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ORIGINAL ARTICLE

Impact of *ADRB2* gene polymorphisms and environmental factors exposure on asthma control in adolescents from Pakistan

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ABSTRACT

Objectives: To explore the association of *ADRB2* Gly16Arg (rs1042713) and Gln27Glu (rs1042714) polymorphisms with asthma control in Pakistani adolescents and explore potential interactions with environmental exposures like tobacco smoke and air pollution.

Methods: This cross-sectional study was conducted from January-June 2022 at University of Sindh and Liaquat University Hospital, Jamshoro and its affiliated respiratory clinics. Adolescents 12-18 years with physician-diagnosed asthma (GINA-2023 criteria) were consecutively recruited. Asthma control was assessed using Urdu Asthma Control Test (ACT; score ≤19=uncontrolled). Spirometry followed ATS/ERS 2019 guidelines. Buccal swabs were used for genotyping *ADRB2* variants by PCR–RFLP. Environmental exposures (tobacco smoke, biomass fuel, residential proximity to roads/industry) were recorded. Associations were analyzed using χ^2 tests, t-tests, and multivariate logistic regression adjusting for confounders. Gene-environment interactions were examined with interaction terms.

Results: Of 100 adolescents (mean age 14.6±1.9 years; 50% female), 54% had uncontrolled asthma. Arg16 allele frequency was 39% and Glu27 allele 22%. Uncontrolled asthma was significantly associated with Arg16 (χ^2=5.12, p=0.024), but not Gln27Glu (p=0.31). Compared with controlled asthma, uncontrolled cases had lower ACT scores (16.5 vs. 20.7, p<0.001) and reduced FEV_1 (77.5% vs. 87.4%, p=0.008). Tobacco smoke exposure independently predicted poor control (AOR 2.51; 95% CI 1.08–5.84; p=0.032). Arg16 carriers exposed to smoke had the highest risk (AOR 3.12; 95% CI 1.01-9.61; p=0.048).

Conclusion: *ADRB2* Arg16 variant was linked with poor asthma control, especially with household tobacco smoke, indicating gene-environment interaction. No significant effect was observed for Gln27Glu. Larger longitudinal studies are warranted.

Keywords: Asthma (MeSH); *ADRB2* gene (Non-MeSH); Polymorphism, Genetic (MeSH); Air Pollution (MeSH); Pharmacogenomics (MeSH); Respiratory Function Tests (MeSH).

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INTRODUCTION

Asthma is one of the most common chronic respiratory diseases worldwide, with a rising burden among children and adolescents. According to the World Health Organization (WHO), it affects over 262 million people and causes more than 455,000 deaths annually.[1] Beyond morbidity and mortality, asthma contributes to substantial socioeconomic costs, school absenteeism, and impaired quality of life. Adolescents represent a particularly vulnerable group, such as physiological transitions, psychosocial stressors, and environmental exposures may influence disease onset, progression, and control.[2]

In South Asia, the prevalence of asthma among adolescents is increasing; however, evidence regarding its genetic and environmental determinants remains limited.[3] Urbanization, air pollution, biomass fuel use, and tobacco smoke are key contributors, yet most genetic studies have been conducted in European and North American populations. The underrepresentation of South Asian cohorts underscores the need for region-specific research to better understand asthma pathogenesis in this setting.

At the molecular level, the β_2-adrenergic receptor (*ADRB2*) regulates airway smooth muscle tone and mediates bronchodilation in response to β_2-agonists, which remain central to asthma therapy.[4] Interindividual variability in treatment response has been attributed to common *ADRB2* polymorphisms, particularly Gly16Arg (rs1042713) and Gln27Glu (rs1042714).[5] Functional studies suggest that the Arg16 allele accelerates agonist-induced receptor down-regulation, reducing responsiveness to β_2-agonists,[6] whereas the Glu27 variant appears to confer resistance to downregulation, potentially offering a protective effect.[7] Together, these variants influence receptor density and signaling, shaping therapeutic outcomes.[8]

Clinical evidence, however, remains inconsistent. Israel et al., reported greater declines in peak expiratory flow among Arg16 homozygotes with regular albuterol use,[9] while Wechsler et al. observed reduced benefit from long-acting β_2-agonists in Arg16 homozygous adolescents.[10] Other studies, however, found no significant associations, suggesting that ethnicity, study design, and methodological differences may account for variability.[11] Meta-analyses highlight this heterogeneity: although overall associations remain inconclusive, subgroup analyses often reveal population-specific effects, with some Asian cohorts demonstrating stronger associations than European

counterparts.[12,13]

Environmental exposures further complicate asthma in South Asia. Traffic-related air pollution, industrial emissions, biomass fuel use, and secondhand smoke are strongly associated with increased risk and severity.[14,15] These factors may interact with genetic susceptibility, modifying disease expression. Graham BL, et al., proposed that asthma results from the interplay between genetic and environmental influences rather than either factor alone.[16] For instance, adolescents carrying *ADRB2* risk alleles and simultaneously exposed to high pollution may experience poorer asthma control compared with peers in cleaner environments. Despite this, gene-environment interactions remain underexplored in South Asian populations.

In summary, while *ADRB2* polymorphisms are implicated in asthma pharmacogenetics, their effects appear context-dependent and may vary across ethnic and environmental settings. The lack of data from South Asia and limited investigation of gene–environment interactions represent important gaps. This study was therefore designed to assess the association of *ADRB2* Gly16Arg and Gln27Glu polymorphisms with asthma control in Pakistani adolescents, while examining their interaction with environmental exposures such as air pollution and tobacco smoke. The findings aim to provide regionally relevant evidence to inform personalized management strategies and improve asthma outcomes in this vulnerable population.

METHODS

This cross-sectional study was conducted from January to June 2022 at Institute of Biotechnology and Genetic Engineering, University of Sindh and the patient samples were collected from Liaquat University Hospital, Jamshoro-Pakistan and its affiliated respiratory clinics. Adolescents aged 12-18 years with physician-diagnosed asthma were consecutively recruited during outpatient visits. The study design was selected to provide a snapshot of both genetic and environmental determinants of asthma control in this age group. Eligibility criteria included adolescents aged 12-18 years with a physician-confirmed diagnosis of asthma according to the Global Initiative for Asthma (GINA) 2023 guidelines.[17] Exclusion criteria were the presence of another chronic respiratory disease, an acute respiratory tract infection within four weeks before enrollment, long-term systemic corticosteroid therapy, or refusal of informed assent/consent by participants or their guardians.

Consecutive sampling was employed for patient recruitment. Although Cochran's formula estimated a required sample size of 384 (with a 10% allowance for non-response, target 423), logistical constraints limited enrollment to 100 adolescents. The study was therefore exploratory and intended to generate hypotheses rather than definitive conclusions.

Asthma control was assessed using the Asthma Control Test (ACT), validated for use in adolescents.[18] The Urdu version was administered by trained staff through face-to-face interviews. ACT scores range from 5 to 25, with a cut-off of ≤19 defining uncontrolled asthma in line with published criteria.

Lung function was evaluated using a portable spirometer (Spirolab III, MIR, Italy). Daily calibration was performed with a 3-L syringe, and testing followed the 2019 American Thoracic Society/European Respiratory Society guidelines.[19] Each participant completed at least three acceptable forced expiratory maneuvers, and the best values for forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio were recorded. Results were expressed as percentages of predicted norms, adjusted for age, sex, and height.

For genetic analysis, buccal swabs were collected using sterile Isohelix SK-2 collection kits (Cell Projects Ltd., UK). DNA extraction was performed using the Qiagen QIAamp DNA Mini Kit (Qiagen, Germany) according to manufacturer's instructions. The Gly16Arg (rs1042713) and Gln27Glu (rs1042714) polymorphisms in the *ADRB2* gene were genotyped using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Primer sequences were as follows: Gly16Arg forward 5′-GCC TTA TGC CAG TGA GGC-3′ and reverse 5′-TGT GGC CAT CCA CTC TGA-3′; Gln27Glu forward 5′-GGC AGA GAC TGA GGA CCA-3′ and reverse 5′-CTG GGT GTT GGC AGA CAA-3′. PCR amplification was carried out using a Bio-Rad T100 thermocycler with initial denaturation at 95 °C for 5 minutes, followed by 35 cycles of denaturation at 95 °C for 30 seconds, annealing at 58 °C for 30 seconds, extension at 72 °C for 45 seconds, and a final extension at 72 °C for 5 minutes. Restriction digestion for Gly16Arg was performed using NcoI (New England Biolabs, Cat. No. R0193S) yielding fragments of 221 and 145 bp, while Gln27Glu was digested with BbvI (New England Biolabs, Cat. No. R0501S), generating fragments of 342 and 126 bp, which were resolved on 3% agarose gels stained with ethidium bromide. Quality control included the use of negative controls, 10% duplicate assays, and Hardy-Weinberg equilibrium testing. Call rates exceeded 98%.

Environmental exposures were assessed using a structured questionnaire adapted from validated studies.[20,21] Household tobacco smoke exposure was defined as the presence of at least one smoker in the home. Additional exposures included the use of biomass fuels (wood, dung, or coal) for domestic heating or cooking, and residence within 100 meters of major roads or industrial facilities, serving as proxies for traffic-related and industrial air pollution. Objective environmental monitoring data such as PM2,5 levels were unavailable; therefore, the limitations of self-reported measures were acknowledged in the analysis.

The study protocol was approved by the Research Ethics Committee of the Institute of Biotechnology and Genetic Engineering (IBGE), University of Sindh, Jamshoro (ERC No: UoS/IBGE/REC-11A/2022/1687; dated 24 August 2022). Written informed consent was obtained from parents or guardians, with assent secured from all adolescent participants. The study was conducted in accordance with the Declaration of Helsinki.

Data were analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed with the Shapiro-Wilk test. Continuous data

(age, body mass index [BMI], ACT scores, spirometry values) were summarized as Mean±Standard deviation (SD), while categorical variables (sex, smoking exposure, biomass use, genotypes) were presented as frequencies and percentages. Comparisons between controlled and uncontrolled asthma groups were made using independent t-tests for normally distributed data, Mann-Whitney U tests for skewed distributions, and X^2 or Fisher's exact tests for categorical data. Logistic regression models were applied to estimate associations between *ADRB2* genotypes and uncontrolled asthma, adjusting for age, sex, BMI, and environmental exposures. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Gene-environment interactions were examined by including product terms (e.g., genotype × smoking exposure) in regression models. Model fit was evaluated with the Hosmer-Lemeshow test, and statistical significance was set at a two-tailed $p<0.05$. Missing data were addressed through complete-case analysis.

RESULTS

A total of 100 adolescents with asthma were enrolled (mean age 14.6±1.9 years; 50% female). *ADRB2* polymorphisms were identified in 46% of participants, while 54% showed no variant. Asthma control was achieved in 46 adolescents (46%), whereas 54 (54%) had uncontrolled disease. Baseline demographic and clinical characteristics are summarized in Table I. Genotype distributions for Gly16Arg and Gln27Glu polymorphisms are presented in Table II. Arg16 homozygotes were more common among adolescents with uncontrolled asthma (27.8%) compared to those with controlled asthma (17.3%), demonstrating a significant association ($p=0.024$). In contrast, Gln27Glu variants showed no significant differences between groups ($p=0.31$).

Multivariate logistic regression (Table III) identified smoking exposure as a significant independent predictor of uncontrolled asthma (AOR 2.51; 95% CI 1.08–5.84; $p=0.032$). Arg16 homozygosity showed a nonsignificant trend toward increased risk (AOR 2.31; 95% CI 0.79–6.77; $p=0.12$). Other factors, including diet, BMI, and physical inactivity, were not significant predictors. Notably, genotype ×

Table I: Demographic and clinical characteristics of patients with controlled and uncontrolled asthma

Parameter	Controlled asthma (n=46)	Uncontrolled asthma (n=54)	p-value
Age (years), Mean±SD	14.4±2.0	14.8±1.8	0.28
Female, n (%)	22 (47.8)	28 (51.9)	0.69
Male, n (%)	24 (52.2)	26 (48.1)	–
BMI (kg/m^2), Mean±SD	20.1 .8	20.9±3.2	0.21
Smoking exposure, n (%)	13 (28.3)	24 (44.4)	0.04*
Diet risk (high fat), n (%)	12 (26.1)	19 (35.2)	0.26
Physical inactivity, n (%)	9 (19.6)	17 (31.5)	0.17
ADRB2 polymorphism present, n (%)	15 (32.6)	31 (57.4)	0.01*
FEV_1 % predicted, Mean±SD	87.4±18.4	77.5±18.4	0.008*
FEV_1/FVC ratio (%)	83.1±8.6	77.4±9.2	0.01*
ACT score, Mean±SD	20.7±3.4	16.5±3.4	<0.001*

*Significant at $p < 0.0$, SD: Standard Deviation in foot notes, n: Frequency.

Table II: Genotypic and allelic frequency distribution of *ADRB2* polymorphisms

Genotype / Allele	Controlled (n=46)	Uncontrolled (n=54)	p-value
Gly16Gly (GG)	21 (45.7%)	16 (29.6%)	0.024*
Gly16Arg (GA)	17 (37.0%)	23 (42.6%)	0.29
Arg16Arg (AA)	8 (17.3%)	15 (27.8%)	0.12
Gln27Gln (QQ)	29 (63.0%)	37 (68.5%)	0.21
Gln27Glu (QE)	14 (30.4%))	13 (24.1%)	0.46
Diet risk (high fat), n (%)	12 (26.1)	19 (35.2)	0.46
Glu27Glu (EE)	3 (6.5%)	4 (7.4%)	0.98

Table III: Multivariate logistic regression predictors of uncontrolled asthma

Predictor	Adjusted OR	95% CI (Lower-Upper)	p-value
Age	1.03	0.85-1.25	0.76
Sex (Female vs Male)	1.12	0.52-2.44	0.77
BMI	1.08	0.95-1.22	0.24
Smoking exposure	2.51	1.08-5.84	0.032*
Physical inactivity	1.42	0.59-3.41	0.44
High-risk diet	1.29	54-3.08	0.57
Arg16 homozygous (AA)	2.31	10.79-6.77	0.12
Gln27Glu variant	0.71	0.29-.76	0.46

*Significant at $p < 0.05$, AOR: Adjusted odds ratio, CI: Confidence interval

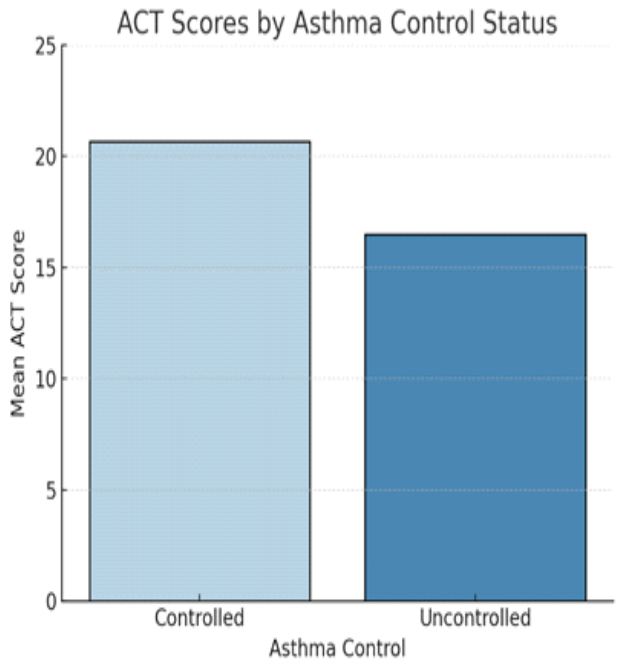

Figure 1: ACT scores by asthma control status (box/violin plot, $p < 0.001$).

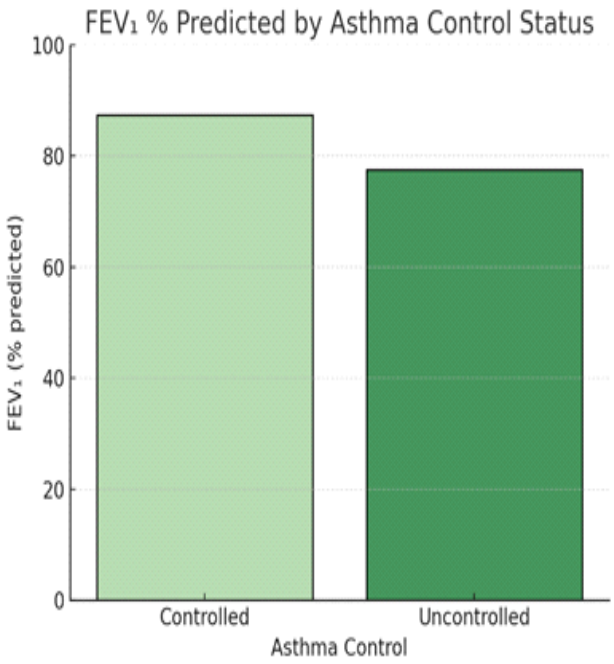

Figure 2: FEV_1 % predicted by asthma control status (box/violin plot, $p=0.008$).

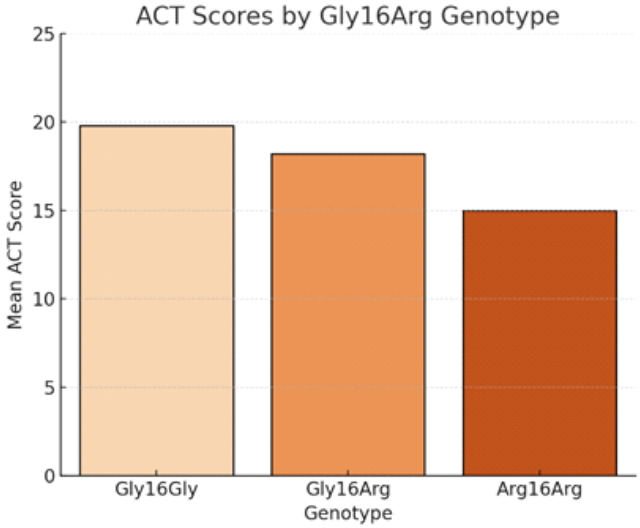

Figure 3: ACT scores by Gly16Arg genotype (Arg16 carriers lower than Gly16 homozygotes, $p<0.05$).

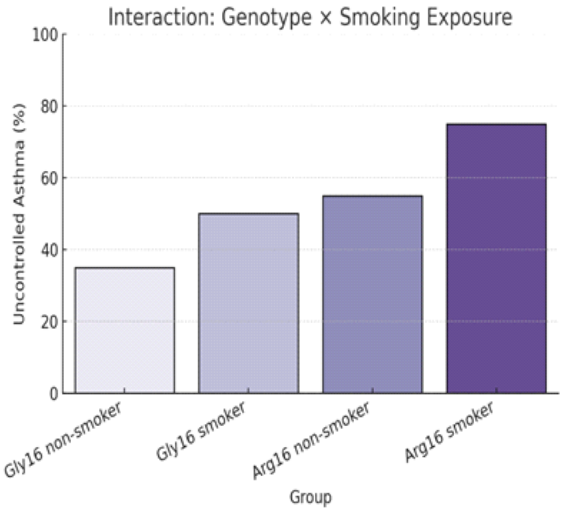

Figure 4: Interaction plot showing higher odds of uncontrolled asthma in Arg16 carriers with smoke exposure ($p=0.048$).

smoking interaction analysis revealed that Arg16 carriers exposed to household smoke had a substantially higher risk of uncontrolled asthma (AOR 3.12; 95% CI 1.01–9.61; $p=0.048$). In this study, the *ADRB2* Gly16Arg polymorphism, particularly the Arg16 allele, was associated with poorer asthma control. Figure 1 shows that ACT scores were significantly lower in adolescents with uncontrolled asthma compared to those with controlled disease ($p <0.001$). Consistently, Figure 2 demonstrates a significant reduction in FEV_1% predicted among the uncontrolled group ($p=0.008$). As illustrated in Figure 3, Arg16 carriers exhibited lower ACT scores than Gly16 homozygotes ($p<0.05$). Notably, Figure 4 highlights a gene-environment interaction, with Arg16 carriers exposed to household tobacco smoke displaying substantially higher odds of uncontrolled asthma ($p=0.048$).

DISCUSSION

In this study, the *ADRB2* Gly16Arg polymorphism, particularly the Arg16 allele, was associated with poorer asthma control among Pakistani adolescents, whereas the Gln27Glu variant showed no significant association. A notable finding was the gene-environment interaction: adolescents carrying the Arg16 allele

who were also exposed to household tobacco smoke had more than a threefold higher risk of uncontrolled asthma. These results underscore the importance of gene-environment interactions in shaping asthma outcomes and provide early evidence from an underrepresented South Asian population.

Our findings align with recent global pharmacogenomic studies. The Pharmacogenomics in Childhood Asthma (PICA) write full form and then abbreviation consortium, which analyzed over 3,000 children and adolescents across diverse ethnic groups, reported that haplotypes containing Arg16 were associated with increased risk of asthma exacerbations among patients treated with inhaled corticosteroids and long-acting β_2-agonists (ICS+LABA).[22] This supports our observation that Arg16 predisposes to poor asthma control, even though our study did not stratify participants by medication use. Similarly, Muchão FP, et al., demonstrated in Brazilian children with acute asthma that Arg16 homozygotes had a higher likelihood of hospital admission compared with Gly16 carriers.[20] Collectively, these studies strengthen the evidence that Arg16 is a risk allele contributing to worse asthma outcomes in adolescents.

In contrast, no significant associations were observed for the Gln27Glu polymorphism. This finding is consistent with some, though not all, prior reports. A systematic review suggested that Glu27 homozygosity may confer modest protection against asthma severity,[24] although such effects appear to vary by ethnicity. The absence of an effect in our cohort may reflect the relatively small sample size, population-specific allele frequencies in South Asia, or the lack of haplotype analysis that could capture interactions between Gly16Arg and Gln27Glu. Overall, our data suggest that Arg16 is the more clinically relevant variant in this setting.

The biological plausibility of these findings is supported by mechanistic evidence. The Arg16 allele has been shown to promote agonist-induced β_2-adrenergic receptor downregulation, reducing responsiveness to bronchodilators over time.[25] This is particularly relevant for adolescents, who often rely heavily on β_2-agonists for symptom relief. Tobacco smoke independently disrupts β_2-receptor function through oxidative stress, inflammation, and receptor internalization.[23] The observed synergism between Arg16 and smoke exposure in our study is therefore biologically credible, as both genetic susceptibility and environmental insult converge on receptor desensitization, thereby amplifying the risk of poor asthma control.

Our results have both clinical and public health implications. Current asthma management guidelines, including GINA 2023, do not recommend routine genotyping for *ADRB2* variants,[14] yet integrating genetic and environmental risk factors may enable more personalized risk stratification. For example, adolescents carrying the Arg16 allele who are also exposed to household tobacco smoke may benefit from closer follow-up, more frequent ACT assessments, and targeted environmental counseling. In low- and middle-income countries, where exposure to tobacco smoke and biomass fuels is widespread, such an approach could contribute to precision public health strategies aimed at reducing asthma morbidity.

These findings should be interpreted cautiously considering several limitations. The sample size (n=100) was below the ideal estimate based on Cochran's formula, limiting statistical power and increasing the risk of type II error. The cross-sectional design precludes causal inference, while reliance on self-reported exposure data without biomarker validation raises the possibility of misclassification bias. Treatment-related variables such as adherence, inhaler technique, and use of ICS or LABA were not systematically documented, potentially confounding genotype–phenotype associations. In addition, haplotype-level analyses and assessments of other relevant *ADRB2* variants, such as Thr164Ile, were not performed. Finally, recruitment from a single geographic area limits generalizability to broader South Asian or global populations.

Future research should address these gaps by recruiting larger, multi-ethnic cohorts across South Asia, employing longitudinal designs, and incorporating objective measures of environmental exposure such as cotinine assays and $PM_{2.5}$ monitoring. Pharmacogenomic trials are needed to evaluate whether Arg16 carriers respond differently to ICS or LABA therapy, as suggested by prior studies.[22,26] Incorporating *ADRB2* variants into polygenic risk scores, alongside environmental risk data, may eventually enable more precise identification of high-risk adolescents and inform targeted interventions.

CONCLUSION

In this study provides preliminary evidence that the *ADRB2* Arg16 allele is associated with poor asthma control in adolescents, particularly in the presence of household tobacco smoke, while Gln27Glu showed no significant role. These findings emphasize the importance of gene-environment interactions in adolescent asthma and highlight the need for larger, prospective studies to confirm clinical relevance. Although insufficient to inform routine clinical practice, our results contribute to the growing evidence base for precision medicine and precision public health in asthma management.

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AUTHORS' CONTRIBUTION

The Following authors have made substantial contributions to the manuscript as under:

AAU & KS: Conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

TS & SN: Analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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