International Journal of Obesity (2013), 1–7

www.nature.com/ijo

ORIGINAL ARTICLE

Impulsivity and genetic variants in *DRD2* and *ANKK1* moderate longitudinal associations between sleep problems and overweight from ages 5 to 11

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OBJECTIVE: Short sleep duration and sleep problems increase risks of overweight and weight gain. Few previous studies have examined sleep and weight repeatedly over development. This study examined the associations between yearly reports of sleep problems and weight status from ages 5 to 11. Although, previous studies have shown that inter-individual differences moderate the effect of short sleep duration on weight, it is not known whether inter-individual differences also moderate the effect of sleep problems on weight. We tested how the longitudinal associations between sleep problems and weight status were moderated by impulsivity and genetic variants in *DRD2* and *ANKK1*.

DESIGN: Seven-year longitudinal study.

PARTICIPANTS: A total of 567 children from the Child Development Project for the analysis with impulsivity and 363 for the analysis with genetic variants.

MEASUREMENTS AND RESULTS: Sleep problems and weight status were measured by mothers' reports yearly. Impulsivity was measured by teachers' reports yearly. Six single-nucleotide polymorphisms located in *DRD2* and *ANKK1* were genotyped. Data were analyzed using multilevel modeling. Higher average levels of sleep deprivation across years were associated with greater increases in overweight ($P = 0.0024$). Sleep problems and overweight were associated at both within-person across time ($P < 0.0001$) and between-person levels ($P < 0.0001$). Impulsivity and two polymorphisms, *rs1799978* and *rs4245149* in *DRD2*, moderated the association between sleep problems and overweight; the association was stronger in children who were more impulsive ($P = 0.0022$), in G allele carriers for *rs1799978* ($P = 0.0007$) and in A allele carriers for *rs4245149* ($P = 0.0002$).

CONCLUSIONS: This study provided incremental evidence for the influence of sleep problems on weight. Findings of *DRD2*, *ANKK1* and impulsivity are novel; they suggest that reward sensitivity and self-regulatory abilities might modulate the influences of sleep on weight gain. The analysis of polymorphisms was restricted to European Americans and hence the results might not generalize to other populations.

International Journal of Obesity advance online publication, 30 July 2013; doi:10.1038/ijo.2013.123

Keywords: sleep problems; overweight; impulsivity; DRD2; ANKK1; children

INTRODUCTION

Short sleep duration and sleep problems are associated with increased risks of overweight and this association is particularly robust in children.[1–3] However, longitudinal studies with repeated assessments of sleep and weight have been lacking. Such studies will be important for examining the continuity of exposure to sleep disturbances and its influences on changes in weight.[3] Evidence suggests improved sleep might be therapeutic in preventing and treating overweight and obesity, but mechanisms by which sleep affects weight have not been well elucidated, and the effect of sleep on weight is modest and of questionable clinical significance.[4] The modest effect might be due to the fact that the effect of sleep on weight varies significantly across individuals. Recent evidence suggests that the association between reported short sleep duration and weight is influenced by individual differences in behavioral traits and obesity genes.[5,6] However, it is not known whether this moderator effect also applies to reported sleep problems. Studies identifying moderating influences on the effect of sleep on weight will shed light on the mechanisms by which sleep affects weight and allow identification of obese persons who might benefit most from sleep modification.

One mechanism by which sleep disturbances lead to increased odds of overweight might involve increased reward-driven eating behavior.[5] Sleep curtailment is followed by increased intake of highly palatable food.[7–9] In addition, measured and reported sleep duration and sleep quality are associated with dopaminergic changes in the striatum, which could lead to increased preference for calorie-dense food following sleep deprivation.[10–12] It is logical to expect that individuals who are predisposed to reward-driven eating behavior would be more prone to overeating and subsequent overweight when they experience sleep disturbances. Genetic variants in *DRD2 and ANKK1* influence the functioning of the dopamine-mediated reward circuitry in the brain and the risks

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Received 28 May 2012; revised 27 May 2013; accepted 26 June 2013; accepted article preview online 5 July 2013

of overeating and obesity,[13,14] and therefore, the predisposition to reward-driven eating behavior. Previous studies have investigated primarily one single-nucleotide polymorphism (SNP), the *TaqIA* polymorphism, among multiple SNPs in *DRD2* and *ANKK1*. As SNPs in close proximity might show strong linkage disequilibrium, previous findings of *TaqIA* polymorphism might have been confounded by other functional variants that are located in these genes. Hence, in this study we examined multiple SNPs that have been previously associated with addictive behaviors in a study that systematically screened the *DRD2/ANKK1* region.[15]

Self-regulatory abilities such as inhibitory control and ability to delay gratification are crucial in regulating reward-driven behavior. Impulsive individuals, often deficient in self-regulation, should be more at-risk for reward-driven eating behavior than non-impulsive ones. Indeed, impulsive children showed reduced weight loss relative to non-impulsive children in response to obesity treatment.[16] In addition, impulsive children are particularly at-risk for maladaptive parenting strategies involving the use of food that increase the risks of overeating and overweight.[17,18] One can hypothesize that impulsive children who are sleep deprived will more likely engage in reward-driven eating behavior compared with non-impulsive sleep-deprived children.

In this study, we examined the association between yearly reports of sleep problems and overweight across 7 years in childhood. It was hypothesized that individuals with higher average levels of sleep problems across years would have higher average levels of overweight, and that levels of sleep problems across years within individuals would be positively associated with levels of overweight over time. It was also hypothesized that higher levels of continued exposure to sleep problems across years would be associated with greater increase in levels of overweight. Finally, it was hypothesized that SNPs in *DRD2* and *ANKK1* and impulsivity would moderate the associations.

PARTICIPANTS AND METHODS

Participants

Data were obtained from the Child Development Project,[19,20] a representative community sample of 585 children from Nashville and Knoxville, TN, USA, and Bloomington, IN, USA. Ethical approval was obtained from the Institutional Review Boards of the universities conducting the study. Eighteen participants who did not provide data in any year from age 5 to age 11 on sleep problems, overweight or impulsivity were excluded from this study, and participants who provided data on some of the years were included. The group of 18 excluded participants did not differ significantly from the sample for this study with respect to socioeconomic status, mother's education, father's education and gender ratio. Data from a total of 567 participants were included in the analysis of the associations between sleep problems and overweight, and the moderation effect of impulsivity. Among them, 430 participants provided data on genetic variants. This sample consisted of 363 self-identified European Americans (51% male), 60 self-identified African Americans (33% male) and 7 participants who either self-identified as 'others' or did not endorse any ethnic category. As population stratification, as denoted by distributional differences in allele frequencies across subsamples, can confound the results of genetic association studies, and small subsamples (for example, 60 African-American children) are statistically underpowered to detect meaningful genetic effects, the analysis of SNPs in this study was restricted to European Americans ($N = 363$).

Measures

Overweight was assessed by mothers' yearly reports from age 5 to age 11 on the Child Behavior Checklist[21] (CBCL). Items consisted of 'overweight' and 'overeating', and were rated on a three-point scale from 0 to 2. Correlations between the two items across the years ranged from 0.52 to 0.78. We collected self-reported height and weight of this sample at age 22 and age 23 and computed body mass indexes (BMIs), respectively. The average of the two items in the CBCL at each year from age 5 to age 11 was significantly correlated with BMI in age 22 and 23 (*r*s ranged from 0.32 to 0.61). In a study tracking reported BMI for 22 years, reported BMIs in childhood were significantly correlated with reported BMIs in young adulthood (*r*s ranged from 0.29 to 0.65).[22] The similar range of moderate-to-strong correlations between the items in the CBCL from age 7 to age 11 and reported BMIs at age 22 and age 23 in this sample can serve as evidence supporting the validity of the items in the CBCL as a measure of weight status. In addition, it has been reported that 60% of mothers reported accurate weight status of their children, and 30% of mothers underestimated their children's weight status.[23] Hence, mother-reported overweight status in this study was likely a stringent indicator.

Sleep problems were assessed by mothers' yearly reports from age 5 to age 11 on the CBCL.[21] Sleep problems were assessed by three items (overtired, sleeps less than others, trouble sleeping) from 0 (never) to 2 (always). Consistent with the small number of and somewhat diverse symptoms, the scale showed a moderate level of internal consistency at every age (αs ranged from 0.35 to 0.59), which was acceptable for the purpose of this study. We collected more detailed data of sleep (for example, mothers' reports on bedtimes and wake times during weekdays and weekends, nap frequency and ratings of sleep adequacy) of this sample beyond the age range of interest in this study, at age 13 and age 15, at which ages the sleep problems scale of the CBCL was also administered. The average scores of the sleep problems scale of the CBCL at age 13 and age 15 were correlated significantly with concurrent reported sleep duration ($rs = 0.27$ and 0.20, respectively). Although the correlations were low-to-moderate and were at ages that were not investigated in the main analysis, they suggested that the sleep problems scale of the CBCL has reasonable validity. Items in the sleep problems scale have also been shown to be correlated with objective measures such as actigraphy[24] and to predict various functional outcomes such as future development of emotional and behavior problems[25] and externalizing symptoms.[26] The three items were averaged to form an index of sleep problems at each time point in this study.

Genotyping. DNA was collected via saliva sample using Oragene collection kits (OraSure Technologies, Bethlehem, PA, USA). Saliva samples were subsequently labeled anonymously and mailed to the laboratory of Dr Alison Goate at Washington University, St Louis (WUSL), MO, USA, where DNA extraction and genotyping occurred. A total six SNPs were genotyped across the *DRD2/ANKK1* complex. At WUSL, initial selection of SNPs was based on prior evidence of association with alcohol dependence phenotypes in family-based association analyses within the Collaborative Study on the Genetics of Alcoholism sample,[15] and genotyping was conducted with a modified single-nucleotide extension reaction, with allele detection by mass spectrometry (Sequenom MassArray system; Sequenom, San Diego, CA, USA). PCR and extension primers (available on request) were designed using MassARRAY Assay Design Version 3.1.2.5. The genotyping success rate for this gene, within this sample, was 99.1%. Haploview[27] was used to estimate linkage disequilibrium across the full set of genotyped SNPs. Pairwise associations between markers in *DRD2/ANKK1* yielded R^2 values ranging from 0.00 to 0.16. The six SNPs were *rs6275*, *rs1799978*, *rs4245149* and *rs12361003* in *DRD2*, and *rs1800497* and *rs4938012* in *ANKK1*. The SNP *rs1800497* is typically referred as the *TaqIA* polymorphism. The coding of the SNPs consisted of values 0, 1 and 2 representing the number of copies of the reference alleles. As most of these SNPs have no known functional variants, the reference alleles were selected arbitrarily based on alphabetical order. Hence, the reference allele was the T allele in SNPs *rs6275* (A/T) and *rs1800497* (C/T), the G allele in SNPs *rs1799978* (A/G), *rs4245149* (A/G) and *rs4938012* (A/G), and the C allele in SNP *rs12361003* (A/C). For SNP *rs1800497* (*TaqIA*), the reference allele corresponded to the A1 allele.

Impulsivity was assessed by seven items (for example, impulsive or acts without thinking, talks out of turn, and disrupts class discipline) in the Achenbach's Teacher Report Form[28] based on teacher's annual reports from age 5 to age 11. This scale showed strong internal consistency (αs ranged from 0.88 to 0.90). Items were averaged to form an index of impulsivity in each year. The impulsivity indexes across years were averaged to give a mean level of impulsivity for each individual. This mean level of impulsivity was then used as a between-person variable instead of a time-varying within-person variable, given that the interest in this study was to test whether a stable trait of impulsivity, which reflects one's self-regulatory resources, would moderate the association between sleep problems and overweight.

Covariates. *Physical activity* and *socioeconomic status* (SES) were controlled for in all analyses, because they could confound the associations between sleep problems and overweight. *Physical activity* was assessed for

each child by the mother's reports of frequency of participating in sports yearly from age 5 to age 11. For example, every mother was asked to list the sports activities that her child participated in, and rate the time the child spent on each of the activities (0—less than average, 2—average and 3—more than average). The sum of the ratings for the listed activities then formed the index for the child's level of physical activity. It was added to the analysis as a time-varying variable. *SES* was calculated for the entire sample in the first year of the study, and was based on parental educational level and occupation. Hollingshead SES scores in this sample ranged from 8 to 66, with a mean of 41.2 (s.d. = 14.1).

Yearly assessments on mother-reported variables (overweight, sleep deprivation and physical activity) were typically obtained within the fall semester of the school year. Yearly assessments on the teacher-reported variable (impulsivity) were typically obtained within the spring semester of the school year.

Statistical analysis

Multilevel modeling was used with multiple years of ratings nested within persons. SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used. Using multilevel modeling, the *inter*-individual variation and the *intra*-individual variation of the levels of sleep problems can be modeled separately. Hence, we were able to test whether individuals with higher average levels of sleep problems across years would have higher levels of overweight, that is, the sleep problems—overweight association at the between-person level, and whether variation in the levels of sleep problems across years within individuals would be positively associated with variation in the levels of overweight across years, that is, the sleep problems—overweight association at the within-person level. All predictors were either group-mean centered or grand-mean centered according to the recommendations in Enders and Tofighi.[29] Interaction terms were formed with group-mean centered predictors as recommended. As scores on the dependent variable, overweight, substantially deviated from a normal distribution (skewness: 1.95–4.63; kurtosis: 2.92–24.58), the pseudo-likelihood estimation method in PROC GLIMMIX was used for parameter estimations. Residual log-likelihood ratio tests were used to compare model fit.

The baseline model consisted of a random linear trend model that captured the change in overweight across years. In the level 1 (within-person) equation, level of overweight of individual i at time t is denoted as $(\text{overweight})_{ti}$; the intercept (the mean level) of overweight across time for individual i is denoted as β_{0i}, the linear change for individual i is denoted as $\beta_{1i}(\text{linear})_{ti}$; and the error is denoted as R_{ti}. In the level 2 (between-person) equations, the means across individuals and the individual-specific residual of the respective regression coefficients (βs) are represented by γs and Us.

Baseline model

Level 1: $(\text{overweight})_{ti} = \beta_{0i} + \beta_{1i}(\text{linear})_{ti} + R_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + U_{0i}$
$\beta_{1i} = \gamma_{10} + U_{1i}$

To test whether sleep problems were associated with overweight within individuals across time (level 1), time-varying sleep problems, denoted as $\beta_{2i}(\text{sleep problems})_{ti}$, were added to the level 1 equation of the baseline model. To test whether variation in the levels of sleep problems across individuals were associated with levels of overweight, the average level of sleep problems across years for each individual, denoted as $\gamma_{01}(\text{sleep problems})_{0i}$ was added to the level 2 equation. Physical activity, denoted as $\beta_{3i}(\text{physical activity})_{ti}$, was a time-varying confounding variable and hence was added to the level 1 equation. SES was a time-invariant confounding variable and hence was added to the level 2 equation. In addition, the average level of sleep problems was also added to the level 2 equation predicting the linear change in overweight to test if children who had high levels of continued exposure to sleep problems would have greater increases in overweight than children who had low typical levels of sleep problems. This sleep problems model was then compared against the baseline model to see if sleep problems improved model fit, and fixed effects coefficients of the main effects were examined to see if sleep problems correlated with overweight at each of the two levels.

Sleep problems model

Level 1: $(\text{overweight})_{ti} = \beta_{0i} + \beta_{1i}(\text{linear})_{ti} + \beta_{2i}(\text{sleep problems})_{ti} + \beta_{3i}(\text{physical activity})_{ti} + R_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(\text{sleep problems})_{0i} + \gamma_{02}(\text{SES})_{0i} + U_{0i}$ $\beta_{1i} = \gamma_{10} + \gamma_{11}(\text{sleep problems})_{1i} + U_{1i}$ $\beta_{2i} = \gamma_{20} + U_{2i}$ $\beta_{3i} = \gamma_{30}$

To test whether the six SNPs and impulsivity moderated the association between sleep problems and overweight, the main effects model was compared with the sleep problems by moderator interaction model to see if adding the interaction effect improved model fit, and if the interaction effect was significant. The main effects model was equivalent to the sleep problems model except that the main effect of the moderator was added in the level 2 equation predicting the intercept. In the sleep problems by moderator interaction models, the effect of the moderator was added in predicting the within-person effect of sleep problems, that is, a cross-level interaction effect as well as in predicting the between-person effect of sleep problems. Adjusted P-value ($0.05/7 = 0.007$) was used for examining significance of the results of the six SNPs to correct for multiple comparisons.

Sleep problems by moderator interaction model

Level 1: $(\text{overweight})_{ti} = \beta_{0i} + \beta_{1i}(\text{linear})_{ti} + \beta_{2i}(\text{sleep problems})_{ti} + \beta_{3i}(\text{physical activity})_{ti} + R_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(\text{sleep problems})_{0i} + \gamma_{02}(\text{SES})_{0i} + \gamma_{03}(\text{Moderator})_{0i} + \gamma_{04}(\text{sleep problems} \times \text{moderator})_{0i} + U_{0i}$ $\beta_{1i} = \gamma_{10} + \gamma_{11}(\text{sleep problems})_{1i} + U_{1i}$ $\beta_{2i} = \gamma_{20} + \gamma_{21}(\text{moderator})_{0i} + U_{2i}$ $\beta_{3i} = \gamma_{30}$.

RESULTS

On average, the level of overweight increased over time as shown in the random linear trend model (baseline model), where the effect of the linear change was significantly greater than 0 ($\gamma_{10} = 0.03$, $P < 0.001$). Adding a random component to the linear change significantly improved the model fit (log-likelihood difference = 1791.0–1057.9 = 733.1, $df = 1$, $P < 0.001$), indicating that there was significant variability across individuals in the change of overweight over time. The sleep problems model fit significantly better than the baseline model (log-likelihood difference = 1057.9–899.9 = 158, $df = 6$, $P < 0.001$). The effects of sleep problems at both the within-person level and the between-person level were highly significant ($\gamma_{20} = 0.15$, $P < 0.001$; $\gamma_{01} = 0.31$, $P < 0.001$), even controlling for physical activity ($\gamma_{30} = -0.004$, $P = 0.16$) and SES ($\gamma_{02} = -0.003$, $P < 0.001$). The effect of sleep problems on the linear change of overweight was significant ($\gamma_{11} = 0.05$, $P = 0.003$), indicating that higher levels of continued exposure to sleep problems across years were associated with greater increases in overweight.

Table 1. Pairwise associations (R^2) among SNPs and Pearson correlations among SNPs and impulsivity

	rs6275	*rs1799978*	*rs4245149*	*rs12361003*	*rs1800497*	*rs4938012*
rs1799978	0.16					
rs4245149	0.00	0.00				
rs12361003	0.03	0.00	0.06			
rs1800497	0.00	0.06	0.00	0.03		
rs4938012	0.09	0.16	0.00	0.05	0.02	
Impulsivity	0.02 (0.644)	0.01 (0.836)	−0.03 (490)	0.03 (0.535)	0.14 (0.005)	−0.06 (0.196)

Abbreviation: SNP, single-nucleotide polymorphism. Numbers in parentheses are *P*-values.

Table 2. Means of sleep problems and overweight and correlations between them by genotype groups and levels of impulsivity

	N	*Mean of overweight*	*Mean of sleep problems*	*Correlation between overweight and sleep problems (95% confidence interval)*
rs6275				
C/C	178	0.33	0.23	0.27 (0.128 to 0.401)
T/C	152	0.30	0.18	0.13 (0.021 to 0.330)
T/T	33	0.17	0.17	0.17 (−0.184 to 0.485)
rs1799978				
A/A	323	0.15	0.15	0.17 (0.062 to 0.274)
G/A	37	0.10	0.16	0.37 (0.052 to 0.620)
G/G	3	0.63	0.19	1.00[a]
rs4245149				
A/A	3	0.57	0.58	0.95[a]
G/A	87	0.16	0.15	0.21 (−0.001 to 0.403)
G/G	273	0.14	0.15	0.13 (0.012 to 0.245)
rs12361003				
A/A	36	0.19	0.16	0.05 (−0.283 to 0.372)
C/A	167	0.16	0.18	0.24 (0.092 to 0.378)
C/C	160	0.13	0.12	0.20 (0.046 to 0.345)
rs1800497				
C/C	237	0.15	0.14	0.25 (0.126 to 0.366)
T/C	112	0.15	0.16	0.15 (−0.037 to 0.327)
T/T	14	0.12	0.29	0.22 (−0.352 to 0.672)
rs4938012				
A/A	39	0.13	0.21	0.12 (−0.203 to 0.420)
G/A	150	0.15	0.15	0.19 (0.031 to 0.340)
G/G	174	0.15	0.14	0.30 (0.158 to 0.430)
Impulsivity				
High	355	0.19	0.17	0.31 (0.213 to 0.401)
Low	212	0.12	0.15	0.17 (0.036 to 0.298)

[a]The sample size is too small for computing the 95% confidence interval.

Table 1 presents the Haploview pairwise associations among SNPs and the correlations between SNPs and impulsivity. Impulsivity was minimally correlated with the SNPs. SNPs were minimally to moderately correlated with each other. Table 2 presents the descriptive statistics of and correlations between sleep problems and overweight by genotype groups and levels of impulsivity. The G allele in *rs1799978* and the A allele in *rs4245149* in *DRD2*, and the G allele in *rs4938012* in *ANKK1* were associated with greater magnitudes of the association between sleep problems and overweight. The association between sleep problems and overweight was also stronger in individuals with high levels of impulsivity (>median) than those with low levels of impulsivity.

Significance tests of moderation effects

Table 3 presents the model fit of the interaction models and respective main effects models. The interaction models for SNPs *rs6275* and *rs12361003* in *DRD2*, and SNPs *rs1800497* and *rs4938012* in *ANKK1* did not fit significantly better than the respective main effects models. This indicated that these SNPs did not significantly moderate the association between sleep problems and overweight. However, the interaction models for SNPs *rs1799978* and SNP *rs4245149* in *DRD2,* and impulsivity each fit significantly better than the respective main effects models. Table 4 presents the parameter estimates of the fixed effects in the better–fit interaction models. The main effects of SNP *rs1799978,* SNP *rs4245149* and impulsivity were not significant. SNP *rs1799978* significantly moderated the association between sleep problems and overweight at the between-person level; the association was stronger among those who carried the G allele in SNP *rs1799978*. SNP *rs4245149* significantly moderated the association between sleep problems and overweight at the between-person level; the association was stronger among those who carried the A allele in SNP *rs4245149*. Impulsivity also significantly moderated the association between sleep problems and overweight at the between-person level; the association was stronger in children who were more impulsive. At the within-person level, the moderation effects of SNP *rs1799978*, SNP *rs4245149* and impulsivity were not significant. This indicated that, although the strength of the association between average levels of sleep problems and overweight across individuals was influenced by SNP *rs1799978*, SNP *rs4245149* and impulsivity, the strength of the association between changes in levels of sleep problems and overweight across time within individuals was not. None of the other SNPs moderated the associations between sleep problems and overweight.

Table 3. Model fit: –2 residual log likelihood

	Main effects models	*Interaction models*
Impulsivity	899.9	893.8[a]
rs6275	401.6	407.0
rs1799978	399.6	391.2[a]
rs4245149	398.9	388.3[a]
rs12361003	400.8	405.2
rs1800497	401.1	406.2
rs4938012	401.5	405.5

[a]Two-way interaction models that fit significantly better than the respective main effects models.

Although we restricted the planned SNPs analyses to European Americans, we have conducted a sensitivity analysis of the models of SNPs, by including those who identified themselves as African Americans and 'others' in the analysis. Results of the analysis of the complete sample showed the same patterns of directions of effects and significance levels of the coefficients. (We planned to analyze only the European-American subsample because the African-American subsample ($N=60$) was too small for any meaningful analysis of SNP × sleep problems interaction effects. Statistical power for such tests ranged only from 6 to 13%. Statistical power for testing such effects in the European-American subsample ($N=363$) ranged from 50 to 85%.)

DISCUSSION

This study confirmed the association between sleep problems and overweight at both the between-person and within-person levels in a community sample of children across the middle childhood years of development. The association at the between-person level replicates previous studies showing that children with higher levels of sleep problems had higher levels of overweight problems compared with other children.[30–33] The present study's test of the association at the within-person level across development was relatively novel. Previous studies have only examined the association between sleep and overweight across development by regressing aggregated data of individuals at a later time point on aggregated data at earlier time points, which could not separate within-person and between-person variation.[30,34,35] An important advantage of the present study's within-person test is that it eliminates influences from unmeasured, potentially confounding between-individual variables, such as parental obesity. Further, we confirmed that children with higher levels of continued exposure to sleep problems across years had greater increases in levels of overweight across years.

Table 4. Unstandardized coefficients of parameter estimates

	Sleep problems × rs1799978 interaction effect model	*Sleep problems × rs4245149 interaction effect model*	*Sleep problems × impulsivity interaction effect model*
Intercept (γ'_{00})	0.169 (0.002)	0.214 (0.005)	0.129 (0.004)
Linear trend (γ'_{10})	0.033 (<0.001)	0.033 (<0.001)	0.035 (<0.001)
Sleep problems (within-person) (γ'_{20})	0.094 (0.021)	0.091 (0.023)	0.154 (<0.001)
Physical activity (γ'_{30})	−0.006 (0.117)	−0.006 (0.117)	−0.004 (0.155)
Sleep problems (between-person) (γ'_{01})	0.209 (0.007)	0.181 (0.020)	0.279 (<0.001)
SES (γ'_{02})	−0.004 (0.002)	−0.003 (0.005)	−0.003 (<0.001)
Moderator (γ'_{03})	0.035 (0.397)	−0.029 (0.367)	0.017 (0.598)
Sleep problems (between-person) × moderator (γ'_{04})	0.643 (<0.001)	−0.462 (<0.001)	0.379 (0.002)
Sleep problems (between-person) × linear trend (γ'_{11})	0.044 (0.044)	0.041 (0.057)	0.055 (0.002)
Sleep problems (within-person) × moderator (γ'_{21})	134 (0.256)	128 (0.090)	0.095 (0.157)

Abbreviation: SES, socioeconomic status. Numbers in parentheses are *P*-values.

Most previous studies on sleep and weight have examined the effect of short sleep duration on weight. Only a few studies have examined the effect of sleep problems other than short sleep duration on weight, showing that irregular sleep and troubles staying asleep were associated with future weight gain and higher BMI.[1,36] Given that the literature on sleep shows that sleep quality and sleep duration are independently associated with childhood internalizing and externalizing problems,[37] school performance,[38] diabetes risk[39] and cardiovascular disease,[40] it is reasonable to hypothesize that sleep problems and short sleep duration might be independently associated with overweight. In this study, mothers' reports on sleep problems showed small-to-moderate levels of association with reported sleep durations. We think that reported sleep problems in this study, instead of being an approximate measure of sleep duration, might actually represent an independent dimension of sleep quality. Future research should examine whether sleep quality and sleep duration independently contribute to risks of overweight and whether the mechanisms involved are similar or different.

This study was the first to our knowledge that tested whether genetic variants in *DRD2* and *ANKK1* moderated the association between sleep problems and overweight. We found that weight status of G allele carriers for SNP *rs1799978* in *DRD2* and A allele carriers for SNP *rs4245149* in *DRD2* was more affected by chronic exposure to sleep problems than the weight status of children who carried the alternative alleles. This finding supports the hypothesis that the reward-processing system might be involved in the mechanism by which sleep problems influences the risks of overweight.[41] Perhaps increasing sleep quality might be a promising target for intervention in prevention and treatment of obesity for children who carry these alleles. Our finding points to a new direction of future research on the relationship between sleep and weight. In addition to impairment of homeostatic regulation of eating,[42–47] sleep problems might specifically influence *reward-driven eating*. If supported by further evidence, reward-driven eating might be the specific target for interventions in individuals who are sleep-deprived.

The functions of SNP *rs1799978* and SNP *rs4245149* are not yet known. Their significant effects in this study might be due to associations with other functional variants that are in linkage disequilibrium with SNP *rs1799978* and SNP *rs4245149*. SNPs *rs1799978* and *rs4245149* were minimally associated with the other four SNPs in this study. It was, therefore, not surprising that the other four SNPs did not show comparable results. The lack of association among SNP *rs1799978* and SNP *rs4245149* in *DRD2*, and SNP *rs1800497* in *ANKK1* (the *Taq1A* polymorphism that has been found to be associated with D2 receptor expression) indicates that these three SNPs likely serve as references for independent biological mechanisms in relation to dopaminergic functioning. Adjustments of *P*-values were made for multiple testing, minimizing the possibility of these significant results being due to chance.

This is the first study to our knowledge that has tested whether the behavioral trait of impulsivity moderates the association between sleep problems and overweight. Results support our hypothesis. Sleep problems affected weight status of impulsive children more strongly than non-impulsive children. If replicated in future studies, this will have important implications. In addition, this suggests that increasing sleep quality might be a promising target for intervention of obesity for children with high levels of impulsivity. Interventions that involve increasing sleep quality in children might reduce the risk of overweight directly through mechanisms by which sleep influences eating and weight regulation as well as indirectly through improving self-regulatory ability. Third, given that sleep problems can impede the development of self-regulatory ability in children[48,49] and given that low self-regulatory ability, often manifested as high levels of impulsivity, can augment the adverse effect of sleep problems on overweight, sleep problems occurring at an early age might produce especially strong and long-lasting influences on the risk of overweight and obesity. This converges with findings from epidemiological studies showing that the association between sleep problems and overweight is stronger and more consistently replicated in children than adults.[2,3,50–55]

One limitation in this study is that weight status was not objectively measured. Although mother reports of weight status were correlated with self-reported BMI at a later age, their accuracy might still be limited, and hence reduce the power to detect significant results. Nonetheless, we did find robust associations between sleep problems and overweight, confirming the findings from previous epidemiological studies. A second limitation is that, both sleep problems and overweight were reported by mothers on the CBCL, the associations between them might be inflated because of common reporter variance. We did additional analyses that showed that the association between sleep problems and overweight remained significant when the common reporter variance was modeled explicitly and the common reporter variance was actually not significant. (We collected both mothers' and fathers' reports of sleep problems and overweight from age 5 to age 9. Using structural equation modeling, we modeled reporters' biases by estimating the common variance between the responses on two variables given by the same reporter, that is, a latent mother-report bias factor and a latent father-report bias factor, in addition to modeling the latent factors of sleep deprivation and overweight by estimating the common variance between two reporters' responses on the same variables. The association between the latent factors of sleep problems and overweight remained significant when the reporters' biases were accounted for in the model and the variance of the latent mother-report bias factor

was not significant, indicating that the association between mothers' reports on sleep deprivation and overweight observed in this study was not be due to common reporter variance.) The third limitation is that, the distribution of the overweight variable substantially deviated from a normal distribution, which might lead to biased parameter estimates. Given concerns about the impact of data non-normality of the parameter estimates, we verified the levels of significance of the results using a non-parametric bootstrapping method that is not affected by the data distribution. Bootstrapping results supported the significance of the findings in this study. (We applied the non-parametric bootstrapping method to create an empirical distribution of each parameter estimate using the resampling function (mcmcsamp) in the lme4 package in R (version 2.15; R core team).[56] This is a bootstrapping method specifically developed for mixed effects models. A total of 10 000 resamples of 363 cases (for models of SNPs) and 567 cases (for models of impulsivity) were generated from the posterior distribution of the parameter estimates of the fitted models using Markov Chain Monte Carlo methods. The means, s.d. and 95% confidence intervals were then estimated for each parameter. The 95% confidence intervals of all the significant effects we found did not include zero, supporting the significance of these effects). A further limitation is that the analysis of SNPs in this study was restricted to the European-American subsample. However, including the 67 non-European-American participants in the analysis did not change the patterns and levels of significance of the results. Results might not be generalizable to other populations. A major strength of this study is its longitudinal design with yearly assessments. Via the use of multi-level modeling, we were able to examine the within-person and between-person variability in sleep problems and overweight, and the association between sleep problems and the *change* in overweight over time. In addition, measures of sleep problems, overweight and impulsivity were obtained from different informants, and multiple SNPs across the *DRD2* and *ANKK1* gene regions were examined.

This study provides novel evidence suggesting that the effect of sleep problems on weight is amplified by high impulsivity and carrying certain alleles in *DRD2*. Findings might suggest that altered reward sensitivity and lack of self-regulatory abilities are implicated in association between sleep problems and weight regulation. Future research on the association between sleep quality and obesity might benefit from considering the mechanisms involving reward-driven food consumption behavior and self-regulation processes in food consumption. Treatment and prevention for pediatric obesity might benefit from improving sleep quality particularly in children who carry certain alleles in the *DRD2* and *ANKK1* genes. Interventions for pediatric obesity might also benefit from helping children build self-regulatory skills.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The Child Development Project has been funded by National Institute of Mental Health Grants MH42498, MH56961, MH57024 and MH57095; Eunice Kennedy Shriver National Institute of Child Health and Human Development Grant HD30572; and National Institute on Drug Abuse Grant DA016903. We thank John Budde and Dr Alison Goate for their contribution to this project through DNA extraction and genotyping of the initial set of genetic markers. We also thank Dr Leslie Rutkowski and Ms Stephanie Dickenson for their advice on statistical analysis.

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