Research in Autism Spectrum Disorders 10 (2015) 1–6

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Autistic spectrum disorder, attention deficit hyperactivity disorder, and psychiatric comorbidities: A nationwide study

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ARTICLE INFO

Article history:
Received 8 October 2014
Received in revised form 15 October 2014
Accepted 17 October 2014

Keywords:
Autism spectrum disorder
Attention deficit hyperactivity disorder
Psychiatric comorbidities

ABSTRACT

Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are both frequently comorbid with other psychiatric disorders, but the comorbid effect of ASD and ADHD relative to the comorbid risk of other psychiatric disorders is still unknown. Using the Taiwan National Health Insurance Research Database, 725 patients with ASD-alone, 5694 with ADHD-alone, 466 with ASD + ADHD, and 27,540 (1:4) age-/gender-matched controls were enrolled in our study. The risk of psychiatric comorbidities was investigated. The ADHD + ASD group had the greatest risk of developing schizophrenia (hazard ratio [HR]: 95.89; HR: 13.73; HR: 174.61), bipolar disorder (HR: 74.93; HR: 19.42; HR: 36.71), depressive disorder (HR: 17.66; HR: 12.29; HR: 9.05), anxiety disorder (HR: 49.49; HR: 50.92; HR: 14.12), disruptive behavior disorder (HR: 113.89; HR: 93.87; HR: 26.50), and tic disorder (HR: 8.95; HR: 7.46; HR: 4.87) compared to the ADHD-alone, ASD-alone, and control groups. Patients with ADHD + ASD were associated with the greatest risk of having comorbid bipolar disorder, depressive disorder, anxiety disorder, disruptive behavior disorder, and tic disorder. The diagnoses of ASD and ADHD preceded the diagnoses of other psychiatric comorbidities. A comprehensive interview scrutinizing the psychiatric comorbidities would be suggested when encountering and following patients with both ASD and ADHD in clinical practice.

1. Background

Both autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders that begin in childhood and usually persist throughout life. They frequently co-occur in the same individuals, although they have very distinct clinical symptoms: ASD exhibits persistent deficits in social communication and social

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http://dx.doi.org/10.1016/j.rasd.2014.10.014
1750-9467/

interaction, and restricted, repetitive patterns of behaviors, interest, or activities, and ADHD manifests the inability to marshal and sustain attention and modulate activity level (Rappley, 2005; Baker, 2013; Lai, Lombardo et al., 2013; Volkow & Swanson, 2013). Previous studies have reported that 20–50% of patients with ADHD exhibit autistic traits or even meet the criteria of ASD, and this comorbidity interferes with their psychopathology, and interpersonal, school, family, and cognitive domains (Rommelse, Franke et al., 2010; Kotte, Joshi et al., 2013). More than 50% of patients with ASD meet the criteria of ADHD, and have higher scores for hyperactivity-impulsivity symptoms (Lee & Ousley, 2006). Several recent large scale genome-wide studies have suggested that ASD and ADHD may share the same genetic susceptibility, which may explain this frequent comorbid phenomenon between ASD and ADHD (Ronald, Simonoff et al., 2008; Nijmeijer, Arias-Vasquez et al., 2010; Goldin, Matson et al., 2013).

Accumulating evidence has shown that patients with ASD and those with ADHD have higher prevalence rates of other psychiatric disorders, including disruptive behavior disorder, mood disorder, and even schizophrenia (Biederman, 2005; Smalley, McGough et al., 2007; Simonoff, Pickles et al., 2008; Joshi, Petty et al., 2010; Joshi, Wozniak et al., 2013). Simonoff et al. assessed psychiatric comorbidities among 112 adolescents with ASD, and found that 70% of participants had at least one comorbid disorder and 41% had two or more, and anxiety disorder, ADHD, and oppositional defiant disorder were most prevalent (Simonoff et al., 2008). Joshi et al. found that patients with ASD suffered from significantly higher current and lifetime prevalence rates of comorbid psychiatric disorders than comparisons, including psychotic disorder, major depression, and anxiety disorder, and further indicated that the comorbidities impaired their school and work function (Joshi et al., 2010; Joshi, Wozniak et al., 2013). Also, patients with ADHD were prevalently comorbid with mood disorder, disruptive behavior disorder, and anxiety disorder (Biederman, 2005; Smalley et al., 2007). Smalley et al. compared 457 adolescents with ADHD with 457 matched controls, and showed that a lifetime diagnosis of ADHD was significantly associated with anxiety disorder (odds ratio [OR]: 2.4, 95% confidence interval [CI]: 1.4–4.2), major depression (OR: 2.48, 95% CI: 1.2–4.9), and disruptive behavior disorders (OR: 17.3, 95% CI: 7.9–38.0) (Smalley et al., 2007). However, the comorbid effect of ASD and ADHD on the trajectory of mental health development and the prevalence of other psychiatric disorders is seldom investigated. Goldin et al. assessed comorbid psychiatric symptoms among 255 children with ASD, 40 with ADHD, and 47 with comorbid ADHD and ASD using the Autism Spectrum Disorders-Comorbidity for children and reported that the ASD + ADHD group had higher scores for tantrum behaviors and irritable mood than the other two groups (Goldin et al., 2013). Jang et al. reported that patients with comorbid ASD and ADHD had higher rates of comorbid psychiatric symptoms, including temper tantrum, depressed mood, avoidance, and conduct behaviors, than those with ASD or ADHD alone (Jang, Matson et al., 2013). However, the above studies, with a small sample size and a cross-sectional study design, evaluated psychiatric symptoms using self- or parents-reported questionnaires only, and not definite psychiatric diagnoses by psychiatrists.

In our study, using the Taiwan National Health Insurance Research Database (NHIRD), we assessed comorbid psychiatric disorders, including schizophrenia, bipolar disorder, depressive disorder, anxiety disorder, disruptive behavior disorder, and tic disorder, among patients with ADHD-alone, ASD-alone, and ADHD + ASD. We hypothesized an additive effect of ASD and ADHD on the comorbidities of other psychiatric diseases.

2. Methods

2.1. Data source

This study was based on data from the NHIRD audited and released by the National Health Research Institute. The National Health Insurance (NHI) program was implemented in 1995, and covers up to 99% of all 23,000,000 residents of Taiwan (http://www.nhi.gov.tw/). Subjects included in the NHIRD are anonymous to protect individual privacy. The database comprises comprehensive information on insured subjects, including demographic data, dates of clinical visits, and diagnoses. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Wu, Chen et al., 2012; Brumpton, Camargo et al., 2013; Chen, Su et al., 2013a,b,c; Shen, Tsai et al., 2013).

2.2. Inclusion criteria for the ADHD-alone group, ASD-alone group, ADHD + ASD group, and control group

One million subjects, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects identified as having ADHD (ICD-9-CM code: 314) or ASD (ICD-9-CM code: 299) by psychiatrists were included as the study group. The study group was divided into three subgroups: ADHD-alone, ASD-alone, and ADHD + ASD. The age- and gender-matched control group (four for every patient in the study cohort) was randomly identified from among the subjects after eliminating study cases and patients who had been given a diagnosis of ADHD or ASD at any time. The psychiatric comorbidities of schizophrenia (ICD-9-CM code: 295.X), bipolar disorder (ICD-9-CM codes: 296.0X, 296.1X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80, 296.81, 296.89), depressive disorder (ICD-9-CM code: 296.2X, 296.3X, 300.4, 311), anxiety disorder (ICD-9-CM code: 300.X except 300.3 and 300.4), and disruptive behavior disorder (ICD-9-CM codes: 312 and 313.81) were identified by psychiatrists. Tic disorder (ICD-9-CM code: 307.2) was also assessed and identified by pediatricians, psychiatrists, and neurologists. All diagnoses were given at least twice by corresponding physicians for diagnostic validity. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed in our study.

2.3. Statistical analysis

In comparing the differences between the four groups (ADHD-alone, ASD-alone, ADHD + ASD, and the control group), analysis of variance (ANOVA) was used for continuous variables and Pearson's χ^2 test for nominal variables. Bonferroni post hoc analysis was also performed. When investigating the risk of psychiatric comorbidities in ADHD + ASD, ADHD-alone, ASD-alone, and the control groups, multiple logistic regressions were performed to calculate the OR with a 95% CI after adjusting for age, gender, and level of urbanization. A two-tailed *P*-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

3. Results

In all, 5694 subjects with ADHD-alone, 725 with ASD-alone, 466 with ADHD + ASD, and 27,540 age-/gender-matched controls were enrolled in our study, with a male predominance. The ADHD + ASD group had an earlier age of ADHD diagnosis (7.64 ± 3.99 vs. 9.68 ± 6.68 years, $p < 0.001$) and ASD diagnosis (7.73 ± 4.29 vs. 11.45 ± 12.44 years, $p < 0.001$) compared to the ADHD-alone and ASD-alone groups, respectively (Table 1). Subjects with ADHD + ASD had a higher prevalence of psychiatric comorbidities, including bipolar disorder (3.4% vs. 1.2% vs. 4.0% vs. 0.1%, $p < 0.001$), depressive disorder (6.4% vs. 5.6% vs. 7.7% vs. 0.6%, $p < 0.001$), anxiety disorder (17.4% vs. 18.3% vs. 7.3% vs. 0.5%, $p < 0.001$), disruptive behavior disorder (8.2% vs. 6.7% vs. 2.1% vs. 0.1%, $p < 0.001$), and tic disorder (7.1% vs. 5.5% vs. 3.6% vs. 0.8%, $p < 0.001$), than the ADHD-alone, ASD-alone, and control groups (Table 1). The ASD-alone group had a higher prevalence of schizophrenia (11.2% vs. 3.0% vs. 0.7% vs. 0.1%, $p < 0.001$) than the ADHD + ASD, ASD-alone, and control groups (Table 1). In addition, the age at diagnoses of ASD and ADHD preceded the age at diagnoses of other comorbid psychiatric disorders (Table 1).

Multiple logistic regression analysis showed that the ADHD + ASD group had the greatest risk of having any psychiatric disorder (HR: 31.50, 95% CI: 25.31–39.19; HR: 28.43, 95% CI: 25.44–31.77; HR: 15.62, 95% CI: 12.77–19.10), schizophrenia (HR: 95.89, 95% CI: 45.39–202.56; HR: 13.73, 95% CI: 7.65–24.64; HR: 174.61, 95% CI: 100.27–304.07), bipolar disorder (HR: 74.93, 95% CI: 37.75–148.75; HR: 19.42, 95% CI: 11.66–32.34; HR: 36.71, 95% CI: 20.11–67.01), depressive disorder (HR: 17.66, 95% CI: 11.69–26.69; HR:12.29, 95% CI: 10.05–15.01; HR: 9.05, 95% CI: 6.42–12.77), anxiety disorder (HR: 49.49, 95% CI: 36.69–66.77; HR: 50.92, 95% CI: 42.15–61.52; HR: 14.12, 95% CI: 10.09–19.77), disruptive behavior disorder (HR: 113.89, 95% CI: 65.61–197.71; HR: 93.87, 95% CI: 59.78–147.41; HR: 26.50, 95% CI: 13.48–52.09), and tic disorder (HR: 8.95, 95% CI: 6.12–13.11; HR: 7.46, 95% CI: 6.24–8.92; HR: 4.87, 95% CI: 3.21–7.38) compared to the ADHD-alone, ASD-alone, and control groups after adjusting for age, gender, and level of urbanization (Table 2).

Table 1
Characteristics of patients with ASD-alone, ADHD-alone, and ASD + ADHD, and the control group.

	Control (a) ($n = 27,540$)	ASD-alone (b) ($n = 725$)	ADHD-alone (c) ($n = 5694$)	ASD + ADHD (d) ($n = 466$)	*p*-value	Post hoc analysis
Gender (M, %)	J	560 (77.2)	4363 (76.6)	401 (86.3)	<0.001	$d > c \sim b \sim a$
Age (years, SD)	14.86 (8.17)	18.34 (13.36)	14.54 (7.33)	13.55 (5.12)	0.553	$b > a \sim c \sim d$
Age at ASD diagnosis (years, SD)	–	11.45 (12.44)	–	7.73 (4.29)	<0.001	$b > d$
Age at ADHD diagnosis (years, SD)	–	–	9.68 (6.68)	7.64 (3.99)	<0.001	$c > d$
Psychiatric comorbidities						
Schizophrenia (*n*, %)	17 (0.1)	81 (11.2)	39 (0.7)	14 (3.0)	<0.001	$a < c < d < b$
Age at schizophrenia (years, SD)	28.20 (10.97)	27.33 (12.91)	20.31 (8.93)	14.45 (4.51)	<0.001	$a \sim b > c > d$
Bipolar disorder (*n*, %)	20 (0.1)	29 (4.0)	68 (1.2)	16 (3.4)	<0.001	$a < c < b \sim d$
Age at bipolar disorder (years, SD)	27.22 (16.20)	27.45 (14.86)	21.17 (11.09)	10.53 (3.64)	<0.001	$a \sim b > c > d$
Depressive disorder (*n*, %)	177 (0.6)	56 (7.7)	334 (5.6)	30 (6.4)	<0.001	$a < c \sim d < b$
Age at depressive disorder (years, SD)	24.97 (12.62)	24.06 (12.55)	19.46 (10.31)	15.71 (6.64)	<0.001	$a \sim b > c > d$
Anxiety disorder (*n*, %)	127 (0.5)	53 (7.3)	1043 (18.3)	81 (17.4)	<0.001	$a < b < c \sim d$
Age at anxiety disorder (years, SD)	23.05 (13.82)	20.61 (12.03)	10.88 (6.75)	9.91 (5.61)	<0.001	$a > b > c \sim d$
Disruptive behavior disorder (*n*, %)	20 (0.1)	15 (2.1)	383 (6.7)	38 (8.2)	<0.001	$a < b < c < d$
Age at Disruptive behavior disorder (years, SD)	10.98 (3.00)	17.98 (12.67)	10.85 (4.09)	10.39 (3.52)	<0.001	$b > a \sim c \sim d$
Tic disorder (*n*, %)	209 (0.8)	26 (3.6)	316 (5.5)	33 (7.1)	<0.001	$a < b < c < d$
Age at tic disorder (years, SD)	7.97 (3.31)	12.87 (8.35)	9.16 (3.25)	9.21 (3.88)	<0.001	$b > c \sim d > a$
Average number of psychiatric comorbidities (*n*, SD)	0.03 (0.17)	0.36 (0.72)	0.38 (0.64)	0.45 (0.77)	<0.001	$d > c > b > a$
Level of urbanization (*n*, %)					<0.001	
1 (Most urbanized)	7766 (28.2)	278 (38.3)	2134 (37.5)	174 (37.3)		
2	8498 (30.9)	231 (31.9)	1887 (33.1)	153 (32.8)		
3	4895 (17.8)	92 (12.7)	885 (15.5)	78 (16.7)		
4	3908 (14.2)	76 (10.5)	533 (9.4)	42 (9.0)		
5 (Most rural)	2473 (9.0)	48 (6.6)	255 (4.5)	19 (4.1)		

ASD, autistic spectrum disorder; ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder.

Table 2
Odds ratio of psychiatric comorbidities among patients with ASD-alone, ADHD-alone, and ASD + ADHD, and the control group.

OR (95% CI)[a]	Control group	ASD-alone	ADHD-alone	ASD + ADHD
Any psychiatric comorbidity	1	15.62 (12.77–19.10)	28.43 (25.44–31.77)	31.50 (25.31–39.19)
Schizophrenia	1	174.61 (100.27–304.07)	13.73 (7.65–24.64)	95.89 (45.39–202.56)
Bipolar disorder	1	36.71 (20.11–67.01)	19.42 (11.66–32.34)	74.93 (37.75–148.75)
Depressive disorder	1	9.05 (6.42–12.77)	12.29 (10.05–15.01)	17.66 (11.69–26.69)
Anxiety disorder	1	14.12 (10.09–19.77)	50.92 (42.15–61.52)	49.49 (36.69–66.77)
Disruptive behavior disorder	1	26.50 (13.48–52.09)	93.87 (59.78–147.41)	113.89 (65.61–197.71)
Tic disorder	1	4.87 (3.21–7.38)	7.46 (6.24–8.92)	8.95 (6.12–13.11)

ASD, autistic spectrum disorder; ADHD, attention deficit hyperactivity disorder; ODD, oppositional defiant disorder; OR, odds ratio; CI, confidence interval.
[a]Adjusted by age, gender, and level of urbanization.

4. Discussion

Our results supported the study hypothesis that patients with dual diagnoses of ADHD and ASD had the greatest likelihood of developing bipolar disorder, depressive disorder, disruptive behavior disorder, and tic disorder, compared to the ASD-alone group, ADHD-alone group, and control group. The diagnoses of ASD and ADHD preceded the diagnoses of the other psychiatric comorbidities. The ADHD + ASD group had an earlier age at diagnosis of schizophrenia, bipolar disorder, depressive disorder, and anxiety disorder than other the three groups.

4.1. ASD, ADHD, and schizophrenia

Several large-scale genome-wide studies supported a shared genetic susceptibility among these three distinct diseases (Chen, Su et al., 2013a,b,c; Lee, Ripke et al., 2013). Gadow et al. assessed 147 patients with ASD and 335 controls, and found that those with ASD had a larger number of more severe symptoms of schizophrenia than the controls, and especially, patients with ASD + ADHD exhibited more severe disorganized thought, disorganized behavior, and negative schizophrenia symptoms than the controls (Gadow, 2012). However, they further indicated that the disorganized behavior and negative symptoms of schizophrenia evidenced the strongest pattern of associations with ASD symptoms (Gadow, 2013). Our epidemiologic results also revealed this association, in that both ASD and ADHD increased the risk of developing schizophrenia.

4.2. ASD, ADHD, and bipolar disorder

Evidence has shown the association between ADHD and bipolar disorder, but the association between ASD and bipolar disorder is seldom investigated, and has shown inconsistent findings (Biederman, 2005; Rappley, 2005; Munesue, Ono et al., 2008; Joshi, Biederman et al., 2013). Munesue et al. assessed 44 children with ASD aged over 12 years, and reported that up to 30% had comorbid bipolar disorder (Munesue et al., 2008). Joshi et al. evaluated 157 youths with bipolar I disorder, and found that 30% met ASD criteria, and the age at onset of bipolar I disorder was significantly earlier in the presence of ASD comorbidity (Joshi, Biederman et al., 2013). Our results also supported a significant association between ASD and bipolar disorder, and ASD + ADHD group had a greatest risk of developing bipolar disorder compared to other three groups. Interestingly, ASD + ADHD group had a much earlier age at diagnosis of bipolar disorder than ASD-alone and ADHD-alone groups.

4.3. ASD, ADHD, and depressive disorder

Both ASD and ADHD patients have an increased likelihood of developing depressive disorder in later life (Biederman, 2005; Rappley, 2005; Smalley et al., 2007; Joshi et al., 2010; Joshi, Wozniak et al., 2013). Joshi et al. reported that more than 70% of adults with ASD met the criteria of major depression in their life, and about 30% suffered from a major depressive episode (Joshi, Wozniak et al., 2013). Our previous finding showed that adolescents with ADHD were more prone to developing depressive disorder (HR: 13.01, 95% CI: 8.99–18.82) in later life than those without (Chen, Su et al., 2013a,b,c). Recent genome-wide studies found a shared susceptible gene among them (Chen, Su et al., 2013a,b,c; Lee et al., 2013). Our current results also supported that both ASD and ADHD were associated with an increased risk of depressive disorder, and ASD + ADHD group increased the depressive disorder further. Emotional dysregulation may be the core manifestation among these three diseases, but this requires further investigation (Mazefsky, Herrington et al., 2013; Musser, Galloway-Long et al., 2013).

4.4. ASD, ADHD, and anxiety disorder

Comorbidity of anxiety disorder was prevalent in both ASD and ADHD patients (Biederman, 2005; Smalley et al., 2007; Simonoff et al., 2008; Joshi, Biederman et al., 2013). Biederman et al. reported that at least 30% of children with ADHD were comorbid with anxiety disorder (Biederman, 2005). Joshi et al. found that children with ASD had significantly higher rates of

multiple (≧2) anxiety disorders, especially social anxiety disorder, agoraphobia, and specific phobia, than the controls (Joshi et al., 2010). Jang et al. suggested that children with ASD and those with ASD + ADHD had higher scores for avoidant symptoms than those with ADHD-alone or those with ASD-alone, and about 8% of patients with ASD + ADHD had severe impairment (Jang et al., 2013). Our results showed that both ASD + ADHD and ADHD-alone groups had the greatest risk of having comorbid anxiety disorder compared to the other two groups after adjusting for age, gender, and level of urbanization.

4.5. ASD, ADHD, and disruptive behavior disorder

Both ASD and ADHD were associated with an increased risk of disruptive behavior disorders, including oppositional defiant disorder and conduct disorder (Biederman, 2005; Smalley et al., 2007; Simonoff et al., 2008; Joshi et al., 2010). Previous evidence suggested that up to 50% and about 10–15% of children with ADHD were comorbid with oppositional defiant disorder and conduct disorder, respectively (Biederman, 2005). This high prevalence was supposed to be related to the core symptoms, especially impulsivity, of ADHD (Biederman, 2005). Simonoff et al. reported that up to 28% of children with ASD met the diagnostic criteria of oppositional defiant disorder (Simonoff et al., 2008). The increased risk of disruptive behavior disorder among patients with ASD may be associated with the deficit in emotional regulation (Mazefsky et al., 2013). Furthermore, Kotte et al. studied the impact of autistic traits on children with ADHD, and found that those with ADHD and comorbid autistic traits had more disruptive behavior disorder and delinquency problems than those with ADHD-alone and the control group, which was compatible with our findings (Kotte et al., 2013).

4.6. ASD, ADHD, and tic disorder

The comorbid prevalence of ADHD and tic disorder ranged from 15% to 34% in previous studies, due to the different methodologies and subject populations (Spencer, Biederman et al., 1999; Schlander, Schwarz et al., 2011). However, the findings concerning the comorbidity between ASD and tic disorder are still inconsistent. Mattila et al. found that up to 25% of children with ASD suffered from tic disorder, but Joshi et al. suggested that the comorbidity of tic disorder did not differ between patients with ASD and the control group (Mattila, Hurtig et al., 2010; Joshi, Wozniak et al., 2013). However, both of these studies had small sample sizes. In our study with a large sample size, we found that both ASD and ADHD patients had a greater risk of tic disorder, and the comorbidity of ASD and ADHD increased this risk further.

5. Limitations

Some limitations of the study should be listed here. First, the prevalence of psychiatric disorders may be underestimated because only those individuals who sought medical help were enrolled. However, the subjects enrolled in our study had diagnoses by board-certified psychiatrists, yielding better diagnostic validity. Second, the NHI database did not provide some information, such as family history, personal lifestyle, and environmental factors. Without this information, we were unable to examine their influence.

6. Conclusion

Our results showed a high prevalence of psychiatric comorbidities among patients with ASD and those with ADHD. Patients with ADHD + ASD had the greatest risk of having comorbid bipolar disorder, depressive disorder, disruptive behavior disorder, and tic disorder than the other three groups. The diagnoses of ASD and ADHD preceded the diagnoses of other psychiatric comorbidities. A comprehensive interview scrutinizing the psychiatric comorbidities in patients is suggested when encountering and following patients with both ASD and ADHD in clinical practice.

Conflict of interest

No conflict of interest.

Funding source

The study was supported by grant from Taipei Veterans General Hospital (V103E10-001).

Financial disclosure

All authors have no financial relationships relevant to this article to disclose.

Contributors

Dr Mu-Hong Chen, Dr Ying-Sheue Chen, and Dr Han-Ting Wei contributed to study conception and design. Dr Mu-Hong Chen and Dr Han-Ting Wei wrote the protocol and manuscripts; Dr Li-Chi Chen, Dr Ya-Mei Bai, Dr Tung-Ping Su, Dr Ying-Sheue Chen, Dr Ju-Wei Hsu, and Dr Kai-Lin Huang assisted with interpretation of data, and the preparation and proof-reading of the manuscript; Dr Ya-Mei Bai, Dr Tzeng-Ji Chen, and Ms Wen-Han Chang provided the advices on acquisition of data and statistical analysis.

Acknowledgement

We thank Mr I-Fan Hu's friendship and support.

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