Risk of Type 2 Diabetes in Adolescents and Young Adults With Attention-Deficit/Hyperactivity Disorder:
A Nationwide Longitudinal Study

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ABSTRACT

Background: Studies have suggested there is an association between attention-deficit/hyperactivity disorder (ADHD) and type 2 diabetes mellitus (DM)–related risk factors, such as obesity, hypertension, and dyslipidemia. However, the association between ADHD and type 2 DM remains unknown.

Methods: Using the Taiwan National Health Insurance Research Database, we enrolled 35,949 adolescents and young adults with ADHD (*ICD-9-CM* code: 314) and 71,898 (1:2) age- and sex-matched controls from 2002 through 2009 and followed up with them until the end of 2011. Participants who developed type 2 DM during the follow-up period were identified.

Results: Adolescents (hazard ratio [HR] = 2.83; 95% CI, 1.96–4.09) and young adults (HR = 3.28; 95% CI, 1.41–7.63) with ADHD had a higher risk of developing type 2 DM than did the controls after adjustment for demographic characteristics, use of ADHD medications and atypical antipsychotics, and medical comorbidities. Individuals with ADHD had a shorter mean ± SD duration between enrollment and onset of type 2 DM (3.17 ± 2.33 vs 4.08 ± 2.11 years, $P = .004$) during the follow-up compared with the controls. Sensitivity analyses after excluding first-year (HR = 2.36; 95% CI, 1.65–3.38) and first-3-year (HR = 1.92; 95% CI, 1.19–3.09) observation periods were consistent. Long-term use of atypical antipsychotics was associated with a higher likelihood of subsequent type 2 DM (HR = 2.82, 95% CI, 1.74–4.58).

Discussion: Adolescents and young adults with ADHD were more likely than non-ADHD controls to develop type 2 DM in later life. In addition, those with ADHD taking atypical antipsychotics exhibited a higher risk. Although correlation does not equal causation, our findings merit further study about the relationship between ADHD and type 2 DM.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood and typically persists to adulthood; it manifests as an inability to marshal and sustain attention and modulate one's activity level and impulsive actions.[1–3] ADHD is highly prevalent in children and adolescents worldwide, affecting approximately 5%–7% of this population, with a male-to-female ratio between 3:1 and 4:1.[1–3] The pathophysiology of ADHD is unclear, and it appears to have a complex etiology. Multiple genetic and environmental factors act together to develop a spectrum of neurobiological vulnerability to ADHD.[1–3]

Several studies[4–7] have suggested an association between ADHD and type 2 diabetes mellitus (DM)–related comorbidities, including hypertension, dyslipidemia, and obesity. A recent meta-analysis[4] of 42 studies that included a total of 728,136 people (48,161 ADHD subjects and 679,975 comparison subjects) reported that both children (odds ratio [OR] = 1.20; 95% confidence interval [CI], 1.05–1.37) and adults (OR = 1.55; 95% CI, 1.32–1.81) with ADHD had a higher risk of obesity than did those without ADHD. Khalife et al[6] assessed ADHD symptoms and body mass index among more than 8,000 children aged 7–8 years and 16 years, respectively; they reported that childhood ADHD symptoms significantly predicted adolescent obesity (OR = 1.91; 95% CI, 1.10–3.33). The National Longitudinal Study of Adolescent Health[5] examined the odds of obesity and hypertension in adulthood in association with retrospectively reported ADHD symptoms; the study revealed that patients with 3 or more hyperactivity-impulsivity (OR = 1.50; 95% CI, 1.22–2.83) or inattention (OR = 1.21; 95% CI, 1.02–1.44) symptoms had an increased risk of obesity compared with those without ADHD symptoms. Moreover, patients with 3 or more hyperactivity-impulsivity symptoms were predisposed to hypertension (OR = 1.24; 95% CI, 1.01–1.51).[5] Spahis et al[7] evaluated the lipid profiles of 37 children with ADHD and 35 controls and found a higher level of free cholesterol in children

Clinical Points

- Studies have suggested there is an association between attention-deficit/hyperactivity disorder (ADHD) and type 2 diabetes mellitus–related risk factors such as obesity.
- Adolescents and young adults with ADHD were more likely to develop type 2 diabetes mellitus in later life.
- Those with ADHD taking atypical antipsychotics exhibited the highest risk of type 2 diabetes mellitus.

with ADHD than in the controls. The association between ADHD and type 2 DM–related comorbidities, particularly obesity, has been documented in recent years; however, few studies have examined whether ADHD is associated with type 2 DM.[8,9] Levitt Katz et al[10] assessed the prevalence of neuropsychiatric disorders in 237 children and adolescents with type 2 DM and observed ADHD in 10 (4.2%) of these patients. Furthermore, Nigg[8] suggested that the obesity risk was overestimated in patients with ADHD because of the increase in obesity rate. Therefore, ADHD as a risk factor for type 2 DM must be monitored and investigated.

In our study, using Taiwan's National Health Insurance Research Database (NHIRD) with a large sample size and longitudinal follow-up study design, we examined the risk of type 2 DM in the later life of adolescents and young adults with ADHD. We hypothesized that adolescents and young adults with ADHD have an increased risk of developing type 2 DM during follow-up compared with those without ADHD.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) is a mandatory universal health insurance program that 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 (NHIRD), which consists of health care data from up to 99% of the entire Taiwan population. The NHRI audits and releases the NHIRD for scientific and study purposes (https://nhird.nhri.org.tw/). Individual medical records included in the NHIRD are anonymous to protect personal privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and prescription. The diagnostic codes used were based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[11–14] The Taipei Veterans General Hospital institutional review board approved this study.

Inclusion Criteria for Patients With ADHD and Controls

Adolescents aged between 10 and 17 years and young adults aged between 18 and 29 years who had a diagnosis of ADHD (*ICD-9-CM* code: 314) by board-certificated psychiatrists based on the diagnostic interviews and their clinical judgment between January 1, 2002, and December 31, 2009, and who had no history of any DM (*ICD-9-CM* code: 250) before enrollment were included as the ADHD cohort. The time of ADHD diagnosis was defined as the time of enrollment. The age-, sex-, and time of enrollment–matched (1:2) control cohort was randomly identified after eliminating the study cases, those who had been given a diagnosis of ADHD 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 December 31, 2011, or to the death). The type 2 DM–related medical comorbidities hypertension, dyslipidemia, and obesity were assessed as the confounding factors in our study. In addition, the use of ADHD medications (methylphenidate and atomoxetine) and atypical antipsychotics during the follow-up was also examined, and subjects were divided into 3 subgroups: nonusers (cumulative defined daily dose [cDDD] during the follow-up < 30), short-term users (cDDD = 30–364), and long-term users (cDDD ≥ 365). In Taiwan, only methylphenidate and atomoxetine were approved for ADHD treatment at the time of the study. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region)[15] was also assessed in our study.

Statistical Analysis

For between-group comparisons, the independent *t* test was used for continuous variables and Pearson χ^2 test for nominal variables, when appropriate. Previous studies calculated the OR only between ADHD and metabolic outcomes because of their cross-sectional study design. In this current study with a longitudinal follow-up study design, Cox regression analysis with an adjustment for demographic data (age, sex, level of urbanization, and income), use of ADHD medications and atypical antipsychotics, and medical comorbidities (hypertension, dyslipidemia, obesity) was used to calculate the hazard ratio (HR) with a 95% CI of type 2 DM among patients with ADHD and controls. Sensitivity analyses were performed to investigate the aforementioned associations after excluding the first year or first 3 years of observation. A subanalysis of the risk of type 2 DM with ADHD stratified by age group (adolescents and young adults) was also performed. A 2-tailed *P* value of < .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 17 software (SPSS Inc, Armonk, NY) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

RESULTS

In all, 35,949 patients and 71,898 age- and sex-matched controls were enrolled in our study, with a mean ± SD age

Table 1. Demographic Data and Incidence of Type 2 DM Among Adolescents and Young Adults With ADHD and the Control Group[a]

Variable	Adolescents and Young Adults With ADHD (N = 35,949)	Controls (N = 71,898)	*P* Value
Age at enrollment, mean (SD), y	12.89 (3.33)	12.89 (3.33)	
Male	28,335 (78.8)	56,670 (78.8)	
Type 2 DM			
n (incidence per 1,000 person-years)	158 (0.83)	79 (0.21)	< .001
Age at diagnosis, mean (SD), y	18.12 (5.21)	18.58 (5.33)	.527
Duration between enrollment and diagnosis of type 2 DM, mean (SD), y	3.17 (2.33)	4.08 (2.11)	.004
Comorbidities			
Hypertension	121 (0.3)	149 (0.2)	< .001
Dyslipidemia	224 (0.6)	217 (0.3)	< .001
Obesity	820 (2.3)	694 (1.0)	< .001
Use of ADHD medications			< .001
Nonuser	14,272 (39.7)	71,497 (99.4)	
Short-term user	15,345 (42.7)	276 (0.4)	
Long-term user	6,332 (17.6)	125 (0.2)	
Use of atypical antipsychotics			< .001
Nonuser	33,818 (94.1)	71,676 (99.7)	
Short-term user	1482 (4.1)	167 (0.2)	
Long-term user	649 (1.8)	55 (0.1)	
Level of urbanization			< .001
1 (most urbanized)	6,716 (18.7)	10,934 (15.2)	
2	10,938 (30.4)	21,126 (29.4)	
3	3,077 (8.6)	7,956 (11.1)	
4	2,544 (7.1)	7,344 (10.2)	
5 (most rural)	12,674 (35.3)	24,538 (34.1)	
Income-related insured amount			< .001
≤ 15,840 NTD/mo	32,490 (90.4)	63,381 (88.2)	
15,841–25,000 NTD/mo	2,914 (8.1)	6,707 (9.3)	
≥ 25,001 NTD/mo	545 (1.5)	1,810 (2.5)	

[a]Values shown as n (%) unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DM = diabetes mellitus. NTD = New Taiwan Dollar.

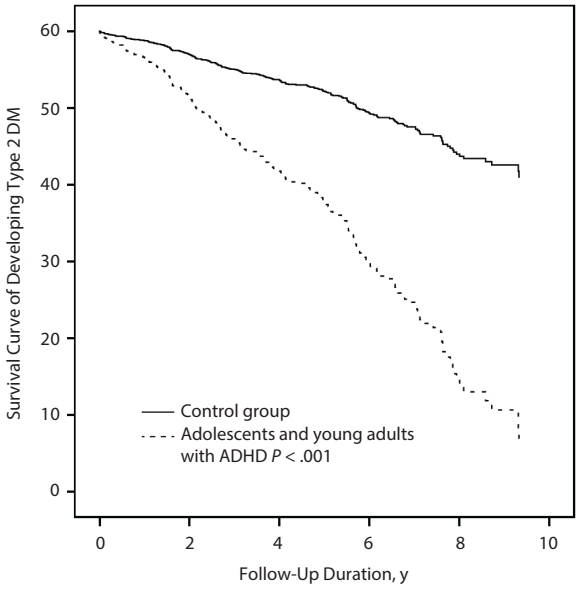
of 12.89 ± 3.33 years and a male predominance (78.8%). Adolescents and young adults with ADHD had an elevated incidence of type 2 DM (0.83 vs 0.21 per 1,000 person-years, $P < .001$) and a shorter duration from enrollment to onset of type 2 DM (3.17 ± 2.33 vs 4.08 ± 2.11, $P = .004$) during the follow-up compared with the controls (Table 1). Individuals with ADHD exhibited a higher prevalence of type 2 DM–related comorbidities, including hypertension (0.3% vs 0.2%, $P < .001$), dyslipidemia (0.6% vs 0.3%, $P < .001$), and obesity (2.3% vs 1.0%, $P < .001$), than did the controls (Table 1). Patients with ADHD had a greater prevalence of long-term use of ADHD medications (17.6% vs 0.2%, $P < .001$) and atypical antipsychotics (1.8% vs 0.1%, $P < .001$) than did those without ADHD (Table 1). Adolescents and young adults with ADHD resided in more urbanized regions ($P < .001$) and had a lower income-related insured amount ($P < .001$).

Kaplan-Meier survival analysis with a log rank test demonstrated that patients with ADHD had a higher likelihood of developing type 2 DM ($P < .001$) than the controls (Figure 1). The crude HR of ADHD for type 2 DM risk was 4.01 (95% CI, 3.06–5.25). Furthermore, Cox regression model with an adjustment of demographic data, use of ADHD medications and atypical antipsychotics, and medical comorbidities revealed that patients with ADHD had an increased risk (HR = 2.84; 95% CI, 2.03–3.97) of developing type 2 DM during the follow-up compared with those without ADHD (Table 2). Subanalysis stratified by age group demonstrated that both adolescents (HR = 2.83; 95% CI, 1.96–4.09) and young adults (HR = 3.28; 95% CI, 1.41–7.63) with ADHD were prone to developing type 2 DM in later life (Table 2). Sensitivity analyses after excluding the first year (HR = 2.36; 95% CI, 1.65–3.38) or first 3 years (HR = 1.92; 95% CI, 1.19–3.09) of observation had consistent findings: ADHD was related to an increased risk of subsequent type 2 DM in later life. Furthermore, hypertension (HR = 1.93; 95% CI, 1.04–3.59), dyslipidemia (HR = 10.80; 95% CI, 7.24–16.12), and obesity (HR = 10.09; 95% CI, 7.25–14.05) were associated with an elevated risk of type 2 DM (Table 2). Long-term recipients (HR = 2.82; 95% CI, 1.74–4.58) of atypical antipsychotics were associated with an increased risk of developing type 2 DM in later life compared with nonusers (Table 2). However, use of ADHD medications (short-term use: HR = 0.99; 95% CI, 0.70–1.40 or long-term use: HR = 0.90; 95% CI, 0.57–1.41) was not related to the risk of subsequent type 2 DM (Table 2).

DISCUSSION

Our findings support the study hypothesis that adolescents and young adults with ADHD have a higher risk of developing type 2 DM during follow-up than do controls. Patients with ADHD were more likely to develop type 2 DM in later life after adjustment for demographic characteristics, the use of ADHD medications and atypical antipsychotics,

Figure 1. Survival Curve of Developing Type 2 DM Among Adolescents and Young Adults With ADHD and the Control Group



Abbreviations: ADHD = attention-deficit/hyperactivity disorder; DM = diabetes mellitus.

and comorbidities. Moreover, young adults; those with comorbid hypertension, dyslipidemia, and obesity; and long-term users of atypical antipsychotics exhibited the highest risk.

Few studies have investigated clinically the association between ADHD and subsequent type 2 DM, despite increasing evidence that patients with ADHD are predisposed to certain type 2 DM–related risk factors, including obesity, hypertension, and dyslipidemia.[4–10] As mentioned, a meta-analysis[4] with a large sample size revealed that both children and adults with ADHD had an approximately 1.5-fold increased obesity risk compared with those without ADHD. Fuemmeler et al[5] identified a linear association between the number of inattentive and hyperactivity-impulsivity symptoms and blood pressure; they also reported an association between hyperactivity-impulsivity symptoms and hypertension risk (OR = 1.04; 95% CI, 1.00–1.09). Our study indicated that the adolescents and young adults with ADHD had a higher prevalence of hypertension, dyslipidemia, and obesity than did the controls. In addition, our results revealed a significant association between ADHD and subsequent type 2 DM. Several studies[16–19] have reported the increased use of atypical antipsychotics in the ADHD population in this decade. For instance, Ben Amor et al[16] reported that the 1-year prevalence of combination therapy with atypical antipsychotics among 9,431 Canadian children and adolescents with ADHD treated with stimulants was 10.8%. Furthermore, Olfson et al[18] observed that among young patients with mental disorders who were treated with antipsychotics in the United States, the most common diagnosis was ADHD in children (52.5%) and adolescents (34.9%). Increasing evidence supports the association between atypical antipsychotic use and type 2 DM in adolescent and young adult populations.[20–23] In our study, compared with the controls and after adjustment for demographic characteristics, use of ADHD medications and atypical antipsychotics, and comorbidities, adolescents and young adults with ADHD exhibited an increased risk of developing type 2 DM in later life. Furthermore, patients with long-term use of atypical antipsychotics and those with comorbid hypertension, dyslipidemia, and obesity were more susceptible to type 2 DM development during the follow-up period. Cortese et al[4] reported that patients receiving medications for ADHD did not have a higher risk of obesity; in accordance with this observation, our results revealed that the use of ADHD medications was not associated with the risk of type 2 DM.

Immunologic dysregulation and proinflammatory cytokine oversecretion may explain the temporal association between ADHD and subsequent type 2 DM.[24–28] Oades

Table 2. Risk of Developing Type 2 DM Among Adolescents and Young Adults With ADHD and the Control Group[a,b]

Variable	Aged < 18 Years, HR (95% CI)	Aged 18–29 Years, HR (95% CI)	Total HR (95% CI)
ADHD, presence vs absence	**2.83 (1.96–4.09)**	**3.28 (1.41–7.63)**	**2.84 (2.03–3.97)**
Comorbidities, presence vs absence			
Hypertension	**3.21 (1.53–6.73)**	1.84 (0.65–5.15)	**1.93 (1.04–3.59)**
Dyslipidemia	**9.20 (5.64–15.02)**	**14.80 (7.32–29.93)**	**10.80 (7.24–16.12)**
Obesity	**13.29 (9.23–19.14)**	**3.33 (1.36–8.15)**	**10.09 (7.25–14.05)**
Use of ADHD medications			
Nonuser	1	1	1
Short-term user	0.86 (0.58–1.28)	1.53 (0.73–3.20)	0.99 (0.70–1.40)
Long-term user	0.83 (0.51–1.37)	1.27 (0.41–3.99)	0.90 (0.57–1.41)
Use of atypical antipsychotics			
Nonuser	1	1	1
Short-term user	1.51 (0.76–2.99)	1.44 (0.49–4.23)	1.59 (0.89–2.81)
Long-term user	**2.73 (1.50–4.99)**	2.10 (0.89–5.00)	**2.82 (1.74–4.58)**

[a]Adjusted by demographic data, use of ADHD medications, use of atypical antipsychotics, and medical comorbidities and with ADHD as a binary variable.
[b]Boldface type indicates statistical significance.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio.

et al[25] compared cytokine levels between patients with ADHD and controls; 6 cytokines, namely, interleukin (IL)-2, IL-6, interferon (IFN)-γ, IL-16, IL-10, and IL-13, showed a marginal increase in the ADHD group. Drtilkova et al[24] revealed that polymorphisms of IL-2, IL-6, and tumor necrosis factor alpha (TNF-α) represent neurodevelopmental risk factors in the etiopathogenesis of ADHD. Furthermore, Rajkovic et al[26] found that patients with type 2 DM exhibited higher concentrations of TNF-α, IL-6, and C-reactive protein (CRP) than did patients without type 2 DM. A meta-analysis[28] of 10 prospective studies involving 19,709 participants and 4,480 cases of type 2 DM revealed a significant dose-response association of IL-6 levels (relative risk [RR]: 1.31; 95% CI, 1.17–1.46) and CRP levels (RR: 1.26; 95% CI, 1.16–1.37) with the risk of type 2 DM. If all of the aforementioned findings are considered, proinflammatory cytokine oversecretion and immunologic dysregulation in ADHD may elevate the risk of subsequent type 2 DM in later life. This notion is consistent with our observation that the adolescents and young adults with ADHD were more likely to develop type 2 DM than were the controls.

The study has several limitations. First, the incidence of type 2 DM may be underestimated because we included only patients who sought medical help and consultation. However, type 2 DM was diagnosed by board-certified pediatricians, internal and family medicine physicians, and endocrinologists on the basis of laboratory examinations; therefore, the diagnostic validity is high. Second, certain information, including the disease severity of ADHD, lifestyle, body mass index, and family history, is unavailable in the NHIRD; therefore, we could not investigate the effects of these parameters in our study.

In conclusion, adolescents and young adults with ADHD had an increased risk of developing type 2 DM in later life after adjustment for demographic characteristics, use of ADHD medications and atypical antipsychotics, and comorbidities. Young adults; those with comorbid hypertension, dyslipidemia, and obesity; and long-term users of atypical antipsychotics were more susceptible to type 2 DM. These findings can inform clinical practice in that type 2 DM should be considered in ADHD even in the absence of other known risk factors and suggest that the use of atypical antipsychotics in individuals with ADHD should be thoroughly evaluated for the benefits and risks. Additional studies are required to elucidate the definite pathophysiology between ADHD and subsequent type 2 DM and to clarify whether prompt intervention for ADHD symptoms reduces the risk of type 2 DM in later life.

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