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Reduced nasal airflow and odor identification in vernal keratoconjunctivitis (VKC): beyond the ocular surface

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Abstract

Background

Vernal keratoconjunctivitis (VKC) is primarily regarded as an ocular inflammatory disease. Whether nasal and olfactory abnormalities are part of its broader clinical expression or simply reflect coexisting atopy remains unclear. This study compared nasal airflow and odor-identification performance between children with VKC and controls and examined whether the observed associations persisted after accounting for atopy.

Methods

This single-centre cross-sectional comparative study included 55 children and adolescents with VKC and 25 controls without VKC. All participants underwent skin prick testing and active anterior rhinomanometry. Odor-identification performance was assessed in participants aged ≥ 6 years using the 12-item U-Sniff test. Atopy was defined by aeroallergen sensitization together with a clinical history consistent with allergic rhinitis. Multivariable logistic regression models including age, sex, VKC, and atopy were used to examine their associations with abnormal rhinomanometry and reduced odor-identification performance.

Results

Abnormal rhinomanometry was more frequent in participants with VKC than in controls (41.8% vs 16.0%). Among the 71 participants with an interpretable U-Sniff result, reduced odor-identification performance was also more frequent in the VKC group (52.1% vs 21.7%). In adjusted analyses, VKC was associated with abnormal rhinomanometry (adjusted odds ratio [aOR] 3.97, 95% confidence interval [CI] 1.09–14.42) and reduced odor-identification performance (aOR 3.95, 95% CI 1.07–14.59). Atopy was also associated with both outcomes (aOR 3.57, 95% CI 1.02–12.50, and aOR 3.50, 95% CI 1.05–11.70, respectively).

Conclusions

VKC was associated with abnormalities in both nasal airflow and odor-identification performance, and these associations persisted after adjustment for age, sex, and atopy. This dual functional involvement challenges a strictly ocular view of VKC and identifies nasal and olfactory function as a potentially overlooked dimension of the disease. Clinicians should therefore consider possible nasal and olfactory involvement when evaluating children with VKC. Larger longitudinal studies are needed to confirm these findings and determine their relationship with disease activity and treatment.

1. Background

Clinical characteristics of VKC

Vernal keratoconjunctivitis (VKC) is a chronic, recurrent inflammatory disease of the ocular surface that predominantly affects boys during childhood and early adolescence. Its course commonly includes exacerbations during spring and summer, although perennial forms and persistence beyond puberty have also been described [1–4]. The clinical presentation typically includes intense itching, photophobia, tearing, foreign-body sensation, and thick mucous discharge, together with giant papillae of the upper tarsal conjunctiva, limbal involvement, or a combination of both [1, 2, 4]. Unlike milder forms of ocular allergy, VKC may involve the cornea and lead to punctate keratopathy, shield ulcers, corneal scarring, keratoconus, or limbal stem cell deficiency [1, 5, 6]. Although its overall prognosis is generally favourable, these complications may cause permanent visual impairment, making early recognition and adequate control of ocular inflammation particularly important in children [2, 3, 5, 6].

Allergic sensitization in VKC

VKC has traditionally been included within the spectrum of allergic eye diseases, but its relationship with systemic allergic sensitization is heterogeneous [2, 7–9]. A systematic review and meta-analysis including 2,122 patients estimated the overall prevalence of allergic sensitization at 57.7%, with house dust mites and pollens representing the most frequently identified allergens [7]. Earlier clinical studies similarly reported negative skin-prick or serum-specific IgE tests in a substantial proportion of patients with VKC [2, 10]. These findings indicate that IgE-mediated mechanisms are relevant but cannot account for the entire clinical and immunological spectrum of the disease [7–9]. Cellular inflammation involving eosinophils and T-helper 2 responses, together with innate and neuroimmune mechanisms, has also been implicated in VKC pathogenesis [8–10]. Allergic sensitization should therefore be regarded as a frequent but non-universal feature of VKC and assessed separately when investigating functional abnormalities extending beyond the ocular surface [7–10].

Upper-airway involvement

This distinction becomes particularly relevant when considering the possible involvement of the upper airways. Although VKC is clinically defined by ocular findings, concomitant nasal and other otorhinolaryngological manifestations have been reported. In a study of 27 children with VKC, symptoms and signs consistent with allergic rhinitis were identified in 37% of participants, while abnormal tympanometric findings were observed in 18.5% [11]. These observations suggest that the clinical expression of VKC may not always be confined to the ocular surface, although they do not establish whether upper-airway abnormalities result from coexisting allergic disease or from mechanisms related more directly to VKC [7, 11]. Objective evaluation of nasal function may therefore help characterize this potential extraocular involvement while accounting for the possible contribution of allergic sensitization.

Olfactory function in pediatric allergic disease

Olfactory function represents another potentially relevant dimension of upper-airway involvement. Smell impairment has been documented in children with seasonal allergic rhinitis, indicating that pediatric

allergic inflammation may affect both nasal symptoms and sensory function. Aksoy et al. reported mild-to-moderate subjective reduced odor-identification performance in 43.2% of children during pollen season and in 32.4% outside pollen season, together with reduced odor-identification performance during seasonal exposure. Olfactory scores were associated with nasal symptom burden but not with acoustic-rhinometry parameters, suggesting that olfactory impairment and anatomical changes in the nasal cavity do not necessarily occur in parallel. Accordingly, anatomical assessment alone may not fully characterize the relationship between nasal involvement and olfactory dysfunction in children [12].

Objective nasal assessment and evidence in VKC

Different objective methods provide complementary information on nasal involvement. Acoustic rhinometry primarily evaluates nasal-cavity geometry and cross-sectional area, whereas rhinomanometry provides a functional assessment based on the relationship between transnasal pressure and airflow [13, 14]. These approaches should therefore not be considered interchangeable, as preserved anatomical measurements do not necessarily exclude altered nasal airflow or increased functional resistance [13]. Evidence specifically addressing olfactory function in VKC remains limited and has mainly been provided by Elsürer et al., who evaluated 39 children with VKC and 32 healthy controls using a modified Connecticut Chemosensory Clinical Research Center test and acoustic rhinometry. Children with VKC showed lower odor-identification and composite olfactory scores than controls, including those without clinically diagnosed allergic rhinitis, whereas odor thresholds and acoustic-rhinometry measurements did not differ significantly between the groups. Moreover, olfactory scores were not correlated with acoustic-rhinometry parameters, further supporting a possible dissociation between olfactory dysfunction and anatomical nasal measurements [14].

Knowledge gap and study aim

These findings provide preliminary evidence of olfactory involvement in VKC but leave two clinically relevant questions unresolved: whether VKC is also associated with a functional alteration of nasal airflow and whether the associations with nasal and olfactory outcomes persist after accounting for allergic sensitization [13, 14]. Accordingly, this study compared rhinomanometric and olfactory findings between children with VKC and controls and examined whether VKC and allergic sensitization were independently associated with abnormal rhinomanometry and impaired olfactory function after adjustment for age and sex.

2. Materials and Methods

Study design and setting

This single-centre observational cross-sectional comparative study was conducted at the Pediatric Allergology Unit of Policlinico Umberto I, Sapienza University of Rome, Italy, between March and June 2025. The study evaluated allergic sensitization, nasal patency, and olfactory function in children and adolescents between 3 and 17 years with vernal keratoconjunctivitis (VKC) and in controls without VKC.

Study population and recruitment

Children and adolescents with a new or previously established diagnosis of VKC who attended the outpatient clinic during the study period were invited to participate as VKC group. The control group comprised children and adolescents without any history or clinical evidence of VKC, who had been referred to the same centre for suspected allergic disease. Children of each group (VKC and controls) which showed sensitization to at least one aeroallergen together with a clinical history of symptoms consistent with allergic rhinitis were considered as atopic, whereas non-atopic subjects had negative Skin Prick Tests and no history of allergic symptoms. At the time of the rhinomanometric and olfactory assessments, atopic controls were not receiving antihistamines, intranasal corticosteroids, or other pharmacological treatments for allergic rhinitis for at least 7 days.

Eligibility criteria

Participants were eligible for the VKC group if they were of pediatric age, had a confirmed diagnosis of VKC, and underwent the scheduled clinical and functional assessments during the recruitment period. Eligibility for the control group required the absence of VKC. Atopic controls were required to have at least one positive Skin Prick Test together with a clinical history consistent with allergic rhinitis, whereas non-atopic controls were required to have negative Skin Prick Tests and no history of allergic symptoms. Participants were excluded if they had chronic upper- or lower-respiratory-tract diseases other than allergic rhinitis or were receiving treatments considered likely to affect rhinomanometric or olfactory outcomes. Inability to complete an individual functional test did not necessarily result in exclusion from the overall study population; these participants were considered non-evaluable only for the corresponding outcome.

VKC diagnosis and clinical assessment

The diagnosis of VKC was established or confirmed cooperatively by a pediatrician and an ophthalmologist on the basis of a compatible clinical history and characteristic ocular findings assessed by slit-lamp examination. Compatible symptoms included recurrent ocular itching, photophobia, tearing, foreign-body sensation, and mucous discharge, while characteristic clinical signs included giant papillae of the upper tarsal conjunctiva, limbal papillae or Horner–Trantas dots, and mixed tarsal–limbal involvement, with or without corneal disease [2, 4, 15]. Demographic and clinical information, including age, sex, current symptoms, previously used therapy, year of diagnosis (if applicable) and any other chronic clinical condition of the child were recorded at enrolment. Allergic sensitization was not required for the diagnosis of VKC, as systemic IgE sensitization represents a frequent but non-universal feature of the disease [7–9].

Assessment of allergic sensitization

Allergic sensitization was assessed by Skin Prick Testing performed on the volar surface of the forearm using standardized allergen extracts supplied by Lofarma S.p.A. (Milan, Italy). The aeroallergen panel included *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, *Cladosporium*

herbarum, cat epithelium, dog epithelium, *Phleum pratense*, *Lolium perenne*, *Cynodon dactylon*, *Parietaria judaica*, *Olea europaea*, *Cupressus arizonica*, *Betula pendula*, *Artemisia vulgaris*, and *Ambrosia artemisiifolia*. Histamine hydrochloride (10 mg/mL) and the allergen diluent were used as positive and negative controls, respectively. Participants were not receiving antihistamine therapy at the time of testing.

Skin reactions were evaluated 15–20 minutes after application. A test was considered positive when the allergen produced a wheal with a mean diameter of at least 3 mm in the presence of valid positive- and negative-control responses [16]. Allergic sensitization was defined as the presence of at least one positive Skin Prick Test. Clinical allergic status was determined by combining Skin Prick Test results with a compatible history of allergic symptoms.

Rhinomanometric assessment

Nasal patency was objectively assessed using active anterior rhinomanometry performed with a Rinopocket ED200 rhinomanometer (MEDI-CARE Solutions s.r.l., Bologna, Italy). Participants were examined in a seated position after an acclimatization period of 5 minutes in a room maintained between 18°C and 22°C. Measurements were obtained before and after nasal decongestion, achieved using xylometazoline hydrochloride administered as two 50-µg actuations into each nostril. Active anterior rhinomanometry was repeated 15 minutes after completion of the decongestant administration under the same measurement conditions [17]. Airflow and transnasal pressure were measured separately for each nasal cavity at a reference pressure of 150 Pa, and total nasal airflow and nasal resistance were subsequently calculated. A reference pressure of 150 Pa is recommended for the standardized reporting and interpretation of active anterior rhinomanometry [13, 17, 18]. Between 1 and 3 technically acceptable measurements were obtained for each participant, and the best technically acceptable measurement was used for the analysis. Rhinomanometric findings were classified according to the height-adjusted reference equation and obstruction categories proposed by Zapletal and Chalupová [18]. Predicted total nasal inspiratory airflow at 150 Pa was calculated as exp [1.69665 + 0.95103 × ln(body height in cm)] mL/s, and the measured total airflow was expressed as a percentage of the predicted value. Normal nasal patency was defined as a total inspiratory airflow ≥ 71% of the predicted value, whereas a value < 71% of predicted was classified as abnormal, corresponding to at least mild nasal obstruction [18]. The binary outcome used in the analysis was based on the pre-decongestion measurement.

Olfactory assessment

Olfactory identification was assessed in participants aged 6–17 years using the 12-item ODOFIN Sniffin' Sticks Kids Identification Test (U-Sniff). The test includes 12 familiar odors - apple, banana, butter, coffee, cut grass, fish, flower/rose, lemon, onion, orange, peach, and strawberry - presented through odor-dispensing felt-tip pens using a four-alternative forced-choice procedure supported by pictorial choice cards [19]. Participants were instructed to refrain from eating, drinking beverages other than tap water, and smoking for at least 15 minutes before testing. The examiner wore odor-free gloves, which were changed for each participant. Before each odor presentation, the corresponding choice card was provided. The cap was then removed and the tip of the stick was positioned approximately 2 cm below

the nose, midway between the nostrils. Participants were instructed to inhale the odor for approximately 3–4 seconds and to select one of the four proposed alternatives. Responses were recorded without providing feedback regarding their correctness. A minimum interval of 30 seconds was maintained between consecutive odor presentations. One point was assigned for each correctly identified odor, resulting in a total score ranging from 0 to 12. Results were interpreted using age-specific normative values based on the 10th percentile. Normosmia was defined by scores ≥ 7 in children aged 6–8 years, ≥ 9 in those aged 9–11 years, and ≥ 10 in participants aged 12–14 or 15–17 years. Scores ≤ 6, ≤8, and ≤ 9, respectively, were classified as reduced odor-identification performance [19]. Children younger than 6 years were not evaluated because the test was validated for participants aged 6 years or older. As this test assesses suprathreshold odor-identification ability and does not measure olfactory threshold, it was not used to diagnose anosmia. The test generated a total score ranging from 0 to 12. Olfactory function was classified as normal or impaired according to Gellrich et al. guidelines. Age-appropriate interpretation is necessary in pediatric populations because olfactory identification performance and test feasibility vary with age and with the format of the assessment [19, 20]. According to the study protocol, children younger than 6 years were considered non-evaluable for the olfactory outcome but remained eligible for the other clinical and rhinomanometric assessments.

Study outcomes

The study outcomes were an abnormal pre-decongestion rhinomanometric result and impaired olfactory function, as defined above. Rhinomanometric and olfactory findings were compared between participants with VKC and controls. The independent associations of VKC and atopy with each functional outcome were examined after adjustment for age and sex. Analyses were conducted using the available outcome-specific data, with participants unable to complete an individual test excluded only from the corresponding analysis.

3. Statistical Analysis

Categorical variables were summarized as absolute frequencies and percentages. Demographic and allergological characteristics were described separately for patients with vernal keratoconjunctivitis (VKC) and controls. Within the allergic subgroup, sensitization was classified into three mutually exclusive categories: seasonal only, perennial only, or combined seasonal and perennial sensitization.

Associations of VKC and allergy with the two functional outcomes, abnormal rhinomanometry (RhinoAltered) and an impaired Sniff Test (SniffAltered), were examined using 2 x 2 contingency tables. When small observed cell counts were present, Fisher’s exact test was considered the primary analysis; Pearson’s chi-square test and the chi-square test with Yates’ continuity correction were also reported for completeness. Effect sizes were expressed as odds ratios (ORs), relative risks, and absolute prevalence differences, with 95% confidence intervals (CIs). Participants with a non-assessable SniffAltered result were excluded only from analyses of olfactory function.

Two multivariable logistic regression models were fitted to determine whether VKC and allergy retained independent associations with the outcomes. RhinoAltered was the outcome in the first model and SniffAltered in the second; sex, age, VKC, and allergy were included as predictors in both models. Results are presented as regression coefficients, adjusted ORs, 95% CIs, and p-values. To improve clinical interpretability, the effect of age was expressed per 12-month increase. Multicollinearity was assessed using the variance inflation factor. Coefficient stability was explored by bootstrap resampling, considering the distribution of the estimates and the proportion of replicates in which each coefficient retained the direction observed in the original sample. Model explanatory performance was quantified using McFadden's pseudo-R^2. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC), with bootstrap 95% CIs. Internal validation was performed by bootstrap resampling with replacement. Mean optimism, defined as the difference between performance in each bootstrap sample and performance obtained when the same fitted model was applied to the original sample, was used to derive the optimism-corrected AUC.

Calibration was explored using the Brier score and the Hosmer–Lemeshow test. ROC curves illustrate apparent discrimination, whereas forest plots display adjusted ORs and their 95% CIs on a logarithmic scale. A p-value < 0.05 was considered statistically significant. The analyses were regarded as exploratory, and no formal adjustment for multiple comparisons was applied because the main hypotheses were specified a priori and involved clinically related exposures and outcomes. Results were therefore interpreted by jointly considering effect size, CI precision, and consistency between bivariable and multivariable analyses. All statistical analyses were performed using Python 3.11, statsmodels version 0.14.6, and NumPy version 2.2.6.

4. Results

Sample Characteristics

The study sample comprised 80 participants, including 55 children with vernal keratoconjunctivitis (VKC) and 25 controls. A marked male predominance was observed in both groups and was more pronounced among patients with VKC: 50/55 (90.9%) versus 20/25 (80.0%) controls. Allergy was present in 41/55 (74.5%) patients with VKC and 15/25 (60.0%) controls. Among allergic participants, seasonal-only sensitization was the most frequent category in both groups, whereas combined seasonal and perennial sensitization was proportionally more common among patients with VKC than among controls.

Demographic and allergological characteristics are summarized in Table 1 and Fig. 1.

Table 1
Demographic and allergological characteristics of the study sample

Variable	VKC (n = 55)	Controls (n = 25)	Total (n = 80)
Number of participants	55	25	80
Male	50 (90.9%)	20 (80.0%)	70 (87.5%)
Female	5 (9.1%)	5 (20.0%)	10 (12.5%)
Allergic	41 (74.5%)	15 (60.0%)	56 (70.0%)
Non-allergic	14 (25.5%)	10 (40.0%)	24 (30.0%)
Seasonal allergy	19/41 (46.3%)	9/15 (60.0%)	28/56 (50.0%)
Perennial allergy	12/41 (29.3%)	4/15 (26.7%)	16/56 (28.6%)
Seasonal and perennial	10/41 (24.4%)	2/15 (13.3%)	12/56 (21.4%)

Data are presented as n (%) or n/N (%), according to the relevant denominator

Associations with Abnormal Rhinomanometry

In the overall sample, rhinomanometry was abnormal in 23/56 (41.1%) allergic patients and 4/24 (16.7%) non-allergic patients, corresponding to an absolute difference of 24.4 percentage points. Abnormal rhinomanometry was therefore more than twice as frequent among allergic participants. Fisher's exact test, considered the primary analysis because of the small count in one cell, showed a statistically significant association (OR = 3.48; 95% CI: 1.05–11.55; p = 0.041).

Pearson's chi-square test yielded a concordant result ($\chi^2 = 4.475$; p = 0.034), whereas Yates' continuity correction produced a more conservative estimate ($\chi^2 = 3.450$; p = 0.063). The magnitude of the OR suggests a potentially clinically relevant association; however, the wide CI indicates limited precision in estimating the true effect size.

Abnormal rhinomanometry was also more frequent among patients with VKC than among controls (23/55, 41.8% vs. 4/25, 16.0%), with an absolute difference of 25.8 percentage points. Patients with VKC had approximately 3.8 fold higher odds of abnormal rhinomanometry than controls (OR = 3.77; 95% CI: 1.14–12.48; p = 0.040, Fisher's exact test). In this comparison, the chi-square test with Yates' continuity correction also remained statistically significant ($\chi^2 = 4.034$; p = 0.045). Agreement across the different statistical approaches makes the association between VKC and abnormal rhinomanometry relatively more consistent than that observed for allergy, although substantial quantitative uncertainty remains.

In the multivariable logistic regression model, with RhinoAltered as the outcome and sex, age, VKC, and allergy as predictors, both VKC and allergy remained statistically significantly associated with abnormal rhinomanometry. After adjustment, VKC had an OR of 3.97 (95% CI: 1.09–14.42; p = 0.036), indicating that, at equivalent values of the other predictors, patients with VKC had approximately fourfold higher odds of

abnormal rhinomanometry than controls. Thus, the association was not explained solely by the higher prevalence of allergy among patients with VKC. Allergy also retained an independent association (adjusted OR = 3.57; 95% CI: 1.02–12.50; p = 0.047), with an estimated magnitude comparable to that of VKC.

Sex and age were not significantly associated with the outcome. However, the CIs, particularly for sex, were too wide to confidently exclude clinically relevant effects. In addition, the lower CI limits for VKC and allergy were close to 1 and the p-values were near the conventional 0.05 threshold. These findings should therefore be interpreted as evidence of independent associations, albeit with limited precision and robustness. The full multivariable model is reported in Table 2 and graphically presented in Fig. 2.

Table 2
Multivariable logistic regression for abnormal rhinomanometry

Predictor	Adjusted OR	95% CI	p
Sex: female vs. male	0.38	0.07–2.18	0.280
Age: 12-month increase	0.90	0.77–1.04	0.157
VKC: yes vs. no	3.97	1.09–14.42	0.036
Allergy: yes vs. no	3.57	1.02–12.50	0.047
Overall model: N = 80; events = 27; McFadden's pseudo-R^2 = 0.123; apparent AUC = 0.722			

Associations with Impaired Olfactory Function

The Sniff Test analysis included 71 participants with an interpretable result; nine children aged < 6 years were excluded because the test was not assessable. Reduced odor-identification performance was present in 25/49 (51.0%) allergic participants and 5/22 (22.7%) non-allergic participants, corresponding to an absolute difference of 28.3 percentage points. Fisher's exact test showed a statistically significant association between allergy and impaired olfactory function (OR = 3.54; 95% CI: 1.13–11.11; p = 0.037), supported by Pearson's chi-square test (χ^2 = 4.974; p = 0.026) and, more marginally, by Yates' correction (χ^2 = 3.893; p = 0.049). Although the observed difference was quantitatively substantial, the CI extending from just above 1 to more than 11 reflects considerable uncertainty regarding the true magnitude of the association.

Impaired olfactory function was also more frequent among patients with VKC than among controls (25/48, 52.1% vs. 5/23, 21.7%), with an absolute difference of 30.4 percentage points. Patients with VKC had approximately 3.9 fold higher odds of reduced odor-identification performance than controls (OR = 3.91; 95% CI: 1.25–12.25; p = 0.021, Fisher's exact test). Pearson's chi-square test (χ^2 = 5.863; p = 0.015) and the continuity-corrected test (χ^2 = 4.684; p = 0.030) were concordant. Compared with the association based on allergy status, the association between VKC and SniffAltered appeared slightly more consistent statistically, although precision remained limited.

In the multivariable model for SniffAltered, both VKC and allergy remained significantly associated with the outcome after mutual adjustment and control for sex and age. VKC had an adjusted OR of 3.95 (95% CI: 1.07–14.59; p = 0.039), indicating that the relationship between VKC and impaired olfactory function could not be attributed solely to the allergic component. Allergy had an adjusted OR of 3.50 (95% CI: 1.05–11.70; p = 0.042), indicating an independent contribution of comparable magnitude.

In this model, the lower CI limits were again only slightly above 1 and the p-values were close to 0.05. The direction of the effects was consistent with the bivariable analyses, but quantitative robustness remained sensitive to sample size and composition. Sex and age were not significantly associated with SniffAltered; however, the wide CIs, particularly for sex, indicate that the model lacked sufficient information to exclude clinically meaningful effects. The full multivariable model is reported in Table 3 and graphically presented in Fig. 3.

Table 3
Multivariable logistic regression for an impaired Sniff Test

Predictor	Adjusted OR	95% CI	p
Sex: female vs. male	1.25	0.25–6.16	0.784
Age: 12-month increase	1.02	0.84–1.24	0.851
VKC: yes vs. no	3.95	1.07–14.59	0.039
Allergy: yes vs. no	3.50	1.05–11.70	0.042

Overall model: N = 71; events = 30; McFadden's pseudo-R^2 = 0.117; apparent AUC = 0.709.

Explanatory Performance and Model Accuracy

The RhinoAltered model showed modest explanatory performance (McFadden's pseudo-R^2 = 0.123) and fair apparent discrimination (AUC = 0.722; bootstrap 95% CI: 0.627–0.842). After bootstrap correction for optimism, the AUC decreased to 0.672, indicating that part of the apparent performance was probably attributable to model fitting within the development sample. The SniffAltered model yielded similar findings: McFadden's pseudo-R^2 = 0.117, apparent AUC = 0.709 (bootstrap 95% CI: 0.628–0.846), and optimism-corrected AUC = 0.653. The Hosmer–Lemeshow tests showed no evidence of lack of fit, although their statistical power is limited in small samples. Overall, the models described internally consistent associations but did not demonstrate sufficient performance for individual-level prediction. Model performance and internal-validation metrics are summarized in Table 4.

Table 4
Performance of the multivariable logistic regression models

Outcome	N	Events	McFadden R^2	AUC	95% CI for AUC	Corrected AUC	Brier	H–L χ^2	H–L p
RhinoAltered	80	27	0.123	0.722	0.627–0.842	0.672	0.193	9.12	0.167
SniffAltered	71	30	0.117	0.709	0.628–0.846	0.653	0.210	5.02	0.542

Corrected AUC: bootstrap optimism-corrected estimate. H–L: Hosmer–Lemeshow test

The ROC curves were not included among the main figures because model discrimination was only fair in the apparent analysis and moderate after correction for optimism. They are nevertheless provided as Supplementary Figures S1 and S2 to fully document model performance. The forest plots were retained in the main text because they simultaneously display the direction of the effects and their limited precision. A visual summary of the study design and principal findings is provided in Fig. 4.

5. Discussion

This study identified a consistent pattern of nasal functional involvement in children with VKC. Abnormal rhinomanometry was observed in 41.8% of patients with VKC compared with 16.0% of controls, while reduced odor-identification performance was found in 52.1% and 21.7%, respectively. These differences remained evident after adjustment for age, sex, and coexisting atopy, with VKC associated with approximately fourfold higher odds of both abnormal rhinomanometry and reduced odor identification. The convergence of the findings across two distinct functional outcomes suggests that the observed involvement was not limited to a single test or dimension of nasal function.

The relationship between VKC and atopy is central to the interpretation of these results. In this study, atopy was not defined by aeroallergen sensitization alone, but by the combination of at least one positive Skin Prick Test and a clinical history consistent with allergic rhinitis. Allergic status was present in 74.5% of patients with VKC and remained associated with both outcomes, with adjusted odds ratios of 3.57 for abnormal rhinomanometry and 3.50 for reduced odor-identification performance. This finding is consistent with the established contribution of allergic inflammation to nasal obstruction and olfactory impairment in children [12, 13]. It is also compatible with the frequent, although non-universal, allergic background of VKC: a systematic review including 2,122 patients estimated the prevalence of allergic sensitization at 57.7%, with inhalant allergens, particularly house dust mites and pollens, most frequently involved [7].

However, the association between VKC and both functional abnormalities persisted after accounting for atopy. The magnitude of the adjusted associations for VKC was comparable to that observed for atopy, suggesting two overlapping but not interchangeable contributions. The composition of the control group strengthens this interpretation. Controls were recruited from the same pediatric allergology centre, and

60% were atopic; they therefore represented an allergy-enriched comparison group rather than a completely healthy population. The differences observed between groups are consequently unlikely to reflect only the presence or absence of allergic rhinitis. At the same time, these findings should not be interpreted as evidence that VKC directly causes nasal or olfactory dysfunction. Rather, they indicate that the associations between VKC and both functional outcomes were not fully accounted for by allergic status.

Previous observations support the existence of an oculo-nasal clinical continuum in VKC. Bozkurt et al. reported symptoms and signs of allergic rhinitis in 37% of children with VKC and abnormal tympanometric findings in 18.5%, suggesting that otorhinolaryngological involvement may accompany the ocular disease [11]. That study did not include an objective assessment of nasal airflow or olfactory performance and could not determine whether the extraocular findings were attributable to concomitant allergic rhinitis. The present results extend those observations by showing that an objective abnormality of nasal airflow remains associated with VKC after adjustment for atopy.

Evidence concerning olfactory involvement in VKC is even more limited. Elsürer et al. evaluated 39 children with VKC and 32 healthy controls using a modified Connecticut Chemosensory Clinical Research Center test. Odor-identification and composite olfactory scores were lower in children with VKC, including those without allergic rhinitis, while impairment was more pronounced when allergic rhinitis coexisted [14]. Our findings are consistent with this general pattern in a different population and with an age-standardized pediatric odor-identification test. More importantly, the multivariable analysis indicates that both VKC and allergic status remained associated with reduced odor-identification performance after mutual adjustment and adjustment for age and sex. The current study therefore supports and refines the hypothesis proposed by Elsürer et al.: allergic rhinitis may aggravate olfactory impairment, but it may not represent its only determinant in children with VKC.

The rhinomanometric findings provide a further element of novelty. Elsürer et al. did not identify significant differences in acoustic-rhinometry parameters between children with VKC and controls, nor a correlation between nasal-cavity measurements and olfactory scores [14]. This is not necessarily inconsistent with our results. Acoustic rhinometry mainly describes nasal geometry, whereas active anterior rhinomanometry evaluates the functional relationship between transnasal pressure and airflow. Preserved cross-sectional measurements may therefore coexist with impaired nasal airflow, particularly in inflammatory conditions in which obstruction is dynamic rather than fixed [13]. The present findings suggest that functional assessment may reveal nasal involvement not captured by anatomical measurements alone. Nevertheless, because the relationship between the two outcomes was not directly examined in our analyses, reduced odor-identification performance cannot be attributed to the rhinomanometric abnormality itself.

Several mechanisms may account for a VKC-associated nasal and olfactory involvement, although none can be demonstrated by the present study. VKC is no longer regarded as a purely IgE-mediated disorder. Its pathogenesis involves eosinophilic and T-helper 2 inflammation, but innate, neuroimmune, hormonal, and non-IgE-mediated pathways may also contribute [8–10]. Proteomic studies and molecular

investigations have further highlighted the involvement of epithelial cells, chemokines, growth factors, metalloproteinases, and neuromediators, supporting a biologically heterogeneous disease rather than a single allergic mechanism [21]. Recent classifications similarly recognize that clinically comparable VKC phenotypes may be sustained by different or mixed inflammatory endotypes [22].

Within this framework, the ocular surface and nasal mucosa may represent connected components of a broader mucosal inflammatory system. Anatomical communication through the nasolacrimal pathway, exposure to common environmental stimuli, and partially shared immune and neural networks provide biologically plausible routes through which ocular and nasal involvement could coexist. The reported immune, nervous, and endocrine components of VKC, together with the limited response of some patients to conventional antiallergic treatments, are also consistent with mechanisms extending beyond immediate IgE-mediated hypersensitivity [23–25]. The complexity observed in refractory VKC, in which systemic comorbidities, environmental exposure and individual inflammatory characteristics can influence the clinical course, further supports this multidimensional interpretation [26]. These mechanisms remain hypothetical in relation to our findings and require direct investigation.

Environmental and mucosal factors may offer additional lines of research. Air pollutants, temperature, solar radiation, and other meteorological variables have been associated with VKC exacerbations and could simultaneously influence the nasal mucosa [27]. The ocular-surface microbiota also participates in epithelial-barrier function and local immune regulation and can be modified by inflammation, environmental exposures, and topical treatments [28]. It is therefore plausible that shared exposures or mucosal responses contribute to the parallel ocular and nasal abnormalities observed in VKC. The present study did not evaluate these pathways, but its findings provide a clinical basis for studies integrating ocular and nasal biomarkers, environmental exposure, and microbiome-related data.

The results also raise a phenotypic question. Established VKC classifications are mainly based on the anatomical distribution and severity of ocular findings, including tarsal, limbal, and mixed forms and graded levels of disease activity [22, 29]. Our observations do not establish a new phenotype, but they suggest that nasal airflow and odor identification may represent additional functional dimensions of the disease. The findings therefore support overlapping associations of allergic status and VKC with nasal and olfactory abnormalities, without establishing a distinct upper-airway phenotype. Rather, atopy appears to contribute to nasal dysfunction, while VKC identifies a further component that may reflect a candidate upper-airway functional phenotype. Confirmation will require studies examining whether this involvement is related to ocular severity, clinical subtype, disease activity, duration, treatment, or specific inflammatory endotypes.

This interpretation has potential clinical implications. Current diagnostic and management recommendations understandably focus on ocular symptoms, corneal involvement, disease grading, and the prevention of visual complications [4, 15, 29, 30]. However, the frequency of the abnormalities observed in our cohort suggests that the clinical assessment of children with VKC could also include questions about nasal obstruction and changes in smell, even when allergic rhinitis is not the predominant clinical concern. A targeted allergological or otorhinolaryngological evaluation may be

appropriate in symptomatic children or in those with persistent or severe VKC. Active anterior rhinomanometry can provide an objective assessment of nasal airflow in pediatric practice, while age-standardized identification tests offer a feasible method for evaluating olfactory performance [13, 19]. The present data do not justify universal instrumental screening, but they argue against considering nasal or olfactory complaints as necessarily unrelated to VKC.

Future studies should determine whether this functional involvement changes with VKC activity and treatment and whether it persists beyond ocular remission. Stratification according to validated ocular severity grades, clinical phenotype, allergen exposure, and seasonal activity would help establish whether nasal abnormalities characterize a specific subgroup [27, 29]. Longitudinal follow-up may be particularly informative because VKC can persist into adulthood or, less frequently, present after puberty [31]. Molecular profiling of tears and nasal samples, including inflammatory, proteomic, neuroimmune, and microbiome-related markers, could clarify whether the ocular and nasal findings share a biological substrate [21, 28]. Finally, newer abbreviated olfactory-identification procedures may permit the inclusion of younger children who cannot reliably complete conventional pediatric tests [20].

In conclusion, children with VKC showed a higher frequency of both abnormal rhinomanometry and reduced odor-identification performance than controls. Allergic status remained associated with both abnormalities after adjustment but did not fully account for their association with VKC. These findings support the hypothesis that VKC may be accompanied by broader upper-airway functional involvement rather than being confined exclusively to the ocular surface. This should currently be regarded as a candidate clinical phenotype requiring confirmation, but it provides a rationale for greater attention to nasal and olfactory symptoms in children with VKC and for future studies exploring the biological links between the ocular surface and the upper airways.

6. Study Strengths and Limitations

The principal strength of this study is its integrated assessment of the relationships among VKC, allergic status, nasal airflow, and olfactory function. The combined use of rhinomanometry and the Sniff Test enabled the evaluation of two complementary dimensions of nasal function, ventilatory and sensory, which are often investigated separately. The inclusion of a control group also allowed direct estimation of the frequency of abnormalities in participants with and without VKC and quantification of the associations using clinically interpretable measures.

A further strength is the use of predefined operational definitions for the outcomes and the classification of allergic sensitization into mutually exclusive categories. The analyses were not limited to bivariable comparisons but included multivariable models evaluating VKC and allergy simultaneously while controlling for sex and age. The concordant direction of the effects in bivariable and multivariable analyses for both outcomes supports the internal consistency of the findings. Bootstrap internal validation, optimism correction of the AUC, and assessment of coefficient stability add methodological rigor by providing a more realistic evaluation of performance than apparent estimates alone.

The study nevertheless has important limitations. The overall sample was small, and the control group included only 25 participants. This limited the precision of the estimates, as reflected by the wide CIs around the ORs. Although the point estimates for VKC and allergy were approximately 3.5–4.0, the ranges compatible with the data included both substantially smaller and considerably larger effects. The findings therefore support the presence of associations but do not allow their magnitude to be estimated precisely.

The number of events was also limited relative to the four predictors included in each model: 27 events for RhinoAltered and 30 for SniffAltered, corresponding to approximately 6.8 and 7.5 events per predictor, respectively. This ratio increases the risk of overfitting, coefficient instability, and overestimation of model performance. The reduction in AUC after bootstrap correction for optimism, from 0.722 to 0.672 for RhinoAltered and from 0.709 to 0.653 for SniffAltered, supports the likelihood that performance observed in the development sample exceeds that expected in independent participants.

Validation was exclusively internal. Bootstrap analysis documented good stability in the direction of the VKC and allergy effects, but it cannot replace external validation; generalizability to other centers or populations therefore remains to be established. The marked male predominance and the inclusion of only 10 female participants also made the estimated effect of sex particularly imprecise. For the Sniff Test, excluding nine children with non-assessable results was methodologically appropriate but further reduced the sample and may have introduced selection if the excluded participants differed systematically from those analyzed.

The observational nature of the study precludes causal inference. The term “independent predictor” denotes an association that persists after adjustment for the included covariates and does not imply that VKC or allergy directly causes abnormal rhinomanometry or olfactory impairment. Residual confounding also cannot be excluded because the models did not include potentially relevant variables such as VKC severity and duration, the presence and severity of rhinitis, allergen exposure, seasonality, treatment, nasal anatomical abnormalities, or other comorbidities.

Dichotomizing originally quantitative measurements, such as rhinomanometric airflow and olfactory test scores, facilitates clinical interpretation but entails information loss and may reduce statistical power. Finally, several associations were evaluated without a formal correction for multiple comparisons. The hypotheses were specified *a priori* and were clinically related, such that a highly conservative correction could increase the risk of false-negative findings; nevertheless, the multiplicity of tests and p-values close to 0.05 require the findings to be considered exploratory. Confirmation will require prospective multicenter studies, larger and more balanced samples, and external validation.

7. Conclusions

Our findings extend the clinical perspective of VKC beyond the ocular surface. Children with VKC showed more frequent impairment of nasal airflow and odor identification, and these associations were not fully explained by coexisting allergic status. Although a distinct phenotype cannot yet be established, nasal

respiratory and olfactory involvement should be regarded as a potentially relevant and overlooked dimension of VKC. Nasal obstruction and olfactory complaints should therefore be actively investigated during clinical assessment. Further longitudinal and mechanistic studies should determine whether this oculo-nasal involvement represents a reproducible VKC-associated phenotype and whether it varies with disease activity or treatment.

Abbreviations

VKC
vernal keratoconjunctivitis
SPT
skin prick test
aOR
adjusted odds ratio
AUC
area under the receiver operating characteristic curve
CI
confidence interval
H–L
Hosmer–Lemeshow
IgE
immunoglobulin E
OR
odds ratio
ROC
receiver operating characteristic.

Declarations

Ethics approval and consent to participate:

The study was conducted in accordance with the Declaration of Helsinki and was approved by Sapienza University Ethical committee (protocol no. 4803). Written informed consent was obtained from the parents or legal guardians of all participants before enrolment.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

EP conceived and designed the study, recruited participants, collected and curated the data, performed the allergological, rhinomanometric and olfactory assessments, interpreted the results, and drafted the manuscript. GB and AG contributed to study design, statistical analysis, and data interpretation. MN performed the ophthalmological assessments. MN, LT, BLC, RC, DGG, CA, and AMZ contributed to conceptualization, supervision, and critical revision of the manuscript; AMZ also coordinated the study. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

Data Availability

The dataset generated and analysed during the current study is not publicly available because it contains participant-level clinical data but is available from the corresponding author on reasonable request.

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Figures

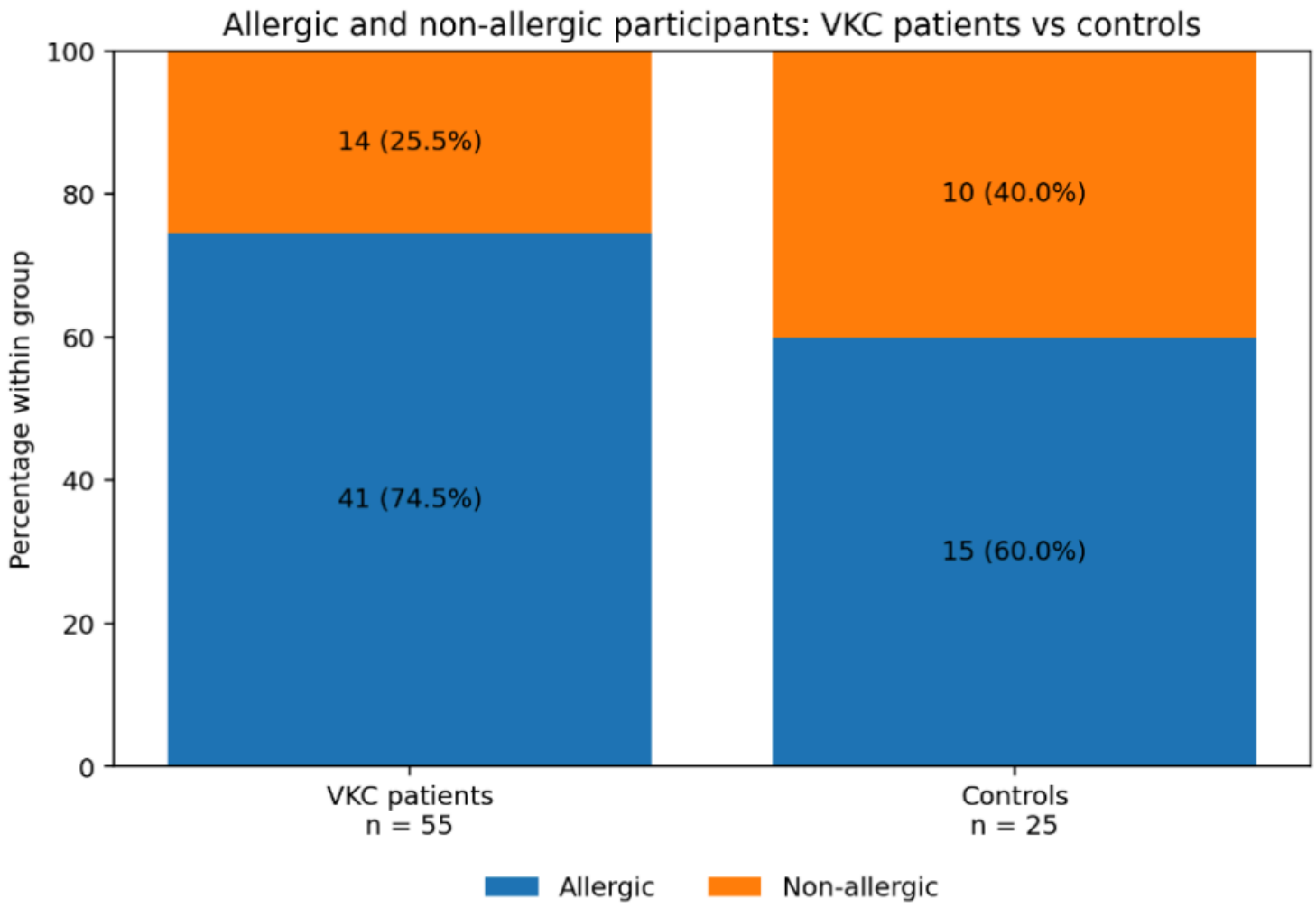


Figure 1

Percentage distribution of allergic and non-allergic children among patients with VKC and controls

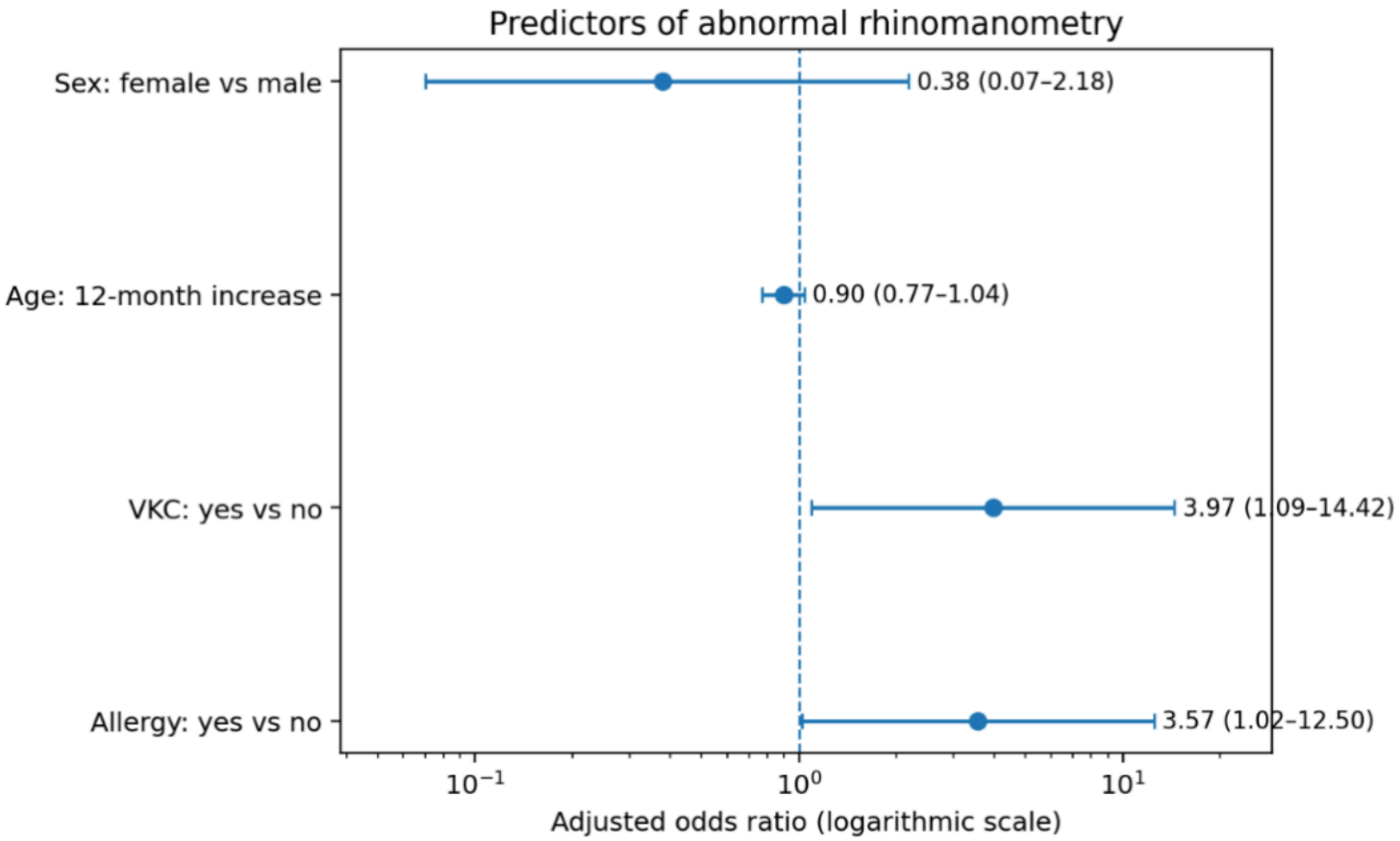


Figure 2

Forest plot of adjusted odds ratios for abnormal rhinomanometry. The horizontal axis is shown on a logarithmic scale, and the vertical line denotes OR = 1. The wide confidence intervals highlight the limited precision of the estimates.

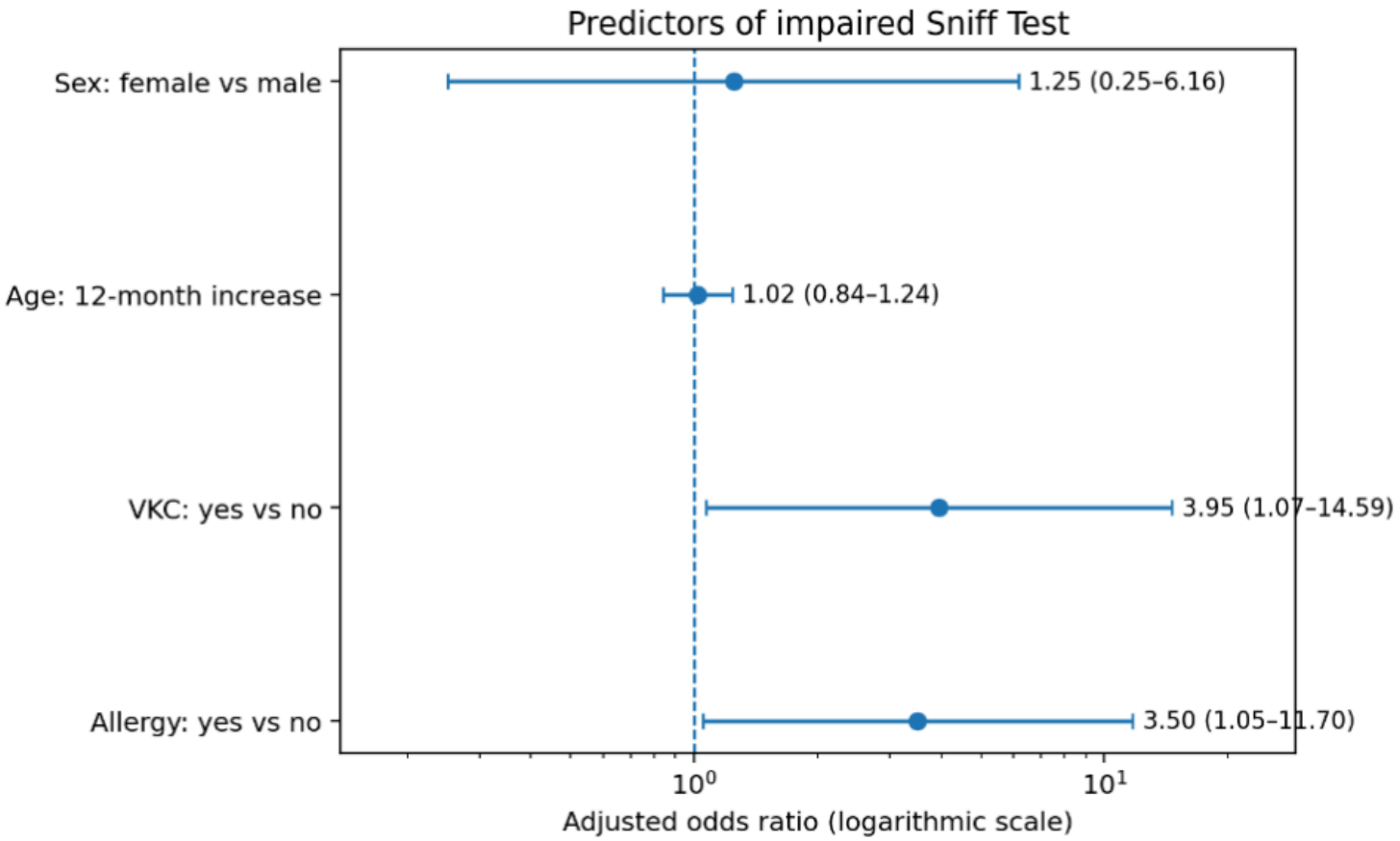


Figure 3

Forest plot of adjusted odds ratios for an impaired Sniff Test. The horizontal axis is shown on a logarithmic scale, and the vertical line denotes OR = 1. The wide confidence intervals highlight the uncertainty of the estimates.

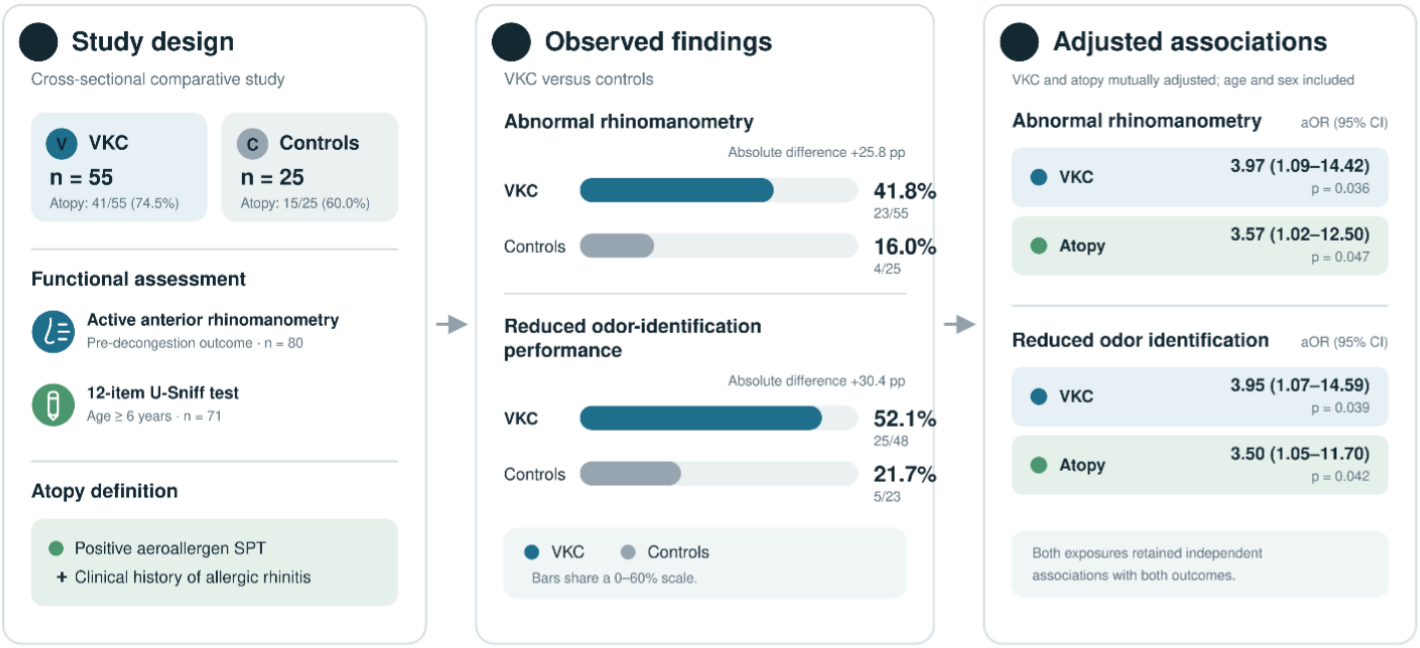


Figure 4

Visual summary of the study design and principal findings

Supplementary Files

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