Childhood social preference predicts lowered risk of insulin resistance in adolescence

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Abstract:

Insulin resistance, hyperinsulinemia, and Type II diabetes are increasingly common among young people in the United States. The quality of social relationships is a predictor of cardiometabolic health among adults, but has not been studied as a predictor of earlier insulin resistance. The purpose of this study was to test whether social preference (likeability) during childhood predicts insulin resistance and a measure of central adiposity during adolescence. Obesity also was examined as one mechanism through which this association occurs. Data came from a long-term longitudinal community study. At approximately age 7, 240 children were rated by their classmates on how liked and how disliked they were (difference score indexes social preference). Nine years later, at age 16, the same children visited the university laboratory where height, weight, and several measures of central adiposity (waist circumference, sagittal diameter, and waist-to-height ratio) were assessed by trained interviewers. Adolescents also provided fasted blood samples, from which HOMA-estimated insulin resistance was assessed. A path model yielded adequate to good fit indices, $\chi 2$ (3, N = 240) = 6.689, p = .08, CFI = .97, RMSEA = .07 [95% CI = .00, .14], sRMR = .03. Results indicated that greater social preference at age 7 was significantly associated with lower IR at age 16. These findings suggest that children who are less liked by their classmates are more likely to demonstrate increased risk of IR. Additionally, BMI at age 15 was positively associated with both IR and WC at age 16. A bootstrapping procedure (10,000 draws) indicated that a child's likeability is associated with IR and WC through the association of likeability with later weight status. The quality of social relationships in childhood is important to consider when trying to understand the recent rise in adolescents' cardiometabolic risk and when considering intervention strategies.

Keywords: Insulin resistance | Peer preference | Obesity

Article:

Abbreviations: IR, insulin resistance; T2D, type II diabetes; HOMA-IR, homeostasis model assessment – insulin resistance; BMI, body mass index; HPA axis, hypothalamus–pituitary–adrenal axis

1. Introduction

The maintenance of homeostatic blood glucose concentrations is a fundamental physiological function necessary for sustaining life. The uptake of glucose into cells is promoted by the pancreatic hormone insulin. Insulin resistance (IR) represents the failure of the body to appropriately respond to insulin and properly manage glucose levels (Lee et al., 2006b); in turn, this can contribute to a state of hyperinsulinemia and eventually lead to Type II diabetes (T2D). T2D is a debilitating chronic disease linked to increased morbidity and mortality in adulthood (e.g., Johansson et al., 2016). Individuals with IR also have an elevated risk of developing other cardiometabolic risk factors, including inflammation, dyslipidemia with increased triglycerides, increased blood pressure, thrombosis, and abdominal obesity (Black, 2003), as well as a greater likelihood of dying from a cardiovascular event (Hanley et al., 2002a,b).

Despite these potentially grave consequences, research on IR has focused largely on adults (e.g., Steinberger et al., 2001). Given the rising prevalence of IR, prediabetes, and T2D among adolescents (Gungor et al., 2005; Menke et al., 2016), it is imperative, however, to identify precursors of adolescent IR in an effort to alter the course of metabolic abnormalities prior to the emergence of clinical endpoints. Among adults, IR is controllable with lifestyle modifications (Long et al., 1994). Furthermore, research increasingly suggests a role for positive social relationships in reducing risk for cardiometabolic disease in adults (Begen and Turner-Cobb, 2015). It remains unclear whether positive social relationships early in life also could promote more favorable health outcomes.

1.1. Social influences on insulin resistance

Work on adults suggests that both the quality and quantity of social relationships are significant predictors of cardiometabolic outcomes (Uchino et al., 1996), and that social support and inclusion in particular come with important physiological benefits (Begen and Turner-Cobb, 2015). Understanding the benefits of positive social relationships may be especially important among school-aged children, because they spend the majority of their time in school and other social contexts (Larson and Verma, 1999). The current study examined whether childhood social preference, a measure of general likability within the peer group, predicts lowered risk of IR in adolescence, and whether this link is mediated by obesity.

1.2. The mediating role of obesity

Extant research on the precursors of adolescent IR primarily highlights the deleterious effects of childhood obesity and obesogenic behaviors (R.-C. Huang et al., 2011a,b; Peplies et al., 2016). For example, children who suffer from adiposity, consume unhealthy foods, and have limited engagement in physical activity are at higher risk for later IR. Given that substantial evidence has also indicated that childhood obesity is a key risk factor for many cardiometabolic disease endpoints (e.g., Sun et al., 2008), it is not surprising that the existing research has focused on the predictive link between obesity and IR in adolescence.

Obesity is also linked to earlier childhood social difficulties, which includes not being liked by one's peers (Harrist et al., 2016a,b). Accordingly, obesity might simply be part of a constellation

of risk factors centered around IR in adolescence. Thus, obesity could potentially represent a mechanistic link between the quality of earlier childhood social relationships and adolescent IR. Evidence for indirect effects of social support on IR risk via obesity comes from adult samples: women who had increased social support were less likely to be prediabetic in older adulthood (Serlachius et al., 2017), and this relation was explained by a reduced risk for obesity. Little is known about these processes earlier in life, but these findings with adults raise the possibility that children's social relationships may represent a critical opportunity for identifying and reversing early cardiometabolic disease risk. This developmental period of childhood is especially significant, because children begin to spend more time with their peers and these peer relationships are changing in both the quantity and quality (Bukowski et al., 2011). Research indicates that prior to age nine, childhood health risk is not necessarily predictive of adult cardiovascular disease (Juonala et al., 2013), suggesting the detrimental effects of early childhood health risks may be reversible.

The primary aim of the current study was to examine whether children's positive social relationships as indexed by social preference was associated with reduced risk for adolescent IR at age 16. Social preference was defined by the difference between a child's level of being accepted versus being rejected by her/his peers in school (Coie et al., 1982). We also examined whether reduced risk for obesity at age 15, as indexed by body mass index (BMI), mediated these links and adjusted for sex, race, socioeconomic status, and depression and generalized anxiety. We selected sex, race, socioeconomic status, depression and generalized anxiety as covariates based on existing literature. Individuals who are female (Lee et al., 2006b), Black (Svec et al., 1992), lower in socioeconomic status (Goodman et al., 2007), and have increased symptoms of depression and anxiety (Hannon et al., 2013) are more likely to have increased cardiovascular risk factors, such as poor health behaviors, higher BMI, and increased oxidative stress, which may directly and indirectly affect their risk of IR. Finally, we included central adiposity at age 16, indexed by waist circumference, as a predicted outcome to account for the concurrent association between central adiposity and IR (Caprio et al., 1995). Although BMI and waist circumference are related to one another, both are independent predictors of cardiovascular risk (Janssen et al., 2002) and risk of IR (Lee et al., 2006a), thus BMI and waist circumference are included in the analysis.

2. Materials and methods

2.1. Participants

The current study included a sample of 240 children (134 females) from the RIGHT Track Study who participated in study assessments at ages 5-, 7-, 10-, 15-, and 16-years old. The original longitudinal project was designed to assess the effect of self-regulation on later development and included a representative sample of children and families from a small southeastern city. The research was approved by the University of North Carolina at Greensboro Institutional Review Board. Additional details about sample recruitment and the adolescent health assessments may be found elsewhere (Smith et al., 2004; Wideman et al., 2016).

The current study included two-hundred and forty participants who had complete data on childhood social preference at age 7. Of the 240 children included in the current study, 211

children had BMI data at age 7, 88 had HOMA-IR data, 122 had BMI data at age 16, and 178 had BMI data at age 15. Due to the nature of our longitudinal study design, HOMA-IR data were only collected on participants who fell within the 16 year age range (16–17 years old) at the time of the assessment, which resulted in missing data. However, adolescents who participated in the fasting glucose assessment at age 16 did not differ on social preference $t(238) = .014$, $p = .989$, sex $t(201) = -.219$, $p = .827$, race $t(201) = -1.411$, $p = .160$, SES at age 5 $t(96) = .698$, $p = .487$, BMI at age 7 $t(58) = -.621$, $p = .537$, BMI at age 15 $t(60) = .049$, $p = .961$, and BMI at age 16 $t(33) = .182$, $p = .856$, compared to those who did not participate in the fasting glucose assessment. Additionally, full information maximum likelihood (FIML) was employed to account for missing data, which results in less biased parameter estimates and appropriate standard errors (Schafer, & Graham, 2002).

Sixty-seven percent of the current study sample identified as White, 27.1 % identified as Black; 55.8 % were female. Children came from economically diverse families. Families' scores on the Hollingshead index (Hollingshead, 1975), a weighted average of parental education and employment, ranged from 14 to 66 ($M = 43.44$, $SD = 10.52$) at age 5. Compared to the original recruitment sample, the current sample did not differ with respect to sex, $\chi^2(1, 443) = 2.86$, $p = .091$, race, $\chi^2(3, 443) = .48$, $p = .924$, SES (age 5), $\chi^2(77, 338) = 73.29$, $p = .599$, and age 7 BMI, $\chi^2(186, 271) = 181.82$, $p = .573$.

2.2. Procedure

When the children were 5, 7, 10, 15, and 16 years old, they came to a university laboratory with their primary caregiver. Mothers completed questionnaires regarding family demographics. Trained experimenters measured weight (kg) and height (cm) at ages 5, 7, 10, 15, and 16; participants self-reported these data with online questionnaires when a laboratory visit was not possible (at ages 15 and 16). At age 7 (2^{nd} grade), the study also included a school-based component during which peers rated study participants on how well they were liked and disliked, using a sociometric nomination procedure described below. At age 16, trained experimenters also measured waist circumference (cm) and standing sagittal diameter (cm).

Participants also provided a fasting blood sample during a morning visit to the university laboratory. Adolescents were fasted from food but allowed *ad libitum* water for at least 10 h prior to their visit. Blood was taken by venipuncture into a serum separator tube. Blood samples were allowed to clot at room temperature for 20 min. Next, they were spun at 3500 rpm for 20 min, then aliquoted into multiple samples for serum storage at −80 °C. Blood samples were batch processed using the Multiplex system (EMD Millipore, Billerica, MA) for assessment of insulin. Glucose was assessed using commercially available ELISA kits (Cayman Chemicals, Ann Arbor, MI).

2.3. Measures

2.3.1. Insulin resistance

HOMA-IR (homeostasis model assessment – insulin resistance) was used to estimate IR in adolescence because of its non-invasiveness and greater specificity and sensitivity compared to

other measures of IR (Keskin et al., 2005). Unlike insulin levels, the HOMA-IR calculation compensates for fasting hyperglycemia. To calculate HOMA-IR, the product of the fasting concentrations of glucose (expressed as millimoles per liter: mmol/L) and fasting concentrations of insulin (expressed as milliunits per milliliter: μU/mL) is divided by a constant (22.5). This formula assumes that normal young subjects have an IR of 1 (Matthews et al., 1985). HOMA-IR was skewed (>3) and kurtotic (>10), therefore it was log transformed for the primary analyses (similar to Lee et al., 2006b). Greater HOMA-IR values indicate higher IR.

2.3.2. Central adiposity

Waist circumference (cm) was used to estimate central adiposity in adolescence. Waist circumference (WC) was measured to the nearest 0.1 cm using a Gulick tension-tape measure by a sex-matched research assistant in a private location in the laboratory. WC was taken at the smallest part of the abdominal area. In addition, a standing sagittal abdominal diameter (SAD) and waist-to-height ratio were used to describe the sample central adiposity characteristics. SAD was taken at the L4-L5 vertebral level to the nearest 0.1 cm using a Holtain-Kahn abdominal caliper (Croswell, UK).

2.3.3. Social preference

Social preference was measured using sociometric peer nominations. The sociometric procedure employed in the current study was a modified version of Coie, Dodge, and Coppotelli's (Coie et al., 1982) original procedure. Children were presented a list of peers within their classroom and allowed to make unlimited nominations of "liked most" and "liked least classmates. Students completed the nomination procedure in an individual interview. All interviews took place at least eight weeks into the school year, so children had an opportunity to become acquainted with their peers. This procedure included cross-gender nominations, which increases internal validity of the measure (Prinstein, 2007) and allows for increased precision and reduced measurement error (Marks et al., 2013). It is the standard assessment procedure used in the current sociometric literature (e.g. Behnsen et al., 2018).

For the current study, peer nomination data were collected in 77 classrooms at 48 schools. To account for differences in class size, these two scores were divided by the number of participating children in the classroom and then standardized. The difference between the standardized "liked most" and "liked least" scores was computed and restandardized to create a measure of social preference, with higher scores indicating greater likability among peers. All students' scores were used to generate standardized scores for our participants. However, for the purposes of the current study, only scores from participants in the long-term longitudinal study were included in the analysis. Thus, the z-scores in the current manuscript are not 'true' z-scores, because they are based on the subsample.

2.3.4. Obesity

Body mass index (BMI) was used to index obesity status, while waist circumference was used to index central adiposity. BMI was computed using the formula weight/(height^2). Age- and sex-adjusted BMI percentiles were assigned according to the Center for Disease Control

(CDC; Centers for Disease Control and Prevention, National Center for Health Statistics 2019) growth charts. CDC guidelines were also used for computing dichotomous overweight/obesity descriptive data. BMI at age 7 and 16 were used as general descriptive variables only (see results) and not included in the analysis. In the analysis, obesity at age 15 (indexed by BMI) was a mediator and central adiposity (indexed by waist circumference) at age 16 was accounted for (similar to the analyses of Serlachius et al., 2017), given the strong influence of central adiposity on IR.

2.3.5. Covariates

Sex was dummy coded 1 = boys, 2 = girls. Socioeconomic status (SES) of the parent at age 5 was measured by the Hollingshead 4-factor index of socioeconomic status, with which an SES score is calculated based a 7-point rating of parent's education and occupation. Race was dummy coded 1 = White, 2 = other. Depression and generalized anxiety symptoms were measured using the diagnostic interview schedule for children version IV (DISC-IV; Shaffer et al., 2000), which provides a symptom count that ranges from 0 to 9 for depression and 0–8 for generalized anxiety.

2.4. Analytic strategy

The continuous outcome variables (HOMA-IR and waist circumference) were predicted by using MPlus 8 (Muthen and Muthen, 2017) to fit a path model. This technique was chosen to test whether childhood social preference had unique associations with adolescent HOMA-IR and with WC, after accounting for demographic characteristics including sex, race, and socioeconomic status. We also considered depression and anxiety symptoms as potential covariates, given research suggesting these factors affect IR (Hannon et al., 2013). However, only 1 % of the participants endorsed any symptoms of depression and less than 6 % of the participants endorsed any symptoms of anxiety at the age of 7, and no participants endorsed clinical levels of depression or anxiety at the age of 7; thus, mental health factors were not considered in future analyses. Adolescent BMI was also included in the model to consider the indirect effect of BMI on the association between childhood social preference and IR and WC in adolescence. Due to the longitudinal nature of our project, the model included missing data due to attrition after two-year recruitment of participants. Full information maximum likelihood (FIML) estimation was used to handle missing data.

3. Results

3.1. Descriptive statistics

In the current sample, 16.8 % of the participants were overweight and 13.0 % of the participants were obese at age 16. These percentages are consistent with recent work from nationally representative cohorts (Gungor et al., 2004). At age 7, 17 % of the participants were overweight and 16.6 % were obese, and BMI at age 7 and 16 were highly correlated ($r = .65$, $p < .01$). Using a definition of HOMA-IR > 4.39 for adolescents (defined by adolescent population estimates found in Lee et al., 2006b), the prevalence of IR among study participants was 14.8 %. Among obese participants at age 16, 75.0 % met criteria for IR.

Descriptive statistics and correlations among study variables are presented in Table 1. The mean of HOMA-IR (2.77 ± 3.49) is similar to recent work from nationally representative cohorts of adolescents (Lee et al., 2006b). Sex differences in study variables were examined. Females had significantly smaller WC than males (2.00, $p < .05$). Racial differences in study variables were examined. White participants had significantly lower BMI at age 15 (t = -2.25, $p < .05$), and had significantly lower HOMA-IR (t = -2.36, $p < .05$). There were no differences in any of the focal variables due to SES.

Table 1. Means, standard deviations, and correlations for HOMA-IR, waist circumference, social preference, BMI, and study covariates.

Variable	1	2	3	4	5	6	7
1. Age 16 HOMA-IR	--	.51**	−.31**	.34**	.04	−.13	.26*
2. Age 16 WC		--	−.31**	.74**	−.19*	−.04	.18
3. Age 7 Social Preference			--	−.24**	.09	.01	−.10
4. Age 15 BMI				--	−.01	−.05	.19*
5. Sex[a]					--	−.10	.05
6. Socioeconomic Status						--	−.21**
7. Race[b]							--
Mean	2.77	79.26	.08	23.70		43.44	
SD	3.49	14.75	.98	5.63		10.52	

HOMA-IR = homeostasis model assessment-insulin resistance; WC = Waist Circumference (cm); BMI = body mass index (kg/m^2).
†p < .10, * p < .05, ** p < .01, ***p < .001.
Note. Total N = 240.
[a] Sex is dichotomized 1 = Males (n = 106, 44 %) 2 = Females (n = 134, 56 %).
[b] Race is defined as 1 = White (n = 161, 67 %) 2 = Non-white (n = 65, 27 %).

T-tests were conducted to examine mean differences in concurrent measures of central adiposity between IR and non-IR participants—overall mean differences, as well as examining these differences separately for males and females (Table 2). Results revealed that participants who met clinical cut-offs for IR were more likely to have greater concurrent central adiposity as indexed by WC (cm), SAD (cm), and a waist-to-height ratio (WHR; cm/cm) than individuals who did not meet clinical cut-offs for IR.

Table 2. Mean values of measures of central adiposity differences between Insulin Resistant and Non-Insulin Resistant Males and Females.

		Waist Circumference (cm)	Sagittal Diameter (cm)	Waist to Height Ratio (cm/cm)
Insulin Resistant	Males	116.00(28.40)***	30.38(8.40)***	0.62(.14)***
	Females	91.29(21.71)***	23.91(6.95)**	0.54(.14)**
Non-Insulin Resistant	Males	79.39(9.28)***	19.64(2.59)***	0.44(.05)***
	Females	73.48(8.62)***	18.40(3.12)**	0.45(.05)**
Insulin Resistant	Total	100.27(26.08)***	26.26(7.80)***	0.57(.14)***
Non-Insulin Resistant	Total	75.74(9.28)***	18.85(2.98)***	0.45(.05)***

†p < .10, * p < .05, ** p < .01, ***p < .001.
N: Males IR = 4, Males Non-IR = 28.
N: Female IR = 7, Female Non-IR = 45.

3.2. Primary analysis

Evaluation of model fit was assessed by examining the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (sRMR), in addition to examining the results of the chi square difference test. Values greater than .95 indicate good model fit for the CFI, values less than .08 indicate good model fit for sRMR, and values less than .05 indicate good model fit and between .05 and .08 indicate acceptable model fit for RMSEA (Bowen and Guo, 2012). A nonsignificant chi square difference test indicates there is evidence that the hypothesized path model is not different from the data (Bowen and Guo, 2012). Using these criteria, the hypothesized model yielded good fit, χ^2 (3, N = 240) = 6.689, p = .08, CFI = .97, RMSEA = .07 [95 % CI = .00, .14], sRMR = .03.

Results indicated that greater social preference at age 7 was significantly associated with lower IR at age 16 [95 %CI = -.159, -.006] (for unstandardized estimates see Table 3; for standardized estimates, see Fig. 1). These findings suggest that children with lower social preference scores are more likely to demonstrate increased risk of IR. Additionally, BMI at age 15 was positively associated with both IR [95 % CI = .005, .037] and WC at age 16 [95 % CI = .985, 2.602] (see Table 3), demonstrating that greater BMI is positively associated with additional risks for health over time.

Table 3. Unstandardized Model Estimates and 95 % Bootstrap Confidence Intervals.

	Estimate	**S.E.**	**Confidence Intervals**	
			Lower	**Upper**
Intercepts				
BMI	21.771***	2.808	16.605	27.750
HOMA-IR	−.597	.300	−1.261	.832k-.018
Waist Circumference	44.615***	9.157	29.323	65.620
Covariances				
HOMA-IR→← Waist Circumference	1.203**	.440	.485	2.238
Direct Paths				
Preference→ HOMA-IR	−.084*	.039	-.159	−.006
Preference→Waist Circumference	−1.499	1.237	−4.148	.706
BMI→HOMA-IR	.022*	.008	.005	.037
BMI→Waist Circumference	1.833***	.458	.985	2.602
Indirect Paths				
Preference→BMI→HOMA-IR	−.030	.016	−.066	−.005
Preference→BMI→Waist Circumference	−2.511*	1.016	−.4.780	−.913

* p<.05, ** p<.01, ***p<.001.

A second aim of this study was to examine the role of obesity as a mechanism that could partially explain the relation between childhood social preference and two indicators of health, IR and WC. To examine this association, a bootstrapping procedure (10,000 draws) was used to test the indirect effect of social preference at age 7 on IR at age 16 and WC at age 16 through BMI at age 15. The bootstrapping procedure minimizes the risk for Type I error and increases power as compared to other similar tests (MacKinnon, Lockwood, & Williams, 2004). The 95 % confidence intervals for the indirect effects between social preference and both IR through BMI at age 15 [95 % CI = -0.07, -.01] and WC through BMI at age 15 [95 % CI = -4.78, -0.91] did not include 0, suggesting a significant indirect effect. Specifically, this indicates that children's social preference was associated with IR and WC in adolescence through its association with BMI at age 15.

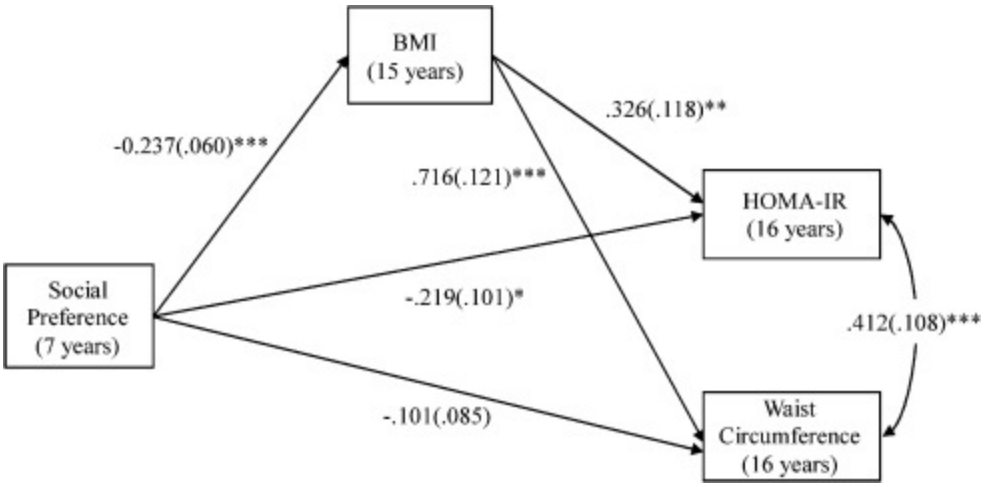

Figure 1. Standardized estimates for the indirect effects model predicting IR and central adiposity. The analyzed model also includes child sex, race, and SES as covariates (not displayed for ease of interpretation).
* p < .05, ** p < .01, ***p < .001.

3.3. Sensitivity analyses

In a set of sensitivity analyses, measures of insulin sensitivity (quantitative insulin sensitivity check index; QUICKI = 1/[log (fasting insulin) + log (fasting glucose)]) measured in μU/mL, and mg/dL respectively) and estimates of pancreatic β-cell function (ratio of fasting insulin to fasting glucose measured in pmol/L and mmol/L respectively; I_F/G_F) (Gungor et al., 2004) were examined as correlates of HOMA-IR and social preference. As expected, HOMA-IR was significantly negatively correlated with QUICKI (r = -.99, $p <$ .01) and positively correlated with I_F/G_F (r = .67, $p <$ .01). Social preference was significantly positively correlated with QUICKI (r = .26, $p <$ .01) and negatively correlated with I_F/G_F (r = -.29, $p <$ .01). This suggests that greater social preference also predicts increased insulin sensitivity and of less impaired β-cell function.

4. Discussion

Insulin resistance (IR) is a major risk factor for the development of Type II diabetes mellitus (T2D) (Lee et al., 2006b) and other cardiovascular diseases (Hanley et al., 2002a,b). Historically, IR has been researched as a condition that primarily afflicts adults, but recent evidence has indicated that the diagnoses of IR, prediabetes, and T2D are increasing among adolescents (Gungor et al., 2005; Menke et al., 2016). Therefore, it is vital to examine the childhood predictors of adolescent IR in order to provide guidance for preventive interventions that may assist in halting and reversing individuals' progression to full-blown metabolic disease during adolescence.

The adult literature suggests that positive social relationships may buffer against the development of IR (Serlachius et al., 2017), but few studies have examined such links in the early life course. Findings from our 9-year prospective longitudinal study revealed that children's social preference at age 7 was associated with lower risk of IR and decreased central adiposity at age 16 and that lower BMI at age 15 mediated these links. Together, these results

highlight the importance of children's positive social relationships for their health, specifically the development of their cardiometabolic risk.

This indirect pathway linking social preference and IR through obesity is expected given the growing literature that links early social experiences with obesity risk and highlights the important role of obesity on IR (e.g. Huang et al., 2011a,b). There are multiple explanations for why children who have increased social preference amongst their peers have a reduced risk of cardiometabolic disease: for instance, children who are liked by their peers might have a buffer against other physiological and psychosocial hazards. A positive consequence of being liked could include increases in "favorable" hormones, such as oxytocin and vasopressin, and a decrease in hormones that are detrimental to health in the long run, such as cortisol (Carter and Keverne, 2009). This physiological response would likely have a positive effect on children's endocrine system and metabolism, resulting in decreased risk for IR over time (Uchino et al., 1996). Indeed, decreased serum cortisol is associated with lowered risk of IR in adolescents (Huybrechts et al., 2014). Social preference may also increase socially-related healthy behaviors, which may also buffer a child from physiological hazards and reduce subsequent IR risk. For example, children who are more socially accepted may spend more time being physically active with their peers (for a review see Fitzgerald et al., 2012), which, in turn, could lead to lower BMI and reduced risk for IR.

So far, our interpretations have focused on the benefits of positive social relationships. However, an alternative explanation for the findings could be explained by the negative effects of low social preference, children who were more rejected than accepted by their peers. For example, children who are less liked by their peers might have increased risk of IR, because they experience heightened psychological stress as a result of not meeting the basic human need of feeling love and acceptance (Baumeister and Leary, 1995). As a result, children who have lower social preference and higher psychological stress might be more likely to struggle with their weight and have increased adiposity. Subsequently, because of increased adiposity there might be insults to their vascular and metabolic systems, which result in increased risk of IR over time. Some evidence has suggested that social isolation in childhood in particular can have a negative effect on adult health as indexed by CRP, an inflammatory biomarker, through increased body mass (Lacey et al., 2014). Children who have low social preference might further withdraw from their peer group and engage in more unhealthy behaviors, such as becoming increasingly sedentary. These unhealthy behaviors could contribute to increased adiposity and increased risk of IR. Further, children who become obese are more likely to be victimized and bullied (Mamun et al., 2013; Robinson, 2006), which could contribute to increased psychological stress and increased BMI and subsequent increased risk of IR.

Additionally, children who have low social preference might have an increased risk of obesity and IR due to their physiological stress response. Stress caused by social rejection may activate an individual's acute phase response and stimulate the release of stress hormones (i.e., epinephrine, glucocorticoids) (Black, 2003). In addition to the acute stress response, children who have low social preference might experience more chronic uncontrollable stress, which could also promote dysregulation of the hypothalamus–pituitary–adrenal axis (HPA axis). Normative patterns of stress hormone release result in temporary increases of glucose and fatty acids as part of a "fight or flight" physiological response to psychological stress—a response that

is essential for protecting the body in an emergency (Brindley and Rolland, 1989; Geer et al., 2014). However, chronic overexposure to glucocorticoids is well known to result in whole-body IR and obesity (Geer et al., 2014). Greater glucocorticoid exposure alters body composition—especially expansion of adipose tissue in the trunk area, such as visceral fat (Lee et al., 2014b) and impairs metabolism and insulin action, resulting in hyperglycemia and dyslipidemia (Geer et al., 2014). As visceral fat depots increase, so does risk for IR (Hewagalamulage et al., 2016), which could explain why obesity had an indirect role on the relation between children's social preference and IR in adolescence. Over time, dysregulation of the HPA axis can overload the physical systems of the body and increase an individual's risk of disease over time (McEwen, 1998).

Thus, increasing social preference may result in more optimal cortisol secretion in children, which may lead to smaller visceral and abdominal fat deposits, and, in turn, reduced risk for IR in adolescence. Notably, however, there is a complex relation between cortisol secretion, obesity and IR. A recent review highlights the roles of both the up- and downregulation of cortisol in the emergence of adipose tissue, and even a hyper-responsive HPA activation in relation to obesity (Rodriguez et al., 2015). Future work should further clarify the complex relation between social preference, optimal cortisol secretion, adiposity, and IR, and consider both the positive and negative physiological and psychological pathways.

4.1. Strengths and limitations

Our study is among the first to identify a predictor of IR risk in adolescence that is not an obesogenic lifestyle factor (i.e., over-eating). Our results are consistent with previous cross-sectional work that indicated that children's social preference predicted their weight status (Harrist et al., 2016a,b) and longitudinal work with adults showing that women's psychosocial characteristics predicted later fasting glucose levels and prediabetes through obesity (Serlachius et al., 2017). We extended this work by examining adolescent IR, which is a direct index of metabolic health and a critical risk factor for T2D.

Although the current study's findings are notable, they are not without limitations. First, although our predictions are longitudinal, they do not establish causality. It is possible that social preference is a result of IR rather than a cause. However, this reverse direction of effects is unlikely considering that our recruitment sample was a healthy group of two-year-olds from the community. We were unable to test this reverse directionality in this sample, however, because we did not assess IR at age 7. It is also possible that children who are previously obese are more likely to be less preferred. This may suggest that the direction of effects should consider that obesity predicts peer preference, which predicts IR risk. Research reports that children with lower total body mass are more likely to be preferred by their peers (Latner and Stunkard, 2003; Strauss and Pollack, 2003).

Second, the current study measures only one aspect of peer relationships, peer preference, which is a general measure of overall likability. However, negative peer-based behaviors related to being disliked have also been linked to health. Bullying, victimization, and stigmatization are overt acts of peer dislike that require an active rejective behavior by peers. The stigmatization of obesity has become particularly salient as obesity rates continue to increase and disliking of

children who are obese has also increased by 40.8 % over the past 40 years (Latner and Stunkard, 2003). Existing literature has shown that children who are overweight or obese are often subject to bullying, victimization, and stigmatization by their peers (Mamun et al., 2013; Robinson, 2006;). Thus, overweight children may become socially isolated, stigmatized, and increasingly harassed leading to increased BMI and increased oxidative stress and subsequent IR risk. Future work should examine the negative effect of these other aspects of peer relationships on IR risk.

Third, transient changes in IR can occur during puberty—increasing at the onset of puberty (Tanner stage 2), and returning to prepubertal levels by the end of puberty (Tanner stage 5) (Moran et al., 1999). We did not assess Tanner stage in our adolescents; however, it is likely that by age 16 nearly all participants had reached Tanner stage 5 with IR values near prepubertal values. Fourth, although the racial/ethnic composition of the sample corresponded to that of the counties from which it was drawn, the sample consisted of mostly White and Black participants. Study hypotheses should also be examined in other racial/ethnic groups, including Latino and Asian youth. Fifth, peer preference only accounts for a small proportion of the variance in IR. However, this does not diminish the importance of the findings of a social variable linked over 10 years to IR in a model that accounts for BMI. Obesogenic variables have a great effect on IR risk, however, intervention studies have consistently demonstrated the difficulty of altering these lifestyle variables (e.g. Dulloo et al., 2017). In contrast, peer preference might provide an easier point of intervention, thus this small effect might have an even larger practical impact. Finally, although we examined the role of obesity as a mechanism that might explain the relation between childhood social preference and adolescent IR, we did not examine other pathways that might explain this predictive association, including health behaviors, such as sports participation, or physiological pathways other than adiposity, such as HPA dysregulation.

4.2. Conclusion

The current study is among the first to identify an early childhood social relationship characteristic, social preference, in the prediction of IR in adolescence. This association was significantly explained by the indirect effect of obesity earlier in adolescence. The identification of social preference as a predictor of later metabolic disease has implications for detecting and preventing IR. Indeed, future research should replicate our findings and begin to examine early intervention approaches for IR that include a focus on children's interpersonal relationships. Social acceptance-based programs in childhood may reduce risk for metabolic and cardiovascular disease for decades to come.

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