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Psychological Symptoms and Insulin Sensitivity in Adolescents

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Abstract

Purpose—Symptoms of psychological distress have been linked to low insulin sensitivity in adults; however, little is known about this relationship in pediatric samples. We therefore examined symptoms of depression and anxiety in relation to insulin sensitivity in adolescents.

Methods—Participants were 136 non-treatment seeking, healthy adolescents (53.2% female) of all weight strata (BMI-z = 1.08±1.08) between the ages of 12 and 18 years (M = 15.16, SD = 1.55). Adolescents completed questionnaire measures assessing depression and anxiety symptoms. Fasting blood samples for serum insulin and plasma glucose were obtained to estimate insulin sensitivity with the quantitative insulin sensitivity check index (QUICKI). Fat mass and fat-free mass were measured with air displacement plethysmography or dual-energy x-ray absorptiometry.

Results—Depressive symptoms were associated with higher fasting insulin and decreased insulin sensitivity even after controlling for fat mass, fat-free mass, height, age, pubertal status, race, and sex ($ps < 0.01$).

Conclusions—As has been described for adults, depressive symptoms are associated with low insulin sensitivity among healthy adolescents. Further experimental and prospective studies are required to determine the directionality of this link.

Keywords

Insulin sensitivity; general psychopathology; depression; children; adolescents

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Low insulin sensitivity is a major physiological precursor to type 2 diabetes and an important risk factor for the development of cardiovascular disease [1]. One of the primary pathways by which decreased insulin sensitivity develops is through excessive gain of body fat. Overweight youth have decreased insulin sensitivity compared to their non-overweight counterparts, placing them at heightened risk for negative health consequences including type 2 diabetes

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[2]. However, evidence from adult studies suggests that psychological factors may also affect insulin sensitivity [3–11]. In overweight and non-overweight adults, sub-clinical and clinical threshold depressive symptoms are correlates of, and potential risk factors for, the development of decreased insulin sensitivity [3,6–10], type 2 diabetes [5,12,13], and other aspects of the metabolic syndrome [4,11]. The degree of psychosocial stress and anxiety symptoms in a large community sample of women also has been shown to be significantly related to measures of insulin sensitivity, even after accounting for body mass index [4]. From a psychophysiological theoretical perspective, depression or anxiety are believed to impact insulin sensitivity through physiological mechanisms such as altered insulin signaling in the brain, pro-inflammatory activation, and/or distress-induced upregulation of counterregulatory hormone systems [14, 15]. In addition, from a behavioral psychology perspective, depression and stress may affect insulin sensitivity, in theory, through their impact on lifestyle factors such as physical inactivity.

Given the possible role that adult studies suggest for depression and anxiety in the development of decreased insulin sensitivity, understanding how these factors are linked to glucose homeostasis during adolescence may be important for identifying early risks for potentially adverse health outcomes. Parents' perceptions of their children's negative emotionality have been found to be associated with children's fasting insulin, particularly among boys, in a large study of Finnish youth ages 6 to 18 years [16]. To our knowledge, however, no studies to date have examined the links between depressive or anxiety symptoms and fasting insulin or measures of insulin sensitivity in youth.

Adolescence represents an important developmental stage for understanding the links between psychological symptoms and insulin sensitivity. During adolescence, normative endocrine changes associated with puberty produce decreased insulin sensitivity relative to childhood. Moreover, adolescence marks a peak time for the onset of depressive symptoms, particularly among girls. Thus, these marked psychological and biological shifts render adolescence an important developmental stage for understanding how symptoms of depression are associated with insulin sensitivity.

We, therefore, investigated whether symptoms of depression and anxiety were associated with insulin sensitivity among adolescents. Based upon prior data, we hypothesized that symptoms of depression and anxiety would be associated with higher fasting insulin and decreased insulin sensitivity. Since previous literature has indicated that sex may act as a moderator of the association between psychological symptoms and insulin sensitivity [9,16], we expected that sex might interact with depression or anxiety and their association with insulin measures, such that the effects would be stronger for girls than for boys.

Methods

Participants and Procedure

Participants were drawn from a sample of healthy volunteers participating in a study examining eating behaviors in youth. Individuals were recruited through flyers posted on public bulletin boards at the National Institutes of Health (NIH), and at local libraries, supermarkets, and high school parent listservs in the Washington, DC greater metropolitan area. The study was also advertised in a local newspaper and posted on free websites. The flyer and advertisement specified that the study was investigating eating behaviors in healthy pediatric volunteers and that no treatment would be provided. Advertisements did not request specific accrual of youth having psychological symptomatology such as depression. Subjects were financially compensated for their participation. For the present study, youth were included if they were between the ages of 12 and 18 years and had a body mass index (BMI; kg/m^2) $\geq 5^{th}$ percentile for age and sex. Individuals were excluded if they had a significant medical disease or abnormal

hepatic, renal, or thyroid function, were undergoing weight loss treatment, or were taking any medication known to affect glucose homeostasis; however, participants were not excluded on the basis of a family history of type 2 diabetes. Adolescents provided written assent and parents gave written consent for participation in the study. This study was approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) institutional review board.

All participants were seen at the outpatient pediatric clinic of the NIH Clinical Center. Adolescents underwent a medical history and a physical examination that included pubertal staging conducted by a pediatric endocrinologist or trained pediatric or family nurse practitioner. Data were recorded on a structured data entry form. Each participant provided blood samples following an overnight fast and subsequently completed questionnaires.

Measures

Anthropometrics—Height and weight were obtained after an overnight fast. Participants were clothed but with shoes removed. Each adolescent's height was measured three times to the nearest millimeter by a stadiometer (Holtain, Crymmych, Wales) calibrated before each adolescent's measurement. Weight was measured to the nearest 0.1 kg with a calibrated digital scale (Scale-Tronix, Wheaton, IL). Participant's height and weight were used to compute BMI. Body composition was assessed with air-displacement plethysmography (Bod Pod; Life Measurement Inc, Concord, CA) or dual-energy x-ray absorptiometry (DXA) using Hologic QDR 4500A equipment (Hologic, Waltham, MD) to assess fat-free mass and body fat mass. Participants' Bod Pod measurements (including weight) were obtained with clothes and shoes removed while participants were in a fasted state. As recommended, we assured that measurements of adiposity were equivalent between the two different assessment techniques by adding 2.29 kg to DXA fat mass, subtracting 2.29 kg from DXA lean mass, and multiplying girls' Bod Pod fat mass by 1.03 [17,18]. Breast and pubertal hair development were assigned according to the stages of Tanner [19,20] and testicular volumes were measured according to Prader [21]. For the purposes of the current study, participants were classified as prepubertal (girl's breast Tanner stage = 1, boy's testicular volume ≤ 3 cc) or pubertal (girl's Tanner stage > 1, boy's testicular volume > 3 cc).

Depressive symptoms—Participants completed the Children's Depression Inventory (CDI), a reliable and well-validated 27-item self-report questionnaire, to assess the extent and severity of depressive symptoms in youth [22]. A total raw score ranging from 0 to 54 is derived from the sum of its items. Total scores that exceed 12 have been proposed as a cut-off for screening for at-risk for clinical depression [23,24]. For the purposes of the current study, a continuous measure of the total score was used. The CDI has demonstrated adequate internal consistency, test-re-test reliability, discriminative validity, and concurrent validity with alternate measures of current as opposed to transient depressive symptoms [25,26].

Anxiety symptoms—The total raw score of the trait scale of the State-Trait Anxiety Inventory for Children (STAIC) was used to assess total symptoms of trait anxiety [27]. Total raw scores that are equivalent to or exceed a T-score of 65 typically are considered clinically at-risk [27]. The STAIC is widely used to assess continuous symptoms of anxiety in community samples, and it has high internal consistency, stability for trait anxiety, and adequate validity [28,29].

Insulin sensitivity—Fasting blood samples for serum insulin and plasma glucose were obtained in the post-absorptive state (i.e., after an overnight fast). Subjects were carefully queried regarding eating and drinking before samples were obtained and informed that they would be compensated for their visits even if they were not fasting. Participants were asked to

return on another day if they reported consuming any calorie-containing foods or beverages on the morning of their blood draw. Plasma for glucose was collected in tubes containing powdered sodium fluoride (which inhibits glycolysis) and measured by the NIH Clinical Center clinical laboratory using an Hitachi 917 analyzer (Roche Diagnostics Indianapolis, IN). Insulin concentrations were determined using a commercially-available immunochemiluminometric assay purchased from Diagnostic Product Corp., Los Angeles, CA and calibrated against insulin reference preparation 66/304. The insulin assay uses a monoclonal anti-insulin antibody and was run on an Immulite2000 machine (Diagnostic Product Corp., Los Angeles, CA). The cross-reactivity of the insulin assay with proinsulin was <8% and with C-peptide was <1%, sensitivity was 2 uU/mL and the mean inter- and intra-assay coefficients of variation were 5.8 and 3.6%, respectively. Insulin sensitivity was calculated according to the quantitative insulin sensitivity check index (QUICKI) [30], in which insulin sensitivity is estimated as 1 divided by the sum of the $\log_{10}$ of fasting glucose (mg/dl) and the $\log_{10}$ of fasting insulin (mIU/L). The QUICKI shows moderate to high correlations with clamp-derived measures of insulin sensitivity in youth [30,31]. Some data suggest slightly better correlations between QUICKI and criterion measures of insulin sensitivity than the homeostatic model assessment (HOMA) [32]. Fasting glucose was not used as an outcome, since fasting measures of insulin sensitivity are much better surrogates for glucose homeostasis in healthy (non-diabetic) samples.

Analytic Plan

Using procedures advocated by Behrens [33], study variables were examined to determine if the assumptions of univariate and multivariate analyses were met. The skew and kurtosis were satisfactory on all variables, and outliers (< 4% of all data points) were adjusted to fall 1.5 times the interquartile range below or above the 25th or 75th percentile. This strategy was used because it minimizes outliers' influence on the characteristics of the distribution, minimally changes the distribution overall, and avoids potential bias associated with eliminating outliers altogether. This correction did not significantly alter the direction or magnitude of any result. Correlations or independent samples t-tests were used to examine the bivariate associations between demographics, anthropometrics, and psychological symptoms with the two dependent variables, fasting insulin and insulin sensitivity. Hierarchical multiple regressions were conducted to determine the main effects of psychological symptoms on insulin measures after controlling for pre-selected demographic variables (age, sex, race, body fat mass, fat-free mass, height, and pubertal status), as well as to determine whether sex interacted with psychological symptoms. We first entered age, pubertal status (prepubertal, pubertal), fat mass, fat-free mass, height, sex (female, male), and race (African American, Caucasian). Then, in the second step, we entered depressive symptoms and anxiety symptoms. Next, we tested for moderation by entering the interactional terms of depressive symptoms by sex and anxiety symptoms by sex [34]. All continuous variables in the interaction terms were mean-centered as recommended [34], in order to avoid problems of multicollinearity. A p value of < 0.05 was considered significant.

Results

Descriptive Information and Bivariate Analyses

Participants were 136 adolescents, with an average age of 15.16 years (SD = 1.55). Eighty-nine (65.4%) participants racially/ethnically self-identified as Caucasian, 47 (34.6%) as Black or African American, and 1 (.7%) as Asian. The sample was comprised of 46.3% adolescents of normal weight (as defined by a BMI < 85th percentile for age and sex), 20.6% overweight (BMI 85th to 95th percentile), and 33.1% obese (BMI > 95th percentile). Similar numbers of boys and girls were of normal weight, overweight, or obese ($\chi^2 = 2.17$, $p = .34$). Examined continuously, BMI-z ranged from −1.68 to 3.20 (M±SD = 1.08±1.08), fat mass from 1.10 to

57.77 kg (M±SD = 22.05±16.04), and lean mass from 28.40 to 87.22 kg (M±SD = 51.40 ±13.38).

Adolescents displayed a broad range of depressive symptoms (Range = 0–19; M±SD = 6.50 ±5.46). As would be expected for a non-treatment-seeking sample, 16.9% (n = 23) of adolescents exceeded a cut-off of 12 (total raw score) on the CDI. There was also a broad range of trait anxiety symptoms (Range = 20–54; M±SD = 30.54±7.14), with one adolescent endorsing what would be considered equivalent to a clinically elevated (T-score ≥ 65) score. Fasting insulin (μIU/mL) ranged from 2.00 to 29.18 (M±SD = 12.33±7.77), and QUICKI scores ranged from .27 to .42 (M±SD = .34±.04).

In bivariate analyses, depressive symptoms were positively correlated with fasting insulin concentrations ($r = .30$, $p < .001$) and inversely correlated with insulin sensitivity ($r = −.24$, $p = .005$). Anxiety symptoms were positively correlated with fasting insulin ($r = .21$, $p = .016$), but were not significantly related to insulin sensitivity ($r = −.13$ $p=.14$).

Multivariate Association of Psychological Variables with Fasting Insulin and Insulin Sensitivity

Demographic and anthropometric variables accounted for a combined 54% of the variance in fasting insulin concentration and 49% of the variance in insulin sensitivity (Table 1). As expected, age was associated with lower fasting insulin and higher insulin sensitivity ($ps < .05$), since adolescents who have completed puberty have improvements in insulin sensitivity. Fat mass was related to higher fasting insulin and lower insulin sensitivity ($ps < .001$) and accounted for the largest standardized coefficients in the fasting insulin and insulin sensitivity models (0.64 and −0.57, respectively). Additionally, height and being female (versus male) were associated with lower insulin sensitivity ($ps < .05$). After accounting for the other variables in Step I, puberty, fat-free mass, and race were not significantly related to insulin measures.

Adding depressive and anxiety symptoms to the equations added an additional, significant 3% of explained variance in fasting insulin and insulin sensitivity ($ps < 0.05$). Depressive ($ps < .02$), but not anxiety ($ps > .10$), symptoms significantly improved the explained variance for both fasting insulin and insulin sensitivity after accounting for anthropometric variables. Greater depressive symptoms were associated with higher fasting insulin and decreased insulin sensitivity.

There were no significant interactions between sex and any psychological measure (all $ps > 0.29$). A small number of participants (n = 16, 11.8%) had a first degree relative with type 2 diabetes. After adjusting for age, sex, race, puberty, and body composition, family history of type 2 diabetes was not significantly related either to fasting insulin ($p = .16$) or to insulin sensitivity ($p = .64$).

Discussion

In a sample of adolescent girls and boys of all weight strata, depressive symptoms showed a small, but significant, association with individual variation in adolescents' fasting insulin and insulin sensitivity even after accounting for the contribution of demographic and anthropometric factors. Although anxiety was associated with fasting insulin in bivariate analyses, anxiety symptoms did not significantly contribute to either model.

Our findings parallel a series of studies in the adult literature that have found links between depressive disorders or severity of depressive symptoms and decreased insulin sensitivity in women and men [3,6–8,11]. Despite meal-level sex differences in depressive symptoms and

insulin resistance, the observed relationship between depression and insulin was not significantly different among adolescent boys and girls. This pattern contrasts with one prior adult study that also explicitly tested for moderation by sex and found an effect only for women [9]. Although further investigation into potential sex differences in adolescents is required, our results preliminarily suggest that depressive symptoms and insulin measures may be related similarly in adolescent boys as well as girls.

Although the present results are cross-sectional and cannot be construed to imply causation, a number of theoretical mechanisms could account for this link. One potential explanation is that depressive symptoms may promote lower insulin sensitivity, independent of their relationship with adiposity, via a number of physiological mechanisms including altered central nervous system insulin signaling, distress-induced up-regulation of humoral systems (e.g., glucocorticoids), and/or pro-inflammatory activation [15,35]. Another possibility is that depressive symptoms contribute to higher fasting insulin and decreased insulin sensitivity through their impact on lifestyle factors such as physical inactivity [36] or eating habits [5]. Evidence in support of this hypothesis includes that adolescent depressive symptoms are associated with greater sedentary behavior [36], which in turn may promote a deleterious metabolic phenotype [37,38]. It is noteworthy that variations in depressive symptoms, even at subclinical levels, were associated with relatively poorer insulin action. Such a pattern is congruent with an existing body of depression research recognizing the detrimental impact of subthreshold adolescent depressive symptoms on health outcomes [39,40].

Alternatively, it is also possible that insulin resistant states may lead to a depressive mood. Yet, we are aware of no studies finding that treatment of insulin resistance (unless in concert with weight reduction) alleviates depressive symptoms. In contrast, the hyperinsulinemia found among adults with full-syndrome depressive disorders has been shown to be ameliorated after treatment for depression [3]. Importantly, replication of this finding among lean and obese adolescents with clinically elevated depressive symptoms is now required. If depressive symptoms contribute to decreased insulin sensitivity in adolescents, the prevention of adolescent depressive symptoms might have the potential to diminish a portion of the risk, at least to some extent, for type 2 diabetes.

Several shortcomings should be noted. The effects of psychological factors on insulin measures were small relative to the effects of anthropometric variables. In particular, fat mass was highly related to fasting insulin and insulin sensitivity. Therefore, even if depressive symptoms and insulin functioning prove to have a causal relationship, interventions that lower depressive symptoms without altering body composition may have a limited impact on insulin sensitivity and vice versa. Study of the links between symptoms and insulin measures is warranted in adolescent samples with clinically elevated symptomatology and may shed greater light on the magnitude of the depression-insulin relationship. Although the QUICKI is a well-validated, reliable estimate of insulin sensitivity that is highly correlated with clamp measurements [30, 31], replication of the observed effects using more sophisticated and precise measurements of insulin sensitivity in larger samples is needed. Other psychological symptoms such as externalizing behavior problems ought to be examined based on prior findings that hostility may be an important risk factor for the metabolic syndrome and cardiovascular disease in adults [9,10] and youth [41]. Another limitation is that we examined only self-reports of psychological symptoms; examination of the associations between parent reports of symptoms and insulin sensitivity should also be undertaken. Finally, in future work it will be important to study potential mechanisms such as physical inactivity [36].

Strengths of the present study include the examination of psychological symptoms and insulin sensitivity in a sizeable sample of adolescents that included both non-overweight and overweight children and the use of reliable and valid measures for estimating these variables.

Although adolescents were not recruited in a truly population-based fashion, participants were recruited for a study measuring plasma hormones pertaining to eating behavior, understood that they would receive no treatment as a result of participation, and had no advanced knowledge of the content of questionnaires or the interview. Thus, we believe that this sample is likely to be reasonably representative of the general population of adolescents and is unlikely to be enriched for youth who were, or were not, especially concerned about eating behavior. Moreover, unlike many prior studies of psychological influences on insulin sensitivity, we examined the associations with psychological symptoms after accounting for the contribution of significant covariates. In particular, controlling for body composition is critical because depressive symptoms have been found to be more common among overweight compared to non-overweight adolescents.

The current study is a preliminary step toward understanding links between psychopathology and insulin sensitivity among adolescents whose metabolic processes are still functioning relatively normally. Longitudinal studies will help elucidate whether these psychological factors are important predictors for, or consequences of, abnormal glucose homeostasis for adolescents.

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Table 1

Multiple hierarchical regressions of psychological symptoms for adolescents' fasting insulin and insulin sensitivity

	Fasting Insulin			QUICKI		
	B	**SE**	***b***	**B**	**SE**	***b***
Step I.						
Age	−0.82	0.38	−0.16*	0.01	0.00	0.21**
Puberty	1.43	1.69	0.06	−0.01	0.01	−0.07
Fat Mass	0.31	0.04	0.64***	−0.001	0.00	−0.57***
Fat-Free Mass	0.04	0.07	0.07	0.00	0.00	−0.02
Height (cm)	0.07	0.09	0.09	0.00	0.00	−0.23*
Sex	−2.15	1.23	−0.14	0.02	0.01	0.23**
Race	−1.73	1.12	−0.10	0.01	0.01	0.08
			$R^2 = 0.54$***			$R^2 = 0.49$***
Step II.						
Depression	0.23	0.10	0.19*	−0.001	0.00	−0.21*
Anxiety	−0.07	0.10	−0.06	0.00	0.00	0.17
			$R^2 = 0.57$***			$R^2 = 0.52$***
			$\Delta R^2 = 0.03$*			$\Delta R^2 = 0.03$*
Step III.						
Depression × Sex	−0.21	0.20	−0.10	0.00	0.00	0.05
Anxiety × Sex	−0.15	0.19	−0.08	0.00	0.00	−0.02
			$R^2 = 0.58$***			$R^2 = 0.52$***
			$\Delta R^2 = 0.01$			$\Delta R^2 = 0.00$

Note: B = unstandardized regression coefficient at each step, *b* = standardized regression coefficient at each step. Puberty is coded 0 = pre-pubertal, 1 = pubertal. Sex: 0 = female, 1 = male. Race: 0 = Other, 1 = Caucasian.

***
$p < 0.001$.

**
$p < 0.01$.

*
$p < 0.05$.