Autism Spectrum Disorders and Metabolic Complications of Obesity

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Objectives To assess for an increased risk of obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis in children with autism spectrum disorders (ASD). Additionally, to determine the rates of prescribed treatment for obesity-related metabolic disorders and to determine whether treatment with psychotropic medications is associated with the development of obesity for children with ASD.

Study design A retrospective 1:5 case-control study was performed by use of the Military Health System database from October 2000 to September 2013. For children with ASD and matched controls, *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes for obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, and prescriptions were obtained. Conditional logistic regression determined ORs and 95% CIs.

Results A total of 48 762 individuals with ASD and 243 810 matched controls were identified. Children with ASD had significantly greater odds of having obesity (OR 1.85; 95% CI 1.78-1.92), having obesity-related disorders, and being prescribed a medication when they had these diseases. In children with ASD, mood stabilizers, antipsychotics, antiepileptic drugs, and selective serotonin reuptake inhibitors were associated with obesity.

Conclusions Children with ASD have an increased risk of obesity and obesity-related metabolic disorders. They are more likely to be prescribed medications to treat these complications, suggesting they may have more severe disease. There is a significant association between the use of some psychotropic categories and a diagnosis of obesity, suggesting that obesity in children with ASD may be partially iatrogenic. *(J Pediatr 2016;178:183-7).*

Autism spectrum disorder (ASD) is a continuum of neurodevelopmental conditions characterized by impairment in social skills, impairment in social communication, and restricted, repetitive behaviors. Patients usually are diagnosed in childhood.[1,2] ASD has an estimated prevalence of 1 in 68 children.[3] Children with ASD frequently have selective eating, manifested by choosing more energy-dense foods; having aversions to certain textures, colors, and smells; and being rewarded with preferred foods for behavioral achievements.[4-6] Physical activities may be more challenging due to motor and social skill deficits,[7-9] and these children may be prescribed psychotropic medications that can cause weight gain.[10-14] A few previous studies have demonstrated a greater incidence of obesity in the ASD population.[15-17] Curtin et al[15] estimated that children with ASD are 40% more likely to be obese compared with children without ASD, but the study was limited by parent-reported data of children's height and weight rather than direct measurements.

Children with obesity have an increased risk of developing related metabolic disorders, such as type 2 diabetes mellitus (T2DM), hypertension (HTN), hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH).[18-20] No previous studies have focused on the prevalence of these comorbid conditions of obesity in children with ASD. It also is unknown how frequently children with ASD are prescribed medications to treat one of these conditions compared with peers with the same condition.

An estimated 30%-60% of children with ASD are prescribed a psychotropic medication to treat behavioral abnormalities.[21] Little is known about the risk of obesity associated with these medications among children with ASD. Broder-Fingert et al[16] evaluated whether psychotropic medications were associated with overweight status or obesity in a cohort of patients with autism and Asperger syndrome and found

ASD	Autism spectrum disorder
BMI	Body mass index
HTN	Hypertension
ICD-9-DM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
MHS	Military Health System
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
RR	Relative risk
SSRI	Selective serotonin reuptake inhibitor
T2DM	Type 2 diabetes mellitus

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no statistically significant association; however, they commented on the possibility that the risk of obesity was so large that the impact of medication is obscured, or that the medication data in the study was incomplete with prescription history, obtained only from within that particular health system. Further evaluation with comprehensive medication data is needed to determine whether psychotropic medications increase the risk of obesity for children with ASD.

We aimed to determine whether children with ASD, compared with other children, have a greater prevalence of obesity and obesity-related metabolic disorders such as T2DM, HTN, hyperlipidemia, NAFLD, and NASH; whether children with ASD were more or less likely to be treated for these conditions with prescription medications; and whether psychotropic medications are associated with an increased risk of obesity among children with ASD.

Methods

A retrospective case-control study was designed with the Military Health System (MHS) database. The MHS database includes data on outpatient visits, inpatient admissions, and prescriptions of all military members and dependents treated in both military and civilian medical facilities in the US and abroad. Cases were defined by the use of a previously validated method.[22,23] Beneficiaries aged 2-18 years who were enrolled in the MHS database between October 2000 and September 2013 and who were given *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for a diagnosis of ASD at 2 separate clinical encounters were identified. Exclusion criteria included ICD-9-CM diagnostic codes for childhood disintegrative disorder and degenerative conditions of childhood such as Rett syndrome, Alpers disease, infantile necrotizing encephalomyelopathy, Leigh disease, and subacute necrotizing encephalopathy (**Table I**; available at www.jpeds.com). Those enrolled in the MHS database at least 6 months before receiving the first ASD diagnosis code and at least 6 months after receipt of the diagnosis were included in the study. Five controls were matched without replacement to each case by age, sex, and enrollment time frame. Each control's enrollment period was then truncated to match the case's enrollment period. The study was reviewed and approved by the responsible institutional review boards.

The MHS database was used, among the identified cases and controls, to identify each of the diagnoses: obesity, T2DM, HTN, hyperlipidemia, NAFLD, and NASH. Children were identified as obese if they had at least 1 encounter with an ICD-9-CM code pertaining to obesity (**Table I**). Those identified as having T2DM included children with at least 1 encounter with an ICD-9-CM code pertaining to T2DM. Children who were prescribed insulin were excluded to minimize possible misclassification of type 1 diabetes mellitus. Those considered to have hyperlipidemia had at least 1 ICD-9-CM code pertaining to elevated lipid levels. In an effort to avoid misclassification bias related to a single visit with an elevated blood pressure, subjects considered hypertensive had at least 2 encounters with an ICD-9-CM code of 401.x, which is the code for essential HTN. Subjects were considered to have NAFLD if they had at least 2 encounters with ICD-9-CM codes pertaining to the diagnosis on separate days. They also met NAFLD criteria if they had 1 encounter with any of the eligible diagnostic codes, as well as a procedure code for a liver biopsy. Because NASH requires the presence of liver inflammation and evidence of hepatic fibrosis, those considered to have NASH were required to have a procedure code for a liver biopsy and at least 1 encounter with ICD-9-CM code 571.5.

In an effort to validate the findings related to obesity, which used ICD-9-CM codes, a subgroup sensitivity analysis was performed. The MHS database was used to obtain height and weight data from children in the study population who were seen in a military treatment facility from October 2008 to September 2013. This subgroup was chosen because anthropometric data, such as height and weight, are available only in the MHS database for patients seen at a military treatment facility after October 2008. The subgroup included children with and without ASD who had a height and weight obtained simultaneously at an outpatient visit. A body mass index (kg/m^2; BMI) and BMI percentile for age was calculated for each subject by the use of a program provided by the US Centers for Disease Control and Prevention.[24] Those with a BMI greater than the 95th percentile were identified as being obese.

Typical treatment for obesity-related metabolic disorders often includes counseling about diet and exercise. We hypothesized that children with ASD were less likely to be responsive to the conservative interventions of diet and exercise changes and were more likely to require prescription treatment for the medical conditions associated with obesity. We evaluated the association of a diagnosis of ASD and the prescription of medication treatment for T2DM, HTN, and hyperlipidemia. There is no standard pharmacologic treatment for the management of NAFLD and NASH. The American Society of Health-System Pharmacists' American Hospital Formulary Service Therapeutic Class Codes were used to identify and categorize medications that typically would be used to treat T2DM, HTN, and hyperlipidemia (**Table II**; available at www.jpeds.com). Three subgroup analyses were performed among those who were diagnosed with T2DM, HTN, and hyperlipidemia. Generalized modeling with a negative binomial distribution was used to determine relative risks (RR) and 95% CIs of children with ASD being prescribed treatment for T2DM, HTN, and hyperlipidemia.

To evaluate whether psychotropic medications were associated with obesity in children with ASD, prescription information, including drug names and number of days supplied, was obtained for each subject in the study sample. For purposes of calculating risk of obesity, a medication was assumed to be taken each day for the number of days supplied. The American Hospital Formulary Service Therapeutic Class Codes were used to identify and categorize the medications into the following categories: mood stabilizers, antipsychotic medications, antiepileptic drugs, selective serotonin reuptake inhibitors (SSRIs), medications to treat attention deficit disorder