

# Interleukin-4 (C590T) Gene Polymorphism in Association with Asthma Severity

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**Background:** A significant link between T allele of the *IL-4* (C590T) gene and developing asthma in some populations was reported. However, no study discussed the link between *IL-4* (C590T) gene polymorphism and asthma severity groups (mild and severe). This study investigated the link between *IL-4* gene variation and asthma severity.

**Methods:** The study included 215 asthmatic patients, of which 102 had mild asthma, and 126 participants were healthy controls. A previously published polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to identify various *IL-4* (C590T) gene polymorphism genotypes.

**Results:** The T allele frequency was higher in mild asthma ( $p=0.002$ ) but not in severe asthma ( $p=0.12$ ) compared to controls. In mild asthma, the CT genotype and (CT+TT versus CC) increased the likelihood of asthma threefold ( $p<0.001$ ,  $0.001$ ). However, no significant association with severe asthma was found in either genetic model. Stratification analysis showed that the C allele and CC genotype increased the risk of severe asthma ( $p=0.01$ ). The recessive genetic model indicated a decrease in the risk of severe asthma (OR=0.5,  $p=0.01$ ) in the non-adjusted regression analysis. Adjusting for age, sex, and other risk factors revealed that the *IL-4* gene polymorphism did not influence the risk of severe asthma (OR=0.92,  $p=0.80$ ); however, being an elderly female with a history of childhood-onset disease and associated nasal polyp (NP) increased the likelihood of severe asthma, OR=1.08, 2.01, 2.36, 8.42;  $p<0.001$ , 0.05, 0.05,  $<0.001$ , respectively.

**Conclusion:** The T allele and CT genotype in the co-dominant genetic model and the (CT+TT) genotype in the recessive model were found to have a higher likelihood of developing mild asthma but not severe asthma; severe asthma was found to be higher in elderly females with a history of childhood-onset disease and associated nasal polyps.

**Keywords:** IL-4 (C590T) gene polymorphism, mild and severe asthma, nasal polyp

## Introduction

Asthma is a common chronic inflammatory disease affecting more than 330 million people worldwide and could develop at any age;<sup>1</sup> however, the first asthma symptoms mostly appear in the childhood.<sup>2</sup> Episodes of bronchial hyper-responsiveness and reversible airway obstruction are the characteristic hallmarks of asthma.<sup>3</sup> The main causes of asthma are not known; however, several factors trigger the pathogenesis cascade of asthma, which include environmental triggers such as pollutants, tobacco smoking, allergens, viral and bacterial infection, and genetic variations.<sup>4,5</sup> The interaction between all these underlying risk factors increases the possibility of asthma presentation and even could determine the disease severity and control.<sup>5</sup> The pathogenesis of asthma is complex, and several immune cells and biomarkers are involved including T-lymphocyte, mast cells and eosinophils, and cytokines such as IL-4, IL-5, and IL-13 plus the immunoglobulin-E (IgE).<sup>6,7</sup>

Interleukin-4 (IL-4) has been shown to play a crucial role in asthma pathogenesis; it influences the isotype switch to the  $\epsilon$  immunoglobulin class, which leads to the production and secretion of immunoglobulin E (IgE) by B lymphocytes.<sup>8</sup> High levels of IgE are a hallmark of allergic diseases, and IL-4 is considered a vital mediator in this process. Additionally, this cytokine is involved in developing airway obstruction through the induction of mucin gene expression, leading to exaggerated mucus production, and contributing to the characteristic airway hyperresponsiveness seen in asthma.<sup>9</sup> Furthermore, IL-4 also increases the expression of eotaxin and other inflammatory cytokines from fibroblasts, which contribute to airway inflammation and lung remodeling in chronic asthma.<sup>9,10</sup>

The *IL-4* gene is located on chromosome 5q31-33 and codes for a protein that binds to the IL-4 receptor.<sup>11</sup> It is highly polymorphic, and divergences in its sequence have been associated with susceptibility to several immune-mediated diseases, including asthma, allergies, and autoimmune disorders.<sup>11-13</sup> Five putative variants have been reported in the promoter region of *IL-4* gene, of which four are rare.<sup>14</sup> The variant – C590T in the *IL-4* gene's promoter region has been associated with increased IgE levels in American<sup>15</sup> and Japanese populations.<sup>16</sup> In-vitro studies suggest that this variant may affect *IL-4* activity by altering the binding affinity to nuclear transcription factors and electrophoretic mobility.<sup>15</sup> However, there is no direct evidence linking this variant to cellular IgE synthesis, and the original association has not been consistently reproduced. Two additional variants have been identified but are not associated with atopy or asthma.<sup>11</sup> The C590T polymorphism in the *IL-4* gene has been extensively studied concerning asthma, and evidence suggests that it may contribute to the development of the disease, as well as its response to treatment.<sup>17</sup>

However, to date, there is no study reporting a link between *IL-4* (C590T) gene polymorphism and severe asthma, and whether there is any difference in its association with mild and/or severe asthma along with other risk factors. This study aimed to investigate whether there is a significant difference in the association of *IL-4 gene* C590T polymorphism between mild and severe asthma.

## Methods

### Patients and Study Design

This case-control study was conducted at Al-Rashed Allergy Center, Kuwait, from October 2022 to March 2023. The study enrolled 215 patients with confirmed bronchial asthma based on clinical diagnosis and reversibility of FEV1%.<sup>18</sup> Additionally, 126 healthy controls with no history of asthma, atopy, or other allergic conditions were included in the study. All participants were Kuwaiti in nationality and recruited during their outpatient clinic visits. Cases with asthma were classified into subgroups according to disease severity, mild and severe asthma. Asthma patients were categorized according to Global Initiative for Asthma (GINA) management recommendation. Mild asthma patients fulfill step 1 and 2 GINA management recommendations. However, patients who fulfilled step 4 or 5 GINA management recommendations were categorized in severe asthma group.

Patients with mild asthma were generally characterized by infrequent symptoms and relatively well-preserved lung function, which minimally impact daily activities. In contrast, severe asthma involves persistent symptoms, frequent exacerbations, frequent use of corticosteroids course and significant limitations in lung function that often require intensive treatment and medical intervention.<sup>18,19</sup>

### Ethics Approval and Consent to Participate

Ethical approval has been obtained from Kuwait University and the Ministry of Health, in accordance with the Helsinki Declaration protocol (Research study number MI02/22, 2022/2010) to ensure that the research is conducted ethically and in compliance with internationally recognized standards. Informed consent has been obtained from all participants involved in the study, as well as their legal guardians, to ensure that they are fully aware of the nature and purpose of the research and have given their voluntary and informed consent to participate.

### Sample Size

The sample size was determined using Minitab 17.1.0.0 for Windows software (Minitab Inc., 2013, Pennsylvania, USA). A type I error of 0.05 and a type II error of 0.2 were considered. Based on Hijazi et al,<sup>20</sup> the proportion of the *IL4* gene -C590T polymorphism in the non-disease cohort was 0.76, and the odds ratio (OR) was 4. Therefore, the minimum

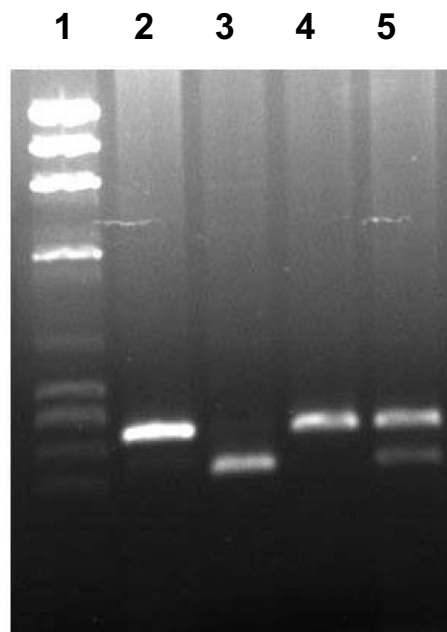
calculated sample size would be 170 for a control: case ratio of 1:1 (85 in each limb) and 183 for a control: case ratio of 2:1 (minimum case=61 and minimum control=122). Moreover, considering Hong et al,<sup>21</sup> assuming an odds ratio of 2, a disease prevalence of about 1%, a minor allele frequency of 5%, complete linkage disequilibrium (LD), and a 5% error rate in an allelic test to achieve 80% power, the minimum total sample size required would be 248 with a 1:1 case/control ratio. Additionally, to achieve a more robust representation of the subgroup of cases with varying degrees of asthma severity (mild and severe), an equal number of mild asthma cases would be needed to achieve 80% study power, assuming a case: case ratio similar to the control: case ratio.

## Sample Collection

About 10 mL of venous blood was collected from all participants under a complete aseptic condition in a plastic syringe and then divided into two tubes; the first tube was without anticoagulant, and the other was with EDTA for DNA extraction. Samples were centrifuged at 4000 g for 10 min to separate the serum plasma and buffy coat containing leukocytes and then frozen at  $-20^{\circ}\text{C}$  for DNA extraction. Genomic DNA extraction was performed from 200  $\mu\text{L}$  blood using the Biospin Whole Blood Genomic DNA Extraction Kit (GentraPuregeneQIAGEN, USA). DNA concentration and purity were analyzed using the NanoDrop™ 1000 Spectrophotometer.

## Genotyping

The primers and procedures used to determine *IL4* gene -C590T, rs2243250 promoter polymorphism, has been described earlier.<sup>20</sup> In which, the genotypes were determined in at least two independent readings to enhance accuracy, and as an additional quality control measure, DNA sequencing of the PCR products was carried out in selected samples. These measures were implemented to ensure the correctness and reliability of the identified genotypes. The C→T transition at codon 590 of the *IL4* gene promoter region abolished a restriction site for *BsmFI* in the T-allele. The polymorphism was detected by *BsmFI* restriction endonuclease digestion of the PCR-amplified product. Agarose gel electrophoresis was used to analyze the cleavage products. Following agarose gel electrophoresis, the cleavage products were detected after staining with Ethidium bromide under UV light (Figure 1). The expected product sizes were 192 and 60 bp for the CC genotype, 252 bp for the TT genotype, and products of 252, 192, and 60 bp for the heterozygous genotype (CT) genotype.



**Figure 1** Detection of *IL-4* gene (C590T) polymorphism genotypes. Lane 1, *HaeIII* cleaved  $\phi\text{X174}$  DNA *M*, size markers; lane 2, un-cleaved PCR product; lane 3, PCR products cleaved with restriction enzyme *BsmFI* from a subject with CC genotype; lanes 4, PCR products cleaved with restriction enzyme *BsmFI* from a subject with TT genotype; lanes 5, PCR products cleaved with restriction enzyme *BsmFI* from a subject with CT genotype.

## Statistical Analysis

Demographic data of patients and control groups were collected in an Excel sheet, along with the genotype of each of the study participant. Minitab for Windows (Minitab Inc, 2013, version 17.1.0.0, Pennsylvania, USA) was used for statistical analysis. The data is represented as mean and standard deviation for numerical data and number (%) for categorical data.

For the dominant model, we calculated it by considering individuals who carried at least one copy of the variant allele as “affected” or “cases”, while those without any copies of the variant allele were designated as “unaffected” or “controls”. This approach allowed us to examine the impact of the variant allele in a binary manner. For the recessive model, we designated individuals as “affected” or “cases” only if they carried two copies of the variant allele. Those with one or no copies of the variant allele were categorized as “unaffected” or “controls” in this model. Comparison between two means was performed using an independent *t*-test and between two or more frequencies through a Chi-square test. Multiple comparisons were corrected using Bonferroni correction methods; the adjusted alpha level was 0.01 for significant threshold.

Logistic regression analysis with adjusted and non-adjusted methods was applied to find the predictive ability of *IL-4* gene polymorphism and severe asthma. All tests were two-sided, and  $p < 0.05$  was considered significant for simple comparison and below 0.01 after correction for multiple comparison.

## Results

### *IL-4* (C590T) Gene Polymorphism in Mild and Severe Subgroup of Asthma

Descriptive data of asthma cases and control were presented in Table 1; both were matched in sex but were significantly younger than the asthmatic patients,  $p = 0.71$  and  $< 0.001$ , respectively.

Table 2 consisted of the three different genetic models used to investigate an association between *IL-4* gene polymorphism and the risk of mild (102 cases) and severe asthma (113); the CC genotype was protective against mild asthma; its frequency was found to be significantly higher in the control group and severe asthma subgroup,  $p < 0.001$  and 0.01, respectively. However, there was an insignificant difference between the control group and severe asthma,  $p = 0.08$ . On the other hand, the CT genotype was significantly linked to mild asthmatic patients,  $p < 0.001$ , and the likelihood of mild asthma increased threefold with this genotype. In contrast with the two polymorphisms mentioned above, the TT genotype did not show any significant association with any of the groups. Moreover, the frequency of the C allele was higher than the T alleles in control, mild, and severe asthmatic subgroups. In the control group and severe asthma subgroup, the frequency of the C allele was significantly higher than in the mild asthma subgroup: 78% versus 62% and 73% versus 62%, respectively,  $p = 0.001$  and 0.003. However, the control and severe asthma subgroups were matched with insignificant differences,  $p = 0.04$ .

In contrast, the frequency of the T allele was significantly higher in the mild asthmatic group compared with both the control group and severe asthma subgroup: 38% versus 22% and 38% versus 27%, respectively,  $p = 0.002$  and  $< 0.001$ . Therefore, the T allele can be considered the risk allele for the associated risk of mild bronchial asthma.

**Table 1** Demographic Data of the Studied Groups

Factors	Control (n=126)		Asthma (n=215)		p
	Mean	SD	Mean	SD	
Age	37.1	15.7	47.4	15.2	$< 0.001^\dagger$
Sex	N	%	N	%	0.71*
F	88	69.84	146	67.91	
M	38	30.16	69	32.09	

**Notes:** Numerical data represented as mean and standard deviation and categorical data as number and percentage,  $^\dagger$ Independent t-test, \*Chi square test,  $p < 0.05$  considered significant.

**Abbreviations:** N, number; SD, standard deviation.

**Table 2** *IL-4* (C590T) Gene Polymorphism in Mild and Severe Asthma

Factors	Control (n=126)		Mild Asthma (n=102)		Severe Asthma (n=113)		P1			P2			P3		
	N	%	N	%	N	%	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
<i>IL-4</i> Genotype															
CC	81	64.29	37	36.27	60	53.1	3.16	1.836 to 5.447	< 0.001*	1.59	0.946 to 2.672	0.08	1.99	1.151 to 3.437	0.01*
CT	35	27.78	52	50.98	44	38.94	2.7	1.560 to 4.687	< 0.001*	1.66	0.963 to 2.854	0.07	1.63	0.949 to 2.804	0.11
TT	10	7.94	13	12.75	9	7.96	1.69	0.710 to 4.042	0.23	1	0.393 to 2.566	0.99	0.59	0.242 to 1.451	0.35
C allele	197/252	78	126/204	62	164/226	73	3.56	1.94 to 6.51	0.001*	2.48	1.08 to 4.10	0.04	1.76	0.460 to 1.372	0.003*
T allele	55/252	22	78/204	38	62/226	27	2.35	1.30 to 3.54	0.002*	1.49	0.95 to 2.32	0.12	3.41	1.75, 6.69	<0.001*
TT	10	7.94	13	12.75	9	7.96	Reference			Reference			Reference		
CC+CT	116	92.06	89	87.25	104	92.04	1.69	0.710 to 4.042	0.23	1.004	0.393 to 2.566	0.99	0.59	0.242 to 1.451	0.35
CT+TT	45	35.71	65	63.73	53	46.9	3.16	1.836 to 5.447	0.001*	1.59	0.946 to 2.672	0.07	1.99	1.151 to 3.437	0.01*
CC	81	64.29	37	36.27	60	53.1	Reference			Reference			Reference		

**Notes:** The data presented as number and percentage, \*Chi square test, with multiple comparison test using Bonferroni methods for correction. P1: Mild asthma vs control, P2: Severe asthma vs control, P3, Mild asthma vs severe asthma, adjusted  $p \leq 0.01$  considered significant.

**Abbreviations:** N, number; OR, odd ratio; CI, Confidence interval.

No significant difference was detected between the three groups in the dominant model,  $p=0.23$ ,  $0.99$ , and  $0.35$ , respectively. However, in the recessive model, the risk of mild asthma increased threefold compared to the control group and twofold to the severe asthma subgroup,  $p=0.001$  and  $0.01$ , respectively.

## Risk Factors and Predictors of Severe Bronchial Asthma

The data on other risk factors and predictors of severe bronchial asthma are presented in Table 3. It showed that patients with severe bronchial asthma were significantly older than mild asthma patients,  $p<0.001$ . Additionally, they had an adult-onset disease and associated nasal polyp (NP),  $p=0.01$  and  $<0.001$ , respectively. In contrast, the frequency of oral corticosteroid (OCS) use was significantly lower,  $p=0.04$ , amongst the severe asthma patients.

The predictors of severe asthma were summarized in Table 4, in which the recessive genetic model of the *IL-4* gene decreased the risk of severe asthma in the non-adjusted model,  $OR=0.5$ ,  $p=0.01$ . However, adjustment of *IL-4* gene polymorphism with age, sex, and associated risk factors showed that the risk of severe bronchial asthma was unaffected

**Table 3** Risk Factors Associated with Severe Asthma

Factors	Mild Asthma (n=102)		Severe Asthma (n=113)		p
	Mean	SD	Mean	SD	
Age	41.2	16.7	53.1	11.7	$<0.001^{\dagger}$
Sex	N	%	N	%	0.71*
Female	68	66.67	78	69.03	
Male	34	33.33	35	30.97	
Risk factors	N	%	N	%	0.01* 0.17* 0.79* 0.07* $<0.001^*$ 0.85* 0.04*
Adult-onset	62	60.78	86	76.11	
Smoking	14	13.73	9	7.96	
DM	8	7.84	10	8.85	
AR	48	47.06	67	59.29	
NP	8	7.84	33	29.2	
Eczema	6	5.88	6	5.31	
OCS	9	8.82	3	2.65	

**Notes:** Numerical data represented as mean and standard deviation and categorical data as number and percentage,  $^{\dagger}$ Independent t-test, \*Chi square test,  $p<0.05$  considered significant.

**Abbreviations:** N, number; SD, standard deviation; DM, diabetes mellitus; AR, allergic rhinitis; NP, nasal polyp; OCS, oral corticosteroid.

**Table 4** Predictors of Severe Asthma

Factors	OR	95% CI	$p^{\dagger}$
Un-adjusted model			
CT+TT	0.50	(0.2909, 0.8691)	0.01
Adjusted model			
Age	1.08	(1.0458, 1.1071)	$<0.001$
Female-Sex	2.01	(0.4609, 1.8166)	0.052
Child-onset	2.36	(0.2226, 1.0189)	0.052
NP	8.42	(2.7888, 25.4086)	$<0.001$
OCS	0.09	(0.0123, 0.5953)	0.006
CT+TT	0.92	(0.4609, 1.8166)	0.80

**Notes:** The test of fitness: Hosmer-Lemeshow test,  $X^2=7.77$ ,  $p=0.45$ ,  $^{\dagger}$ The test of significant: Logistic regression models,  $p<0.05$  considered significant.

**Abbreviations:** OR, odd ratio; CI, confidence interval; NP, nasal polyp; OCS, oral corticosteroid.

by the *IL-4* gene polymorphism, OR=0.92,  $p=0.80$ . The risk factors associated with developing severe asthma were being an elderly female with a history of childhood-onset disease and associate NP, OR=1.08, 2.01, 2.36, and 8.42;  $p<0.001$ , 0.05, 0.05, and  $<0.001$ , respectively. On the other hand, OCS use decreased the risk of severe asthma, OR=0.09,  $p=0.006$ .

## Discussion

The current study was the first of her kind; it highlighted the difference between mild and severe asthma in correlation with *IL-4* (C590T) gene polymorphism. The data showed that mild and severe asthma was different in associated risk factors and genetic risk. The frequency of C alleles in severe asthma was significantly higher than in mild asthma, and the risk of severe asthma increased twice with the CC genotype; it was protective against mild asthma but not severe asthma. Additionally, despite the overall frequency of C alleles being higher than T alleles in both asthmatic subgroups and control, the T alleles were the associated risk for mild asthma. A supporting study by Zhang et al<sup>22</sup> stated that the *IL-4-590C>T* polymorphism might be linked to bronchial asthma in Uyghur children, and the T allele was more frequent in asthmatic Uyghur children; the study established that the genetic variation leads to increase IgE level and airway obstruction (FEV1%). Childhood asthma differs from adult asthma in its pathogenesis, as it is influenced by underdeveloped immune responses and the continued growth of lung function. Typically, childhood asthma is associated with allergic reactions to various allergens, such as pollens. This type of asthma is usually mild to moderate in severity and can be controlled effectively with proper medication adherence.<sup>23</sup>

An older Kuwaiti study<sup>20</sup> denied any association between adult asthma and *IL-4* (C590T) gene polymorphism, even with a different phenotypic classification of asthma (hay fever, eczema, and positive skin prick test group), in addition to finding similar frequencies of C alleles and T alleles in all studied groups (asthmatic, non-asthmatic and control). This discrepancy between the present data and the older study could be related to the difference in patient selection; Hijazi et al<sup>20</sup> focused on patients with uncontrolled asthma and all cases collected from the hospital during an exacerbation; however, the present study was tented to be community-based style; the collection of cases and control happened during routine outpatient's clinic visits. Another study found that asthma susceptibility is linked to the C allele and CC genotype of the *IL-4-590C>T* gene polymorphism and considered that a possible cause of asthma.<sup>23</sup> Additionally, multiple studies suggested that a higher frequency of T alleles in control may be protective against developing asthma.<sup>24-26</sup>

To better understand the connection between the *IL-4-590C>T* gene polymorphism and asthma, a recent meta-analysis conducted a subgroup analysis. However, it was found that there was no significant association. This could be due to various factors, such as differences in sample size, ethnicity, source of control sample, and genotyping methods.<sup>27</sup> While genetic and environmental factors both play a role in the development of asthma, there is still much to learn about genetic variation and severe asthma.<sup>28</sup> Previous research has suggested that asthma is caused by multiple genes rather than just one gene having a significant impact.<sup>27</sup>

A meta-analysis found that specific variations (SNPs) in the *IL4* gene are linked to asthma susceptibility in Caucasian-European populations, especially SNPs like rs2070874 (C-33T) and rs2243250 (C-589T), which are located in the gene's promoter region. Notably, rs2070874 is one of the most frequently reported SNPs associated with asthma risk, especially in Caucasian and Asian populations, and it's particularly tied to the severity of the condition.<sup>29</sup>

This study emphasized the importance of host-related risks in the development of severe asthma, in addition to the genetic variability of the *IL-4-590C>T* gene. The CT+TT genotype was found to be protective against severe asthma in a recessive genetic model, but it increased the risk of mild asthma by twice as much. However, other risk factors were found to play a more significant role in predicting severe asthma, rather than the *IL-4-590C>T* gene polymorphism. Elderly females were found to be twice as likely to develop severe asthma based on an adjusted regression analysis model. A Korean national database study showed that asthma was more severe in elderly females and associated with higher morbidity and mortality.<sup>30</sup> The underlying cause is still unclear, but some studies suggest that sex hormones like estrogen and progesterone may contribute to the clinical features of asthma.<sup>31-33</sup> Further investigation is needed to clarify the underlying mechanisms of severe asthma in elderly females, but the variation of *IL-4-590C>T* gene polymorphism could be considered a contributing factor.

The current data showed that the frequency of NP was higher in severe asthmatic patients than in mild asthma, and the coexistence of NP increased the risk of severe asthma eightfold more. In concordance with meta-analysis, NP was

independently associated with severe asthma.<sup>34</sup> Severe asthma and nasal polyps frequently coexist in some individuals, often called “asthma with nasal polyps”.<sup>35</sup> Chronic inflammation is the characteristic hallmark of asthma and NP; it is characterized by overactive immune responses and an imbalance in specific cytokines, particularly IL-4, IL-5, and IL-13, which promote inflammation, tissue remodeling, and eosinophilic response.<sup>35,36</sup>

Mohammadi et al found a significant association between TT and CT genotypes at the *IL-4* C590T promoter gene and NP.<sup>37</sup> However, a contrary study from Korea showed that T alleles were protective against non-asthmatic and asthmatic nasal polyps.<sup>38</sup> On the other hand, the Iranian study reported a lack of association between the *IL-4* C590T promoter gene and NP.<sup>39</sup>

A longitudinal study that followed individuals with severe asthma for 10 years found that 83% of those who experienced severe asthma symptoms between the ages of 14 and 55 tended to respond well to their medication. However, the risk of persistent severe asthma was linked to other factors like low socioeconomic status, a high number of other health conditions, and non-adherence to medication during the first year of diagnosis.<sup>40</sup> Surprisingly, sex and typical risk factors for childhood asthma did not play a role in the continued presence of severe asthma in this group.<sup>40</sup>

Our data showed that the frequency of adult-onset emergence asthma was significantly severe, even though, for those who started their asthma in childhood and persisted till adulthood, the risk of severe asthma increased twice. Asthma symptoms can last throughout childhood, adolescence, and adulthood for some people. However, many children with asthma show improvement and fewer symptoms during their school years.<sup>41</sup> Boys with a milder and less allergic form of the disease tend to have a better prognosis.<sup>42</sup> Nonetheless, it's not clear if symptom remission means that the underlying problem has disappeared, as airway hyper-responsiveness and inflammation can persist even without visible symptoms.<sup>41</sup> Some women with impaired lung function can develop asthma symptoms in adulthood,<sup>43</sup> but it's uncertain whether this represents a new onset or a relapse of childhood asthma. Both relapse and adult-onset asthma symptoms have been linked to allergic disease, sensitization, and airway hyper-responsiveness.<sup>44</sup> Smoking has been associated with the persistence, relapse, and new onset of asthma symptoms in adulthood,<sup>45,46</sup> although the underlying mechanisms are not fully understood.

Even though the study had an appropriate sample size, it had some limitations. The most important one is that it only discussed one genetic variation, while asthma pathogenesis involves multiple and complex genetic factors. Therefore, one gene-variability could not fully explain the association. Additionally, the researchers were unable to measure the level of IL-4 in serum for all groups studied, which could have reflected the gene's variability, expression, and function in each group.

However, the study's strength came from its stratification of adult asthma by severity and exploration of host-related risk factors along with genetic variability.

In conclusion, the data showed that T alleles, CT genotype in the co-dominant genetic model, and (CT+TT) genotype in the recessive model were significantly associated with mild asthma, not severe asthma. The *IL-4* (C590T) gene polymorphism did not independently affect the risk of severe asthma. However, elderly females with a history of childhood-onset disease and associated nasal polyps had an increased risk of severe asthma up to 8 times.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Acknowledgement

The authors would like to acknowledge Dr. Ahmed Maher for his contributions to data collection.

## Funding

This research received funding from Kuwait University Research Sector, project number (M102/22).



## Funding

This research received funding from Kuwait University Research Sector, project number (M102/22).

## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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