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REVIEW

Tackling nasal symptoms in athletes: Moving towards personalized medicine

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Abstract

Adequate nasal breathing is indispensable for athletes, and nasal symptoms have been shown to interfere with their subjective feeling of comfortable breathing and quality of life. Nasal symptoms are caused by either structural abnormalities or mucosal pathology. Structural pathologies are managed differently from mucosal disease, and therefore, adequate diagnosis is of utmost importance in athletes in order to choose the correct treatment option for the individual. Literature suggests that nasal symptoms are more prevalent in athletes compared to the general population and certain sports environments might even trigger the development of symptoms. Given the high demands of respiratory function in athletes, insight into triggering factors is of high importance for disease prevention. Also, it has been suggested that athletes are more neglectful to their symptoms and hence remain undertreated, meaning that special attention should be paid to education of athletes and their caregivers. This review aims at giving an overview of nasal physiology in exercise as well as the possible types of nasal pathology. Additionally, diagnostic and treatment options are discussed and we focus on unmet needs for the management and prevention of these symptoms in athletes within the concept of precision medicine.

KEYWORDS
ENT, precision medicine, rhinitis, sinusitis, sports

1 | INTRODUCTION

For elite athletes, an optimal health state is indispensable in order to deliver their best athletic performances. Athletes who undertake intense aerobic exercise meet metabolic demands by significantly increasing minute ventilation, making the airways one of their most important organ systems. The link between strenuous exercise and asthma has been a long-standing source of research and debate, but more recently, interest in the upper airways of athletes has gained more attention. Although it has been demonstrated that the nasal airway contributes only for 10% of minute ventilation at maximal exercise intensity,[1] the nose plays an important role in respiratory physiology due to its position at the entry of the airways. The most important functions of the nasal mucosa are to humidify and heat up the inhaled air; however, it is also the first barrier to encounter and respond to environmental particles such as allergens, pathogens or irritants.[2]

Athletes seem to suffer more frequently from nasal symptoms compared to the non-sporting population,[3] and some data in literature suggest that factors related to the excessive ventilation and/or environmental exposures might be a causal factor for upper airway dysfunction.[4,5]

Up till now, very little data exist on the difficulties that may arise while choosing the adequate treatment strategy for this patient group that presents with specific demands related to their occupation.

The aim of this review is to give an overview on what is currently known on the relevance and causes of the different types of nasal dysfunction in athletes. Additionally, the different treatment options with their place within the anti-doping regulations as well as the open questions and unmet needs for the management of this patient group are discussed with an outlook towards further research necessities.

2 | ROLE OF SINONASAL DISEASE ON WELL-BEING AND PERFORMANCES IN ATHLETES

Thanks to filtration, humidification and heating of the inhaled air, nasal breathing is more comfortable than oral breathing and human beings are innate nose breathers at rest. The nasal septum and turbinates that are responsible for these functions create a high-resistance airway passage inside the nose. During exercise, this resistance leads to an increased breathing effort sensation and when this sensation becomes too uncomfortable, the individual will switch from nasal to oral breathing.[6] Time points at which this occurs are very variable among subjects, but it is believed to occur when laminar nasal airflow becomes turbulent.[7] Oral breathing has been shown to be more efficient than nasal breathing[8] which also implicates that blocking the nose does not form a limiting factor when looking at objective exercise parameters such as VO_2 max.[9]

2.1 | Impact on quality of life (QOL)

Despite this finding that impaired nasal breathing does not directly impair objective physiological outcome, multiple studies have shown a clear impact of nasal symptoms on patients' quality of life (QOL)[10-12] which might indirectly interfere with athletic performances. Katelaris surveyed 214 Olympic athletes and found that those who suffered from a seasonal allergic rhinitis (AR) reported significantly lower QOL scores than non-allergic athletes, which improved as the pollen count declined.[13] Walker recently published that QOL related to nasal symptoms, as measured by the Sinonasal outcome test (SNOT) 22 questionnaire, was significantly lower in athletes compared to sedentary controls[3] and lower in athletes suffering from nasal symptoms compared to healthy athletes.[14] This questionnaire comprises 22 questions related to sinonasal symptoms as well as related functional and emotional impairment, each scored from 0 to 5 (0 = not impaired; 5 = severely impaired). Surda demonstrated that this effect was greatest in swimmers as measured by the rhinoconjunctivitis quality of life questionnaire (RQLQ).[15] The RQLQ is a self-administered questionnaire evaluating seven domains of functional impairment related to rhinoconjunctivitis symptoms that are all scored on a 7-point scale (0 = not impaired, 6 = severely impaired). These higher RQLQ results in swimmers were confirmed by Bougault who even showed a normalization of nasal symptoms and QOL after a 2-week resting period.[4]

2.2 | Impact on sleep

Another indirect link between nasal symptoms and athletic performances is the impact on sleep. Multiple papers have shown the detrimental effect of rhinitis, and especially nasal congestion, on sleep.[16] A recent meta-analysis demonstrated that patients with AR score significantly higher on sleep disturbances and sleep latency tests and that they have lower sleep efficiency scores and report more frequent use of sleep medications compared to controls, as measured by the Pittsburgh Sleep Quality Index and polysomnography. They also report more nocturnal dysfunctions, such as insomnia and sleep-related breathing disorders, than individuals without nasal symptoms, as well as more daytime dysfunction including difficulty waking up and daytime dysfunction.[17] Conversely, there is more and more evidence that poor sleep quality can directly impact the performances of athletes[18] with sleep restriction studies showing adverse impacts on anaerobic power, isometric force, cortisol level and even shorter running distances on a 30-min treadmill exercise.[18,19] Also decreased sport-specific performances have been reported after (partial) sleep-deprivation.[20,21]

2.3 | Impact on athletic performance

Unfortunately, very little studies have evaluated the direct impact of nasal dysfunction on athletic performances; however, there are some papers available that suggest the presence of this link; a recent questionnaire-based study including more than 600 marathon runners demonstrated that over 80% of athletes suffering from AR reported an impact on their performances, based on how often their training activities were disturbed (reduced, postponed or shifted to indoor)during the pollen season.[22] 12.5% of the runners could not at all exercise because of pollen allergy during the season and another

10% of participants was affected in more than every second training units/sessions. Another questionnaire-based study questioned recreational athletes suffering from self-reported exercise-induced rhinitis and found that around 45% of these individuals answered 'yes' to the question whether their nasal symptoms adversely affected their athletic performances in a moderate or severe way.[23]

3 | TYPES AND PREVALENCE OF NASAL DYSFUNCTION IN ATHLETES

Nasal dysfunction can arise from either mucosal dysfunction or deformity of the anatomical structures. Mucosal dysfunction can be induced by multiple factors and can either present as rhinitis which causes symptoms of nasal obstruction, rhinorrhea, nasal itch and sneezing,[24] while rhinosinusitis patients have additional symptoms of facial pain and smell loss.[25]

3.1 | Infectious rhinitis

Viral rhinitis or 'common cold' is one of the most common diseases worldwide, and it was the principal reason for athletes to consult a doctor during both the Summer and Winter Olympic Games of 2000–2002.[26,27] Interestingly, elite athletes suffer more frequently from commons colds compared to recreational athletes[28] and they were more common in athletes with pre-existing nasal symptoms.[3] Data suggest that long-distance running increases the likelihood of having a common cold during heavy training or in the period following a marathon.[28-32] These findings imply a potential link between acute physical stress and susceptibility to upper respiratory tract infection. An exercise-induced decrease in immunoglobulin (Ig) A secretion is the most commonly reported explanation, although a study from Peters failed to show this link.[32] Other mechanisms that have been suggested are a decreased NK-cell activity and/or lymphocyte proliferative response after strenuous exercise,[33] but clear evidence is lacking. Also, it should be noted that in 30%–40% of studied cases no pathogen could be identified,[2] so the infectious component might be overestimated and other causes might lay at the base of the nasal dysfunction.

3.2 | Allergic rhinitis

Allergic inflammation is the most common cause of chronic rhinitis and responsible for inducing nasal symptoms after allergen exposure in a sensitized individual through an IgE-induced pathway.[34] A recent systematic review mentions a prevalence of AR in athletes ranging from 21% to 56.5%[35] which is comparable to the prevalence in the general population. When looking at specific sports populations however, aquatic athletes seem to suffer more frequently from AR compared to land-based athletes.[36] This might be explained by the fact that chlorination products might predispose to allergic sensitization[37]; however, this could not be confirmed by in vivo[38] nor in vitro[5] studies. It has been suggested that strenuous exercise may contribute to the development of allergic sensitization after showing a potential shift of the T lymphocyte population towards a T helper 2 subtypes upon excessive exercise.[39,40] To our knowledge, no study has demonstrated a causal relationship between exercise and allergic sensitization.

3.3 | Non-allergic and mixed rhinitis

Non-allergic rhinitis (NAR) is defined as a chronic rhinitis in the absence of infection or systemic allergen-specific IgE and comprises a very heterogenous patient group.[41] In everyday life, an overlap between AR and NAR is very frequently seen and addressed as mixed rhinitis. So far, reliable data on the occurrence of NAR in the athlete population are scarce but studies reporting on mixed rhinitis show a prevalence as high as 74% in athletes.[35]

Within all sports disciplines, NAR is again most frequently reported in aquatic athletes, possibly due to exposures to pool chlorination products. Several studies showed a significantly higher prevalence of NAR in swimmers compared to non-swimming athletes and controls.[3] Gelardi and colleagues showed that within a population of swimmers with rhinitis, 76% had NAR of whom 35% presented with a neutrophilic nasal inflammation.[42] Another study confirmed this neutrophilic nasal influx in swimmers, in combination with an increased MCT compared to controls.[42,43] A recent study showed an increase of neuropeptides and epithelial injury markers in nasal secretions of swimmers after training, suggesting a direct irritant effect on the airway mucosa of the chlorination products, which has also been shown in a mouse model of chlorine-induced airway hyperreactivity.[38] Also, air pollution might induce non-allergic dysfunction: the nasal mucociliary clearance time (MCT) was prolonged in runners who ran in polluted streets when compared to running in the woods,[44] although the inflammatory response to exposure to pollutants seems more mitigated in athletes compared to sedentary controls.[45]

3.4 | Nasal hyperreactivity

Nasal hyperreactivity (NHR) which is a frequent hallmark of rhinitis is characterized by the induction of nasal symptoms upon encounter of unspecific environmental stimuli and is believed to play an important role in athletes.[46,47] Exposure to cold temperatures is one of the most important triggers for NHR.[48,49] The perception of cold temperature is regulated by transient receptor potential melastatin 8 (TRPM8), a cation channel belonging to the TRP superfamily.[50,51] In the lungs, cold-mediated activation of TRPM8 leads to increased expression of several cytokine and chemokines,[51] suggesting a close involvement of TRMP8 in airway inflammatory responses induced by cold air. Li, 2011 #532}. Cold-induced NHR can be an issue for winter sports athletes; which has been confirmed by Bonadonna who reported on a prevalence of almost 50% of cold-induced rhinorrhea in over a hundred skiers, independent from their atopy state.[52] Also, exposures to environmental irritants such as pollution and chlorination products in outdoor and aquatic athletes might induce rhinitis symptoms in those with pre-existing rhinitis with NHR, even in the absence of a direct irritant effect. This reaction is most likely also provoked via activation of the sensory nerves expressing TRP receptors since TRPA1 has been emerged as the major airway irritant detector.[53]

3.5 | Exercise-induced rhinitis

It has been postulated that laborious exercise has a direct negative effect on nasal functioning and can lead to 'exercise-induced rhinitis'. In healthy individuals, exercise promotes a decrease in nasal airway resistance due to an increased sympathetic tone upon a rise in the arterial pCO2[54]; however, in patients suffering from pre-existing rhinitis, isometric exercise induces conversely an increase in nasal resistance, probably due to an abnormal neurogenic regulation of the nasal mucosa in these patients.[48] There are also data that strenuous exercise can lead to rhinitis symptoms and nasal inflammatory changes by itself. One study found a nasal neutrophil influx after a 20-km race in combination with a significantly prolonged MCT after the race.[55] At the level of the lower airways, two distinct exercise-induced phenotypes are described: exercise-induced asthma (EIA) and exercise-induced bronchoconstriction (EIB). EIA implies a background of airway hyperresponsiveness that may be exacerbated by exercise. EIB implies airway hyperresponsiveness that is solely triggered by exercise. It can be accepted that the same holds true for rhinitis and a distinction between exercise-induced rhinitis (EIR) and exercise-induced nasal hyperreactivity (EINHR) can be a topic for future discussion.

3.6 | Rhinosinusitis

To our knowledge, hardly anything is known about rhinosinusitis in athletes. Gelardi mentions in his study that 3% of swimmers had an acute rhinosinusitis[42] and one other study describes sinonasal mucosal hypertrophyin divers, possibly due to pressure differences.[56] However, to our knowledge, no study has investigated the presence of chronic rhinosinusitis (CRS) in the athletic population, although an increased prevalence lies within the line of expectation since infection and atopy are considered to be risk factors for CRS.[25]

3.7 | Structural pathology

Not all nasal symptoms are due to mucosal pathology, and structural abnormality of the nasal septum, pyramid or tip is one of the most common reasons for nasal obstruction[57] and might be congenital or acquired. In these patients, nasal airway resistance is increased, which can lead to reduced or uncomfortable nasal breathing.[58] The impact of this nasal obstruction on QOL is measured by the nasal obstruction evaluation (NOSE) questionnaire that consists of five questions scored from 0 (no problem) to 4 (severe problem) and even includes the question about the individual's ability to get enough air through his/her nose during exercise, highlighting the importance of a patent nasal airway during sports. In certain contact sports, nasal trauma is a frequent complication that can potentially lead to structural pathology. This was confirmed by Passali who demonstrated in seventeen boxers a significantly higher nasal resistance, compared to the normal population reference values.[59] Other studies that support the importance of structural pathology in exercise are the studies that discuss the effect of nasal dilators that decrease the nasal resistance and are discussed below.

4 | MECHANISMS OF UPPER AIRWAY ILLNESSES IN ATHLETES

Although more and more attention has gone towards the mechanisms of asthma symptoms in athletes, studies focusing on upper airway pathophysiology in this population are rather scarce. However, the upper airway epithelium is the gateway keeper of the respiratory tract and continuously exposed to environmental molecules and physical strains. It consists of several cell types, each playing their role in modulating mucosal homeostasis.[60] Several mechanisms that interfere with this homeostasis may be involved in the development of upper airway symptoms in athletes[29,61] (Figure 1). When looking at the lower airways, the classical theory explaining EIB states that the increased ventilation during intense exercise induces water loss, cooling and dehydration of the airway mucosa which lead to a secondary stimulation of the cholinergic receptors. But there is more and more evidence that increased ventilation and sport-specific environmental factors (eg pollution, cold air or chlorination products) can cause a direct epithelial damage, inducing airway inflammation.[62] Additionally, also the sensory nerves can detect and respond to both cold temperatures[63] and humidity[64] via the TRP receptors. With regards to the concept of the global airway, one can speculate that similar mechanisms are playing at the level of the upper airways. The potential interplay between these exogenous and endogenous factors is depicted in Figure 1.

5 | DIAGNOSIS

Diagnosis starts with taking a thorough history about symptoms, sport environment and a possible link between these two. Questions about triggering factors or symptom improvement after a resting break or treatment are useful. Clinical examination should include both evaluation of the external and internal nose. The general aspect of the nasal mucosa, the nasal septum and the nasal valve can be appreciated with anterior rhinoscopy. Nasal endoscopy offers the advantage of a global evaluation of the nasal cavity and sinus outflow tracts.[65] Examination of the external nasal pyramid and tip with valve tests will give information about important structural abnormalities, nasal valve dysfunction and alar collapse.[66]

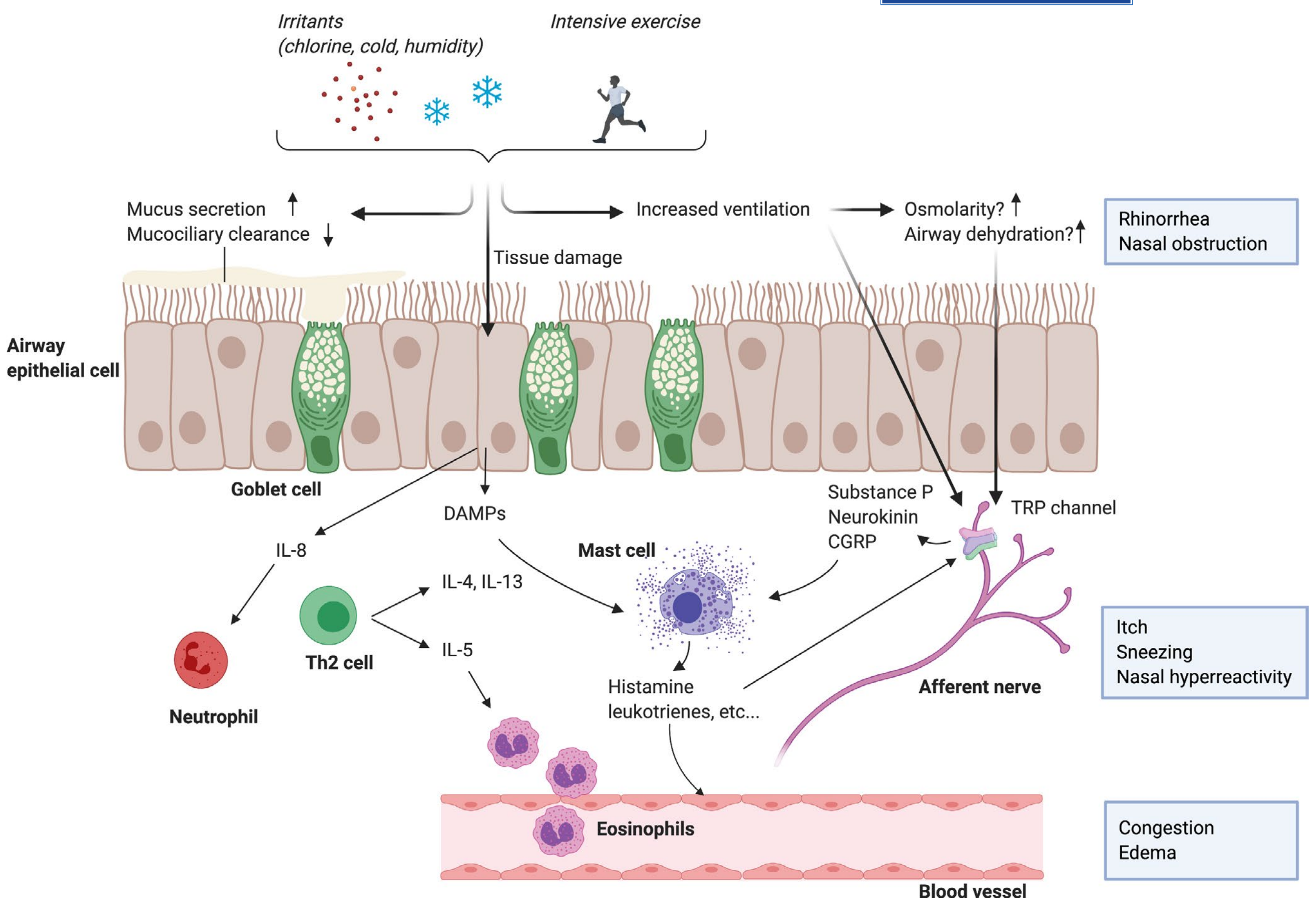

FIGURE 1 Immunological mechanisms contributing to upper airway symptoms in athletes. Different sport-specific exogeneous triggers to which athletes are exposed (cold, pollution, environmental irritants, increased ventilatory flow) are believed to trigger the respiratory sinonasal epithelium, as well as the underlying nervous system. This activation can lead to the direct induction of nasal symptoms such as rhinorrhea, itch and NHR. Long-term or repetitive exposure to these triggers might lead to an activation of the innate and adaptive immune system, inducing a more chronic nasal inflammation. Th2: T helper 2 lymphocyte; IL: interleukin; TRP: transient receptor potential; CGRP: calcitonin gene-related peptide. Created with BioRender.com

Technical examinations such as anterior rhinomanometry, acoustic rhinometry and peak nasal inspiratory flow measurements and can be used to objectify reported nasal blockage and measure nasal resistance.[67] However, these objective measurements do not always correspond well with symptoms of nasal obstruction and results should always be correlated with subjective parameters.

Every athlete with airway symptoms should be screened for allergies as a causal factor of rhinitis. The validated AQUA questionnaire is often used to identify athletes with allergic disease.[68] Although a useful screening tool (specificity of 97.1% when score >5), the sensitivity is quite low (58.3%)[69] and might be due to the fact that athletes often misinterpret the cause of their nasal symptoms as being allergic or not. Since several of the epidemiological studies in athletes are based on this questionnaire,[70,71] the current prevalence of AR among athletes remains unclear. However, the final diagnosis of AR is based upon a correlation between typical nasal symptoms and the systemic detection of allergen-specific IgE, either by skin prick test (SPT) or in the serum.[72] One Polish study that combined data from the AQUA questionnaire with SPT and previous doctor diagnosis in 220 Olympians found a clear mismatch between self-reported AR (27%), SPT-confirmed AR (21%) and doctor-diagnosed AR (9%).[73]

When allergic symptoms and systemic IgE detection do not correlate, a specific nasal allergen challenge (NAC) can be considered.[74] Nasal cold-dry air (CDA) challenge can objectify the presence of NHR.[49] Unlike exercise-induced bronchoconstriction (EIB), no specific test is currently available to diagnose exercise-induced rhinitis which is consequently solely based on history and self-reporting.

6 | TREATMENT OPTIONS

Different types of nasal pathology in athletes should be treated according to the respective guidelines.[24,25,75] However, due to the World Anti-Doping Agency (WADA) regulations,[76] athletes ought to adhere to strict regulations in terms of pharmacological treatment. Treatment differs between mucosal and structural pathology and options are summarized in Table 1.

TABLE 1 Treatment options for nasal symptoms in athletes according to the causal pathology and the current WADA regulations[72]

Treatment/ intervention	Disease	WADA rules	Notes
Trigger avoidance	AR, NAR, CRS	Allowed	Not always feasible to achieve.
Saline douchings	AR, NAR, ARS, CRS	Allowed	Very safe and cheap treatment option recommended as an adjunct for all mucosal pathology Might be considered specifically for symptomatic swimmers after leaving a chlorinated pool
Decongestants	Infectious rhinitis, ARS	Allowed: phenylephrine, phenylpropanolamine, adrenaline, xylometazoline and synephrine Allowed in limited concentrations: cathine, ephedrine and methylephedrine, pseudoephedrine Not allowed: sympathomimetic amines	Overuse can lead to rhinitis medicamentosa with paradoxal chronic nasal obstruction
Intranasal corticosteroids	AR, NAR, ARS, CRS	Allowed, TUE is not required	Transient side effects: minor epistaxis, nasal dryness and irritation of nose and throat Golden standard for chronic mucosal sinonasal pathology
Oral corticosteroids	Severe therapy-resistant AR	Allowed with TUE. Indications are rare for AR	Gastro-intestinal, cardiovascular, ocular, psychiatric side effects. Avascular necrosis, suppression of HPA axis, osteopenia, diabetes mellitus, increased infection rate
Antihistamines	AR	Allowed	Side effect: first-generation antihistamines can have a sedative effect. Second-generation and later antihistamines are less sedative
Cromoglycates	AR	Allowed	Less effective in suppressing nasal symptoms than antihistamines
Antileukotrienes	AR	Allowed	Comparable efficacy to antihistamines, but no sedation
Allergen Immunotherapy	AR	SLIT: Allowed SCIT: Allowed	Immunotherapy should be started before competition Local and systemic side effects are reported, more in SCIT than in SLIT Exercise is prohibited on day of injection for SCIT
Nasal dilators	Structural pathology	Allowed	No clear effect on physiological parameters, however, beneficial effect on subjective breathing
Surgery	Structural pathology, AR, NAR, CRS	Permitted	(Rhino)septoplasty is an option for medically resistant nasal obstruction in the presence of structural abnormalities Turbinoplasty can be considered in medically resistant, reversible nasal obstruction due to turbinate hypertrophy Endoscopic sinus surgery is an option in CRS patients in whom maximal medical therapy has failed

Abbreviations: AR, allergic rhinitis; NAR, non-allergic rhinitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TUE, therapeutic use exemption; HPA, hypothalamic-pituitary-adrenal.

6.1 | Treatment of mucosal pathology

6.1.1 | Trigger avoidance

A very safe, cheap and adequate treatment option is the avoidance of triggering agents.[77] For AR patients, this means allergen avoidance, but for all athletes suffering from NHR, exposure to unspecific triggers such as airway irritants, pollution and cold temperatures should be circumvented whenever possible. For some athletes, this may be hard to accomplish; winter sports athletes cannot avoid exposure to cold temperatures and outdoor athletes will always be exposed to pollens and/or pollution. Also, for swimmers, exposure to chlorination products is basically unavoidable. In indoor pools, trichloramine is the chlorination by-product that is most closely related with respiratorysymptoms[78,79] and the WHO regulations demand a maximum level of 0.5 mg/m^3 trichloramine in the air of indoor swimming pools.[80] Yet, in most countries, regular monitoring of swimming pool water and air is rarely performed.

6.1.2 | Saline douches

Nasal douching is cheap and safe, and an important part of the management of both rhinitis and rhinosinusitis that do not interfere with the WADA regulations. Especially in symptomatic athletes exposed to irritants (swimmers, runners in polluted areas), this is a valuable option. Since the WHO recommends to shower and clean off the chlorine after exposure to a chlorinated swimming pool,[80] it seems logical to clean the nasal mucosa after swimming, although no data are available on the action of nasal saline douchings in rhinitis prevention.

6.1.3 | Decongestants

Short-course treatment with nasal or oral decongestant can be beneficial in treating a common cold but should be limited to a maximum of 7 days. WADA allows some decongestants (caffeine, phenylephrine, phenylpropanolamine, adrenaline, xylometazoline and synephrine) and restricts others to a certain dose ((methyl)ephedrine <10 μg/ml and pseudoephedrine <150 μg/ml in urine). Most other decongestants, especially those containing sympathomimetic amines or stimulants are currently prohibited by the WADA.[76] The list of prohibited drugs changes annually, so physicians should verify when prescribing these products to athletes. Moreover, the use of oral decongestants can lead to a series of side effects such as tachycardia, tremor, insomnia, elevated heart rate and blood pressure, which can be problematic for athletes. Unfortunately, in many countries, these drugs are available on an over-the-counter base and therefore athletes need to be counselled about the actual prohibited substances.

Decongestants do not have a part in the treatment of AR, NAR or CRS because of the risk of inducing rhinitis medicamentosa, a decongestant-induced paradoxical swelling of the nasal mucosa.

6.1.4 | Glucocorticosteroids

Intranasal steroids (INS) as a maintenance treatment are the first therapy of choice in moderate/severe and persistent AR, CRS and most forms of NAR.[24,25,75] In athletes specifically, they have shown to reduce symptoms and improve QOL significantly for AR.[81] Furthermore, they are known to have a beneficial effect on asthma symptoms.[24] Interestingly, the use of INS has been reported to revert the paradoxical increase in nasal resistance upon isometric exercise which is seen in NAR[48] and might therefore be the ideal treatment for athletes with NAR and/or exercise-induced rhinitis.

The use of INS is presently permitted by WADA without a therapeutic use exemption (TUE).[76] However, literature suggests that athletes may not be fully aware of those regulations since several studies show that athletes with rhinitis are much less adherent to their INS compared to non-athletes; Surda showed that chronic nasal medication was significantly less taken by elite swimmers with nasal symptoms (18%) compared to symptomatic non-sporting controls (67%),[3] and Walker showed that elite hockey players were much less adherent to their INS compared to non-elite players and sedentary controls.[14] Adverse effects of INS include minor epistaxis, crusting, nasal dryness and irritation of the throat and nose; however, most of these side effects are transient and rarely require stopping INS treatment, even on a long-term base.

It is worthwhile mentioning that WADA allows physicians to treat severe AR with systemic glucocorticosteroids under the TUE rule. However, in view of the possible side effects, indications for treating AR with oral or depot steroids are extremely rare and preserved for uncontrolled AR with severe symptoms not responding to any other medical therapy including allergen immunotherapy (AIT).[82]

6.1.5 | Antihistamines

Antihistamines are a first-line treatment for athletes suffering from AR and are currently allowed by the WADA regulations.[76] They are very effective for treating histamine-induced symptoms such as rhinorrhea, sneezing and itch, but are somewhat less effective on nasal obstruction[83] and therefore often combined with INS. Surprisingly, two RCTs have also shown a beneficial effect of topical azelastine in NAR patients,[84,85] probably due to secondary effects on neuropeptide release. In most countries, a combination formulation of intranasal azelastine with the INS fluticasone propionate (MP-029) is available and has been shown to be effective in reducing symptoms in a population of both AR and NAR patients [86] with a specific reduction of NHR in AR patients.[87]

The above-mentioned study by Walker, however, has shown that antihistamines were rarely used by elite hockey players when compared to recreational players or non-sporting controls.[14] It was believed to be due to the athletes' fear of side effects of these kinds of drugs or misperception of WADA regulations. Nonetheless, it is well known that second-generation antihistamines are much less sedative than older antihistamines and cardialarythmias are only seen with overdosing.[88,89] Topical antihistamines have no side effects but 4
the disadvantage of shorter duration of activity.[24]

6.1.6 | Cromoglycates

Cromolyns are mast cell stabilizers that can be used intranasally. They are moderately effective in treating mast cell-related nasal symptoms (itch, rhinorrhea, sneezing)[24] but inferior to antihistamines. Despite their short half-life and duration of activity, they show a very good safety profile and are at the moment authorized by the WADA's regulation.[76]

6.1.7 | Antileukotrienes

Leukotriene receptor antagonists block the functions of leukotrienes on the local environment and have been shown to have an efficacy in AR patients comparable to antihistamines[24] and might be an added value in athletes suffering from AR with concomitant asthma.[90] In contrast to antihistamines, they do not cause sedation and they are currently also permitted by the WADA regulation.[76]

6.1.8 | Allergen immunotherapy

Allergen immunotherapy is the only disease-modifying treatment option for athletes suffering from AR, because of its capability to induce immune tolerance leading to long-term disease control.[91] Multiple studies have proven that AIT is effective in reducing symptoms and rescue medication, as well as in improving QOL in the general AR population.[91] AIT is administered either subcutaneously (SCIT) or in a sublingual way (SLIT) with SCIT being slightly more effective but SLIT showing a better safety profile. Both types are permitted by the WADA regulations.[76] SCIT usually precludes performing exercise on the administration day, which should be a factor to be considered in athletes.

To our knowledge, there is only one study that included athletes on AIT; this German questionnaire-based study compared athletes with AR treated by AIT to athletes with AR treated by either pharmacological or non-pharmacological alternative treatments.[22] Although appropriate statistical calculations are missing, they show that in athletes treated by AIT, the pollen season had a lower effect on their trainings, compared to AR athletes treated by other means. These results might be biased by the fact that AIT patients per definition have sought medical help and are in medical follow-up, while this is not necessarily the case for the other groups. Interestingly, a post hoc analysis showed that the majority of athletes were not aware or had misbeliefs about the different anti-allergic treatment options, which is not very different from the general population. Practically, when prescribed in athletes, it is recommended to start AIT a few months before the competitive season because the initial phase can be accompanied with local or systemic side effects, more so for SCIT than for SLIT.

6.2 | Treatment of structural pathology

6.2.1 | Nasal dilators

Nasal dilators can be either fixed on the nasal dorsum or introduced in the nostrils, in order to open up the nasal valve region and reduce airflow resistance at this highly resistant area. These dilators are an elegant, non-surgical solution for alar insufficiency, leading to an important increase of nasal flow and good patient satisfaction in the general population.[92] They became very popular in the late eighties in the athletic population because they were initially believed to

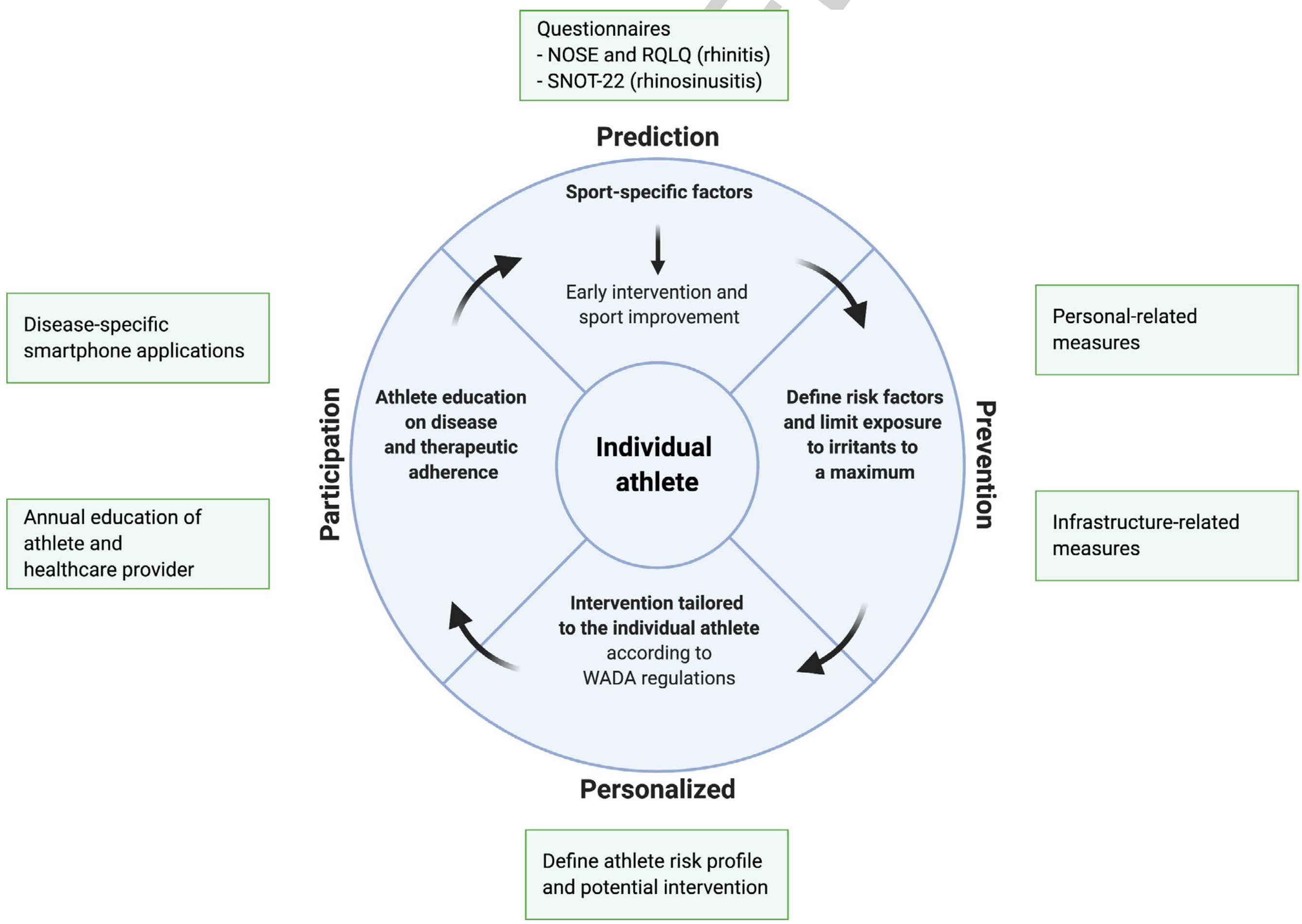

FIGURE 2 Implementation of personalized medicine to the management of an athlete with nasal symptoms. SNOT-22: sinonasal outcome test-22 questionnaire; RQLQ: rhinoconjunctivitis quality of life questionnaire; NOSE: nasal obstruction symptom evaluation. Created with BioRender.com

improve performances. Dinardi recently reviewed the effects of external nasal dilators on physical exercise[93] and performed one study using an internal nasal dilator.[94] Most of the studies reviewed are of limited methodological quality and fail to demonstrate an objective effect on total VO_2max, heart rate or total exercise time,[93] but some studies indicate that nasal dilators can improve subjective exertion rates[95] and nasal breathing[96] during exercise. This corresponds to what is found in the non-athletic population where nasal dilators can also improve subjective nasal breathing in patients with nasal valve dysfunction. It needs to be noted that almost all of the exercise-based studies were performed in asymptomatic healthy athletes; only one has considered nasal dilators in adolescents with AR.[97] However, none of these studies reported on rhinoscopy findings or data on structural abnormalities such as septal deviation or valve pathology in the tested athletes, which would be the key determinants for the therapeutic effect of nasal dilators.

6.2.2 | Surgery

Nasal surgery can be a treatment option for medically resistant nasal obstruction due to structural pathology at the level of the nasal bones or cartilage.

Septoplasty is the most commonly performed surgical ENT intervention in adults; however, due to a lack of controlled trials, clear evidence on its effectiveness is currently lacking.[98] One of the possible reasons for septoplasty failure could be an unaddressed nasal valve insufficiency. In this case, septorhinoplasty could bring a solution, although also for this type of intervention, evidence on functional benefit is mostly lacking. Endoscopic sinus surgery is indicated in CRS patients who fail to respond to maximal medical therapy.[25]

To our knowledge, apart from one study showing a benefit of early reduction of sport-induced nasal fracture,[99] no studies are available on the benefit of nasal surgery in athletes. As is the case for the general population, the key factor is to make the correct surgical indication and mucosal pathology should be excluded and/or treated before deciding on surgical intervention.

7 | RECOMMENDATIONS FOR THE APPLICATION OF PERSONALIZED MEDICINE

It goes without saying that not every therapeutic option mentioned in the previous paragraph is suitable for every athlete that suffers from nasal symptoms. In order to offer an optimized treatment to every symptomatic athlete, we suggest to follow

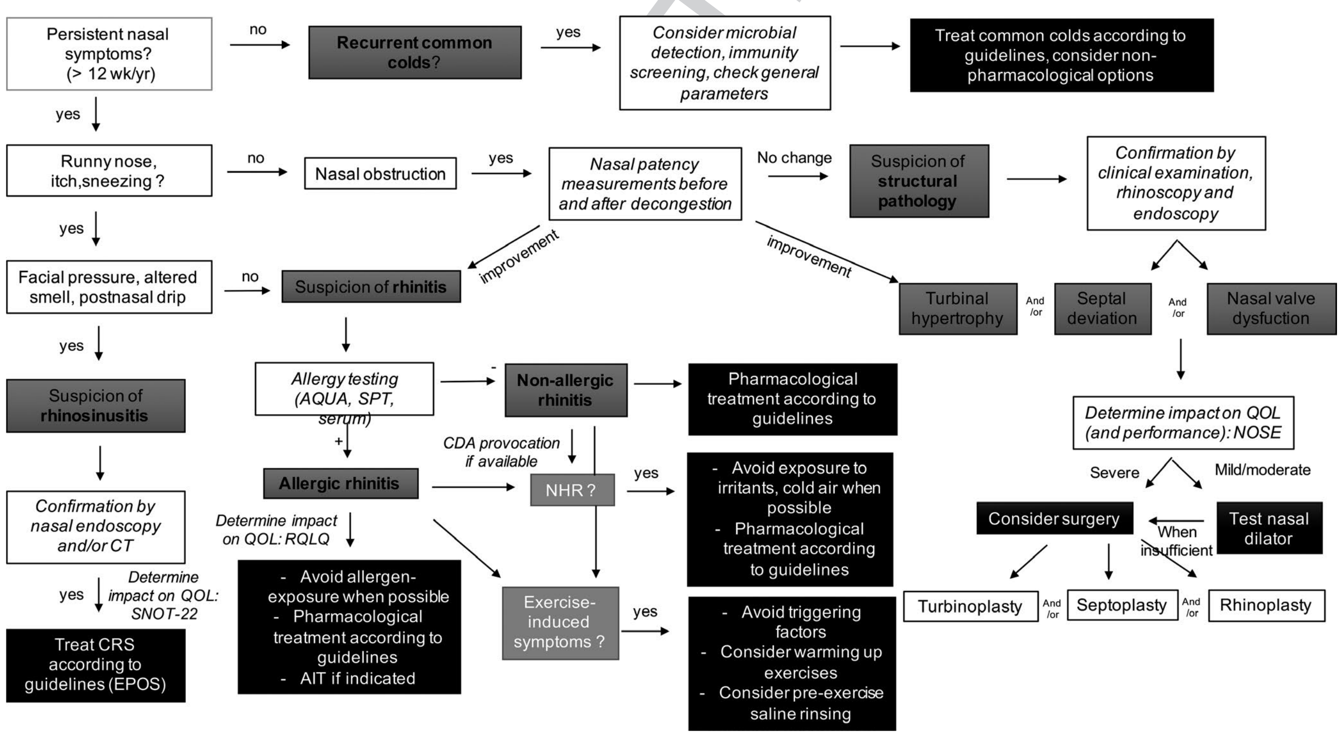

FIGURE 3 Diagnostic flow chart of a hypothetical athlete presenting with nasal symptoms. The flow chart is based on initial type and timing of symptom presentation. By combining elements from history with clinical examination, rhinoscopy, nasal endoscopy, imaging, nasal patency measurements and technical examinations, an adequate differential diagnosis can be made in an athlete with nasal symptoms. When a diagnosis has been made, the impact on QOL (determined by means of specific questionnaires) and sports performance will determine the velocity by which more advanced therapeutic strategies will be initiated. AQUA: allergy questionnaire for athletes; SPT: skin prick test; QOL: quality of life; SNOT-22: sinonasal outcome test-22 questionnaire; RQLQ: rhinoconjunctivitis quality of life questionnaire; NOSE: nasal obstruction symptom evaluation questionnaire; NHR: nasal hyperreactivity

TABLE 2 Application of the 4P's-concept of personalized medicine for the management of nasal symptoms within the athletic population

P	Problem	Proposed solution
Prediction	Certain sport-specific factors are believed to predispose to upper airway symptoms	Screen athletic populations at risk (eg aquatic sports, ultra-endurance athletes) regularly for upper airway symptoms.
	Certain athletes will be bothered more by nasal symptoms than others	Evaluation of the **impact on QOL** of the nasal symptoms by QOL-specific questionnaires: • NOSE (nasal obstruction) • RQLQ (rhinitis) • SNOT-22 (rhinosinusitis) → moving up treatment scheme more rapidly in patients with severe impact
	Outdoor athletes suffering from seasonal allergies will suffer more during pollen seasons	**Perform allergy testing** (AQUA +SPT/serum test) **in symptomatic athletes** in order to predict and manage the symptomatic period depending on a specific country's pollen season
	Rhinitis and rhinosinusitis are risk factors in the development of asthma or BHR	Screen athletes with rhinitis and rhinosinusitis for lower airway problems
Prevention	Environmental airway irritants can trigger and/or cause nasal symptoms	**Avoid irritants where possible**: Aquatic athletes: • non-chlorinated pools if available. • Monitor and adapt environmental levels of chlorination (by) products. Outdoor athletes should avoid training in (highly) polluted environments
	Outdoor athletes suffering from seasonal allergies will suffer more during pollen seasons	**Athletes with seasonal allergies should be treated accordingly** (AH, AIT) when performing outdoor during the allergy season **or train indoor**
	Exposure to cold-dry air induces NHR	Pre-exercise warm-up respiratory exercises? (to be investigated)
	Increased ventilation might induce dehydration of the nasal mucosa	Pre-exercise saline nasal douching? (to be investigated)
Personalization	Different types of nasal symptoms require different management options	**Individual diagnosis and adaptation of therapeutic option accordingly**: • structural vs. inflammatory pathology • allergic vs. non-allergic cause of inflammation • rhinitis vs. rhinosinusitis **Follow diagnostic algorithm**
Participation	Adherence to prescription drugs has been shown difficult in athletes	**Information and education of athletes** and physicians about • their disease and its impact • action of prescribed drugs • known side effects of drugs • prohibition status by WADA can increase adherence. Smartphone applications might play a role

Note: Priorities are highlighted in bold.

Abbreviations: AH, antihistamine; AIT, allergen immunotherapy; BHR, bronchial hyperreactivity; NHR, nasal hyperreactivity; NOSE, nasal obstruction symptom evaluation; QOL, quality of life; RQLQ, rhinoconjunctivitis quality of life questionnaire; SNOT, sinonasal outcome test; WADA, world anti-doping agency

the concept of precision-based medicine, which is based on the 4P's: prediction, prevention, personalization and participation[100] (Figure 2). By predicting which athletes are at risk to develop nasal symptoms and which of them will be most bothered by them, early interference might prevent the development of symptoms or their interference with athletic performances. Reducing exposures to sensitized allergens and irritants wherever possible can prevent the development or aggravation of nasal symptoms. By investing in an adequate diagnosis of the cause and type of nasal symptoms, a more personalized therapeutic strategy can be offered to the symptomatic athlete. A diagnostic algorithm, including history, clinical examination, endoscopy, imaging and technical exams, can help the physician to obtain an adequate diagnosis (Figure 3). Following this diagnostic algorithm, there can be decided upon more or less advanced therapeutic interventions according to the impact of the symptoms on QOL and/or performances. For most of the athletes that suffer from rhinitis or rhinosinusitis, pharmacological treatment will be part of their management scheme. However, therapeutic adherence is an important issue in athletes[22] and participation of both patient and healthcare provider forms an essential part of their treatment. They should be informed about their disease and its impact, efficacy of pharmacological and

TABLE 3 Open Research questions and unmet needs in the field of nasal disease in athletes are mentioned in the left column. In the right column proposals are given for studies that can answer these questions. AR: allergic rhinitis; NAR: non-allergic rhinitis; CRS: chronic rhinosinusitis. EIR: exercise-induced rhinitis

Open research questions	Future study perspectives
Accurate epidemiological knowledge on different types of upper airway pathology	Design proper epidemiological studies in large and variable populations of athletes, including correct definitions of AR, NAR and CRS, preferably with doctor visits for proper diagnosis.
The direct impact of nasal symptoms on athletic performances	More studies investigating sport-specific performances in athletes with nasal symptoms due to AR (in and out of season) or structural pathology (before and after surgery).
Knowledge on the concept of EIR	• Study whether post-endurance rhinitis is due to either infectious, environmental or endogenous triggers. • Properly designed mechanistic studies on the effect of strenuous exercise on the nasal airway physiology / immunology. • Properly designed mechanistic studies on the effect of different sport-related environmental factors on the nasal airway physiology / immunology.
Diagnosis and management of EIR	• Studies to evaluate symptoms and nasal patency in patients before and after exercise. • Development of a test to diagnose EIR • Investigating the effects of pre-exercise warm-up exercises or nasal humidification on nasal symptoms
The role and management of nasal structural pathologies in athletes	• Mapping the presence of structural pathologies within the athletic population and their effects on subjective nasal breathing and sports performances • Studying the objective and subjective effects of nasal dilators in athletes with nasal valve dysfunction.

non-pharmacological treatments, possible side effects and how they fit within the WADA regulations. Since WADA regulations change constantly, updated and country-specific information on the prohibited status of medication can be sought via the website of Global Drug Reference Online (Globaldro).[101] Disease-specific smartphone applications delivering patient education and following symptoms might be useful in this regard. A list of strategies that can be applied for the implementation of the 4 P's is given in Table 2.

8 | UNMET SCIENTIFIC NEEDS AND FUTURE PERSPECTIVES

Due to a lack of knowledge, evidence and attention for the impact of nasal symptoms on athletic performances in athletes, several unmet needs persist regarding this topicy.[105,106] First of all, more well-designed epidemiological studies are needed, involving both experts in sports medicine as well as in upper airway pathology, in order to get a proper idea about the occurrence of the different types of rhinitis and rhinosinusitis, using proper definitions and diagnosis by specialists. This could not only give us an indication about the true frequency of this problem, but also about the (sport-related) risk factors for both allergic and non-allergic subtypes. Ideally, these studies need to include questions and outcome parameters of athletic performances in order to determine a possible direct impact of upper airway symptoms on the athlete's performance.

In the last decades, a lot of research has been devoted to investigate mechanisms, diagnosis and management of EIB. Unfortunately, this does not hold true for its upper airway counterpart and at present, we are not sure whether EIR is a true concept and how it should be defined. Adequately set-up studies investigating athletes from variable sports categories and variable sport-specific environments should examine functional and immunological changes in the nasal airway before and after exercise. Gaining more insight in mechanisms of upper airway symptoms in athletes related to exercise and unfavourable circumstances will lead to a better clinical diagnosis and individual-tailored treatment in athletes.

Within this regard, various non-pharmacological interventions, such as pre-exercise nasal saline rinses or warm-up exercises, that might interfere with sport-related strains on the upper airway mucosa, need to be investigated.

Currently, basically nothing is known about the impact of nasal structural abnormalities leading to a narrow nasal valve area on nasal breathing during exercise, despite the fact that increased nasal flow generally worsens the valve problem. None of the studies that investigate the effects of nasal dilators in athletes have looked at the presence of septal deviations or nasal valve dysfunction, while this is a key aspect to consider when prescribing devices that open up the nasal valve. Since elective surgery is often not easy to fit into a busy training scheme, nasal dilators might be a good (temporary) option in athletes that suffer from nasal valve dysfunction. A proposal for future studies that can be designed in order to answer the above-mentioned questions and needs is made in Table 3.

9 | CONCLUSION

Regarding the obvious importance of adequate breathing for athletes, a lot of attention has been paid to lower airway symptoms in this population. Because of the minor effects of improving nasal patency on objective physiological exercise parameters, nasal symptoms are often overlooked in athletes. However, in addition to the well-known impact of nasal symptoms on QOL in general, subjective exercise parameters such as exertion perception and breathing comfort are affected by nasal dysfunction. Therefore, we plead for an increased awareness for nasal symptoms in the athletic population in order to improve early diagnosis and provide precision-based treatment options to athletes suffering from nasal dysfunction.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

HV: initiative, conception, drafting, revising, submission of paper; BS: researching for and drafting of paper; BD: conception, drafting, revising of paper; CM: conception, drafting, revising of paper; LD: conception, drafting, revising of paper; HP: conception, drafting, revising of paper; HC: conception, drafting, revising of paper; RP: conception, drafting, revising of paper; SS: conception, drafting, revising of paper; SP: conception, drafting, revising of paper; WA: conception, drafting, revising of paper; SB: conception, drafting, revising of paper.

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