and highest level of parental education.

Genotyping

Children's DNA was collected in 2010, when they were 9 to 11 years old, using an all-in-one system (OG-500 DNA; Oragene) for the collection, stabilization, transportation, and purification of DNA from saliva. Children were asked to spit into a small vial, and samples were immediately mixed with stabilizing solution and stored at room temperature until assayed. The target single-nucleotide polymorphism (rs53576) was assayed using an assay platform (Taqman SNP Genotyping Assays; ThermoFisher Scientific) with a mix (Taqman Genotyping MasterMix; ThermoFisher Scientific) containing the amplification primers and target locus probes and run on a polymerase chain reaction system (7900HT; Applied Biosystems). The results were analyzed with a software program (SDS; Applied Biosystems), and a data plot provided genotype calls for the samples.

Table 1 lists the genotype distribution for *OXTR* among children included in these analyses, which was in Hardy-Weinberg equilibrium. χ^2 Analyses revealed no significant group differences in age, sex, or racial/ethnic minority status. Consistent with previous literature[19,33] and because of small numbers of homozygous *A* carriers found in the population, individuals were categorized based on the presence of the *A* allele (ie, *AA*/*AG* vs *GG*).

Anthropometric Outcomes

Height, weight, and triceps skinfold thickness were collected during a calendar year when children were in third, fourth, or fifth grade depending on the cohort wave. Children were weighed and measured without shoes or heavy clothing by trained staff using standard protocols and equipment. Body mass index was calculated as weight in kilograms divided by height in meters squared. Because children's BMI values differ based on age and sex, they were converted to *z* scores according to the US Centers for Disease Control and Prevention age- and sex-adjusted reference growth curves. Triceps skinfold thickness (in millimeters) was averaged across 2 repeated measurements on the right arm using calibrated calipers (Holtain Skinfold Caliper; Holtain Limited).

Covariates, including child sex, age, and race/ethnicity, were assessed via parental report. Because of the small numbers for most subgroups and moderate percentage of multiracial/multiethnic participants, racial/ethnic group status was calculated as a dichotomous variable reflecting "minority" vs white racial/ethnic groups.

Statistical Analysis

Examination of the *OXTR* polymorphism and SES main effects, and their interaction, was conducted using multivariable linear regression within a software program (SPSS, version 21; IBM). Minority status was included as a covariate in both models. Child age and sex were included as covariates in skinfold analyses and were previously adjusted within the calculation of BMIz. All analyses were performed using standardized variables. Significant interactions ($P < .05$) were probed in line with extant DNS research and as outlined by Aiken and West[34] by examining effect estimates from the full-sample covariate-adjusted model for the association between SES and BMIz and skinfold thickness separately for each genotype. Then, each of these within-group slope estimates was plotted across the range of SES within the sample to aid interpretation.

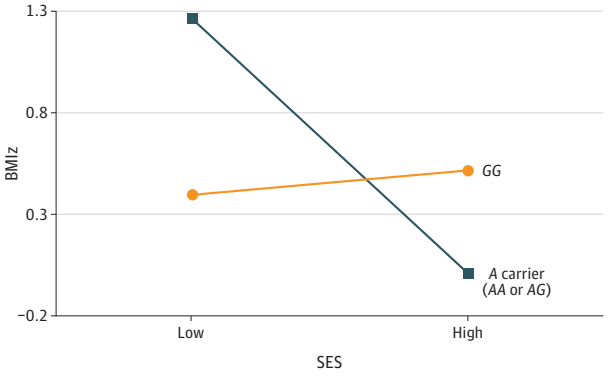
Results

Characteristics of the original sample and the subsample used for this study are summarized in **Table 2**. The genotyped subsample (n = 192) was less racially/ethnically diverse and had families with higher incomes and greater educational attainment compared with nongenotyped children, reflecting the higher rate of loss of contact with lower-SES and minority fami-

Table 2. Characteristics of the Original Sample and the Subsample Used for This Study

Characteristic	Nongenotyped Sample (n = 146)	Genotyped Subsample (n = 192)
Age at kindergarten entry, mean (SD), y	5.28 (0.33)	5.34 (0.31)
Age at anthropometric assessment, mean (SD), y	9.99 (0.47)	10.03 (0.47)
Sex, No. (%)		
Female	67 (45.9)	96 (50.0)
Male	79 (54.1)	96 (50.0)
Race/ethnicity, No./total No. (%)		
White	35/130 (26.9)	101/184 (54.9)
African American	37/130 (28.5)	20/184 (10.9)
Asian	17/130 (13.1)	16/184 (8.7)
Latino	7/130 (5.4)	6/184 (3.3)
Multiracial/multiethnic	32/130 (24.6)	37/184 (20.1)
Other	2/130 (1.5)	4/184 (2.2)
Total household income, $		
Mean (SD)	6.28 (2.99)	7.67 (2.36)
No./total No. (%)		
<10 000	7/127 (5.5)	6/189 (3.2)
10 000-19 999	12/127 (9.4)	4/189 (2.1)
20 000-29 999	7/127 (5.5)	9/189 (4.8)
30 000-39 999	20/127 (15.7)	2/189 (1.1)
40 000-49 999	6/127 (4.7)	9/189 (4.8)
50 000-59 999	8/127 (6.3)	9/189 (4.8)
60 000-79 999	13/127 (10.2)	27/189 (14.3)
80 000-99 999	14/127 (11.0)	36/189 (19.0)
100 000-149 999	22/127 (17.3)	52/189 (27.5)
150 000-199 999	11/127 (8.7)	28/189 (14.8)
≥200 000	7/127 (5.5)	7/189 (3.7)
Level of parental education		
Mean	4-y College degree	4-y College degree
No./total No. (%)		
Less than high school degree	3/131 (2.3)	5/191 (2.6)
Completed high school	12/131 (9.2)	6/191 (3.1)
Some college or 2-y degree	37/131 (28.2)	18/191 (9.4)
4-y College degree	26/131 (19.8)	31/191 (16.2)
Some graduate or professional school	12/131 (9.2)	27/191 (14.1)
Professional or graduate degree	41/131 (31.3)	104/191 (54.5)

Figure 1. Socioeconomic Status (SES) and Oxytocin Polymorphism Interaction Predicting Standardized Body Mass Index *z* Score (BMIz)



Children with an *A* allele in low SES families had the highest BMIz, while those in high SES families had the lowest BMIz. *GG* children were unaffected by their SES environment.

lies after the initial study was completed. However, this level of income and education is still largely representative of populations in the San Francisco Bay area. Of genotyped children, a subsample of 186 (mean age, 10.3 years; age range, 9.4-11.3 years; 93 female [50%]) of the original sample of 338 (55.3%) typically developing children had complete SES, growth, and genetic data across the longitudinal study. The mean (SD) SES composite of standardized total income and highest level of parental education was 0.21 (0.80). Other mean (SD) values were 1.42 (0.07) m for height, 37.12 (8.86) kg for weight, 0.38 (0.97) for BMIz, and 11.10 (4.20) mm for skinfold thickness.

Bivariate correlations between variables are listed in the eTable in the Supplement. In addition, there was a significant sex difference in skinfold thickness, with girls having increased skinfold thickness (mean [SD], 12.31 [4.23] mm) compared with boys (mean [SD], 9.91 [3.85] mm).

The results from the multivariable linear regression analyses testing the associations among SES, *OXTR* allelic variation, and BMIz, adjusting for racial/ethnic minority status (with BMIz adjusted for age and sex), revealed a significant interaction between SES and *OXTR* (β = 0.18; *P* = .04). Examination of the covariate-adjusted within-group effect estimates by genotype revealed a negative association between SES and BMIz for *A* allele carriers (n = 97), such that a 1-SD increase in SES was associated with a decrease in BMIz of 0.28 (95% CI, −0.47 to −0.09) (US Centers for Disease Control and Prevention age- and sex-normed distribution *z* scores), whereas SES was unrelated to BMIz for *GG* genotyped children (n = 89) (*b* = 0.03; 95% CI, −0.21 to 0.26). Using these within-group effect estimates, **Figure 1** shows that SES was related to BMIz only for children with the *A* allele, with *A* carriers exhibiting the highest BMIz in low SES environments and the lowest BMIz in high SES environments.

In the second multivariable linear regression model, adjusting for the effects of age, sex, and race/ethnicity, the interaction between SES and the *OXTR* polymorphism was significantly associated with skinfold thickness (β = 0.17; *P* = .01). Examination of the covariate-adjusted within-group effect estimates by genotype revealed a negative association between SES and skinfold thickness for *A* allele carriers (n = 97), such that a 1-SD increase in SES was associated with a decrease in skinfold thickness of 0.95 (95% CI, −1.77 to −0.12) mm, whereas SES was unrelated to skinfold thickness for *GG* genotyped children (n = 89) (*b* = 0.17; 95% CI, −0.42 to 1.45). Using these within-group effect estimates, **Figure 2** shows that SES was negatively associated with skinfold thickness only for *A* allele carriers, such that *A* carriers demonstrated the greatest thickness if in lower SES families but the least thickness if in high SES families.

The results from both models tested met the full criteria for identifying a genuine DNS interaction.[13] These findings are summarized in the eAppendix in the Supplement.

Discussion

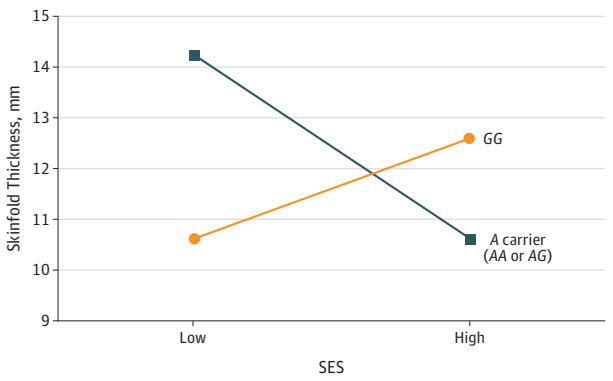
These study findings provide the first evidence, to our knowledge, that the *OXTR* OT receptor polymorphism confers differential susceptibility to the effects of SES on childhood obesity risk. Socioeconomic status was related to obesity risk only for children with the *A* allele, such that *A* carriers exhibited the highest BMIz and skinfold thickness in low SES environments but the lowest BMIz and skinfold thickness in high SES environments. The interaction effect was replicated across 2 related but distinct measures of adiposity, strengthening confidence in the reliability of each association.

Oxytocin is increasingly recognized as an important influence on metabolic regulation, appetite, and reward-driven eating processes and as such is a key potential driver of obesity.[21,22,27,35,36] Our findings add to this literature and suggest that individuals carrying the *A* allele of the OT receptor polymorphism may be more susceptible to both positive and negative environmental influences. Consistent with DNS theory, this pattern indicates that the *A* allele is best conceptualized as a sensitivity allele rather than as a risk allele. This interpretation is consistent with the findings from a 2012 study[15] in children demonstrating that *OTXR* genetic variation enhanced sensitivity to the social environment, such that *A* carriers were found to have the lowest levels of resilient functioning when maltreated but the highest levels of resilient functioning when not maltreated. Indeed, an article reviewing human OT studies suggested that OT enhances perception of both positive and negative social cues,[37] which may be a mechanism for such effects, and posits that *A* carriers may also show enhanced benefits from healthier environments. Given that the *A* allele is associated with less efficacious OT binding and that OT administered therapeutically results in increased social cognition and prosocial behavior,[37] children with this variant growing up in stressful environments may have a more limited capacity for coping with stress and thus experience unique, greater risk for childhood obesity through the stress pathway.

Consistent with the literature, we found no main effect of *OTXR* genotype on child adiposity, suggesting a more complex association between the polymorphism and body composition in humans than in animals. This result is not surprising given the tremendous variability in human physical, social, and food environments relative to those of research animals. Given that OT may enhance sensitivity to positive and negative social environment factors[8] and that OT feeding associations in mice differed as a function of social ranking and social environment,[26] it is important to consider how future mechanistic work can inform our understanding of these associations and their development over the life course in humans.

The preponderance of empirical evidence in support of DNS theories to date has come from the neuropsychological literature, although other health outcomes have been explored as well.[11-14] Evidence has emerged supporting application of the DNS model to predict obesity or obesogenic behavior, including 3 studies examining genetic moderation of the association between social factors and BMI,[38] emotional eating,[39] and dietary intake.[40] Our results parallel those by Silveira and colleagues,[40] who found that the negative association between family income and dietary fat intake depended on genetics in a DNS manner for female adolescents: girls carrying the 7-repeat allele of the *DRD4* (OMIM 126452) gene living in low-income families had increased fat intake compared with noncarriers, whereas girls carrying the 7-repeat allele and living in higher-income families had decreased fat intake relative to noncarriers. As such, in addition to informing our understanding of the complex determinants of health outcomes, our findings bolster the emerging body of empirical evidence for organismic (including genotypic) factors producing DNS to social environmental influence with respect to obesity risk. Further investigation of gene × environment interactions may provide important information regarding the etiology of childhood obesity, specifically how an individual's allelic variation may enhance sensitivity to both positive and negative environmental exposures and through which pathways or, alternatively, produce a relative impermeability to environmental influence. These areas are exciting new directions for research and hold potential for important practice implications.

Figure 2. Socioeconomic Status (SES) and Oxytocin Polymorphism Interaction Predicting Skinfold Thickness



Children with an *A* allele in low-SES families had the highest skinfold thickness, while those in high-SES families had the lowest skinfold thickness. *GG* children were unaffected by their SES environment.

Limitations

As with all studies, this study had limitations. We did not measure eating behavior, which may be a proximal mechanism of influence on child adiposity and is associated with OT. Our relatively small sample (for gene × environment interaction analyses) was diverse and moderately heavy, and the genotyped subsample had a somewhat higher SES than the children who were lost to follow-up, suggesting bias in attrition, so the results may not generalize to other samples. Also, although using a racially/ethnically diverse sample was a strength of this study, adjusting for minority status in analyses was not likely to fully address potential genetic confounds of race/ethnicity. Additional

limitations stem from controversy within the field surrounding examination of gene × environment interaction effects.[41-43] Our interaction findings may possibly reflect 2 false-positive results (type I error), which are possible in any scientific study but less likely than false-negative results in smaller samples.[43] Novel reports of interactions such as ours are thought to be particularly vulnerable, although the present study was based on a strong set of a priori hypotheses and understanding of specific biological and behavioral mechanisms derived from a growing body of experimental human and animal studies. In addition, we only examined 2 models, each with the same genotype; therefore, our study did not increase risk of type I error through multiple hypothesis testing. Indeed, it is particularly compelling that the interaction effect replicated in significance and in pattern of association across both objectively measured outcomes. Furthermore, our effect size was moderate and may reflect that our sample possessed a broad range of environmental exposure, and the genotype of interest was not rare and thus provided sufficient instances of genetic variation, optimal circumstances for the detection of "true" gene × environment interaction effects.[43] However, replication in an additional cohort of young children would further strengthen confidence in our results.

Conclusions

In summary, our findings provide preliminary evidence that risk for childhood obesity is attributable, at least in part, to genetic sensitivity to socioeconomic environments. The results highlight the substantial disparities in risk for poor metabolic health among some individuals and suggest a novel way to identify children at greatest risk for becoming overweight or obese within levels of SES to focus behavioral obesity prevention efforts on this population. In addition, although evidence is just emerging and the mechanisms need to be more clearly articulated, clinical implications of this work could ultimately include peripheral OT infusion as treatment for childhood obesity, with this approach already being conducted in early trials with adults. In the clinicaltrials.gov registry, almost 400 completed, ongoing, or future-funded investigations in humans list OT in preclinical trials to reduce caloric intake, gastric emptying, and obesity.[23] Finally, our findings indicate that the effects of gene × environment interaction interactive processes are evident early in human development, underscoring the temporal urgency of implementing prevention and treatment plans.

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Author Contributions: Dr Bush had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bush, Allison, Boyce.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bush, Allison, Miller.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bush, Allison.
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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(5):483-490.

2. Dixon JB. The effect of obesity on health outcomes. *Mol Cell Endocrinol*. 2010;316(2):104-108.

3. Halfon N, Larson K, Slusser W. Associations between obesity and comorbid mental health, developmental, and physical health conditions in a nationally representative sample of US children aged 10 to 17. *Acad Pediatr*. 2013;13(1):6-13.

4. Workgroup APaCHL. AAP agenda for children strategic plan poverty and child health. American Academy of Pediatrics; 2015. https://www.aap.org/en-us/about-the-aap/aap-facts/AAP-Agenda-for-Children-Strategic-Plan/pages/AAP-Agenda-for-Children-Strategic-Plan-Poverty-Child-Health.aspx#sthash.XFQRXClo.dpuf. Accessed October 3, 2016.

5. McLaren L. Socioeconomic status and obesity. *Epidemiol Rev*. 2007;29:29-48.

6. Adler NE, Ostrove JM. In: Adler NE, Marmot M, McEwen B, Stewart J, eds. *Socioeconomic Status and Health in Industrial Nations—Social*. Vol 896. Bethesda, MD: Psychological, and Biological Pathways; 1999:3-15.

7. Schreier HM, Chen E. Socioeconomic status and the health of youth: a multilevel, multidomain approach to conceptualizing pathways. *Psychol Bull*. 2012.

8. Dallman MF, Pecoraro NC, La Fleur SE, et al. Glucocorticoids, chronic stress, and obesity. *Prog Brain Res*. 2006;153:75-105.

9. Rossen LM, Schoendorf KC. 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(10):698-704.

10. El-Sayed Moustafa JS, Froguel P. From obesity genetics to the future of personalized obesity therapy. *Nat Rev Endocrinol*. 2013;9(7):402-413.

11. Bush NR, Boyce WT; Cicchetti D, ed. *Developmental Psychopathology*. Hoboken, NJ: John Wiley & Sons Inc; 2015.

12. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary-neurodevelopmental theory. *Dev Psychopathol*. 2011;23(1):7-28.

13. Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. For better and for worse: differential susceptibility to environmental influences. *Curr Dir Psychol Sci*. 2007;16(6):300-304.

14. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol Bull*. 2009;135(6):885-908.

15. Cicchetti D, Rogosch FA. Gene × environment interaction and resilience: effects of child maltreatment and serotonin, corticotropin releasing hormone, dopamine, and oxytocin genes. *Dev Psychopathol*. 2012;24(2):411-427.

16. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci*. 2011;12(9):524-538.

17. Lucht MJ, Barnow S, Sonnenfeld C, et al. Associations between the oxytocin receptor gene (*OXTR*) and affect, loneliness and intelligence in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(5):860-866.

18. Saphire-Bernstein S, Way BM, Kim HS, Sherman DK, Taylor SE. Oxytocin receptor gene (*OXTR*) is related to psychological resources. *Proc Natl Acad Sci U S A*. 2011;108(37):15118-15122.

19. Tost H, Kolachana B, Hakimi S, et al. A common allele in the oxytocin receptor gene (*OXTR*) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc Natl Acad Sci U S A*. 2010;107(31):13936-13941.

20. Uvnas-Moberg K, Petersson M. Oxytocin, a mediator of anti-stress, well-being, social interaction, growth and healing [in German]. *Z Psychosom Med Psychother*. 2005;51(1):57-80.

21. Ho JM, Blevins JE. Coming full circle: contributions of central and peripheral oxytocin actions to energy balance. *Endocrinology*. 2013;154(2):589-596.

22. Klockars A, Levine AS, Olszewski PK. Central oxytocin and food intake: focus on macronutrient-driven reward. *Front Endocrinol (Lausanne)*. 2015;6:65.

23. Blevins JE, Baskin DG. Translational and therapeutic potential of oxytocin as an anti-obesity strategy: insights from rodents, nonhuman primates and humans. *Physiol Behav*. 2015;152(pt B):438-449.

24. Morton GJ, Thatcher BS, Reidelberger RD, et al. Peripheral oxytocin suppresses food intake and causes weight loss in diet-induced obese rats. *Am J Physiol Endocrinol Metab*. 2012;302(1):E134-E144. doi:10.1152/ajpendo.00296.2011

25. Sclafani A, Rinaman L, Vollmer RR, Amico JA. Oxytocin knockout mice demonstrate enhanced intake of sweet and nonsweet carbohydrate solutions. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(5):R1828-R1833.

26. Olszewski PK, Allen K, Levine AS. Effect of oxytocin receptor blockade on appetite for sugar is modified by social context. *Appetite*. 2015;86:81-87.

27. Takayanagi Y, Kasahara Y, Onaka T, Takahashi N, Kawada T, Nishimori K. Oxytocin receptor–deficient mice developed late-onset obesity. *Neuroreport*. 2008;19(9):951-955.

28. Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J Clin Endocrinol Metab*. 1995;80(2):573-579.

29. Qian W, Zhu T, Tang B, et al. Decreased circulating levels of oxytocin in obesity and newly diagnosed type 2 diabetic patients. *J Clin Endocrinol Metab*. 2014;99(12):4683-4689.

30. Ott V, Finlayson G, Lehnert H, et al. Oxytocin reduces reward-driven food intake in humans. *Diabetes*. 2013;62(10):3418-3425.

31. Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci U S A*. 2009;106(50):21437-21441.

32. Boyce WT, Obradovic J, Bush NR, Stamperdahl J, Kim YS, Adler N. Social stratification, classroom climate, and the behavioral adaptation of kindergarten children. *Proc Natl Acad Sci U S A*. 2012;109(suppl 2):17168-17173.

33. Sturge-Apple ML, Cicchetti D, Davies PT, Suor JH. Differential susceptibility in spillover between interparental conflict and maternal parenting practices: evidence for OXTR and 5-HTT genes [published correction appears in *J Fam Psychol*. 2013;27(1):75]. *J Fam Psychol*. 2012;26(3):431-442.

34. Aiken LS, West SG. *Multiple Regression: Testing and Interpreting Interactions*. Newbury Park, CA: Sage Publications; 1991.

35. Camerino C. Low sympathetic tone and obese phenotype in oxytocin-deficient mice. *Obesity (Silver Spring)*. 2009;17(5):980-984.

36. Blevins JE, Graham JL, Morton GJ, et al. Chronic oxytocin administration inhibits food intake, increases energy expenditure, and produces weight loss in fructose-fed obese rhesus monkeys. *Am J Physiol Regul Integr Comp Physiol*. 2015;308(5):R431-R438.

37. Bartz JA, Zaki J, Bolger N, Ochsner KN. Social effects of oxytocin in humans: context and person matter. *Trends Cogn Sci*. 2011;15(7):301-309.

38. Carr KA, Lin H, Fletcher KD, et al. Two functional serotonin polymorphisms moderate the effect of food reinforcement on BMI. *Behav Neurosci*. 2013;127(3):387-399.

39. van Strien T, Snoek HM, van der Zwaluw CS, Engels RC. Parental control and the dopamine D2 receptor gene (*DRD2*) interaction on emotional eating in adolescence. *Appetite*. 2010;54(2):255-261.

40. Silveira PP, Gaudreau H, Atkinson L, et al. Genetic differential susceptibility to socioeconomic status and childhood obesogenic behavior: why targeted prevention may be the best societal investment. *JAMA Pediatr*. 2016;170(4):359-364.

41. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. 2011;168(10):1041-1049.

42. Rutter M, Thapar A, Pickles A. Gene-environment interactions: biologically valid pathway or artifact? *Arch Gen Psychiatry*. 2009;66(12):1287-1289.

43. Kraemer HC. Determining gene moderation of environmental risk factors for a mental disorder: a "perfect storm" of methodological problems. *Int J Methods Psychiatr Res*. 2012;21(3):185-194.