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Title Page

Independent association among suicidal ideation, asthma, and bronchial hyperresponsiveness in adolescents

Running Head

Suicidal ideation in asthmatic adolescents

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Key words: asthma, adolescent, bronchial hyperresponsiveness, suicidal ideation

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Abbreviations

BDI: Beck Depression Inventory

BHR: bronchial hyperresponsiveness

ISAAC: International Study of Asthma and Allergies in Childhood

SIQ: Suicidal Ideation Questionnaire

Text

Asthma is a known risk factor for suicide-related behaviors in adolescents.¹ In particular, an association between asthma and suicidal behaviors has been reported in US high school students² and Taiwanese³ adolescents. However, most previous studies have used self-reported questionnaires to determine whether asthma was present², and others used hospital registries.³ Moreover, the role of potential confounders has not been fully investigated.

Although the questionnaire-based determination of asthma may be convenient to evaluate its prevalence in large populations, questionnaires are prone to false positives. Hence, the use of objective measures such as video questionnaires or bronchial provocation tests is recommended. Furthermore, as smoking, depression, and decreased pulmonary function are associated with both asthma and suicidal ideation, these variables may confound the association between asthma and suicidal ideation and accordingly cause difficulty in identifying an independent relationship.

In our current study, we recruited 1097 Korean students from three high schools. The three schools were randomly selected in the administrative districts to high, middle, and low areas based on tax amount of the previous year in Seoul. The assessment was conducted during one

of the classes, with assist from the teachers. The students completed the informed consent and the questionnaires. All students from the school of middle socioeconomic status area, a subgroup of 651 adolescents, underwent pulmonary function tests, with the methacholine challenge test. There was no exclusion criteria. This study was approved by the institutional review boards of Asan Medical Center (IRB No. 2014-0064). The presence of asthma was determined by using 3 distinct measures: self-reported questionnaires of allergic symptoms, video questionnaires, and the methacholine challenge test. We used the modified Korean version of the International Study of Asthma and Allergies in Childhood questionnaire, which is a validated tool for assessing allergic symptoms and diagnosis in Korean children and adolescents.⁴ Moreover, we used a video questionnaire developed by the International Study of Asthma and Allergies in Childhood.⁵ Students with positive responses to any of the 5 video clips when only considering the last 1 year were designated as having current asthma. Students who had positive responses when considering their entire lifetime, except for the past year, were considered to have previous asthma. The remaining patients were considered to not have asthma. In addition, bronchial hyperresponsiveness (BHR) was measured using the methacholine challenge test. The methacholine provocative concentration that caused a 20% reduction in the forced expiratory volume in 1 second (FEV₁) (PC20) was determined, and a cut-off value of 16 was used. Finally, students with concurrent BHR and recent wheezing symptoms were considered to have definite asthma.

Additional information was also collected through self-reported questionnaires: Gender, age, monthly family income, maternal educational level, and smoking status. For active smoking, we asked whether the student ever smoked cigarette and whether the student smoked cigarette during last month, and categorized the students into three exclusive groups: current smoker, previous smoker, and non-smoker. For passive smoking, we asked “How often do you smell tobacco in your environment?” and grouped the answers into three groups:

never, less than 3 times a week, and three times a week or more. Data on antidepressant medication or other past psychiatric histories were not collected.

In addition, we assessed the presence of suicidal ideation with the Korean adolescent form of the Suicidal Ideation Questionnaire (SIQ-JR).⁶ The SIQ-JR is a self-reported questionnaire that is used worldwide to predict and prevent suicidal attempts in adolescents during the first screening stage. Since this was a screening test of normal population, a cut-off score of 23 was used.⁷ With regard to potential confounders, depression status was determined using the Beck Depression Inventory (BDI)⁸; subjects with scores >13 were considered to have depression.

Approximately 10.4% of the students reported suicidal ideation; students with depression were more likely to do so (33.3% vs. 2.5%, $p < 0.0001$). Suicidal ideation was not significantly associated with gender, age, income, maternal educational level, or active smoking status. Subjects who were exposed to passive smoking tended to exhibit suicidal ideation (12.4% (>3/week) vs. 10.5% (<3/week) vs. 7.7% (no passive smoking); $p = 0.080$). Moreover, students with a suicidal ideation were more likely to have a lower FEV₁ (99.15 ± 12.05 vs. 102.4 ± 12.58 ; $p = 0.0405$) though the difference is clinically insignificant.

Students with wheezing symptoms or current asthma were more likely to be exposed to active and passive smoking, whereas students with current asthma or BHR were more likely to be depressed (Table 1). The association between asthma-related outcomes and suicidal ideation was significant, after adjusting for demographic variables and smoking status (odds ratio [95% confidence interval {CI}]): 1.95 [1.23–3.08] and 4.02 [1.34–12.48]). After further adjustments for depression status and pulmonary function, the level of significance remained strong. Furthermore, students with definite asthma were 5.23 times more likely to have

suicidal ideation, even after controlling for depression status and FEV₁ (95% CI, 1.37–19.94; Table 2).

We investigated the association between asthma and suicidal ideation in a sample of Korean high school students. To our knowledge, our current study is the first to use the methacholine challenge test along with a self-reported questionnaires to determine whether a student is affected by asthma. Moreover, we used 4 distinct definitions to establish the diagnosis of asthma: self-reported questionnaire, video questionnaire, BHR, and concurrent BHR with recent wheezing symptoms. All 4 definitions indicated similar results, which emphasized the significance of the association between asthma and suicidal behaviors in adolescents. Moreover, this association was independent of potential confounders, including active and passive smoking, depression status, and pulmonary function.

Our current findings notwithstanding, additional studies linking asthma and BHR with suicidal behaviors are needed. Asthma is a chronic inflammatory disease involving alterations in pro-inflammatory cytokine and inflammatory metabolite levels. The systemic inflammation in asthma activates the kynurenine pathway and disturbs the tryptophan metabolite levels, which then modulates neuroinflammation and subsequently affects suicidal behavior.⁹ Asthmatic patients with BHR show higher serum levels of tryptophan, kynurenine, and quinolic acid—all involved in the kynurenine pathway—compared with healthy persons.¹⁰ This supports the hypothesis that students with asthma, particularly those with BHR, are more likely to have suicidal ideation, and that the underlying relationship may involve the kynurenine pathway via increased airway inflammation. Oxidative stress, which has been hypothesized as a mediator of prenatal stress and atopic dermatitis, could be another possible candidate.¹¹ Apart from such possible underlying pathways, a direct causal relationship, unmeasured confounders, or common genetic link may also explain this association.^{1,12} Another potential cause of suicidal ideation in asthmatic adolescents is the use

of corticosteroids, which may induce adverse psychiatric symptoms.¹² However, the proportion of participants taking medication was too small to test this hypothesis. Also, no student was using oral steroids to control asthma.

The association between asthma and suicidal ideation was independent of potential confounders, including active and passive smoking, depression status, and pulmonary function. However, due to the cross-sectional design of our analysis, we could not clarify whether the considered variables acted as confounders or mediators. Among these three variables, smoking and depression may play a role in mediating the relationship between asthma and suicidal behavior, since smoking and depression are known to be associated with various pro-inflammatory reactions. On the other hand, the third variable, pulmonary function, has little relationship with inflammation in itself, which we thought may be a confounder rather than a mediating variable. However, since the association remained statistically significant after adjusting for all variables, we posit that the relationship is independent of them.

In summary, the association between asthma and suicidal ideation was examined in adolescents by using the methacholine challenge test to ascertain the presence of asthma. This association was found to be independent of potential confounders, including smoking, depression and pulmonary function.

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Table 1. The association between demographic characteristics and asthma-related outcomes

	Wheezing symptoms during the last 12 months (8.7%)		Current asthma (15.3%)		Previous asthma (7.9%)		BHR* (13.4%)		Definite asthma† (2.6%)	
	%	p value	%	%	p value	%	p value	%	p value	
Gender										
Male	8.0		15.0	7.8		10.9		1.6		
Female	9.1	0.460	15.5	8.7	0.751	14.4	0.240	3.0	0.325	
Age (years)										
15	11.3		16.5	8.7		15.3		2/6		
16	6.8		13.8	8.7		10.5		1.9		
17	8.4	0.022	16.0	7.5	0.638	15.5	0.198	4.6	0.334	
Monthly family income										
<\$5000	8.0		15.8	8.2		12.4		1.7		
\$5000–\$7000	10.6		16.5	8.3		12.9		4.2		
>\$7000	7.6	0.153	13.6	8.6	0.753	15.0	0.707	2.0	0.217	

Maternal educational level									
High school	7.9		16.0	5.5		12.1		1.8	
University	9.4		15.7	9.3		14.4		3.4	
Graduate school	6.3	0.311	11.1	9.4	0.088	10.3	0.554	0.0	0.262
Active smoking									
Current smoker	21.1		30.6	5.6		9.1		0.0	
Previous smoker	9.7		14.5	13.7		13.0		2.2	
Non smoker	8.3	0.021	15.0	8.0	0.018	13.5	0.913	2.7	0.279
Passive smoking									
≥3/week	11.1		16.6	8.5		14.2		2.4	
<3/week	9.0		16.4	9.0		11.2		2.1	
No passive smoking	5.3	0.012	11.4	6.7	0.076	17.5	0.169	4.2	0.438
Depression status									
Depression	10.4		25.4	7.4		17.8		2.9	
No depression	8.2	0.153	11.9	8.7	<.0001	11.7	0.044	2.5	0.785

*BHR: Bronchial hyperresponsiveness (Defined as methacholine provocative concentration that caused a 20% reduction in the forced expiratory volume in 1 second (FEV₁) (PC20) less than 16 mg/ml)

†Concurrent bronchial hyperresponsiveness (PC20 less than 16 mg/ml) and wheezing symptoms during the last 12 months

Table 2. Association between asthma-related outcomes and suicidal ideation

	N/total N	%	Suicidal ideation (yes vs. no)		
			Model 1	Model 2	Model 3*
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Wheezing symptoms during the last 12 months	148/ 1697	8.7%	1.95 (1.23–3.08)	2.03 (1.19–3.47)	2.50 (1.10–5.70)
Current asthma, ascertained by video questionnaire (vs. no asthma)	249/ 1625	15.3%	2.36 (1.62–3.44)	1.48 (0.96–2.28)	2.45 (1.25–4.77)
Bronchial hyperresponsiveness (PC20<16)	87/651	13.4%	2.21 (1.18–4.14)	1.83 (0.89–3.75)	1.64 (0.80–3.37)
Definite asthma†	17/651	2.6%	4.02 (1.34–12.48)	5.83 (1.50–22.69)	5.23 (1.37–19.94)

*Analyses were limited to students with data on pulmonary function (N=651).

†Concurrent bronchial hyperresponsiveness (CP20<16) and wheezing symptoms during the last 12 months

Model 1: adjusted for sex, age, income, maternal education, active smoking, and passive smoking

Model 2: Model 1 + depression status

Model 3: Model 2 + forced expiratory volume in 1 second. (Value=measured value/predicted value×100; the predicted value was based on age, sex, height, mass, and ethnicity)