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Apparently healthy adults with high serum gamma-glutamyl transferase levels are at increased risk of asthma development in the near future: a Korean nationwide cohort study

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Abstract. – OBJECTIVE: Serum gamma-glutamyl transferase (GGT), an indicator of oxidative stress and/or a chronic inflammatory process, is associated with the levels of leukotrienes and other inflammatory mediators that play a critical role in the pathogenesis of asthma. This study aimed at investigating whether apparently healthy subjects with higher serum GGT levels at a national health check-up are at an increased risk of developing asthma in the near future.

PATIENTS AND METHODS: We analyzed 564,213 Korean adults, aged 20-80 years who underwent a national general health examination, including measurement of baseline serum GGT between 2003 and 2015, using data from a large-scale representative cohort of the Korean population. Data were analyzed using a Cox proportional hazards regression analysis.

RESULTS: In total, 516,956 participants were included in the final analysis. During the mean follow-up period of 8 years (standard deviation, 4.0), 7,439 incident asthma events occurred. We then classified the male and female participants according to quartiles of blood GGT levels (males: ≤ 20, 21-30, 31-51, and ≥ 52 IU/L; females: ≤ 12, 13-16, 17-22, and ≥ 23 IU/L, respectively). The adjusted hazard ratio (aHR) for incident asthma was significantly greater for subjects in the highest GGT quartile than for those in the lowest GGT quartile (aHR, 1.47; 95% confidence intervals, 1.36-1.59). Further, there was a significant linear trend across quartiles with regard to asthma (p_{trend}<0.001). We estimated the optimal cut-off values (using the minimum *p*-value approach) as 35 IU/L for the total population, 35 IU/L for males, and 36 IU/L for females, respectively.

CONCLUSIONS: Clinicians should be aware of the risk of incident asthma in healthy subjects with elevated GGT levels. Our findings advance our understanding of asthma pathogenesis.

Key Words:
Asthma, Gamma-glutamyl transferase, Oxidative stress.

Introduction

Asthma is a chronic inflammatory airway disease characterized by recurrent episodes of wheezing, dyspnea, chest tightness, and coughing[1], affecting a large number of children and adults[2]. Patients with asthma are treated with a combination of long-term maintenance therapy (i.e., maintenance medications) and short-term therapy (i.e., reliever medications)[3]. Leukotriene receptor antagonists (LTRAs) are a class of maintenance medications for asthma[3]. LTRAs function by suppressing inflammatory mediators of bronchoconstriction [i.e., leukotriene (LT) C_4, LTD_4, and LTE_4][4] and are primarily administered as adjunctive therapy to inhaled corticosteroids in patients with moderate-to-severe asthma, although they may also be utilized as an alternative to inhaled corticosteroids for mild persistent asthma[3].

Gamma-glutamyl transferase [GGT; enzyme commission number (EC) 2.3.2.2.], a protein routinely measured during a health check-up, is a ubiquitous enzyme that plays a pivotal role in the metabolism of glutathione[5], which is the most important cellular antioxidant in humans[6]. While the current nomenclature recommends the use of the name GGT, some authors have continued to use the older name gamma-glutamyl transpeptidase[5].

Elevated serum GGT levels indicate oxidative stress and/or an inflammatory process[7] and are associated with chronic inflammatory diseases[8,9]. Further, high serum GGT levels are associated with high levels of LTs and other inflammatory mediators that play critical roles in the pathogenesis of asthma and airway bronchoconstriction[10]. Although laboratory studies have reported a possible positive association between serum GGT and asthma[10], no epidemiological studies have

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corroborated this relationship. Therefore, we aimed at determining whether apparently healthy adults with higher serum GGT levels at a national health check-up were at an increased risk of developing asthma in the near future.

Patients and Methods

Study Subjects

We performed a large-scale general population-based study to determine the association between serum GGT levels and incident asthma. This study utilized data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a large-scale representative cohort of the Korean standard population[11,12]. The study protocol was approved by the Institutional Review Board of the Armed Force Medical Command (AFMC-18-IRB-047).

Individuals aged 20-80 years underwent a general health examination, including measurement of baseline serum GGT levels, between 2003 and 2015. Asthma was defined using the criteria of the International Classification of Disease, 10th revision (ICD-10), code J45 (asthma) and/or code J46 (status asthmaticus) at least three times, and the use of asthma-related medications, including inhaled corticosteroids, long- and short-acting β_2-agonists, and/or LTRAs[11] in the following 8 years.

Information on age, sex, residence (rural *vs.* urban)[13-16], history of diabetes mellitus, stroke, hypertension, atrial fibrillation, Charlson comorbidity index, smoking, alcohol consumption, and physical activity[17] was collected through health interviews. Trained medical staff, following a standardized procedure, conducted the anthropometric measurements. Weight and height were obtained with participants wearing light indoor clothing and no shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated using the following formula: weight (kg)/[height (m)]^2. Systolic and diastolic blood pressures (BPs) were measured twice in a seated position after a 5 min rest using a standard mercury sphygmomanometer. The average of the two measurements was used for the analysis. Physical activity was assessed with a seven-day recall method using the Korean version of the International Physical Activity Questionnaire short form[17]. According to the questionnaire, individuals who engaged in vigorous intensity physical activity at least three times per week were categorized into the regular exercise group. After a 12-hour overnight fasting, blood samples were drawn from an antecubital vein and immediately dispatched to a central testing institute where the plasma and serum were separated by centrifugation. The fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were analyzed. The serum GGT levels were measured using an enzymatic method.

Statistical Analysis

Data were analyzed using Cox proportional hazards regression and presented as hazard ratios (HRs) with 95% confidence intervals (CIs) using SPSS (version 25.0; IBM Corp., Armonk, NY, USA) and R software (version 3.1.1; R Foundation, Vienna, Austria)[18]. Outcomes were adjusted for confounding factors [Model 1: age (20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years), sex, and frequency of alcohol consumption (<1, 1-2, 2-3, 3-4, and ≥ 5 drinks per week) and Model 2: Model 1 + region of residence (rural *vs.* urban), BMI (< 25, 25-30, and ≥ 30 kg/m^2), systolic BPs (continuous), fasting blood glucose (continuous), hemoglobin (continuous), serum total cholesterol (continuous), ALT (continuous), AST (continuous), history of diabetes mellitus, stroke, hypertension, and atrial fibrillation, Charlson comorbidity index, household income (low, middle, and high), smoking (never been a smoker, ex-smoker, and current smoker), and physical activity (zero, one to two, three to four, five to six, and seven sessions per week)][19,20]. Statistical significance was set at $p < 0.05$.

Results

Characteristics of the Study Subjects

A total of 564,213 adults, aged 20-80 years, were enrolled in the NHIS-NSC, of which 516,956 (91.6%) met the study criteria. Subjects were excluded if the questionnaire was incomplete (n = 29,781), their blood test results were missing (n = 1,420), there was a previous diagnosis of asthma based on a general health examination (i.e., previous assignment of the J45 or J46 ICD-10 codes), and/or if there was a history of previous use of asthma-related medications (n = 38,439) (Figure 1). The 516,956 enrolled participants were followed up for a mean of 8.0 years (standard deviation: 4.0).

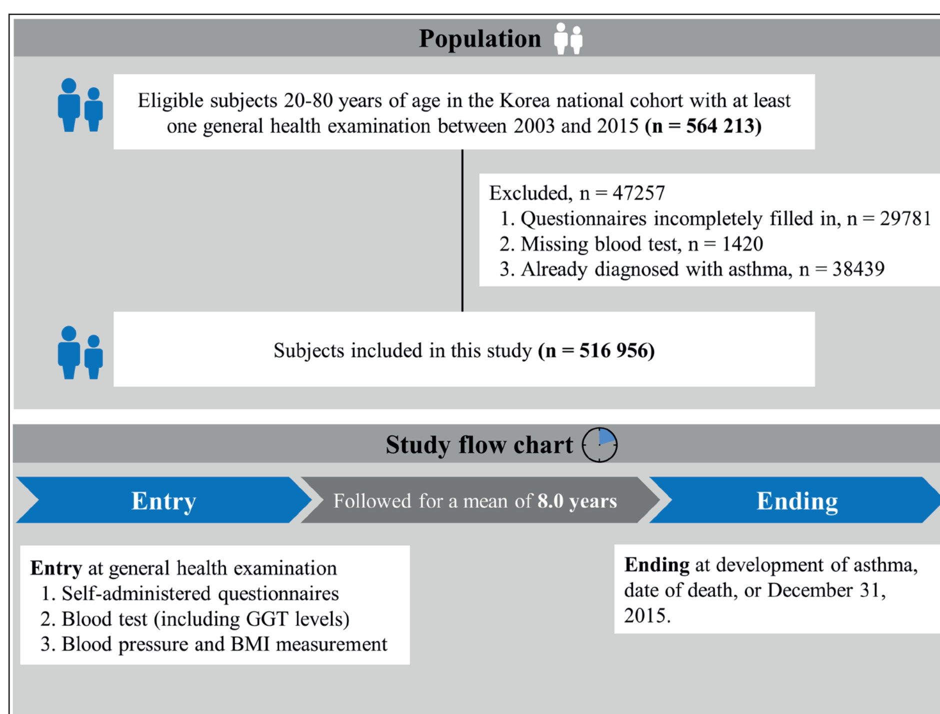

Figure 1. Disposition of study subjects from the Korean National Cohort. Abbreviations: BMI, body mass index; GGT, gamma-glutamyl transferase.

Comparison of Asthma Prevalence with Regard to Serum GGT Levels During the Follow-Up Period

During the follow-up period, 7,439 incident asthma events occurred. The subjects with incident asthma were categorized by sex according to quartiles of blood GGT levels (males: ≤ 20, 21-30, 31-51, and ≥ 52 IU/L; females: ≤ 12, 13-16, 17-22, and ≥ 23 IU/L). Among all participants, 142,319 (27.5%) were in quartile one (1Q), 128,373 (24.8%) in 2Q, 118,685 (23.0%) in 3Q, and 127,579 (24.7%) in 4Q (Table I). Analysis of all subjects indicated that the aHR for incident asthma was significantly greater for subjects in the highest GGT quartile (4Q) than for those in the lowest GGT quartile (1Q) (aHR = 1.47; 95% CI = 1.36 to 1.59). Furthermore, there was a significant linear trend across quartiles ($p < 0.001$) (Table II).

HRs for Incident Asthma Using Optimal Cut-Off Values for GGT During the Follow-Up Period

We estimated the optimal cut-off values [using the minimum *p*-value approach, according to GGT levels with Cox regression (Model 2)] as 35 IU/L for the total population, specifically, 35 IU/L for males and 36 IU/L for females. We then used these cut-off points to categorize the participants into two groups. The results indicated that the aHR for incident asthma was significantly greater for subjects with higher serum GGT levels in the total population (1.32; 95% CI = 1.25 to 1.40), particularly in males (1.30; 95% CI = 1.22 to 1.40) and females (1.41; 95% CI = 1.25 to 1.58) (Table II).

Discussion

The present study aimed at determining whether apparently healthy adults aged 20-80 years with a high serum GGT level at a routine health checkup are more likely to develop asthma than those with a low serum GGT level within the next 8 years (mean: 8.0, standard deviation: 4.0), using a large population-based cohort. We found that apparently healthy adults with higher serum GGT levels are at an increased risk of developing near future asthma compared with those with lower serum GGT levels. To the best of our knowledge, this is the first large population-based cohort study to determine that apparently healthy adults with high serum GGT concentrations have an in-

Table I. Demographic and clinical characteristics of subjects from the Korean national cohort (n = 516,956) according to serum GGT quartile.

		Quartiles of GGT (IU/L)*			
Characteristic	**Entire cohort**	**Q1**	**Q2**	**Q3**	**Q4**
Total (%)	516,956 (100)	142,319 (27.5)	128,373 (24.8)	118,685 (23.0)	127,579 (24.7)
Age, years (SD)	49.82 (14.00)	46.58 (13.96)	48.61 (14.64)	51.08 (14.14)	52.44 (12.49)
Sex, male (%)	263,868 (51.0)	68,788 (48.3)	64,043 (49.9)	64,707 (54.5)	66,330 (52.0)
Region of residence, n (%)					
Rural	246,527 (47.7)	67,286 (47.3)	61,841 (48.2)	56,851 (47.9)	60,549 (47.5)
Urban	270,429 (52.3)	75,033 (52.7)	66,532 (51.8)	61,834 (52.1)	67,030 (52.5)
Body mass index, kg/m^2					
< 25	362,712 (70.2)	121,006 (85.0)	97,422 (75.9)	76,383 (64.4)	67,901 (53.2)
25-30	135,695 (26.2)	20,046 (14.1)	28,316 (22.1)	37,468 (31.6)	49,865 (39.1)
≥ 30	18,549 (3.6)	1,267 (0.9)	2,635 (2.1)	4,834 (4.1)	9,813 (7.7)
Systolic blood pressure, mmHg, mean (SD)	121,91 (16.02)	117,65 (14.43)	120,15 (15.23)	123,29 (15.91)	127,14 (16.91)
Fasting blood glucose, mg/dL, mean (SD)	95.26 (27.02)	90.38 (20.12)	92.59 (23.23)	96.13 (27.48)	102,58 (34.26)
Hemoglobin, g/dL, mean (SD)	13.96 (1.62)	13.69 (1.65)	13.89 (1.60)	14.11 (1.59)	14.19 (1.61)
Serum total cholesterol, mg/dL, mean (SD)	191,81 (42.37)	196,37 (38.87)	188,52 (39.69)	196,37 (38.87)	205,18 (48.83)
ALT, IU/L, mean (SD)	24.89 (26.46)	16.31 (8.41)	19.93 (12.13)	25.41 (16.61)	38.97 (45.25)
AST, IU/L, mean (SD)	25.04 (21.07)	20.48 (14.17)	22.01 (9.95)	24.57 (13.03)	33.62 (34.80)
History of diabetes mellitus, n (%)	16,536 (3.2)	4,531 (3.2)	4,062 (3.2)	3,852 (3.2)	4,091 (3.2)
History of stroke, n (%)	2,210 (0.4)	573 (0.4)	516 (0.4)	545 (0.5)	576 (0.5)
History of hypertension, n (%)	37,313 (7.2)	10,058 (7.1)	9,339 (7.3)	8,678 (7.3)	9,238 (7.2)
History of atrial fibrillation, n (%)	1,238 (0.2)	307 (0.2)	312 (0.2)	318 (0.3)	301 (0.2)
Charlson comorbidity index, n (%)					
0	410,351 (79.4)	112,960 (79.4)	101,711 (79.2)	94,187 (79.4)	101,493 (79.6)
1	96,000 (18.6)	26,466 (18.6)	24,062 (18.7)	22,023 (18.6)	23,449 (18.4)
≥ 2	10,605 (2.0)	2,893 (2.0)	2,600 (2.0)	2,475 (2.1)	2,637 (2.1)
Household income					
Low (0-39 percentile)	117,042 (22.6)	32,703 (23.0)	28,643 (22.3)	26,029 (21.9)	29,667 (23.3)
Middle (40-79 percentile)	214,920 (41.6)	59,171 (41.6)	52,776 (41.1)	49,127 (41.4)	53,846 (42.2)
High (80-100 percentile)	184,994 (35.8)	50,445 (35.4)	46,954 (36.6)	43,529 (36.7)	44,066 (34.5)
Smoking					
Never been a smoker	325,208 (62.9)	99,156 (69.7)	83,723 (65.2)	70,592 (59.5)	71,737 (56.2)
Ex-smoker	45,618 (8.8)	10,958 (7.7)	11,100 (8.6)	11,597 (9.8)	11,963 (9.4)
Current smoker	146,130 (28.3)	32,205 (22.6)	33,550 (26.1)	36,496 (25.0)	43,879 (34.4)
Alcohol consumption, drinks per week					
< 1	320,970 (62.1)	102,110 (71.7)	84,258 (65.6)	70,211 (59.2)	64,391 (50.5)
1-2	137,432 (26.6)	33,946 (23.9)	34,488 (26.9)	33,912 (28.6)	35,086 (27.5)
3-4	41,656 (8.1)	4,899 (3.4)	7,371 (5.7)	10,709 (9.0)	18,677 (14.6)
≥ 5	16,898 (3.3)	1,364 (1.0)	2,256 (1.8)	3,853 (3.2)	9,425 (7.4)
Physical activity, sessions per week					
0	237,393 (45.9)	64,320 (45.2)	58,290 (45.4)	54,755 (46.1)	60,028 (47.1)
1-2	129,146 (25.0)	35,262 (24.8)	32,080 (25.0)	30,022 (25.3)	31,782 (24.9)
3-4	66,178 (12.8)	18,420 (12.9)	16,617 (12.9)	15,185 (12.8)	15,956 (12.5)
5-6	11,492 (8.1)	11,492 (8.1)	10,206 (8.0)	8,656 (7.3)	8,775 (6.9)
7	45,110 (8.7)	12,825 (9.0)	11,180 (8.7)	10,067 (8.5)	11,038 (8.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.
*GGT is expressed for sex-specific quartiles (males: ≤ 20, 21-30, 31-51, and ≥ 52 IU/L; females: ≤ 12, 13-16, 17-22, and ≥ 23 IU/L).

creased risk of near future asthma development.

Asthma is one of the most prevalent chronic lung diseases among adults[1]. Despite vigorous investigations to date, we have limited knowledge regarding the pathogenesis and pathophysiology of this complex disease[2]. Therefore, differentiating subjects at risk of future asthma is of great clinical concern. Although asthma is a complex disease[2], mounting evidence has shown the critical role of reactive oxygen species in the development of asthma[21]. For example, when airway cells and tissues come in contact with oxidative stress

Table II. Hazard ratios for incident asthma among subjects in different sex-specific serum GGT quartiles* (n = 516,956).

GGT Quartile	N (%)	Asthma events	Person-years	Asthma incidence rate§	Hazard ratio (95% CI)					
					Crude	*p* for trend	Model 1‡	*p* for trend	Model 2†	*p* for trend
Q1	142319 (27.5)	1245	874200	2.84	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2	128373 (24.8)	1874	1115840	3.36	**1.19 [1.11 to 1.28]**	**<0.001**	**1.14 [1.07 to 1.23]**	**<0.001**	**1.16 [1.08 to 1.25]**	**<0.001**
Q3	11 8685 (23.0)	1886	1090671	3.46	**1.25 [1.16 to 1.34]**		**1.14 [1.06 to 1.24]**		**1.16 [1.07 to 1.26]**	
Q4	127579 (24.7)	2434	1056336	4.61	**1.69 [1.58 to 1.81]**		**1.47 [1.36 to 1.59]**		**1.51 [1.39 to 1.65]**	
Optimal cut-off points for GGT**										
Whole population										
Low (<35 IU/L)	384482 (74.4)	5005	3080712	3.25	1.00 (reference)		1.00 (reference)		1.00 (reference)	
High (≥35 IU/L)	132474 (25.6)	2434	1056336	4.61	**1.46 [1.39 to 1.53]**	**<0.001**	**1.31 [1.24 to 1.38]**	**<0.001**	**1.32 [1.25 to 1.40]**	**<0.001**
Men										
Low (<35 IU/L)	154370 (58.5)	2221	1245948	3.57	1.00 (reference)		1.00 (reference)		1.00 (reference)	
High (≥35 IU/L)	109498 (41.5)	2048	874335	4.68	**1.33 [1.26 to 1.42]**	**<0.001**	**1.29 [1.21 to 1.38]**	**<0.001**	**1.30 [1.22 to 1.40]**	**<0.001**
Women										
Low (<36 IU/L)	231341 (91.4)	2801	1844430	3.04	1.00 (reference)		1.00 (reference)		1.00 (reference)	
High (≥36 IU/L)	21747 (8.6)	269	172334	3.12	**1.40 [1.26 to 1.56]**	**<0.001**	**1.38 [1.24 to 1.55]**	**<0.001**	**1.41 [1.25 to 1.58]**	**<0.001**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.
* GGT is expressed for sex-specific quartiles (males: ≤20, 21-30, 31-51, and ≥52 IU/L; females: ≤12, 13-16, 17-22, and ≥23 IU/L).
§ Asthma incidence rate is expressed as per 10000 persons per 5 years.
‡ Risk factors were adjusted for age (20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years), sex, and frequency of alcohol consumption (<1, 1-2, 2-3, 3-4, and ≥5 drinks per week).
† Risk factors were adjusted for age, sex, frequency of alcohol consumption, region of residence (rural *vs.* urban), body mass index (<25, 25–30, and ≥30 kg/m²), systolic blood pressure (continuous), fasting blood glucose (continuous), hemoglobin (continuous), serum total cholesterol (continuous), ALT (continuous), AST (continuous), history of diabetes mellitus, stroke, hypertension, and atrial fibrillation, Charlson comorbidity index, household income (low, middle, and high), smoking (never smoker, ex-smoker, and current smoker), and physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week).
** The optimal cut-off values (estimated using the minimum *p*-value approach according to GGT levels with Cox regression [model 2]) were estimated as 35, 35, and 36 IU/L in the whole population, males, and females, respectively.
Number in bold indicates a significant difference ($p < 0.05$).

induced by environmental pollutants, infections, allergens, inflammatory reactions, or decreased levels of antioxidants and reactive oxygen species levels escalate and lead to various destructive effects within the airways via numerous pathophysiological conditions[22].

To date, no epidemiological studies have shown a possible association between GGT levels and asthma risk. Our observations from the present study partly correspond with the current knowledge that a significantly positive association exists between serum GGT and chronic low-grade inflammatory diseases, including cardiovascular diseases[8,9], metabolic syndromes[8,9], atherosclerosis[23], various liver diseases[24], several cancers[25], COPD[26], and all-cause mortality[27]. However, no epidemiological research has delineated the associations between serum GGT levels and asthma development, a chronic low-grade respiratory tract disease[28].

Serum GGT levels are frequently measured as part of the blood test panel for routine health check-ups. GGT is a microsomal membrane-binding protein that is present both in serum and on the external surface of most human cells, including lung epithelial cells[10]. It is a protective enzyme that hydrolyzes the gamma-glutamyl bond of the antioxidant glutathione (L-γ-glutamyl-L-cysteinyl-glycine) and glutathione S-conjugate and plays an important role in maintaining glutathione homeostasis (i.e., regulating oxidative stress)[29]. An *in vitro* study showed that two members of the GGT gene family (GGT1 and GGT5) convert LTC_4 to LTD_4 in A549 epithelial lung cancer cells and primary bronchial epithelial cells[10]. LTs are a family of inflammatory mediators that are important in the pathogenesis of asthma and airway bronchoconstriction. They are derived from various cells, including epithelial cells, endothelial cells, and mast cells during acute asthma attacks and from eosinophils during chronic bronchoconstriction[30].

There are underlying mechanisms that may explain the significant positive relationship between high serum GGT levels and the risk of asthma development (Figure 2). Allergens, viral infections, platelet-activating factors, aspirin, exercise, and sulfur dioxide may increase reactive oxygen species, which up-regulate serum GGT levels and convert leukotriene C_4 (LTC_4, a glutathione S-conjugate) to LTD_4, followed by LTE_4[30,31]. Of these, LTD_4 is the most potent molecule for the development of bronchoconstriction and inflammation[31]. Since serum GGT is considered a protective enzyme contributing to glutathione homeostasis, a high serum GGT level may reflect increased oxidative stress. Corresponding well with this plausible mechanism, the present findings indicate that apparently healthy subjects with a high serum GGT level measured at a general health check-up are more likely to develop asthma, which is linked with elevated oxidative stress and low-grade chronic inflammation. Therefore, the positive association between high serum GGT levels and the risk of future asthma development may suggest that high serum GGT levels are associated with the risk of future asthma development via oxidative stress. GGT itself has pro-oxidant effects, especially in the presence of transitional metals such as iron[32].

Strengths and Limitations

The main strengths of our study include the nationwide cohort design, which minimizes sampling bias, the large sample size (n = 516,956), long-term follow-up (mean: 8.0 years), and adjustments for various potential confounding factors, including BMI, age, and sex. Nevertheless, the present study had some limitations. First, the asthma diagnosis was established based on ICD-10 codes, which may be inaccurate in real life. However, many studies have validated other electronic health record data using similar methods. Second, we were unable to analyze the different subtypes or severities of asthma because the NHIS-NSC does not provide these data. Third, we could not account for some potential confounding factors (i.e., vitamin D level, sleep quality, or psychological status) because our claims-based data were not systematically obtained. Fourth, due to the nature of the claimed data, we only examined adults aged 20-80 years. Additionally, since the current study was conducted only in the Korean population, we could not differentiate between possible ethnic differences. The risk of asthma development in subjects with high serum GGT levels might be associated with their genetic background; thus, further research is warranted in other ethnic groups. Fifth, we were unable to measure intracellular GGT levels in bronchial tissues because this requires an invasive procedure. However, in agreement with the present findings, previous studies[10] have shown that exosomes from lung epithelial cells contain GGT1, which functions in the transcellular conversion of LTC_4 to LTD_4. In addition, a part of the GGT in the measured plasma is bound to exosomes, which contributes to the cascade of inflammatory reac-

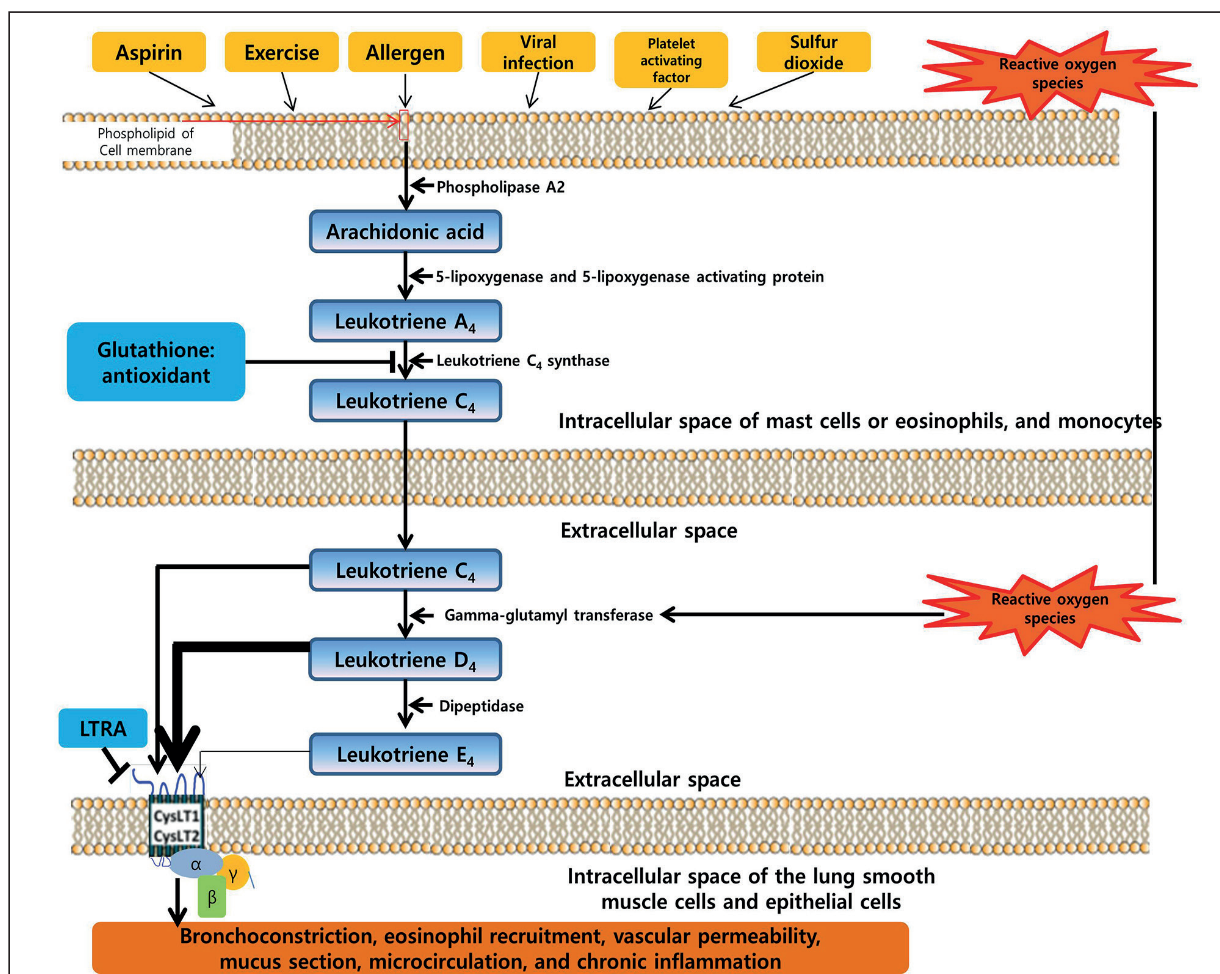

Figure 2. Schematic diagram showing how GGT converts leukotriene C_4 to leukotriene D_4, which then bind to cysteinyl leukotriene 1 and 2 receptors on the surface of the epithelial or smooth muscle cells of the lungs, which then causes bronchoconstriction, eosinophil recruitment, vascular permeability, mucus secretion, and chronic inflammation, which are all biochemical characteristics of asthma.
Abbreviations: GGT - gamma-glutamyl transferase; LTRA - leukotriene receptor antagonist.

tions and is associated with asthma risk and its severity[33]. Sixth, this was a retrospective cohort study, rather than a prospective study, and relied exclusively on medical insurance claim-based data to identify participant outcomes. Finally, although we found an association between high serum GGT levels and asthma risk in the near future, the results may not be of diagnostic utility because asthma is a complex disease with many etiological factors[2].

Conclusions

Apparently healthy adults with high serum GGT levels measured during a routine health check-up are more likely to develop incident asthma in the subsequent 8 years. We speculate that serum GGT levels may be used as a predictor of asthma during routine health check-ups. The present findings advance our understanding of the pathogenesis of asthma and suggest that clinicians should discern the risk of incident asthma in apparently healthy adults with increased serum GGT levels. Future prospective studies are warranted to corroborate the present findings and to determine whether they have any diagnostic utility for asthma in a real clinical setting.

Financial Support

None.

Ethics Approval and Consent to Participate

The study protocol was approved by the institutional review board of Armed Force Medical Command (AFMC-18-IRB-047). Consent to participate is not applicable due to its retrospective nationwide cohort design.

Consent for Publication

Not applicable due to its retrospective nationwide cohort design.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Dong Keon Yon conceived of the study, carried out, analyzed the data, and drafted and revised the manuscript; David Myung Soo Shin drafted and revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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