



Hypertension and diabetes mellitus as risk factors for asthma in Korean adults: the Sixth Korea National Health and Nutrition Examination Survey

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Background: Asthma is a chronic inflammatory disease that may associate with other chronic diseases such as hypertension and diabetes. We observed the effects of blood pressure (BP), fasting blood glucose (FBG), haemoglobin A1c (HbA1c) and insulin on asthma in Korean adults.

Methods: Data from 5045 adults were taken from the 2015 Sixth Korea National Health and Nutrition Examination Survey and analysed using a multiple logistic regression model.

Results: By age, the probability of asthma occurrence was 1.02 times higher (adjusted odds ratio [aOR] 1.02 [95% CI 1.01 to 1.03]). Specifically, asthma occurrence was increased in individuals >66 years of age (aOR 2.40 [95% CI 1.22 to 4.72]). The probability of asthma occurrence in females was higher than in males (aOR 1.73 [95% CI 1.02 to 2.84]). Hypertension and systolic blood pressure (SBP) were found to increase the probability of asthma occurrence by 1.43- and 1.03-fold, respectively. Diabetes mellitus (DM) was another factor that increased with the occurrence of asthma (aOR 1.75 [95% CI 1.06 to 3.02]). The probability of asthma occurrence was not increased with the FBG level, whereas HbA1c (aOR 1.38 [95% CI 1.03 to 1.84]) and insulin levels (aOR 1.02 [95% CI 1.01 to 1.04]) were shown to increase the occurrence of asthma.

Conclusions: Age, sex, hypertension, SBP, DM, HbA1c and insulin levels are all factors that may influence the occurrence of asthma in Korean adults. In particular, hypertension and diabetes emerge from the present study as potential associated factors for the development of asthma.

Keywords: asthma, blood pressure, diabetes mellitus, haemoglobin A1c, hypertension, insulin

Introduction

Asthma is a chronic inflammatory disease that affects as many as 334 million people worldwide, with an increasing prevalence in most countries, as evidenced by a 2010 WHO report.¹ Although diagnosis and treatment of asthma has improved over the past 2 decades, it is still a disease that significantly increases healthcare one word costs and decreases work productivity. In Korea, the prevalence of diagnosed asthma increased from 0.7% in 1998 to 2.0% in 2008² and to 2.4% from 2007 to 2011.³ Additionally, the loss of quality-adjusted life years (QALYs) due to asthma is about 400 per 100 000 people per year, which is the sixth largest disease burden of any chronic disease.⁴ By age, the prevalence of asthma is 5–9% in childhood and decreases to 3% in young adults; however, the prevalence of asthma after the age of 50

y increases, showing a peak of 6.8–12%.⁵ Because Korea is one of the fastest aging societies in the world, the prevalence of asthma in the elderly suggests that the socio-economic burden of asthma may increase even further.

Hypertensive patients with comorbid asthma show increased asthma morbidity⁶ and previous epidemiological studies have observed that asthma patients suffer arterial hypertension at a higher rate than those without asthma.^{6,7} The relationship between hypertension and asthma may be synergistic and due to common mechanisms such as vascular remodelling and endothelial abnormalities (e.g. abnormal contraction and proliferation of smooth muscle cells).^{8,9} Both pulmonary and cardiovascular regulation are under autonomic control and there are many interdependent parts, which may explain the relationship between asthma and hypertension. Thus,

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considering the epidemiological association and potential pathophysiological interaction, it is reasonable to suspect that asthma and hypertension would correlate with each other and share some common factors.

Diabetes mellitus (DM) is another common comorbid condition among adult patients with asthma. The prevalence of comorbid DM and asthma has been shown to range from 5% to 16%, as demonstrated by previous studies.^{10,11} Also, diabetic patients show an increased risk for other respiratory diseases, such as chronic obstructive pulmonary disease, pulmonary fibrosis and pneumonia, compared with those without diabetes.¹² In order to improve disease management and health outcomes, it is vital to understand the impact of DM, hypertension and other metabolic/cardiovascular conditions on asthma, particularly in high-risk communities. There is already some evidence to suggest a link between cardiovascular/metabolic health problems and asthma;^{13,14} however, these relationships are poorly understood and the role of environmental risk factors in these relationships has yet to be explored. In addition to asthma, chronic diseases such as hypertension and DM account for a large portion of the medical expenditures of Korean adults, and this is increasing year by year. There have been few studies on the effects of hypertension and DM on asthma in Korean adults and, in particular, there have been no studies investigating the influence of fasting blood glucose (FBG), haemoglobin A1c (HbA1c) and insulin on asthma. Thus the purpose of this study was to investigate the risk of asthma in hypertensive and diabetic populations from a large survey of Korean adults.

Methods

Samples and setting

The subjects of this study were Korean adults who provided data via the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI-3; 2015), administered by the Korea Centers for Disease Control and Prevention. The KNHANES's investigating methodology has been well described in previous studies.¹⁵ In brief, the survey consists of a health interview, a nutritional survey and a health examination. All participants were given physical examinations by trained staff and answered a questionnaire. A total of 7380 subjects, of which 5045 were adults >20 y of age, had their data analysed (Figure 1).

Measuring methods

General characteristics included age, sex, smoking, amount of smoking, body mass index (BMI), hypertension, DM and education level. The asthma-related characteristics included age of onset, present asthma care, medication and asthma diagnosis. Whether the patient suffered from asthma was determined by asking them, 'Have you ever been diagnosed with asthma by a doctor in your entire life?'; 3.1% of respondents (158 people) answered 'yes' and 96.9% (4887 people) answered 'no'.

Three blood pressure (BP) readings were taken at regular intervals in a stable state. The mean of the second and third BPs was measured as the final systolic blood pressure (SBP) and final diastolic blood pressure (DBP). Blood sampling was performed in the morning, after fasting for ≥ 8 h, by cubital vein puncture

using a vacutainer needle with blood drawn into a vacuum tube. FBG was measured by the hexokinase ultraviolet method and analysed with a Hitachi Automatic Analyzer 7600-210 (Hitachi, Marunouchi, Japan) using Pureauto S GLU (Sekisui, Osaka, Japan) reagent. The HbA1c assay was measured by a high-performance liquid chromatography assay analysed with a Tosoh G8 instrument (Tosoh, Shiba, Japan) using HLC-723G8 HbA1c (Tosoh). The insulin measurement was performed using the electrochemiluminescence method and analysed with a Cobas 8000 instrument (Roche, Basel, Switzerland) using Elecys insulin (Roche).

Data analysis

All data analysis of the study subjects was done by complex sampling design analysis so that the sample data results were representative of the general population. General characteristics were summarized as frequency, percentage, mean and standard deviation for quantitative variables. Group comparisons between the asthma-diagnosed group and the non-asthma group were analysed by a t-test and χ^2 test for general characteristics, BP, FBG, HbA1c and insulin levels. Multiple logistic regression analysis was performed to identify factors influencing asthma. The adjusted odds ratio (aOR) and 95% CI for each variable were calculated as the dependent variable for the diagnosis of asthma. ORs >1 indicate a positive influence on asthma prevalence and ORs <1 indicate a negative influence on asthma prevalence compared with the reference. A two-tailed p-value <0.05 was considered statistically significant. The collected data were analysed using SPSS WIN 24.0 software (IBM, Armonk, NY, USA).

Ethical consideration

We used the National Health and Nutrition Examination Survey (approval no. 117002) data according to Article 17 of the Statistical Law. Personal information about the subjects was collected via a unique, non-identifiable number code, thus guaranteeing the anonymity and confidentiality of the subjects. All subjects consented to the study. Data collection occurred over a 48-week period. This study was made available on 7 April 2017, after the researchers approved the use of the data, in accordance with the rules for disclosure and management of source data set forth by the Korea Centers for Disease Control and Prevention.

Results

Multiple general characteristics were associated with the rate of asthma occurrence in Korean adults. The mean age of the study participants was 56.20 y in the asthma-diagnosed group and 52.02 y in the non-asthma group. By age, asthma was most prevalent in patients >66 y of age (42.4%). There was a significant difference in asthma prevalence according to age ($p < 0.001$). The probability of asthma occurrence in female subjects (66.5%) was higher than that for male subjects (33.5%). In the non-asthma group, there were more females (56.9%) compared with males (43.1%). The difference in asthma prevalence according to sex was significant ($p = 0.016$).

There was no significant difference in asthma prevalence according to smoking ($p = 0.387$) and amount of smoking

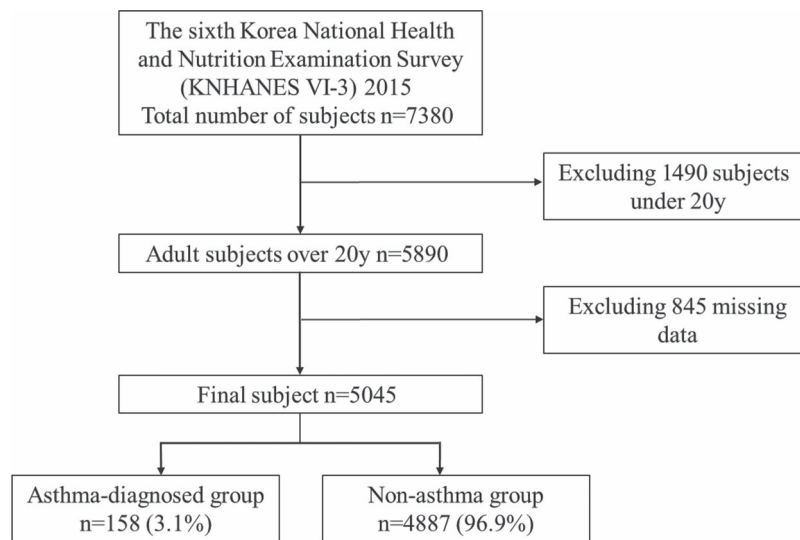


Figure 1. Flow chart of the study population.

($p=0.182$). For BMI, the probability of obesity occurrence in the asthma-diagnosed group ($24.59 \pm 3.76 \text{ kg/m}^2$) was higher than for the non-asthma group ($23.93 \pm 3.45 \text{ kg/m}^2$) ($p=0.018$). There was a significant difference in asthma prevalence according to BMI ($p=0.019$). For hypertension, the probability of hypertension occurrence in the asthma-diagnosed group (36.7%) was higher than for the non-asthma group (25.8%). The difference in asthma prevalence according to DM diagnosis was significant ($p=0.015$). For education, the below elementary graduated group (39.2%) showed a higher prevalence in the asthma-diagnosed group, while the non-asthma group showed a higher prevalence in the high school graduated group (32.8%). There was a significant difference in asthma prevalence according to education level ($p<0.001$). In the asthma-diagnosed group, the age of onset was often before 19 y of age (19.6%), but it was non-relevant (100%) in the non-asthma group ($p<0.001$). In the asthma-diagnosed group, significantly more patients stated that they do not presently see a healthcare professional for their asthma (61.4%) compared with those who do ($p<0.001$). Additionally, 50.0% of the asthma-diagnosed group had no medication to treat their asthma ($p<0.001$). Thus, in the analysis of general characteristics, the variables that showed significant differences included age, sex, hypertension, DM, education level, present asthma care and medication treatment (Table 1).

More individuals were diagnosed with hypertension in the asthma-diagnosed group compared with the non-asthma group. SBP was higher in the asthma-diagnosed group than in the non-asthma group, but DBP was not significantly different between the asthma and non-asthma populations. More individuals were diagnosed with DM in the asthma-diagnosed group than the non-asthma group. There was no significant difference in FBG between the asthma-diagnosed group and the non-asthma group ($p=0.061$). However, there was a significant difference in HbA1c levels ($p=0.002$) and insulin levels ($p=0.010$) between the asthma-diagnosed group and the non-asthma group (Table 2).

Significant factors associated with the diagnosis of asthma include age, sex, hypertension, SBP, DM, HbA1c and insulin levels (Table 3). The factors affecting the occurrence of asthma are

indicated by multivariate logistic regression analysis. By age, the probability of asthma occurrence was 1.02 times higher (95% CI 1.01 to 1.03; $p=0.003$). Specifically, the occurrence of asthma was 0.71-fold lower (95% CI 0.36 to 1.05; $p=0.091$) in the 36–50 y age group and 0.72-fold lower (95% CI 0.37 to 1.08; $p=0.091$) in the 51–65 y age group compared with the 20–35 y age group, but the values were not significant. At an age of >66 y, the probability of asthma occurrence was 2.40-fold greater than in the 20–35 y age group (95% CI 1.22 to 4.72; $p=0.042$). The probability of asthma occurrence in females was 1.73 times higher than in males (95% CI 1.02 to 2.84; $p=0.042$). The smoking group had an increase in the risk of asthma occurrence of 1.25-fold (95% CI 0.79 to 1.98; $p=0.329$) compared with the non-smoking group, but the values were not significant. The occurrence of asthma was 1.41-fold higher (95% CI 0.17 to 11.32; $p=0.861$) in the 1–10 cigarettes group, 1.88-fold higher (95% CI 0.24 to 12.76; $p=0.546$) in the 11–20 cigarettes group and 2.00-fold higher (95% CI 0.27 to 14.60; $p=0.747$) in the >21 cigarettes group compared with the non-smoking group. However, none of these values were significant. As the BMI (kg/m^2) increases, the occurrence of asthma increases by 1.02-fold (95% CI 0.90 to 1.14; $p=0.958$). In the BMI classification, the occurrence of asthma increases in overweight subjects by 1.69-fold (95% CI 0.85 to 3.37; $p=0.131$) and in obese subjects by 1.37-fold (95% CI 0.82 to 2.30; $p=0.222$), but these values were not significant. The hypertension-diagnosed group had a 1.43 times higher asthma occurrence compared with those without hypertension (95% CI 1.09 to 2.10; $p=0.046$) and with a higher SBP there was a 1.03 times greater probability of asthma occurrence (95% CI 1.01 to 1.25; $p=0.036$). The probability of asthma occurrence in the DM-diagnosed group was 1.75 times higher than the non-DM group (95% CI 1.06 to 3.02; $p=0.048$). Additionally, the probability of asthma occurrence was 1.38 times higher in individuals with high HbA1c levels (95% CI 1.03 to 1.84; $p=0.031$) and 1.02 times higher in individuals with higher insulin levels (95% CI 1.01 to 1.04; $p=0.015$). Thus, in Korean adults, the probability of asthma occurrence is greater in hypertensive and diabetic individuals.

Table 1. General characteristics of the asthma-diagnosed and non-asthma groups

Variables	Category	Asthma-diagnosed group, n (%)	Non-asthma group, n (%)	p-Value
Age (y), mean \pm SD		56.20 \pm 18.91	52.02 \pm 16.35	0.002
	20–35	30 (19.0)	933 (19.1)	<0.001
	36–50	26 (16.5)	1268 (25.9)	
	51–65	35 (22.2)	1499 (30.7)	
Sex	>66	67 (42.4)	1187 (24.3)	
	Male	53 (33.5)	2108 (43.1)	0.016
	Female	105 (66.5)	2779 (56.9)	
	Smoking	Non-smokers	136 (86.1)	4062 (83.1)
Amount of smoking (per day), mean \pm SD	Smokers	22 (13.9)	825 (16.9)	
		1.66 \pm 5.11	2.32 \pm 6.07	0.182
	None	136 (86.1)	4062 (83.1)	0.677
	1–10 cigarettes	12 (7.6)	382 (7.8)	
	11–20 cigarettes	9 (5.7)	383 (7.8)	
BMI (kg/m ²), mean \pm SD	>21 cigarettes	1 (0.6)	60 (1.2)	
		24.59 \pm 3.76	23.93 \pm 3.45	0.018
	Normal weight (<23.0)	51 (32.5)	2035 (41.7)	0.019
	Overweight (23–24.9)	36 (22.9)	1174 (24.1)	
Hypertension	Obese (\geq 25)	70 (44.6)	1671 (34.2)	
	Yes	58 (36.7)	1259 (25.8)	0.002
	No	100 (63.3)	3628 (74.2)	
DM	Yes	24 (15.2)	459 (9.4)	0.015
	No	134 (84.8)	4428 (90.6)	
Education level	Below elementary school	62 (39.2)	1135 (23.4)	<0.001
	Middle school graduate	12 (7.6)	537 (11.1)	
	High school graduate	44 (27.8)	1586 (32.8)	
	University graduate or greater	40 (25.3)	1584 (32.7)	
Age of onset (y)	<19*	31 (19.6)	0 (0.0)	<0.001
	20–29	13 (8.2)	0 (0.0)	
	30–39	18 (11.4)	0 (0.0)	
	40–49	26 (16.5)	0 (0.0)	
	50–59	27 (17.1)	0 (0.0)	
	60–69	21 (13.3)	0 (0.0)	
	>70	21 (13.3)	0 (0.0)	
	N/A	0 (0.0)	4887 (100)	
Present asthma care	Yes	61 (38.6)	0 (0.0)	<0.001
	No	97 (61.4)	0 (0.0)	
	N/A	0 (0.0)	4887 (100)	
Medication	Regular treatment to prevent deterioration and manage asthma symptoms	31 (19.6)	0 (0.0)	<0.001
	Irregular treatment only during symptoms	48 (30.4)	0 (0.0)	
	No treatment	79 (50.0)	0 (0.0)	
	N/A	0 (0.0)	4887 (100)	

*Data for asthma onset were collected from subjects' previous medical records.

Table 2. Characteristics of hypertension and diabetes in asthma-diagnosed and non-asthma groups

Variables	Asthma-diagnosed group, n (%)	Non-asthma group, n (%)	p-Value
Hypertension (mmHg)			
SBP	122.15 ± 17.08	119.29 ± 17.40	0.043
DBP	73.81 ± 9.24	74.87 ± 10.29	0.204
DM			
FBG (mg/dl)	105.05 ± 33.55	101.14 ± 24.71	0.061
HbA1c (%)	5.90 ± 0.97	5.70 ± 0.79	0.002
Insulin (mU/L)	10.19 ± 9.89	8.43 ± 8.09	0.010

Table 3. Factors associated with asthma

Variables	Category	aOR (95% CI)*	p-Value*
Age (y)	20–35 (reference)	1.02 (1.01 to 1.03)	0.003
	36–50	0.71 (0.36 to 1.05)	0.091
	51–65	0.72 (0.37 to 1.08)	0.077
	>66	2.40 (1.22 to 4.72)	0.042
Sex	Male (reference)		
	Female	1.73 (1.02 to 2.84)	0.042
Smoking	Non-smokers (reference)		
	Smokers	1.25 (0.79 to 1.98)	0.329
Amount of smoking (per day)	None (reference)	1.01 (0.98 to 1.03)	0.861
	1–10 cigarettes	1.41 (0.17 to 11.32)	0.491
	11–20 cigarettes	1.88 (0.24 to 12.76)	0.546
	>21 cigarettes	2.00 (0.27 to 14.60)	0.747
BMI (kg/m ²)	1.02 (0.90 to 1.14)	0.958	
	Normal weight (reference)		
	Overweight (23–24.9)	1.69 (0.85 to 3.37)	0.131
Hypertension	Obese (≥25)	1.37 (0.82 to 2.30)	0.222
	Non-hypertension group (reference)		
	Hypertension-diagnosed group	1.43 (1.09 to 2.10)	0.046
DM	SBP	1.03 (1.01 to 1.25)	0.036
	DBP	0.10 (0.97 to 1.02)	0.818
	Non-DM group (reference)		
	DM-diagnosed group	1.75 (1.06 to 3.02)	0.048
	FBS (mg/dl)	1.01 (0.98 to 1.01)	0.14
Education level	HbA1c (%)	1.38 (1.03 to 1.84)	0.031
	Insulin (mU/L)	1.02 (1.01 to 1.04)	0.015
	Below elementary school (reference)		
	Middle school graduate	1.54 (0.87 to 2.74)	0.138
High school graduate	0.95 (0.43 to 2.09)	0.888	
Over university graduate	1.14 (0.70 to 1.85)	0.602	

*ORs and p-values were from a multiple logistic regression model adjusted for age, sex, smoking, amount of smoking, BMI and education level.

Discussion

Various sociodemographic characteristics, such as age, sex, education and age of onset, are associated factors for asthma prevalence.¹⁶ In this study, there was a significant difference in the probability of asthma occurrence between the sexes. Our results are in agreement with a number of previous studies that have reported a preponderance of women suffering from asthma.^{16,17} Interestingly, it has also been reported that females tend to have a higher rate of severe asthma.¹⁸ A partial explanation for the sex differences in asthma presentation is variations in the hormone receptor oestrogen receptor 1, which has been linked to airway hyperresponsiveness and an accelerated decline in lung function in the female population.¹⁹ In our study, the incidence of asthma occurrence was increased after the age of 66 y. The prevalence of asthma in elderly people is notably high and is rapidly increasing in the aging society of Korea. In the early 2000s, Korean national epidemiological data showed the prevalence of asthma was 12.8% for those 20–45 y of age, 14.6% for those 46–65 y and 23.6% for those ≥66 y in a survey of 9266 adults and 2026 adolescents.²⁰ According to the results from the International Study of Asthma and Allergies in Childhood,²¹ the prevalence of asthma in Korean adolescents <12 y of age was 12.5–18%, decreasing to 7.5–18% in adolescents 12–18 y of age. Similar to our results, the frequency of asthma was higher in adults (especially in elderly people) compared with children and young adults.

In this study, hypertension was found to be a significant comorbidity in the asthma population. Our results are in agreement with previous results indicating that the presence of asthma and hypertension is associated and more prominent in adults (particularly in females compared with males).⁶ Household environmental risk factors and asthma were strongly related with physician-diagnosed hypertension compared with those without a diagnosis of hypertension.⁷ Hypertensive status could increase susceptibility to asthma development due to pathways or pathological mechanisms associated with both asthma and hypertension, including those involved in both airway and vascular remodelling. Recent studies have suggested that pathways involved in the differentiation and regulation of smooth muscle cells may be a component of these two diseases. Specifically, endothelin (a family of peptides that influence vasoconstriction and vasodilation) dysfunction has been shown to play an integral role in the pathology of asthma and hypertension.^{22,23} Moreover, myosin II has been shown to abnormally contract smooth muscle cells in the pathology of both asthma and hypertension.²⁴ We observed that SBP is a significant factor increasing the risk for asthma occurrence. Thus additional studies will be required to define and better assess the influence of SBP on the risk of asthma development. In addition, protocols should be established to more uniformly treat the co-occurrence of asthma and other chronic diseases, with special emphasis on continuity of management.

In this study, DM was one of the important factors significantly associated with asthma occurrence. The probability of asthma occurrence in the DM-diagnosed group was 1.50-fold higher than the non-asthma group. Our results are similar to those from a study that found a twofold increased risk of DM among patients with asthma compared with those without.²⁵ Our results are also

consistent with findings in which women with a history of asthma were at an increased risk for diabetes.²⁶ We observed that higher HbA1c levels increase the risk of asthma occurrence by 1.37 times. This finding is consistent with a study that showed HbA1c levels were higher in asthmatic children than in healthy controls²⁷ and HbA1c levels are increased significantly in non-diabetic adult patients with asthma.²⁸ It should be noted, however, that many studies have emphasized that blood glucose levels are increased in asthma patients who take high doses of inhaled or oral corticosteroids. Suissa et al.²⁹ demonstrated that inhaled corticosteroid significantly increased the risk of diabetes onset and diabetes progression in asthmatic or chronic obstructive pulmonary disease patients in a large nested case-control study. Thus there is the possibility that patients with asthma may receive some medications, including glucocorticoids, that may affect BP or glycaemic control. As shown in Table 1, 61.4% of asthma-diagnosed patients do not presently receive care for their asthma. Furthermore, 50% of such patients have not received any medication. Therefore we assumed that the treatment of asthma (such as with glucocorticoids) may not have impacted our data significantly. There is some uncertainty about the medications taken by patients that may affect BP or glycaemic control due to the cross-sectional design of the study. Thus more detailed follow-up studies are needed.

We found that insulin levels are associated with an increased probability of asthma occurrence in Korean adults. Our results are consistent with those of a study documenting that individuals with the highest levels of insulin resistance have greater odds of currently having asthma compared with obese individuals with the lowest levels of insulin resistance.³⁰ In an *in vitro* study, insulin infusion significantly reduced certain immune mediators, including interleukin 4, the key type 2 T helper cytokine associated with asthma. Thus insulin has been shown to suppress the expression of genes and mediators related to asthma.³¹ Both basic and prospective clinical research studies are needed to clarify whether organ-specific compensatory asthma is the pathophysiological mechanism by which insulin resistance potentiates the association between insulin levels and asthma and whether drugs that target insulin resistance can reduce asthma morbidity in patients. Furthermore, based on the results of this study, asthma prevention and management programmes should include management of hypertension and diabetes.

Our study's notable strength is that it may be the first report to identify the association between chronic diseases and asthma in Korean adults.

Conclusions

This study indicates that hypertension and diabetes are potential associated factors for the development of asthma in Korean adults. Although the causes of asthma are principally genetic and environmental, this disease can be sufficiently prevented and treated through basic management. This study provides insights that could improve public medical care by identifying associated factors that can be treated as a means of asthma prevention and management. In the future, long-term follow-up studies identifying the time of asthma onset in association with the presentation of other chronic diseases

will be helpful in guiding treatment by further elucidating the association between asthma and other chronic diseases.

Authors' contributions: KHL participated in the design of the study and performed data analysis. HSL designed the study and wrote the manuscript, with comments from the co-author.

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Competing interests: None declared.

Ethical approval We used the National Health and Nutrition Examination Survey (approval no. 117002) data according to Article 17 of the Statistical Law. This study was made available on 7 April 2017, after the researchers approved the use of the data, in accordance with the rules for disclosure and management of source data set forth by the Korea Centers for Disease Control and Prevention.

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