ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Maternal and Pediatric Nutrition

The *FTO* rs9939609 Variant Is Associated with Cardiometabolic Disease Risk and Dietary Energy Intakes in Children with Mental Health Disorders

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ABSTRACT

Background: Second-generation antipsychotics (SGAs) are used to treat children for mental health disorders but in some children they cause cardiometabolic complications including weight gain and type 2 diabetes. Genetic variants can place a child at risk of developing these metabolic complications. The fat mass and obesity-associated (*FTO*) rs9939609 A allele has been associated with obesity and dietary energy intakes in healthy children but its relation to metabolic complications in SGA-treated children is not known.

Objectives: This study investigated the association of the *FTO* rs9939609 variant and SGA treatment with cardiometabolic complications and dietary intakes in children with mental health disorders.

Methods: A cross-sectional population of children (≤18 y; $n = 506$) with mental health disorders that were SGA-treated ($n = 197$) and SGA-naïve ($n = 309$) were recruited through the Department of Psychiatry at BC Children's Hospital. Dietary intakes were estimated using 3-d food records in a subset of children ($n = 73$).

Results: Genotype frequencies were not different between SGA-treated (TT genotype 42.6%, TA genotype 38.6%, AA genotype 18.8%) and SGA-naïve (TT 41.1%, TA 39.5%, AA 19.4%) children. Children with the A allele had lower BMI *z*-sores compared with the TT genotype (0.84 ± 1.19 compared with 1.19 ± 1.36; $P = 0.005$, adjusted for ethnicity). We observed an interaction between *FTO* genotype and SGA status on fasting glucose ($P = 0.036$). SGA-naïve children with the A allele had higher fasting glucose than those with the TT genotype (4.96 ± 0.35 compared with 4.81 ± 0.35 mmol/L; $P = 0.001$), in adjusted models (age, sex, ethnicity, and BMI *z*-score). This was not observed in SGA-treated children. Children with the A allele had higher daily total energy intakes compared with the TT genotype (1994 ± 619 compared with 1814 ± 484 kcal/d; $P = 0.048$), in adjusted models (age, sex, ethnicity, and BMI *z*-score); no effect of SGA-treatment was observed.

Conclusions: Our findings suggest the A allele of the *FTO* rs9939609 variant is associated with higher BMI in children with mental health disorders, but only in those not treated with SGAs. *Curr Dev Nutr* 2022;6:nzac014.

Keywords: children, youth, second-generation antipsychotics, obesity, type 2 diabetes, dietary intake

Manuscript received December 8, 2021. Initial review completed January 20, 2022. Revision accepted January 25, 2022. Published online January 29, 2022.
This research was supported by a grant from BC Mental Health and Substance Use Services to AMD and CP. AMW is supported by a Bertram Hoffmeister postdoctoral fellowship from BC Children's Hospital Research Institute and by Becas-Chile, Agencia Nacional de Investigación y Desarrollo. AMD is supported by an Investigator Grant from BC Children's Hospital Research Institute.
Author disclosures: The authors report no conflicts of interest.

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Abbreviations used: *FTO*, fat mass and obesity-associated gene; *IRX3*, iroquois-related homeobox 3 gene; SGA, second-generation antipsychotic.

Introduction

The prevalence of mental health disorders in children and youth (≤18 y of age) has been estimated to be ∼14% in Canada (1). Common mental health disorders during childhood include anxiety disorder, depressive disorders, bipolar disorder, autism spectrum disorder, and attention deficit hyperactivity disorder. Many of these children are increasingly being treated with second-generation antipsychotics (SGAs), also known as atypical antipsychotics (2–4). Treatment with SGAs is associated with metabolic complications such as rapid and excessive weight gain, elevated fasting glucose, insulin resistance, hypertension, and dyslipidemia (5, 6). A 3-fold greater risk of type 2 diabetes has been reported in children treated with antipsychotics compared with untreated controls (7–9).

Interestingly, metabolic complications develop in approximately half of SGA-treated children (10), suggesting the potential contribution of other factors such as genetic susceptibility (11). Currently, there is no way to identify SGA-treated children at risk of metabolic complications. We previously reported that the T allele of the C677T variant of the gene encoding methylenetetrahydrofolate reductase (*MTHFR*) (12) and the Met allele of the Val158Met variant of the gene encoding catechol-*O*-methyltransferase (*COMT*) (13) are associated with higher blood pressure and fasting blood glucose in SGA-treated, but not SGA-naïve children. However, these variants were found in only ∼25% of

SGA-treated children with metabolic complications, suggesting further genetic factors and/or other environmental factors place children at risk of metabolic complications.

A genome-wide association study identified a relation between the A allele of the rs9939609 variant in the fat mass and obesity-associated gene (*FTO*) and higher BMI and obesity in children and adults (14). Further studies have confirmed the association between the *FTO* rs9939609 A allele and surrogate markers of adiposity in children, including greater weight and BMI *z*-scores, and total fat mass (15–17). In addition, an association between the *FTO* rs9939609 variant and type 2 diabetes has been reported independent of BMI in adults (18, 19), suggesting a direct relation between *FTO* and type 2 diabetes.

FTO encodes an RNA demethylase (20) that is highly expressed in the hypothalamus, the region of the brain that regulates appetite; it has been postulated that *FTO* might play a role in food intake regulation and energy homeostasis. A few published studies in children support this concept. For example, children ($n = 3337$; aged 8–11 y) with the AA genotype of the *FTO* rs9939609 variant were reported to have reduced satiety compared with those with the TT genotype (15). Another study reported that food intake was greater during a test of eating in the absence of hunger in young children ($n = 131$; aged 4–5 y) with the AA genotype compared with those with the TT genotype (21). Further, others have reported that overeating is more common in children ($n = 190$; aged 6–19 y) with the A allele compared with children with the TT genotype (17). Dietary energy intakes were higher during a test meal in children ($n = 76$; aged 4–10 y) with the A allele compared with those with the TT genotype (16).

We hypothesize that given the potential role of *FTO* in food intake regulation and energy homeostasis, the *FTO* rs9939609 variant can contribute to rapid weight gain and cardiometabolic complications in SGA-treated children. One study reported that the *FTO* rs9939609 variant was not associated with weight gain in young children ($n = 181$; aged 8 y) with autism spectrum disorder after 8 wk of risperidone treatment (22), but relations with other cardiometabolic risk factors and dietary energy intakes were not assessed. The objective of this study was to determine if the *FTO* rs9939609 variant is associated with cardiometabolic disease risk in SGA-treated and SGA-naïve children with mental health disorders. The secondary objective was to explore if the *FTO* rs9939609 genotype is associated with dietary energy intakes and interaction with SGA treatment.

Methods

Study design and participants

This was a cross-sectional study designed to determine the relation between the *FTO* rs9939609 variant, SGA treatment, and several markers of cardiometabolic health in children with mental health disorders. Participants were recruited through the Child and Adolescent Psychiatry department at British Columbia Children's Hospital between June 2008 and April 2018. The inclusion criteria were children between the ages of 6 and 18 y with a mental health diagnosis who were treated with an SGA for ≥7 d (SGA-treated) or children who were not receiving an SGA and had never received an SGA for >7 d (SGA-naïve). Children with a disorder/disease known to affect metabolism (type 1 diabetes, type 2 diabetes, polycystic ovary syndrome, Crohn disease, etc.), a diagnosed eating disorder, treatment with medications known to affect metabolism (glucocorticoids, β blocker, levothyroxine, etc.), genetic syndromes (Prader–Willi syndrome, Down syndrome, etc.), fetal alcohol spectrum disorder, and/or inborn errors of metabolism were excluded.

This research was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the University of British Columbia Clinical Research Ethics Board and the Children's and Women's Health Centre of British Columbia Research Ethics Board. Parents or legal guardians provided written informed consent, and children provided written assent where capable. Study participants were not compensated for participation in the study. Study participants were assigned a unique study number at enrolment in the study, which did not include any personal information that could identify the participant. Only this number was used on research-related information collected about the participant during the course of this study. The information on the study number and link to the study participant identification are kept in a paper file in a locked filing cabinet in the office of AMD. The study participants consented to the data being used for scientific publication. There was no direct benefit to the child for participating in this study. However, abnormal metabolic blood test results were provided to the parent/guardian of the study participant, and with permission, to their treating physician.

Demographic information was collected including sex and self-reported ethnicity. Medical records were reviewed to obtain information on the mental health disorder diagnoses (by a board-certified psychiatrist), and dose and duration of SGA treatment.

Genomic DNA extraction and genotyping

Buccal epithelial cells were collected from the participants by scraping the inner cheek with collection swabs (Puritan Medical Products). Genomic DNA was isolated using the QIAamp DNA Mini Kit (Qiagen). Genotyping of the *FTO* rs9939609 variant was completed using Taqman SNP Genotyping reagents and a 7500 Real-Time PCR System (Applied Biosystems).

Anthropometric assessments

Height was measured to the nearest 0.1 cm (Seca 240 Stadiometer) and weight to the nearest 0.1 kg (Tronix Scale 5002). Waist circumference was measured to the nearest 0.1 cm at the level of the umbilicus using a nonelastic flexible tape; an average of 2 measurements was used. Waist circumference *z*-scores were standardized for age and sex based on NHANES, cycle III (23). Elevated waist circumference was defined as ≥90th percentile for age and sex (24). BMI z-scores were standardized for age and sex based on the WHO growth charts (25); overweight was defined as a BMI *z*-score ≥1 SD and <2 SD for age and sex; obesity was defined as a BMI *z*-score ≥2 SD.

Clinical assessments

Blood pressure was assessed using a Dinamap automated monitor (PRO 100-400; GE Medical Systems). Children were seated in a chair with their back supported and feet on the floor; their right arm was supported and positioned at the heart level and fitted with an appropriately sized cuff. After 5 min of seated rest, systolic blood pressure and diastolic blood pressure were measured; an average of 3 readings was used. Blood pressure percentiles were standardized for age, sex, and height.

TABLE 1 Demographic characteristics of the participants[1]

	All children ($n = 506$)	SGA-naïve ($n = 309$)	SGA-treated ($n = 197$)
Age, y	12.87 ± 3.03	13.39 ± 2.74	12.05 ± 3.27
Male sex, *n* (%)	292 (57.7)	161 (52.1)	131 (66.5)
European ethnicity, *n* (%)	403 (79.6)	238 (77.0)	165 (83.8)
Primary psychiatric diagnosis, *n* (%)			
Anxiety disorder	130 (25.7)	79 (25.6)	51 (25.9)
Depressive disorders	103 (20.4)	85 (27.5)	18 (9.1)
ADHD	74 (14.6)	35 (11.3)	39 (19.8)
Mood disorders	37 (7.3)	18 (5.8)	19 (9.6)
Psychotic disorders	32 (6.3)	18 (5.8)	14 (7.1)
Pervasive developmental disorder	31 (6.1)	9 (2.9)	22 (11.2)
Adjustment disorders	29 (5.7)	29 (9.4)	0 (0.0)
Disruptive behavior disorder	9 (1.8)	1 (0.3)	8 (4.1)
Oppositional defiant disorder	8 (1.6)	3 (1.0)	5 (2.5)
Other disorders	53 (10.5)	32 (10.4)	21 (10.7)
Current SGA, *n* (%)			
Risperidone			104 (52.8)
Quetiapine			68 (34.5)
Aripiprazole			17 (8.6)
Olanzapine			4 (2.0)
Ziprasidone			2 (1.0)
Paliperidone			1 (0.5)
Lurasidone			1 (0.5)
FTO rs9939609 genotype, *n* (%)			
TT	211 (41.7)	127 (41.1)	84 (42.6)
AT	198 (39.1)	122 (39.5)	76 (38.6)
AA	97 (19.2)	60 (19.4)	37 (18.8)

[1]Data presented as mean ± SD, unless otherwise indicated. ADHD, attention deficit hyperactivity disorder; *FTO*, fat mass and obesity-associated gene; SGA, second-generation antipsychotic.

Elevated blood pressure was defined as ≥90th percentile (age 1–13 y) or ≥120/80 mmHg (age ≥13 y) (26).

A fasting (overnight ≥8 h) blood sample was collected by venipuncture, and plasma glucose, insulin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations were quantified by the clinical laboratory at BC Children's Hospital. Elevated LDL cholesterol was defined by a plasma LDL cholesterol ≥3.37 mmol/L; elevated total cholesterol was defined as plasma total cholesterol ≥5.18 mmol/L; elevated plasma triglycerides was defined as plasma triglycerides ≥1.47 mmol/L (24). Insulin resistance was estimated using the updated version of the homeostatic model assessment calculator (HOMA2-IR, version 2.2.3) (27).

Dietary assessment

Three-day food records were collected on 2 weekdays and 1 weekend day; only the data from the subset of the participants (recruited between 2012 and 2018) who provided complete records were used to estimate dietary macronutrient intakes as described previously (28). Participants or their parents/guardians were instructed to record all food, drinks, and supplements consumed. The dietary information was checked for clarity, and all items consumed were confirmed by the research staff. Food records were analyzed using the Food Processor Nutrition Software (version 10.13.1.0; ESHA Research) with the Canadian Nutrient File or USDA database. Daily average total energy and macronutrient intakes were estimated.

Statistical analyses

Data distribution normality was assessed by the Kolmogorov–Smirnov test and visually assessed by histograms and Q-Q plots. All variables were normally distributed and are presented as mean ± SD. Differences in *FTO* rs9939609 variant genotype frequencies by SGA status were assessed using a χ^2 test. Associations between *FTO* rs9939609 genotype (TT compared with TA/AA), cardiometabolic disease risk factors, and SGA status were determined by separate linear general models for continuous variables and logistic regression models for categorical variables. Models were adjusted for age, sex, BMI *z*-score, and ethnicity, as indicated. If an interaction between the *FTO* genotype and SGA status was observed, the effect of the *FTO* rs9939609 genotype was determined separately in SGA-treated and SGA-naïve groups.

In a subset of participants, the interaction and relation of the *FTO* rs9939609 TT genotype and SGA status on dietary total energy and macronutrient intakes were determined by separate general linear models. Models were adjusted for age, sex, BMI *z*-score, and ethnicity, as indicated. All statistical analyses were performed using SPSS Statistics (version 27.0; IBM Corp). A P value ≤ 0.05 was considered statistically significant.

Results

Participant characteristics

A total of 506 children were included in this analysis: 197 SGA-treated children and 309 SGA-naïve children. The demographic characteristics of the participants are presented in **Table 1**. SGA-treated children were younger and had a higher percentage of males compared with the SGA-naïve children. The most common primary psychiatric diagnoses were anxiety disorder, depressive disorder, and attention deficit hyperactivity disorder. Risperidone and quetiapine were the most prescribed

TABLE 2 Cardiometabolic disease risk factors[1]

	All children		SGA-naïve		SGA-treated	
	TT	TA/AA	TT	TA/AA	TT	TA/AA
Anthropometrics						
BMI z-score	1.19 ± 1.36	0.84 ± 1.19	0.98 ± 1.29	0.66 ± 1.19	1.52 ± 1.41	1.13 ± 1.14
Overweight,[2] *n* (%)	43 (22.8)	54 (21.6)	26 (22.6)	31 (20.5)	17 (23.0)	23 (23.2)
Obesity,[3] *n* (%)	56 (28.0)	49 (19.6)	24 (20.9)	22 (14.6)	29 (39.2)	27 (27.3)
Waist circumference z-score	0.70 ± 0.98	0.54 ± 0.94	0.55 ± 0.99	0.37 ± 0.96	0.92 ± 0.94	0.78 ± 0.85
Elevated waist circumference,[4] *n* (%)	55 (31.4)	57 (25.0)	26 (25.2)	26 (19.5)	29 (40.3)	31 (32.6)
Blood pressure						
Systolic blood pressure percentile	66.2 ± 27.7	63.0 ± 28.4	63.6 ± 28.3	62.3 ± 28.0	70.5 ± 26.2	64.2 ± 29.22
Diastolic blood pressure percentile	62.2 ± 24.1	57.3 ± 27.2	61.0 ± 24.5	55.8 ± 26.5	64.3 ± 23.3	59.6 ± 28.1
Elevated blood pressure,[5] *n* (%)	65 (35.1)	88 (35.3)	39 (33.6)	51 (33.3)	26 (37.7)	37 (38.5)
Glucose homeostasis						
Fasting glucose, mmol/L	4.87 ± 0.35	4.96 ± 0.34	4.81 ± 0.35	4.96 ± 0.35	4.97 ± 0.33	4.97 ± 0.34
Impaired fasting glucose,[6] *n* (%)	6 (3.3)	13 (5.4)	2 (1.8)	7 (5.0)	4 (5.6)	6 (6.1)
Fasting insulin, pmol/L	57.69 ± 43.87	54.98 ± 37.21	54.37 ± 33.10	53.65 ± 37.94	62.61 ± 56.11	56.83 ± 36.26
Elevated fasting insulin,[7] *n* (%)	13 (7.3)	23 (9.8)	6 (5.6)	10 (7.3)	7 (9.7)	13 (13.3)
HOMA2-IR	1.08 ± 0.80	1.04 ± 0.69	1.01 ± 0.61	1.01 ± 0.71	1.20 ± 1.01	1.09 ± 0.67
Blood lipids						
Total cholesterol, mmol/L	4.37 ± 0.87	4.22 ± 0.80	4.23 ± 0.77	4.12 ± 0.74	4.59 ± 0.97	4.37 ± 0.85
Elevated total cholesterol,[8] *n* (%)	33 (17.8)	29 (11.4)	11 (9.8)	12 (8.0)	22 (30.1)	17 (16.2)
LDL cholesterol, mmol/L	2.58 ± 0.78	2.45 ± 0.72	2.47 ± 0.67	2.37 ± 0.65	2.75 ± 0.91	2.56 ± 0.78
Elevated LDL cholesterol,[9] *n* (%)	25 (13.8)	30 (12.3)	12 (10.9)	11 (7.8)	13 (18.3)	19 (18.6)
HDL cholesterol, mmol/L	1.33 ± 0.35	1.35 ± 0.38	1.31 ± 0.32	1.34 ± 0.38	1.36 ± 0.40	1.37 ± 0.38
Lowered HDL cholesterol,[10] *n* (%)	29 (16.0)	45 (18.4)	19 (17.3)	28 (19.6)	10 (14.1)	17 (16.7)
Triglycerides, mmol/L	1.03 ± 0.52	0.92 ± 0.47	0.99 ± 0.44	0.93 ± 0.48	1.09 ± 0.62	0.92 ± 0.45
Elevated triglycerides,[11] *n* (%)	25 (13.4)	33 (13.0)	16 (14.2)	18 (12.1)	9 (12.3)	15 (14.3)

[1]Data presented as mean ± SD, unless otherwise indicated. HOMA2-IR, updated homeostatic assessment model of insulin resistance; SGA, second-generation antipsychotic.
[2]Overweight, BMI ≥1 SD and <2 SD for age and sex.
[3]Obesity, BMI ≥2 SD for age and sex.
[4]Elevated waist circumference, waist circumference ≥90th percentile for age and sex.
[5]Elevated blood pressure, ≥90th percentile (1–13 y) or ≥120/80 mmHg (≥13 y).
[6]Impaired fasting glucose, fasting glucose ≥5.6 mmol/L.
[7]Elevated fasting insulin, fasting insulin ≥100 pmol/L.
[8]Elevated total cholesterol, plasma total cholesterol ≥5.18 mmol/L.
[9]Elevated LDL cholesterol, plasma LDL cholesterol ≥3.37 mmol/L.
[10]Lowered HDL cholesterol, plasma HDL cholesterol <1.03 mmol/L.
[11]Elevated triglycerides, plasma triglycerides ≥1.47 mmol/L.

TABLE 3 Association between *FTO* rs9939609 genotype and SGA status with cardiometabolic risk factors[1]

	Interaction between *FTO* genotype and SGA status *P* value	*FTO* genotype *P* value	SGA status *P* value	*FTO* genotype	
				SGA-naïve *P* value	SGA-treated *P* value
BMI *z*-score	0.756	0.005	0.001		
Waist circumference *z*-score	0.792	0.078	0.001		
Systolic blood pressure percentile	0.516	0.474	0.853		
Diastolic blood pressure percentile	0.540	0.092	0.323		
Fasting glucose	0.036			0.001	0.994
Fasting insulin	0.420	0.909	0.055		
HOMA2-IR	0.357	0.969	0.066		
Total cholesterol	0.931	0.056	0.023		
LDL cholesterol	0.934	0.064	0.111		
HDL cholesterol	0.601	0.506	0.676		
Triglycerides	0.141	0.074	0.242		

[1]Associations determined using general linear models adjusted by ethnicity for anthropometric and blood pressure variables, and adjusted by age, sex, ethnicity, and BMI *z*-score for fasting plasma concentration variables. *FTO*, fat mass and obesity-associated gene; HOMA2-IR, updated homeostatic assessment model of insulin resistance; SGA, second-generation antipsychotic.

SGAs. The median (IQR) duration of SGA treatment was 7.0 (3.0–14.8) mo. The *FTO* rs9939609 genotype distribution was not different between SGA-treated and SGA-naïve children (Table 1). The A allele frequency was 58.3% for all children; 57.4% in the SGA-treated children, and 58.9% in the SGA-naïve children.

Cardiometabolic risk factors

The anthropometric and other cardiometabolic parameters are presented in **Table 2**. SGA-treated children had significantly higher BMI *z*-scores (1.30 ± 1.27 compared with 0.80 ± 1.24; $P = 0.001$) and a greater odds of overweight and/or obesity (≥1 SD; OR = 2.17; 95% CI: 1.19, 3.95; $P = 0.012$) than SGA-naïve children in adjusted models (by ethnicity). SGA-treated children had significantly higher waist circumference *z*-scores (0.84 ± 0.89 compared with 0.45 ± 0.98; $P = 0.001$) and greater odds of elevated waist circumference (≥90th percentile; OR = 1.95; 95% CI: 1.02, 3.74; $P = 0.045$) than SGA-naïve children in adjusted models (by ethnicity).

Relations between the *FTO* genotype and SGA status on anthropometric and cardiometabolic risk factors are shown in **Table 3**. No interactions between the *FTO* genotype and SGA status on BMI *z*-scores or waist circumference *z*-scores were observed. Children with the *FTO* rs9939609 A allele had lower BMI *z*-scores compared with children with the TT genotype in a model adjusted for ethnicity ($P = 0.005$; **Figure 1**, Table 3).

An interaction between the *FTO* rs9939609 genotype and SGA status was observed for fasting glucose concentrations ($P = 0.036$) in an adjusted model (age, sex, ethnicity, and BMI *z*-score). SGA-naïve children with the A allele had higher fasting glucose concentrations compared with children with the TT genotype ($P = 0.001$); this was not observed in SGA-treated children.

SGA-treated children had higher plasma total cholesterol concentrations (4.45 ± 0.91 compared with 4.16 ± 0.75 mmol/L; $P = 0.023$) and elevated plasma total cholesterol (≥5.18 mmol/L; OR = 3.88; 95% CI: 1.74, 8.65; $P = 0.001$) compared with SGA-naïve children in an adjusted model (by age, sex, ethnicity, and BMI *z*-score). No effect of the *FTO* genotype on fasting lipids was observed.

Dietary intake

Daily dietary total energy and macronutrient intakes estimated from the 3-d food records in a subset of the participants are presented in **Table 4**. There was no interaction between *FTO* rs9939609 genotype and SGA status on total energy intakes. Children with the *FTO* A allele consumed on average 180 kcal more than children with the *FTO* TT genotype in a model adjusted for age, sex, ethnicity, and BMI *z*-score ($P = 0.048$; Tables 4 and 5). No differences in total energy intakes were observed between SGA-treated and SGA-naïve children.

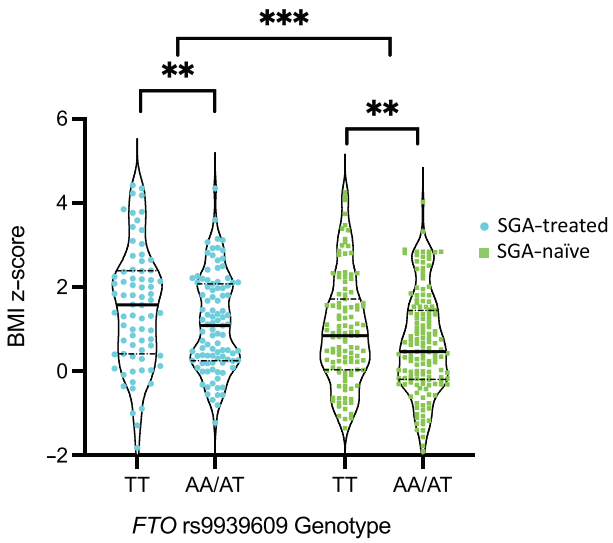

FIGURE 1 BMI *z*-scores in SGA-treated and SGA-naïve children by *FTO* rs9939609 genotype. Individual data points presented. Violin plots show the density of the data points, median (solid line), and 25th and 75th percentiles (dashed line). **Significant effect of *FTO* genotype, $P < 0.01$; ***significant effect of SGA treatment, $P = 0.001$. *FTO*, fat mass and obesity-associated gene; SGA, second-generation antipsychotic.

TABLE 4 Daily dietary total energy and macronutrient intake[1]

	All children		SGA-naïve		SGA-treated	
	TT ($n = 30$)	TA/AA ($n = 43$)	TT ($n = 12$)	TA/AA ($n = 23$)	TT ($n = 18$)	TA/AA ($n = 20$)
Total energy, kcal	1814 ± 484	1994 ± 619	1597 ± 525	1889 ± 442	1959 ± 406	2116 ± 769
Protein, g	62.9 ± 19.7	73.8 ± 23.4	61.7 ± 22.4	69.3 ± 18.9	63.7 ± 18.3	79.0 ± 27.2
% energy	13.9 ± 2.29	15.0 ± 2.41	15.5 ± 2.37	14.7 ± 2.23	12.9 ± 1.57	15.3 ± 2.63
Carbohydrates, g	251 ± 71.5	269 ± 101	211 ± 67.5	247 ± 75.7	277 ± 62.7	295 ± 121
% energy	55.1 ± 5.90	54.0 ± 9.28	53.1 ± 5.60	52.9 ± 11.5	56.5 ± 5.85	55.2 ± 5.82
Fat, g	64.1 ± 19.4	70.2 ± 25.1	57.4 ± 20.6	68.6 ± 24.0	68.6 ± 17.8	72.0 ± 26.8
% energy	32.0 ± 5.76	31.6 ± 6.62	32.4 ± 5.78	32.3 ± 7.15	31.7 ± 5.90	30.7 ± 6.02

[1]Data are 3-d average presented as mean ± SD. SGA, second-generation antipsychotic.

An interaction between the *FTO* rs9939609 genotype and SGA status was observed for dietary protein intakes (as percentage of total energy, $P = 0.003$) in an adjusted model (by age, sex, ethnicity, and BMI *z*-score) (**Table 5**). SGA-treated children with the A allele consumed more protein (2.39% of total energy) than SGA-treated children with the TT genotype ($P = 0.004$, Table 5). No effect of the *FTO* genotype on total protein intakes was observed in SGA-naïve children. No relations between the *FTO* rs9939609 genotype or SGA status on carbohydrate or fat intakes were observed.

Discussion

In this study, we examined whether the *FTO* rs9939609 variant is associated with greater cardiometabolic complications and dietary energy intakes in SGA-treated and SGA-naïve children with mental health disorders. We postulated that given the potential role of *FTO* in food intake regulation and energy homeostasis (15–17, 21), children with the *FTO* rs9939609 A allele would be more susceptible to SGA-related cardiometabolic complications. We observed 3 main findings. First, both SGA-naïve and SGA-treated children with the *FTO* rs9939609 A allele had lower BMI *z*-scores compared with SGA-naïve and SGA-treated children with the TT genotype. This finding is in contrast to others who have reported higher BMI *z*-scores in children with the A allele compared with the TT genotype (15–17). Further, no interaction between the *FTO* rs9939609 genotype and SGA treatment on BMI *z*-scores was observed. Second, SGA-naïve children with the *FTO* rs9939609 A allele had higher fasting plasma glucose concentrations than SGA-naïve children with the TT genotype. This association between *FTO* genotype and fasting plasma glucose was not seen in SGA-treated children, Third, as predicted, in a subset of the children, those with the *FTO* rs9939609 A allele had greater dietary total energy intakes compared with children with the TT genotype. No interaction between the *FTO* variant and SGA treatment on dietary total energy intakes was observed. However, SGA-treated children with the A allele had higher protein intake compared with SGA-treated children with the TT genotype. This was not seen in SGA-naïve children.

The *FTO* rs9939609 A allele was the first identified (14), and one of the most replicated genetic variants associated with elevated BMI and obesity in children (29, 30). In contrast, our study found children with the A allele had lower BMI *z*-scores compared with children with the TT genotype. The mostly likely explanation for our discrepant finding is the differences in the populations that were studied. In the current study, we assessed children with a confirmed mental health disorder diagnosis, whereas the previously published studies (15–17) were conducted in children representing the general population or in otherwise healthy children with no information on mental health disorders. However, similar to what we report here, a previous study conducted in children ($n = 225$) with autism spectrum disorder reported no relation between risperidone-related weight gain and the *FTO* rs9939609 variant (31). Moreover, other studies that assessed both children and adults with mental health disorders have reported no relations between the *FTO* rs9939609 variant and weight gain or BMI (32–34). Taken together, this suggests that the impact of the *FTO* rs9939609 A allele on BMI might not be relevant in children with mental health disorders.

There are no published studies in children with mental health disorders that have interrogated the relation between the *FTO* rs9939609 variant and fasting glucose concentrations. Interestingly we observed an

TABLE 5 Associations between *FTO* rs9939609 genotype and SGA status with dietary energy and macronutrient intakes[1]

	Interaction between *FTO* genotype and SGA status *P* value	*FTO* genotype *P* value	SGA status *P* value	*FTO* genotype	
				SGA-naïve *P* value	SGA-treated *P* value
Total energy intake (kcal)	0.731	0.048	0.286		
Protein (% energy)	0.003			0.231	0.004
Carbohydrates (% energy)	0.808	0.508	0.067		
Fat (% energy)	0.667	0.889	0.431		

[1]Associations determined using general linear models adjusted by age, sex, ethnicity, and BMI *z*-score. *FTO*, fat mass and obesity-associated gene; SGA, second-generation antipsychotic.

interaction between the *FTO* rs9939609 variant and SGA treatment on fasting glucose concentrations, with higher fasting plasma glucose concentration observed only in SGA-naïve children with the A allele. This is similar to findings of others who have also reported higher fasting glucose concentrations in those with the A allele (19, 35, 36). The lack of a relation between the A allele and fasting plasma glucose concentrations in SGA-treated children could be due to the greater effect of SGAs on glucose metabolism (11), diluting any effect of the A allele. SGAs may affect blood glucose by 2 different pathways that occur independent of each other or in concert. First, blood glucose concentrations may become elevated in SGA-treated children secondary to the development of obesity and insulin resistance. This is supported by studies that report children treated with antipsychotics have a 3-fold greater risk of type 2 diabetes compared with untreated children (7, 8). Second, SGAs may have direct effects on the insulin producing β-cells of the pancreas. We have reported that children treated with quetiapine have reduced insulin secretion (insulinogenic index) during an oral-glucose-tolerance test (37). Further, a recent study in a mouse model reported β-cell dysfunction, glucose intolerance, and impaired insulin secretion in female mice treated with aripiprazole (38).

Our finding of a positive relation between the *FTO* rs9939609 A allele and dietary total energy intakes is consistent with previous studies conducted in children (16, 21, 39–41) and supports the role of *FTO* in food intake regulation. Moreover, reduced satiety, increased food responsiveness, and overeating have been reported in children with the A allele compared with those with the TT genotype (15, 17, 42). Interestingly, we observed an association between *FTO* genotype and dietary energy intakes from protein only in SGA-treated children; however, the association was small and is unlikely to be clinically relevant. Discrepant findings have been reported on the relation between the *FTO* rs9939609 variant and macronutrient intakes. Some studies have reported no associations with macronutrient intakes (39, 41), whereas others have reported a positive association between the A allele and dietary fat intake in children (40, 43). Inconsistent findings have also been reported in adults (44). However, one study reported that the A allele was associated with lower total energy intakes and higher protein intake in adults (45).

Interestingly, children with the *FTO* rs9939609 A allele had lower BMI *z*-scores despite higher dietary energy intakes. However, this could have been impacted by the small number of children in the subset that completed dietary assessment relative to the number of children that were genotyped. Nonetheless, this observation might be due to differences in energy expenditure and/or activity between the groups. We were unable to assess energy expenditure in the current study. We previously reported that ~59% of children with mental health disorders (SGA-treated and SGA-naïve) met physical activity guidelines of ≥60 min of activity per day (46). The most likely explanation for our findings is that the medications and/or the pathology of the mental health disorder counteract the effect of *FTO* on body composition and food intake regulation. The SGA medications typically target serotonin and dopamine receptors (11); it is probable that SGAs and/or mental illness affect the hypothalamus and interfere with the role of *FTO* in this brain region.

Although the functional effect of the *FTO* rs9939609 variant is still unclear, the location of the variant in an intron at the 5′ end of the gene suggests the variant could interfere with *FTO* transcriptional regulation rather than protein function. The main functional effect of the variant is on appetite and food intake regulation (17, 21). A study reported that *FTO* rs9939609 variant impacts food intake through effects on the corticolimbic activation pathway (47). An alternative explanation might relate to changes in the gene expression of adjacent genes involved in energy metabolism. It has been reported that the *FTO* rs9939609 variant interacts with the promotor of the iroquois-related homeobox 3 gene (*IRX3*) and enhances expression, indirectly affecting adipocyte function, energy metabolism, and body weight (48, 49). Recent evidence suggests increased expression of *IRX3* with the *FTO* rs9939609 A allele in adipose tissue in children with a BMI <1.28 SD for age and sex and greater adipocyte *IRX3* expression, negatively correlated with BMI compared with children with overweight and obesity (BMI ≥1.28 SD for age and sex) (50).

There are several strengths and some limitations to our study. The strengths of our study include the large sample size of children with mental health disorders ($n = 506$). We adjusted all the statistical analyses for relevant covariates including age, sex, ethnicity, and BMI *z*-score. Our study is limited because of the cross-sectional design. However, given the population of children, it is difficult to prospectively follow a large cohort of children with mental health disorders receiving SGA treatment because of high rates of attrition and medication changes during the course of their illness. There are also well-known limitations with self-reported dietary intake data, particularly related to measurement errors in estimating food portions/sizes. The possibility of response bias related to social desirability might also influence dietary information reported by the participant's parents or caregivers.

In summary, our findings suggest that the *FTO* rs9939609 A allele is associated with lower BMI *z*-scores and higher dietary energy intakes in children with mental health disorders, and with higher plasma fasting glucose concentration in SGA-naïve children. Given metabolic complications are common in children with mental health disorders, especially in those treated with SGAs, further research to understand which genetic variants can predict children at risk of developing metabolic complications is required.

Acknowledgments

We acknowledge Mikaela Barker, who assisted with collection of some of the dietary information from the children.

The authors' responsibilities were as follows—AMD and CP: designed the research; YFN and AMH: conducted the research; AMW: analyzed data and wrote the first draft of the manuscript; AMD: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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