Risk of Developing Type 2 Diabetes in Adolescents and Young Adults With Autism Spectrum Disorder: A Nationwide Longitudinal Study

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OBJECTIVE

Studies have suggested the association between autism spectrum disorder (ASD) and type 2 diabetes mellitus (DM)–related risk factors, such as obesity and dyslipidemia. However, the association between ASD and type 2 DM remains unknown.

RESEARCH DESIGN AND METHODS

We used the Taiwan National Health Insurance Research Database for enrolling 6,122 adolescents and young adults with ASD and 24,488 age- and sex-matched control subjects between 2002 and 2009 and monitored them until the end of 2011. Participants who developed type 2 DM during the follow-up period were identified.

RESULTS

Adolescents (hazard ratio [HR] 2.71 [95% CI 1.64–4.48]) and young adults (HR 5.31 [95% CI 2.85–9.90]) with ASD had a higher risk of developing type 2 DM than those without ASD, after adjustment for demographic data, atypical antipsychotics use, and medical comorbidities. Sensitivity analyses after excluding first year (HR 3.03 [95% CI 2.03–4.51]) and first 3-year (HR 2.62 [95% CI 1.62–4.23]) observation periods were consistent. Short-term (HR 1.97 [95% CI 1.20–3.23]) and long-term (HR 1.64 [95% CI 1.02–2.63]) use of atypical antipsychotics were associated with a higher likelihood of subsequent type 2 DM.

CONCLUSIONS

Adolescents and young adults with ASD were more likely to develop type 2 DM during the follow-up. In addition, those with ASD using atypical antipsychotics exhibited a high risk. Therefore, further research is necessary to investigate the common pathophysiology of ASD and type 2 DM.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social cognition, interaction, and communication as well as by repetitive behavior and restricted interests (1–3). Population reports have revealed a consistent and significant rise in ASD prevalence worldwide of ~0.6–0.7%; the latest large-scale studies have estimated a 1–2% increase (1–3). Males are 2 to 3 times more likely to be affected by ASD than are females, indicating the crucial role of sex-linked factors at the genetic, endocrine, epigenetic, and environmental levels in the pathophysiology of ASD (1–3). However, the precise etiology of ASD remains unclear.

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Growing evidence has revealed the association between ASD and type 2 diabetes mellitus (DM)–related risk factors, such as obesity and dyslipidemia (4–7). For example, Egan et al. (5) assessed the rate of obesity in 273 children with ASD and reported that ~10% of the assessed children were obese according to their BMI. de Vinck-Baroody et al. (4) compared the prevalence of obesity between 2,769 children with ASD and non-ASD control subjects and reported that ASD was associated with an increased risk of obesity (odds ratio [OR] 1.16 [95% CI 1.05–1.28]). A 25-year follow-up outcome study of ASD in adulthood revealed that obesity was one of the most common medical comorbidities (8). Tyler et al. (6) assessed the rate of metabolic syndrome in 108 adults with ASD and reported 34.9% for obesity, 31.5% for dyslipidemia, and 19.4% for hypertension. Furthermore, adult patients with ASD were more likely to be diagnosed with dyslipidemia than the control group (OR 2.0 [95% CI 1.2–3.4]) (6). Few studies, however, have investigated the potential link between ASD and type 2 DM. Jones et al. (8) monitored 92 patients with ASD from their childhood to adulthood and found that ~10% of the patients were diagnosed with type 2 DM in their adulthood. Several genetic studies also suggested that ASD and type 2 DM may share similar common gene polymorphisms, such as glyoxalase I (GLO1) C419A polymorphism (9,10). The above studies have several limitations, however, including a small sample size, a cross-sectional study design incapable of clarifying the temporal association between ASD and type 2 DM, and an adult ASD population instead of an adolescent population.

We used the Taiwan National Health Insurance Research Database (NHIRD), which has a large sample size, and a longitudinal follow-up study design to investigate the risk of type 2 DM among adolescents and young adults with ASD. We hypothesized that patients with ASD were more likely to develop type 2 DM in later life compared with those without ASD.

RESEARCH DESIGN AND METHODS

Data Source

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely, the NHIRD, which consists of health care data from >97% of the entire Taiwan population (http://www.nhi.gov.tw/). The NHRI audits and releases the NHIRD for scientific and study purposes. Individual medical records included in the NHIRD are anonymous to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and prescriptions. The diagnostic codes used were based on the ICD-9-CM. The NHIRD has been used extensively in many epidemiologic studies in Taiwan (11–14).

Inclusion Criteria for Individuals With ASD and the Control Group

Adolescents aged 10–17 years and young adults aged 18–29 years who had a diagnosis of ASD (ICD-9-CM code 299) by board-certificated psychiatrists between 1 January 2002 and 31 December 2009, and who had no history of any DM (ICD-9-CM code 250) before enrollment, were included as the ASD cohort. The time of ASD diagnosis was defined as the time of enrollment. The control cohort, which was matched by age, sex, and time of enrollment (1:4), was randomly identified after eliminating the study individuals, those who had been given a diagnosis of ASD at any time, and those with any DM before enrollment. Diagnosis of type 2 DM (ICD-9-CM code 250.x0 and 250.x2, x = 0–9) given by pediatricians, internal medicine physicians, endocrinologists, and family medicine physicians based on the laboratory examination, was identified during the follow-up (from enrollment to 31 December 2011 or to the death). Medical comorbidities related to type 2 DM, including hypertension, dyslipidemia, and obesity, were assessed as the confounding factors in our study. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. The use of atypical antipsychotics was also examined and divided into three subgroups: nonusers (cumulative defined daily dose [cDDD] during the follow-up <30), short-term users (cDDD = 30–364), and long-term users (cDDD ≥365). Level of urbanization from level 1 (most urbanized region) to level 5 (least urbanized region) was also assessed in our study (15).

Statistical Analysis

For between-group comparisons, the independent *t* test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate. The Cox regression model was used to investigate the hazard ratio (HR) with a 95% CI of type 2 DM after adjusting for demographic data (age, sex, level of urbanization, and income), use of atypical antipsychotics, and medical comorbidities (hypertension, dyslipidemia, obesity) among patients with ASD and the control group. Sensitivity analyses were performed to investigate the above associations after excluding the first year or first 3 years of observation. We also performed a subanalysis of the risk of type 2 DM with ASD stratified by sex and by age groups: adolescents (<18 years) and young adults (18–29 years). A two-tailed *P* value of <0.05 was considered statistically significant. Data processing and statistical analyses were performed with SPSS 17 software (IBM Corp., Armonk, NY) and SAS 9.1 software (SAS Institute Inc., Cary, NC).

RESULTS

Our study enrolled 6,122 adolescents and young adults aged 15.25 ± 4.60 years and 24,488 control subjects matched for age and sex, with a male predominance (80.0%). The ASD cohort exhibited an increased incidence of type 2 DM (2.63 vs. 0.63 per 1,000 person-years, $P < 0.001$) and a shorter duration at onset of type 2 DM (mean [SD] 3.42 [2.11] vs. 5.35 [2.31] years, $P < 0.001$) compared with the control group (Table 1). Adolescents and young adults with ASD had a higher prevalence of dyslipidemia (2.0% vs. 1.6%, $P = 0.017$), obesity (2.7% vs. 1.1%, $P < 0.001$), and long-term use of atypical antipsychotics (16.0% vs. 0.1%, $P < 0.001$) than the control subjects (Table 1). Patients with ASD resided in less urbanized regions ($P < 0.001$) and had a lower income-related insured amount ($P < 0.001$).

Kaplan-Meier survival analysis with a log-rank test demonstrated that adolescents and young adults with ASD had a higher likelihood of developing type 2

Table 1—Demographic data and incidence of type 2 DM among adolescents and young adults with ASD and the control group

	Adolescents and young adults with ASD (*n* = 6,122)	Control group (*n* = 24,488)	*P* value
Age at enrollment, years (SD)	15.25 (4.60)	15.25 (4.60)	
< 18 years, *n* (%)	4,844 (79.1)	19,376 (79.1)	
18–29 years, *n* (%)	1,278 (20.9)	5,112 (20.9)	
Male sex, *n* (%)	4,896 (80.0)	19,584 (80.0)	
Type 2 DM, *n* (1,000 person-years)	95 (2.63)	92 (0.63)	<0.001
Age at diagnosis, years (SD)	22.22 (5.89)	23.06 (6.49)	0.359
Duration between enrollment and type 2 DM diagnosis, years (SD)	3.42 (2.11)	5.35 (2.31)	<0.001
Comorbidities, *n* (%)			
Hypertension	61 (1.0)	241 (1.0)	0.948
Dyslipidemia	122 (2.0)	380 (1.6)	0.017
Obesity	166 (2.7)	273 (1.1)	<0.001
Use of atypical antipsychotics, *n* (%)			<0.001
Nonuser	4,153 (67.8)	24,371 (99.5)	
Short-term user	990 (16.2)	82 (0.3)	
Long-term user	919 (16.0)	35 (0.1)	
Level of urbanization, *n* (%)			<0.001
1 (most urbanized)	1,053 (17.2)	7,315 (29.9)	
2	1,884 (30.8)	7,499 (30.6)	
3	549 (9.0)	4,429 (18.1)	
4	495 (8.1)	3,365 (13.7)	
5 (most rural)	2,141 (35.0)	1,880 (7.7)	
Income-related insured amount, *n* (%)			<0.001
≤15,840 NTD/month	5,548 (90.6)	17,849 (72.9)	
15,841–25,000 NTD/month	534 (8.7)	4,556 (18.6)	
≥25,001 NTD/month	40 (0.7)	2,083 (8.8)	

NTD, New Taiwan dollar.

DM ($P < 0.001$) than the control group (Fig. 1). The Cox regression model showed that ASD increased the risk of developing type 2 DM (HR 3.25 [95% CI 2.23–4.75]) after adjusting for demographic data, use of atypical antipsychotics, and medical comorbidities (Table 2). Sensitivity analyses after excluding the first year (HR 3.03 [95% CI 2.03–4.51]) or first 3 years (HR 2.62 [95% CI 1.62–4.23]) of observation had consistent findings: ASD was associated with an elevated risk of subsequent type 2 DM in later life (Table 3). Subanalysis stratified by age group revealed that adolescents (HR 2.71 [95% CI 1.64–4.48]) and young adults (HR 5.31 [95% CI 2.85–9.90]) with ASD were both prone to developing type 2 DM during the follow-up compared with the control subjects (Table 2). Subanalysis stratified by sex further found that males (HR 2.93 [95% CI 1.87–4.59]) and females (HR 4.44 [95% CI 2.14–9.21]) with ASD both had an elevated risk of subsequent type 2 DM compared with those without ASD (Table 4). The risk of developing type 2 DM did not differ significantly (HR 0.65 [95% CI 0.42–1.01]) between males and females with ASD. Furthermore, hypertension (HR 2.09 [95% CI 1.22–3.58]), dyslipidemia (HR 11.11 [95% CI 7.65–16.13]), and obesity (HR 3.46 [95% CI 2.16–5.53]) were related to an increased risk of type 2 DM (Table 2). Short-term users (HR 1.97 [95% CI 1.20–3.23]) and long-term users (HR 1.64 [95% CI 1.02–2.63]) of atypical antipsychotics were both associated with an elevated risk of developing type 2 DM in later life compared with nonusers (Table 2).

CONCLUSIONS

The findings of our study confirmed the study hypothesis that adolescents and young adults with ASD had a higher incidence of type 2 DM in later life than those without ASD. Adolescents and young adults with ASD were more likely to be diagnosed with type 2 DM during the follow-up after adjustment for demographic data, atypical antipsychotics use, and medical comorbidities. Young adults with ASD exhibited the highest risk.

Clinically, fewer studies have investigated the relationship between ASD and type 2 DM, despite growing evidence showing that patients with ASD are prone to certain type 2 DM–related risk factors, including obesity, hypertension, and dyslipidemia (4–8). Our study revealed that adolescents and young adults with ASD had a higher prevalence of dyslipidemia and obesity than did the control group; in addition, the results indicated a significant link between ASD and subsequent type 2 DM. Figure 1 further showed that the cumulative risk of developing type 2 DM increased gradually with the longer follow-up period among patients with ASD, indicating that the long-term clinical course of ASD may play an important role in the development of type 2 DM. Moreover, several studies have reported the increased prevalence of atypical antipsychotics use in the ASD population in these decades (16–20) and revealed the association between the use of atypical antipsychotics and type 2 DM in the adolescent and young adult populations (21–24). In our study, compared with the control group and after adjustment for demographic data, use of atypical antipsychotics, and medical

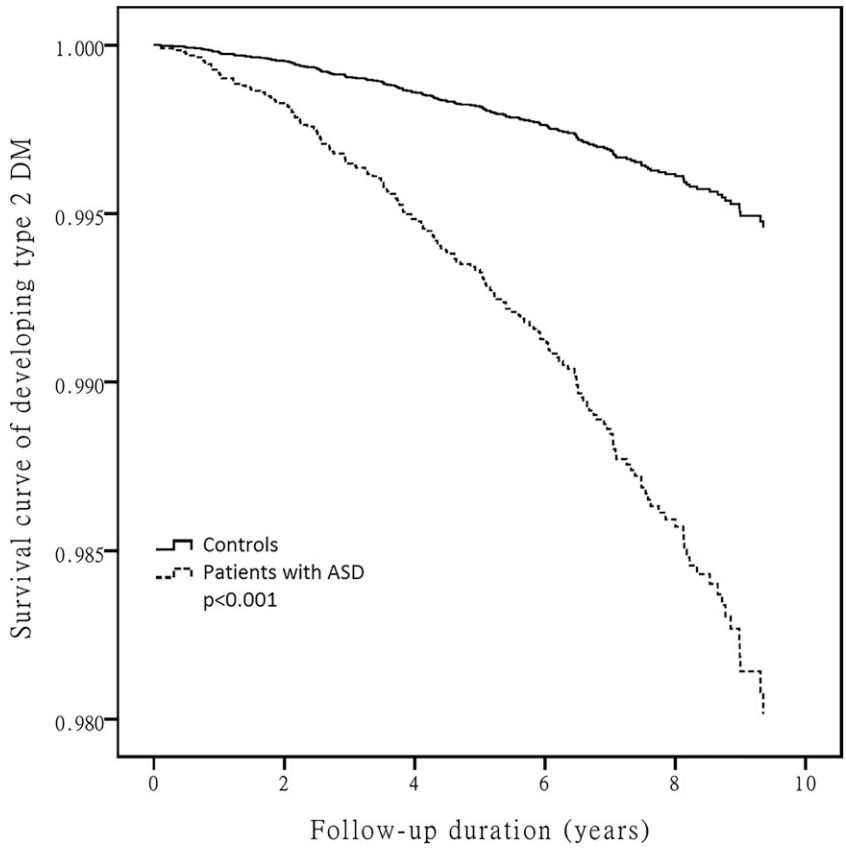

Figure 1—Survival curve of developing type 2 DM among adolescents and young adults with ASD and the control group.

comorbidities, adolescents and young adults diagnosed with ASD exhibited an increased likelihood of developing type 2 DM in later life; furthermore, those with short-term and long-term use of atypical antipsychotics were susceptible to type 2 DM development during the follow-up period. We also found that dyslipidemia and obesity were associated with the risk of developing type 2 DM among males with ASD and that hypertension and dyslipidemia increased the likelihood of subsequent type 2 DM among females with ASD. This result may imply the sex effect in the pathophysiology between ASD and type 2 DM and type 2 DM–related metabolic disorders. Further studies may be required to clarify this potential difference.

Table 2—Risk of developing type 2 DM among adolescents and young adults with and without ASD

	<18 years HR (95% CI)	18–29 years HR (95% CI)	Total HR (95% CI)
ASD, presence vs. absence*	**2.71 (1.64–4.48)**	**5.31 (2.85–9.90)**	**3.25 (2.23–4.75)**
Comorbidities, presence vs. absence			
Hypertension	0.79 (0.24–2.69)	**3.19 (1.71–5.94)**	**2.09 (1.22–3.58)**
Dyslipidemia	**15.70 (9.15–26.93)**	**9.07 (5.47–15.06)**	**11.11 (7.65–16.13)**
Obesity	**4.29 (2.28–8.07)**	**2.87 (1.37–6.00)**	**3.46 (2.16–5.53)**
Use of atypical antipsychotics			
Nonuser	1	1	1
Short-term user	1.39 (0.94–3.02)	1.74 (0.89–3.42)	**1.97 (1.20–3.23)**
Long-term user	**2.35 (1.23–4.50)**	0.78 (0.39–1.56)	**1.64 (1.02–2.63)**

Boldface type indicates statistical significance. *Adjusted by demographic data, use of atypical antipsychotics, and medical comorbidities and ASD as a binary variable.

Furthermore, increasing evidence suggests the potential association between maternal metabolic disorders (obesity and type 2 DM) and childhood ASD (25–27). Krakowiak et al. (25) and Xiang et al. (27) found that maternal metabolic disorders, such as preexisting maternal type 2 DM and gestational DM, were associated with a higher likelihood of ASD relative to the control subjects. This evidence and our new finding may suggest that metabolic disorders (type 2 DM, gestational DM, and obesity) in mothers may increase the risk of ASD and type 2 DM in their offspring. Further clinical studies would be required to elucidate this association.

Shared common genes between ASD and type 2 DM may increase the risk of type 2 DM in patients with ASD (9,10,28–31). GLO1, an enzyme involved in the detoxification of methylglyoxal and in limiting the advanced glycation end products formation, is crucial in autism susceptibility and type 2 DM disease progression (9,10,29,31). In addition, Belligni et al. (28) reported that a patient with a de novo duplication on chromosome 17p13.1 involving neuroligin 2, ephrin B3, and GLUT type 4 genes manifested obesity, type 2 DM, intelligence disability, and autistic traits. Additional genome-wide association studies are necessary to identify more susceptible candidate genes for the risk of type 2 DM in patients with ASD.

Moreover, immune dysregulation and proinflammatory cytokine oversecretion may explain the temporal association between ASD and subsequent type 2 DM (32–37). A recent meta-analysis comprising 17 studies with a sample size of 743 participants with ASD and 592 control subjects investigated the cytokine aberrations in ASD and determined that concentrations of interleukin (IL)-1β ($P < 0.001$), IL-6 ($P = 0.03$), IL-8 ($P = 0.04$), and interferon-γ ($P = 0.02$) were significantly higher in participants with ASD than in the control group (37). Another meta-analysis including 10 prospective studies with 19,709 participants and 4,480 individuals with type 2 DM identified a significant dose–response association of IL-6 levels (relative risk 1.31 [95% CI 1.17–1.46]) and CRP levels (relative risk 1.26 [95% CI 1.16–1.37]) with the risk of type 2 DM (38). Cieślak et al. (33) indicated that proinflammatory cytokines,

Table 3—Sensitivity tests of developing type 2 DM among adolescents and young adults with and without ASD

	Total HR (95% CI)	≥1 year HR (95% CI)	≥3 years HR (95% CI)
ASD*			
Absence	1	1	1
Presence	**3.25 (2.23–4.75)**	**3.03 (2.03–4.51)**	**2.62 (1.62–4.23)**

Boldface type indicates statistical significance. *Adjusted by demographic data, use of atypical antipsychotics, and medical comorbidities and ASD as a binary variable.

such as IL-1β, IL-6, tumor necrosis factor-α, and interferon-γ, were involved in the apoptosis of pancreatic β-cells. Considering the preceding findings altogether, the interrelationship of proinflammatory cytokine secretions and immune dysregulation in ASD may increase the risk of subsequent type 2 DM in later life, consistent with our findings that adolescents and young adults with ASD were more likely to develop type 2 DM compared with the control group during follow-up.

Finally, a few previous studies suggested the potential link between ASD and type 1 DM (39,40). Freeman et al. (40) reported that the prevalence of ASD in children with type 1 DM may be greater (0.90% vs. 0.34–0.67%) than that in the general population. However, Harjutsalo et al. (41) and Iafusco et al. (42) failed to validate this association. In our study, we found that adolescents and young adults with ASD had an increased risk of developing type 2 DM in later life. Further studies may be required to elucidate the biological link between ASD and type 1 and type 2 DM.

Several study limitations exist. First, the incidence of type 2 DM may be underestimated because we included only patients who sought medical help and consultation. However, in our study, the diagnosis of type 2 DM was made by board-certificated pediatricians, internal and family medicine physicians, and endocrinologists on the basis of laboratory examinations; therefore, the diagnostic validity is high. Second, although the prevalence of obesity in Asian countries, such as Japan, South Korea, and Taiwan, is indeed much lower than that in Western countries, such as U.S. (43), the prevalence of obesity in our study may be still underestimated because only those who sought medical help and consultation for obesity would be identified in the NHIRD. However, the diagnosis of obesity was given by board-certificated physicians, yielding an improved diagnostic validity. Third, certain information, including disease severity of ASD, personal lifestyle, BMI, blood pressure, and family history, is unavailable in the Taiwan NHIRD; therefore, we could not investigate the effect of these parameters in our study.

In conclusion, adolescents and young adults with ASD had an increased risk of developing type 2 DM in later life compared with those without ASD after adjustment for demographic data, atypical antipsychotics use, and medical comorbidities. Participants with ASD who used short- and long-term atypical antipsychotics were susceptible to type 2 DM. These results may remind the clinicians working with patients with ASD to more closely monitor their body weight and lipid profiles and to try to prevent or delay the onset of type 2 DM. Furthermore, additional studies are necessary to investigate the mechanism underlying the association between ASD and subsequent type 2 DM and to elucidate whether a prompt intervention for ASD reduces the risk of type 2 DM in later life.

Table 4—Risk of developing type 2 DM among adolescents and young adults with and without ASD, stratified by sex

	Male HR (95% CI)	Female HR (95% CI)	Total HR (95% CI)
ASD, presence vs. absence*	**2.93 (1.87–4.59)**	**4.44 (2.14–9.21)**	**3.25 (2.23–4.75)**
Comorbidities, presence vs. absence			
Hypertension	1.56 (0.79–3.09)	**6.05 (2.41–15.24)**	**2.09 (1.22–3.58)**
Dyslipidemia	**9.95 (6.29–15.73)**	**16.74 (8.87–31.56)**	**11.11 (7.65–16.13)**
Obesity	**4.31 (2.51–7.42)**	1.62 (0.58–4.48)	**3.46 (2.16–5.53)**
Use of atypical antipsychotics			
Nonuser	1	1	1
Short-term user	**2.11 (1.14–3.92)**	1.07 (0.45–2.57)	**1.97 (1.20–3.23)**
Long-term user	**1.95 (1.12–3.41)**	0.69 (0.25–1.88)	**1.64 (1.02–2.63)**

Boldface type indicates statistical significance. *Adjusted by demographic data, use of atypical antipsychotics, and medical comorbidities and ASD as a binary variable.

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