



Research report

Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: A nationwide longitudinal study



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ABSTRACT

Background: Previous cross-sectional studies have suggested a comorbid association between atopic dermatitis (AD) and depressive disorder as well as anxiety disorders, but the temporal relationship was not determined.

Methods: Using the Taiwan National Health Insurance Research Database, 8208 AD patients aged 12 and older without psychiatric history and age-/sex-matched (1:1) controls between 1998 and 2008 were enrolled in our study and followed to the end of 2011. Subjects who developed major depression, any depressive disorder, and anxiety disorders during the follow-up were identified.

Results: The Cox regression analysis after adjusting for demographic data and atopic comorbidities demonstrated that patients with AD had an elevated risk of developing major depression (hazard ratio [HR]: 6.56, 95% confidence interval [CI]: 3.64–11.84), any depressive disorder (HR: 5.44, 95% CI: 3.99–7.44), and anxiety disorders (HR: 3.57, 95% CI: 2.55–4.98). Stratified by age group, both adolescents and adults with AD were prone to developing major depression (HR: 4.26, 95% CI: 1.39–13.13; HR: 7.56, 95% CI: 3.75–15.23), any depressive disorder (HR: 4.38, 95% CI: 2.09–9.18; HR: 5.66, 95% CI: 4.01–7.99), and anxiety disorders (HR: 5.40, 95% CI: 2.02–14.39; HR: 3.36, 95% CI: 2.38–4.80).

Conclusions: AD in both adolescence and adulthood increased the risk of developing major depression, any depressive disorder, and anxiety disorders in later life. Further studies would be required to clarify the possible underlying mechanism between AD and depression as well as anxiety disorders.

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1. Introduction

Atopic dermatitis (AD) has been regarded as a chronic inflammatory and pruritic skin disorder and was characterized by intense pruritus, lichenification, dry skin, and eczematous inflammation (Leung, 1999; Rothe and Grant-Kels, 1996). AD usually occurred in early life and may persist throughout a lifetime with a waxing and waning clinical course (Leung, 1999; Rothe and Grant-Kels, 1996). Population-based studies demonstrated an increasing prevalence of AD in the past four decades, affecting about 10–20% of children and adolescents in United States (Shaw et al., 2011) and at least 7% of adults worldwide (DaVeiga, 2012;

Harrop et al., 2007; Odhiambo et al., 2009). Hwang et al. (2010) determined that 9.6% of children and adolescents and 6.7% of the whole population suffered from AD in Taiwan. Because of the chronicization of the disease clinical course, AD has been deemed to show a great impact on the health care and the quality of life of the patients (White et al., 1990). Previous studies also suggested the potential roles of environmental factors and psychosocial stress in the exacerbation of AD (Senra and Wollenberg, 2014; Chida et al., 2008).

A growing body of evidence reported the association between atopic diseases and depression as well as anxiety symptoms/disorders (Chen et al., 2013a, 2013b, 2013c; Ginsburg et al., 1993; Hashiro and Okumura, 1997; Mancuso et al., 2008; Opolski and Wilson, 2005; Slattery and Essex, 2011; Van Lieshout et al., 2009). Some clinical and community studies provided the evidence of a link between asthma and anxiety disorders (Opolski and Wilson, 2005; Slattery and Essex, 2011) as well as between asthma and depression

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in adults and adolescents (Mancuso et al., 2008; Opolski and Wilson, 2005; Van Lieshout et al., 2009). For example, Slattery and Essex (2011) followed 367 adolescents for the development of psychiatric problems, and found that both allergic rhinitis and asthma were associated with anxiety disorders in an additive manner. Assessing 257 with asthma, Mancuso et al. (2008) reported a positive association between patient-reported depressive symptoms and asthma severity ($p=0.007$). Our previous studies also supported a temporal association between allergic rhinitis and major depression as well as asthma and major depression (Chen et al., 2013a, 2013b, 2013c, 2014). On the contrary, previous studies investigating the relationship of AD with depression or anxiety disorders were much limited with controversial findings (Ginsburg et al., 1993; Hashiro and Okumura, 1997; Slattery and Essex, 2011). Evaluating the mood symptoms among 45 patients with AD and 34 healthy controls, Hashiro and Okumura (1997) showed that those with AD had a higher prevalence of depression symptoms and psychosomatic symptoms, but not anxiety symptoms, compared to the controls. Ginsburg et al. (1993) reported a study of 34 adult patients with AD and 32 controls, and found those with AD often exhibited chronically anxious states. However, Slattery and Essex (2011) suggested that there was no significant relationship of depression and anxiety symptoms with a lifetime history of AD. The inconsistent findings between AD and depression and anxiety disorders may be due to the various study methodologies and limitations in previous studies, including a small sample size, the use of a self-reported symptom questionnaire instead of a psychiatrist-given diagnosis, and a cross-sectional study design rather than a longitudinal follow-up study design. Furthermore, previous studies did not adjust for the atopic comorbidities in the regression model and cannot elucidate the independent or mediating effect of AD in the development of depression and anxiety disorders.

In the current study, using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal follow-up study design, we investigated the risk of major depression and anxiety disorders among adolescents and adults with AD. We hypothesized that patients with AD had an increased likelihood of subsequent major depression and anxiety disorders in the later life.

2. Materials and methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was implemented in 1995 and covers up to 99% of all 23,000,000 residents of Taiwan at this time. Demographic and medical information on insured residents, including date of birth, sex, residence location, the diagnosis, and the visiting dates were recorded in the NHIRD, which was audited and released by the Taiwan Department of Health and the Bureau of NHI. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used for the diagnosis. The completeness and accuracy of the NHIRD have been affirmed by the Department of Health and the Bureau of NHI through audit. The NHIRD has been used extensively in many epidemiological studies in Taiwan (Chen et al., 2013a, 2013b, 2013c; Li et al., 2012; Shen et al., 2013).

2.2. Inclusion criteria of patients with AD and the control group

Adolescents aged between 12 and 17 years and adults aged 18 years and older with a diagnosis of AD (ICD-9-CM: 691 or 691.8) given by board-certified dermatologist, pediatricians or rheumatologists and without any psychiatric disorder (ICD-9-CM code: 290–319) between January 1, 1998 and December 31, 2008, were included

in our study. The age- and sex-matched control group (one for every patient in the study cohort) was randomly identified after eliminating study case group, subjects who had been given a diagnosis of AD anytime, and those with any psychiatric disorder before the enrollment. These subjects were followed up to December 31st, 2011 for having diagnoses of major depression (ICD-9-CM codes: 296.2X and 296.3X) and any depressive disorder (ICD-9-CM codes: 296.2X, 296.3X, 300.4 and 311) and anxiety disorders (ICD-9-CM codes: 300 except 300.04 and 300.03) given by board-certified psychiatrists. Because of the high comorbidity of other atopic diseases with AD, comorbid atopic diseases, including asthma (ICD-9-CM codes: 493, 493.0, 493.1 or 493.9) diagnosed by internists, pulmonologists, rheumatologists, or pediatricians; allergic rhinitis (ICD-9-CM code: 477) given by internists, pulmonologists, rheumatologists, otolaryngologists, family physicians or pediatricians, and allergic conjunctivitis (ICD-9-CM codes: 372.05, 372.10 and 372.14) diagnosed by ophthalmologists, were also identified as confounding factors. All diagnoses were given at least twice by corresponding physicians or psychiatrists for improved diagnostic validity. Level of urbanization based on the postal code (level 1 to 4: level 1: most urbanized region; level 4: least urbanized region) was assessed in our study.

2.3. Statistical analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and Chi-squared test for nominal variables, where appropriate. Multivariate Cox regression analyses were performed to investigate the hazard ratios (HR) with 95% confidence intervals (CI) of major depression, any depressive disorder, and anxiety disorders after adjusting for demographic data (age at enrollment, sex, level of urbanization, and income-related insured amount) and atopic comorbidities. In addition, we also performed the Cox regression analyses to elucidate the age effect (adolescence or adulthood) in the risk of developing depression and anxiety disorders among patients with AD because some previous studies suggested the brain functioning in adolescence may differ from that in adulthood (Kessler and Wang, 2008; Paus et al., 2008). 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 21 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.2 (SAS Institute, Cary, NC, USA).

3. Result

Overall, 8208 patients with AD and 8208 age- and sex- matched controls were included in our study, with a mean age of 32.60 ± 16.06 years and a female predominance (60.1% vs. 39.9%) (Table 1). Patients with AD had a higher incidence of developing major depression (1.42 vs. 0.20 per 1000 person-years, $p < 0.001$), any depressive disorder (4.32 vs. 0.74 per 1000 person-years, $p < 0.001$) and anxiety disorders (2.83 vs. 0.70 per 1000 person-years, $p < 0.001$) than the control group during the follow-up period (Table 1). In addition, a higher prevalence of asthma (7.8% vs. 2.6%, $p < 0.001$), allergic rhinitis (30.5% vs. 15.1%, $p < 0.001$) and allergic conjunctivitis (21.4% vs. 10.7%, $p < 0.001$) was noted in patients with AD than in the control group (Table 1). Those with AD resided less on the urbanized region ($p < 0.001$) and had a higher income ($p < 0.001$) (Table 1).

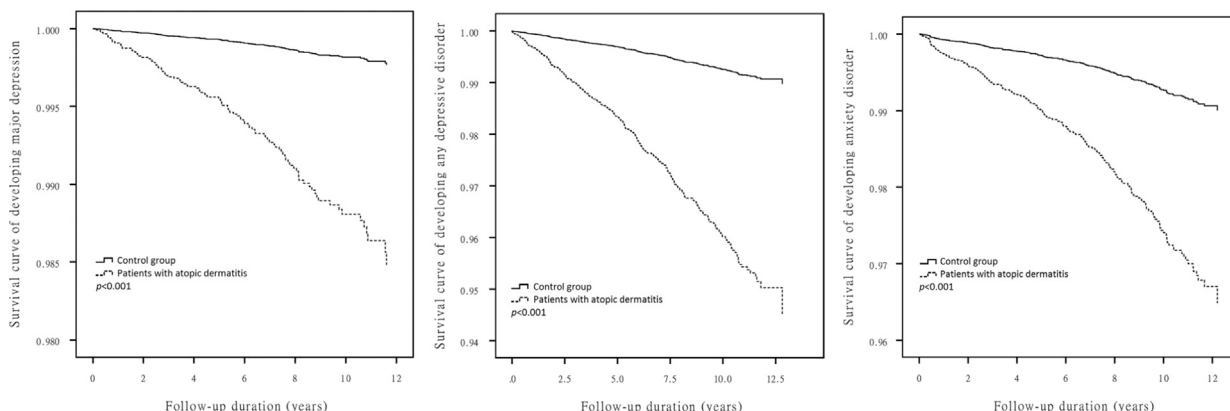
The Kaplan–Meier survival curve with a log-rank test indicated that patients with AD had a significantly higher risk of developing major depression, any depressive disorder, anxiety disorders than the control group ($p < 0.001$) (Fig. 1). After adjusting for demographic data and atopic comorbidities, the Cox regression model showed that patients with AD had an increased risk of developing major depression (HR: 6.56, 95% CI: 3.64–11.84), any depressive

Table 1

Demographic data and incidence of depression and anxiety disorders of patients with atopic dermatitis and the control group.

	Patients with atopic dermatitis (n=8208)	Controls (n=8208)	p-Value
Age at diagnosis of atopic dermatitis/enrollment (years, SD; n, %)	32.60 (16.06)	32.60 (16.06)	
< 18 years	1568 (19.1)	1568 (19.1)	
≥18 years	6640 (80.9)	6640 (80.9)	
Sex (M, %)	3272 (39.9)	3272 (39.9)	
Major depression (n, 1000 person-years)	91 (1.42)	13 (0.20)	< 0.001
Age at diagnosis (years, SD)	36.16 (15.10)	34.02 (17.60)	0.641
Duration between enrollment and diagnosis of major depression (years, SD)	4.80 (3.08)	5.76 (2.83)	0.291
Any depressive disorder (n, 1000 person-years)	273 (4.32)	48 (0.74)	< 0.001
Age at diagnosis (years, SD)	37.85 (16.99)	38.94 (18.77)	0.687
Duration between enrollment and diagnosis of any depressive disorder (years, SD)	4.60 (3.03)	6.26 (2.84)	< 0.001
Anxiety disorders (n, 1000 person-years)	180 (2.83)	45 (0.70)	< 0.001
Age at diagnosis (years, SD)	38.71 (16.98)	37.00 (13.04)	0.529
Duration between enrollment and diagnosis of anxiety disorders (years, SD)	4.62 (3.19)	6.98 (2.87)	< 0.001
Allergic comorbidities (n, %)			
Asthma	641 (7.8)	214 (2.6)	< 0.001
Allergic rhinitis	2501 (30.5)	1244 (15.1)	< 0.001
Allergic conjunctivitis	1759 (21.4)	884 (10.7)	< 0.001
Level of urbanization (n, %)			< 0.001
1 (most urbanized)	3441 (41.9)	4269 (52.0)	
2	1467 (17.9)	1527 (18.6)	
3	3129 (38.1)	2130 (26.0)	
4 (most rural)	171 (2.1)	282 (3.4)	
Income-related insured amount			< 0.001
≤ 15,840 NTD/month	2986 (36.4)	2978 (36.3)	
15,841–25,000NTD/month	2553 (31.1)	2883 (35.1)	
≥ 25,001NTD/month	2669 (32.5)	2347 (28.6)	

SD: standard deviation; NTD: New Taiwan Dollar.

**Fig. 1.** Survival curve of developing mood disorders among patients with atopic dermatitis and the control group.

disorder (HR: 5.44, 95% CI: 3.99–7.44), and anxiety disorders (HR: 3.57, 95% CI: 2.55–4.98) (Table 2). Stratified by age group, both adolescents and adults with AD were prone to developing major depression (HR: 4.26, 95% CI: 1.39–13.13; HR: 7.56, 95% CI: 3.75–15.23), any depressive disorder (HR: 4.38, 95% CI: 2.09–9.18; HR: 5.66, 95% CI: 4.01–7.99), and anxiety disorders (HR: 5.40, 95% CI: 2.02–14.39; HR: 3.36, 95% CI: 2.38–4.80) (Table 2). Besides, allergic rhinitis was associated with an increased risk of any subsequent depressive disorder (HR: 1.36, 95% CI: 1.04–1.77) and anxiety disorders (HR: 1.80, 95% CI: 1.32–2.44) in adult population (Table 2).

4. Discussion

The study results supported our study hypothesis that patients with AD had an elevated likelihood of subsequent major depression, any depressive disorder, and anxiety disorders compared to the controls after adjusting for demographic data and atopic comorbidities. Furthermore, AD both in adolescence and in adulthood was

associated with a vulnerability of developing depression and anxiety disorders in later life.

In the clinical aspect, symptomatology of AD, particularly the torturing pruritus and the feeling of being disfigured by the eczematous skin lesions, imposed a severe psychological burden among patients with AD and often had an enormous impact on their everyday quality of life (Buske-Kirschbaum et al., 2001; Jafferany, 2007). In a culture that values smooth skin, a disfigured skin may cause stigmatization (Schmid-Ott et al., 1999) and make the sufferers avoid their social activities (Senra and Wollenberg, 2014). Those cosmetic consequences resulted from AD would impair interpersonal relationships, social standing, and self-esteem (Humphreys and Humphreys, 1998). Wittkowski et al. (2004) recruited a total of 125 adults through the National Eczema Society of United Kingdom and revealed that AD-related perceptions of stigma were of particular importance in predicting AD-related quality of life and depression and anxiety symptoms. In addition, chronic pruritis dermatosis may play an important role in the development of sleep disturbances, anxiety, irritability, and depression (Yang et al., 2010; Koblenzer, 1997; Roza et al., 2003). Ellis et al. (2012) further concluded that even

Table 2Risk of developing mood disorders among patients with atopic dermatitis and the control group^a.

	< 18 years HR (95% CI)	≥18 years HR (95% CI)	Total HR (95% CI)
Atopic dermatitis, presence vs. absence	4.26 (1.39–13.13)	7.56 (3.75–15.23)	6.56 (3.64–11.84)
Allergic comorbidities, presence vs. absence			
Asthma	1.96 (0.59–6.46)	1.80 (0.88–3.68)	1.61 (0.87–2.96)
Allergic rhinitis	0.76 (0.29–1.98)	1.36 (0.84–2.20)	1.15 (0.74–1.77)
Allergic conjunctivitis	1.47 (0.59–3.67)	1.15 (0.68–1.95)	1.18 (0.75–1.85)
Any depressive disorder	4.38 (2.09–9.18)	5.66 (4.01–7.99)	5.44 (3.99–7.44)
Atopic dermatitis, presence vs. absence			
Allergic comorbidities, presence vs. absence			
Asthma	1.41 (0.65–3.06)	1.19 (0.75–1.91)	1.16 (0.78–1.72)
Allergic rhinitis	1.23 (0.69–2.21)	1.36 (1.04–1.77)	1.30 (1.02–1.66)
Allergic conjunctivitis	1.27 (0.70–2.27)	1.13 (0.84–1.52)	1.13 (0.86–1.47)
Anxiety disorders	5.40 (2.02–14.39)	3.36 (2.38–4.80)	3.57 (2.55–4.98)
Atopic dermatitis, presence vs. absence			
Allergic comorbidities, presence vs. absence			
Asthma	2.24 (0.92–5.43)	1.01 (0.57–1.79)	1.11 (0.70–1.78)
Allergic rhinitis	0.99 (0.47–2.10)	1.80 (1.32–2.44)	1.60 (1.20–2.12)
Allergic conjunctivitis	1.43 (0.69–2.95)	1.25 (0.88–1.77)	1.23 (0.90–1.68)

HR: hazard ratio; CI: confidence interval; NA: not available.

^a Adjusted by demographic data and allergic comorbidities and atopic dermatitis as a binary variable.

in patients with a mild presentation of AD, the psychosocial and economic burden of the disease can produce profound influence, including early retirement, decreasing desire for sex, somatization and mood symptoms. As mentioned in the Section 1, previous studies suggested a trend association between AD and depression as well as anxiety although the results were still very inconsistent (Ginsburg et al., 1993; Hashiro and Okumura, 1997; Slattery and Essex, 2011). Our current study with a large sample size and a longitudinal follow-up re-confirmed the relationship of AD with an increased risk of subsequent major depression and anxiety disorders after adjusting for demographic data and comorbid atopic diseases.

A shared genetic susceptibility to atopic diseases and depression as well as anxiety may explain the increased risk of developing depression and anxiety disorders among patients with AD (Wright, 2005; Wamboldt et al., 2000). Examining the covariance of atopic disorders and depressive symptoms by fitting the competing genetic and environmental model, a Finnish Twin Cohort study consisted of 1337 monozygotic and 2506 dizygotic twin pairs supported the hypothesis that there was a genetic link between atopic diseases and psychological distress including depression or anxiety (Wamboldt et al., 2000). Weitkamp and Stancer (1989) showed that HLA-region genes contributed to the higher likelihood to major depression, and Smeraldi et al. (1978) demonstrated that HLA-A29 and HLA-BW22 frequencies were significantly elevated among patients with mood disorders compared to the controls. But, the above studies also claimed that HLA-region genes may account for this observation but were not the only factor in susceptibility to mood disorders (Weitkamp and Stancer, 1989; Smeraldi et al., 1978).

Immunological dysregulation and alteration caused by the atopic inflammation, including a prominent Ig-E mediated atopic response and an over-secretion of proinflammatory cytokines (i.e., interleukin [IL]-1, IL-6, tumor necrosis factor alpha [TNF-α]), may contribute to the risk of depression and anxiety disorders (Bieber, 2008; Peng and Novak, 2014). Several evidences supported that a dysregulated secretion of proinflammatory cytokines during atopic responses would penetrate the blood-brain barrier (Yarlagadda et al., 2009) and activated abnormal neuroimmunological mechanisms involving some specific neural circuits related to emotional modulation (Raison et al., 2006; Raison and Miller, 2013). For example, Ishiui et al. (2009) found that patients with AD exhibited bilateral activation of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and dorsolateral prefrontal cortex (DLPFC). Dysfunction of the DLPFC and

ACC has been suggested to play an important role in depression and anxiety disorders (Du et al., 2012; Konarski et al., 2007; Zeng et al., 2012). The atopy-related neuroimmunological changes, as in a vicious cycle, impaired gradually the specific brain functioning and neural circuitry involved in emotional regulation and cognition. It may explain the sequential phenomenon of AD developing first and depression and anxiety coming later. But the underlying pathophysiology between AD and depression and anxiety disorders required further investigation.

Regarding the influence of AD on the risk of depression and anxiety disorders in adolescence and adulthood, Slattery et al. (2011) reported that adolescents with AD had a higher prevalence of anxiety (31%) and depressive (17%) disorders, and Chrostowska-Plak et al. (2013) demonstrated that adults with AD complained of more depression and sleep symptoms and lower health-related quality of life. Kadyk et al. (2004) further expressed that adolescents with AD seemed to suffer from a more diminished quality of life compared to the older group. But, interestingly, in our study, we found that adults with AD had about 7 times and 3 times increase in the risk of developing major depression and anxiety disorders, respectively, and adolescents with AD exhibited a reversed pattern of having an about 4 times and 5 times increase in the major depression and anxiety disorders, respectively. This result may indicate that AD in adolescence may be more likely linked to anxiety disorders and AD in adulthood was associated with depressive disorder. A possible reason which may explain this finding is that anxiety disorders always developed since childhood and preceded the occurrence of depressive disorder, and major depression usually occurred in the early adulthood or midlife (Paus et al., 2008; Jones, 2013). However, further studies may be required to clarify the different roles of AD in adolescence or adulthood in the risk of depression and anxiety disorders.

Some study limitations need to be addressed. First, database from the Bureau of National Health Insurance did not provide some of the information, such as disease severity, personal lifestyle, and environmental factors. Hence, we cannot evaluate the influence of those factors. Second, the incidence of major depressive disorder, any depressive disorder and anxiety disorders may be underestimated because only people with medicine-seeking behaviors were enrolled. In addition, those subjects enrolled in our study had board-certified psychiatrists' diagnoses, providing improved validity, compared to the previous studies with self-reported questionnaires, although it was still possible that the significant heterogeneity in the assessment was

likely to be present due to the absence of standardized instruments for diagnosis. Third, NHIRD is an anonymous database to protect personal medical privacy. We cannot know the information about subjects' parents, siblings, and family history of any psychiatric disorders or atopic diseases. Finally, we would inform the large confidence intervals in the regression models, indicating a wide variability in the sample which weakened the precision of our results. Further clinical studies would be required to re-validate our findings.

In conclusion, our study was the first longitudinal cohort study to suggest that adolescents and adults with AD had a higher risk of the further development of major depressive disorder, any depressive disorder, and anxiety disorders. The mental health among those patients with AD should be more evaluated and emphasized in the clinical practice. Further studies would be required to investigate the underlying disease mechanisms between AD and depression as well as anxiety and to examine whether proper treatment of AD and comorbid atopic diseases could prevent the development of depression and anxiety disorders or decrease those symptoms.

Contribution

Dr CMC, Dr MHC, and Dr SJT designed the study, wrote the protocol and manuscripts; Dr ACY, Dr TPS, Dr YMB, Dr JWH, Dr KLH, and Dr CTL assisted with the preparation and proof-reading of the manuscript; Dr MHC, Dr TJC, and Ms WHC provided the advices on statistical analysis.

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There is no further role in any step of the present study.

Conflict of interest

We declared that there is no conflict of interest.

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