# Distinguishing science from pseudoscience in commercial respiratory interventions: An evidence-based guide for health and exercise professionals

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## ABSTRACT

Respiratory function has become a global health priority. Not only is chronic respiratory disease a leading cause of worldwide morbidity and mortality, but the COVID-19 pandemic heightened attention on respiratory health and the means of enhancing it. Subsequently, and inevitably, the respiratory system has become a target of the multi-trillion-dollar health and wellness industry. Numerous commercial, respiratory-related interventions are now on sale, coupled to therapeutic and/or ergogenic claims that vary in their plausibility: from the reasonable to the absurd. Moreover, legitimate and illegitimate claims are often conflated in a wellness space that lacks regulation. The abundance of interventions, the range of potential therapeutic targets in the respiratory system, and the wealth of research that varies in quality, all confound the ability for health and exercise professionals to make informed risk-to-benefit assessments with their patients and clients. This review focuses on numerous commercial interventions that purport to improve respiratory health, including nasal dilators, nasal breathing, generalized and systematized breathing interventions (such as pursed-lips breathing), respiratory muscle training, canned oxygen, various nutritional supplements, and inhaled L-menthol. For each intervention we describe the premise, examine the plausibility, and systematically contrast commercial claims against the published literature. The overarching aim is to assist health and exercise professionals to distinguish science from pseudoscience and make pragmatic and safe risk-to-benefit decisions.


**Key words:** asthma; COPD; exercise; disease; lung function; nutrition; pulmonary.

## 1.0 INTRODUCTION

The human respiratory system comprises the upper respiratory tract (nasal and oral cavities, pharynx, and larynx), lower respiratory tract (trachea, and bronchial tree), lung parenchyma, pulmonary vasculature, and respiratory muscles (e.g., diaphragm, abdominals, obliques, intercostals). Under neural control from central and peripheral chemoreceptors and respiratory centers in the brain, the respiratory system transfers oxygen from the atmosphere to the pulmonary circulation and carbon dioxide in the opposite direction. With a few notable exceptions (e.g., high-intensity exercise, hypoxic environments), the healthy respiratory system is unlikely to present a significant limitation to gas exchange or $O_2$ transport (Dempsey et al. 2020).

In recent years, the respiratory system has become a target of the multi-trillion-dollar commercial health and wellness industry. Therein, numerous respiratory-related products and strategies (e.g., respiratory muscle training devices, nasal strips, deep breathing regimens) are sold to the consumer alongside therapeutic and/or ergogenic claims that vary in their plausibility: from the reasonable (mitigate stress, improve perceptions, improve lung and respiratory muscle function); to the questionable (increase oxygen transport, “boost” immune function); to the absurd (increase “energy flow” and promote healing). Furthermore, due to lax regulations in the wellness space and little obligation for marketing to conform to scientific or ethical standards, it is common for legitimate and illegitimate claims to be conflated (Tiller et al. 2022). The current ‘wellness’ paradigm thus makes it difficult for health and exercise professionals to make informed risk-to-benefit assessments with their patients and clients.

Several factors underpin the accelerating commercial popularity of respiratory-related interventions, the most pertinent being the COVID-19 pandemic which has heightened attention on respiratory health and potential means of enhancing it. But even before COVID-19, chronic respiratory disease (such as chronic obstructive pulmonary disease [COPD]) was a leading cause of morbidity and mortality (World Health Organization 2022), conferring a considerable and growing economic burden (Ehteshami-Afshar et al. 2016). Respiratory disease has also received growing coverage in the media owing to the pressing issue of climate change and worsening air quality (Barnes et al. 2013). Respiratory function has thus become a global health priority. To

compound the problem, respiratory physiology is a complex discipline that is poorly understood by the public, and its mechanisms can thus be easily misappropriated for commercial gain.

This review explores a number of commercial interventions that purport to influence aspects of the respiratory system to improve respiratory function, respiratory health, and/or exercise responses. The interventions selected for inclusion were nasal dilators, nasal breathing, generalized and systematized breathing interventions (including pursed-lips breathing), respiratory muscle training, canned oxygen, various nutritional supplements, and inhaled L-menthol. For each intervention we describe its premise, examine its plausibility, and contrast commercial claims against the published literature. The overarching aim of this paper is to provide an evidence-based guide for health and exercise professionals—to help them distinguish science from pseudoscience in respiratory physiology and assist them in making safe and pragmatic risk-to-benefit decisions.

### 1.1 Methods

In January 2022, the first and corresponding authors (CRI and NBT, respectively) convened a meeting of recognized experts in the fields of respiratory medicine and exercise physiology. After several rounds of discussion, all authors agreed that the products/strategies to be included should be non-medical, commercial interventions, excluded if they were controlled drugs and/or regulated by the FDA as “medical devices”. The list was not exhaustive but instead limited to the interventions most prevalent in the health and wellness industry and that were coupled to the most conspicuous claims. A list of commercial claims was then compiled from websites, press releases, and relevant media, after which peer-reviewed articles were searched via PubMed (no date restriction). The literature search-terms comprised the relevant intervention (e.g., nasal dilators, respiratory muscle training, etc.) alongside various combinations of the following: breathlessness; dyspnea; lung; lung function; pulmonary; respiratory; respiratory function; respiratory health; respiratory symptoms; pathophysiology. All article types—meta-analyses, systematic reviews, randomized-controlled trials (RCTs), exploratory studies, confirmatory studies, and case reports—were included, and the reference lists of

articles selected for inclusion were manually searched for additional literature. A first draft of the manuscript was collated, and after several rounds of discussion and refinement, all authors agreed upon the evidence summaries and recommendations and approved the final work. Most of the correspondence was carried out virtually/electronically.

## 2.0 EVIDENCE REVIEW

### 2.1 Nasal dilators

*2.1.1 Premise and plausibility.* External nasal dilators (ENDs) are applied horizontally to the skin of the nasal dorsum whereas internal nasal dilators (INDs) are placed inside the nostrils. Both purportedly increase nostril patency by preventing the nasal wings from collapsing during inspiration (Dinardi et al. 2014). The devices were originally developed to aid with sleep-related issues (e.g., snoring and apnea) but their widespread use at the Atlanta Olympic Games in 1996 made them popular with exercisers and athletes (Dinardi et al. 2014). Using magnetic resonance imaging, Bishop *et al.* (2016) showed that an END (Breathe Right®) evoked significant enlargement of the anterior nasal passage when compared to a placebo. Using acoustic rhinometry, Griffin et al. (1997) observed increased nasal valve area with the same device. Although ENDs had no effect on plethysmography-derived measures of nasal resistance (Vermoen et al. 1998) or maximum expiratory flows (Di Somma et al. 1999) in healthy individuals, others have shown that ENDs increased nasal inspiratory flow during normal and forced breathing (Vermoen et al. 1998; Di Somma et al. 1999). Thus, ENDs likely improve nostril patency by supporting the lateral nasal vestibular walls, manifesting as a slight increase in inspiratory nasal flow at rest and during maximal inspiratory maneuvers. The bulk of literature has focused on whether there is any subsequent clinical or ergogenic benefit.

*2.1.2 Literature*. Articles were excluded if nasal dilators were simultaneously applied with other breathing interventions. Most studies on nasal dilators evaluated their effect on sleep-related issues including sleep quality, snoring, and obstructive sleep apnea; generally showing subjective (but not objective) outcomes. For example, using ENDs, Wenzel *et al*. (1997) reported improved subjective ratings of nose breathing at rest but no changes in objective (polysomnography-derived) measures of obstructive sleep apnea. Similarly, several non-placebo-controlled studies showed improved subjective ratings of sleep quality (e.g., insomnia severity, sleep-disordered breathing) and quality of life with ENDs (Krakow et al. 2006; Gelardi et al. 2019). When an IND (Nas-Air®) and an END (Breathe Right®) were compared, the former conferred better subjective ratings of sleep quality (assessed via visual analogue scale) (Gelardi et al. 2019). One placebo-controlled study in patients with upper-airway resistance syndrome found that

desaturation time during sleep (the percentage of time that $SpO_2$ was >2% below waking values) was significantly lower with an END (Breathe Right®) versus placebo (9.1 vs. 12.2%), but there were no other effects on cardiorespiratory variables, sleep architecture, or sleep latency (Bahammam et al. 1999).

Data on snoring are equivocal. Research by Gelardi *et al*. (2019) reported that snoring time was reduced with both an IND and END, whereas Wenzel *et al*. (1997) showed that ENDs had no effect on the frequency of snoring events. When healthy subjects with nasal congestion were randomized to an END group (Breathe Right®) or a placebo group for two weeks, both devices equally improved subjective ratings of sleep quality and subjective ratings of nasal congestion, suggesting a potent placebo effect (Noss et al. 2019). Lastly, Sadan et al. (2005) showed that nasal dilators, when used by females during childbirth, improved subjective ratings of "ease of breathing" but had no effect on objective markers of labor progression or recovery. Collectively, the data suggest that nasal dilators (mainly ENDs) may improve perceptions of nasal breathing and subjective ratings of sleep quality. However, they are unlikely to influence objective markers of obstructive sleep apnea (Camacho et al. 2016) and the data on snoring frequency and duration are equivocal. In fact, several authors have proposed ENDs as an effective placebo intervention in RCTs that explore treatment options in obstructive sleep apnea (Amaro et al. 2012; Yagihara et al. 2017).

On the premise that ENDs increase some measures of nasal patency and nasal inspiratory flow, their potential to improve exercise capacity has also been explored. Despite a few reports of favorable outcomes (Griffin et al. 1997; Dinardi et al. 2013, 2017), a recent systematic review and meta-analysis of 19 articles concluded that ENDs elicited "no improvement in $\dot{V}O_2$max, HR and RPE outcomes in healthy individuals during [maximal or submaximal] exercise" (Dinardi et al. 2021). Other studies, using esophageal balloon catheters, report no effect of ENDs on inspiratory elastic work, inspiratory resistive work, or expiratory resistive work during submaximal or maximal exercise (O'Kroy et al. 2001). There was also no effect of ENDs on recovery of $\dot{V}O_2$, $\dot{V}_E$, or HR after exercise when compared to a placebo or a no-intervention control (Thomas et al. 2001); and no effect of ENDs on blood lactate responses after exercise in sedentary or endurance

trained women (Boggs et al. 2008). Thus, nasal dilators appear to have no meaningful influence on exercise performance or physiological variables during or after exercise.

The commercial claims of one specific IND (Turbine™) have been scrutinized by several studies, all showing no benefit on respiratory mechanics or exercise tolerance. One such study, a sham-controlled trial using esophageal balloon catheters to measure respiratory mechanics during incremental cycling, showed that INDs did not reduce the work of breathing and had no effect on exertional dyspnea or exercise capacity (Schaeffer et al. 2021). Another RCT tested the effect of the Turbine™ on 20-km cycling time-trial performance, reporting no influence on mean power output (Adams and Peiffer 2017). Favorable data from a clinical trial posted on the manufacturer's website have not been peer reviewed or published at the time of this writing.

*2.1.3 Evidence Summary and Recommendations.* Primary outcomes from the literature on nasal dilators are summarized in **Figure 1**. Both ENDs and INDs enlarge and stabilize the nasal valves thereby mitigating their collapse during high flow inspiration and increasing inspiratory nasal airflow during maximal inspiratory efforts. Current evidence suggests that nasal dilators may improve perceptions of nasal breathing and subjective ratings of sleep quality but are unlikely to influence objective markers of obstructive sleep apnea. The data on snoring frequency and duration are equivocal. Most studies show no effect of nasal dilators on cardiorespiratory function or ratings of perceived exertion during exercise, no effect on exercise capacity, and no effect on physiological variables during the acute phase of recovery.

## 2.2 Nasal breathing

*2.2.1 Premise and plausibility.* In humans, nitric oxide (NO) is a vasodilator (Morris and Rich 1997) and mild bronchodilator (Kacmarek et al. 1996), first identified in expired gas in the 1990s (Gustafsson et al. 1991). Functionally, the two NO isoforms are "constitutive" and "inducible" NO, with most being produced in the paranasal sinuses (Ricciardolo 2003). In fact, the paranasal sinuses produce considerably greater amounts of NO than either the mouth or the trachea (56 vs. 14 vs. 6 ppb, respectively; (Törnberg et al. 2002)). It has been suggested that nasally-derived NO can evoke airway smooth muscle relaxation, inhibit smooth muscle proliferation, and protect against excessive

bronchoconstriction (Ricciardolo 2003). Others suggest that nasal breathing might attenuate pulmonary hypertension by vasodilating the pulmonary vasculature (Settergren et al. 1998). Although exogenous (supplementary) NO is known to reduce vascular resistance and increase pulmonary blood flow in healthy and patient populations (Settergren et al. 1998; Crespo et al. 2010), the concentration of endogenous (nasally-derived) NO is considerably lower than the concentrations used in NO-enriched air (Törnberg et al. 2002). Therefore, an important consideration is whether increased NO uptake via nasal breathing exerts meaningful effects in healthy or patient populations.

*2.2.2 Literature*. Articles were excluded if they reported on exogenous (supplementary) NO inhalation as opposed that which was nasally derived, if they studied exhaled NO as a tool for assessing airway inflammation, or if nasal breathing was studied in combination with other breathing interventions (e.g., deep/slow breathing). Using single photon emission computed tomography during separate bouts of upright nasal or oral breathing in healthy adults, Crespo *et al*. (2010) found that nasal breathing elicited blood flow redistribution from caudal and dorsal regions of the lung to the less-perfused cranial and ventral regions. For the otherwise poorly perfused lung regions, such as the apical region, this represented a 24% increase in blood flow. Similar effects were observed when exogenous NO mixtures were inhaled orally, supporting the hypothesis that the mechanism of blood flow redistribution was mediated by NO. Others showed that nasal breathing increased oxygen tension across the chest wall (assessed using transcutaneous electrodes) in healthy subjects versus oral breathing (Lundberg et al. 1996), although the effects were very small and the clinical significance thus unclear.

Limited data also suggest a possible therapeutic benefit of nasal breathing in patients with respiratory disease. For example, intubated patients who were unable to rebreathe their own nasally-derived NO exhibited an 18% increase in $PaO_2$, and an 11% decrease in pulmonary vascular resistance index, when gas derived from the patient's nose was aspirated and fed into the inspiration limb of the ventilator (Lundberg et al. 1996). Although the exact mechanism was unclear, the authors postulated that sinus-derived NO may act as an “aerocrine messenger” that selectively dilates vessels supplying well-ventilated areas of the lung. Pulmonary vascular resistance also decreased in patients recovering from thoracic surgery when they engaged in nasal

versus oral breathing, although there was no difference in $O_2$ and $CO_2$ partial pressures of arterial and mixed venous blood between the two breathing techniques (Settergren et al. 1998). Pertinently, exogenous NO inhaled orally at “nasal physiologic concentrations” of 10–100 ppb evoked pulmonary vasodilatation and improved pulmonary gas exchange in patients with acute respiratory distress syndrome (Mourgeon et al. 1997) and acute respiratory failure (Gerlach et al. 1993). Collectively, these data support the notion that nasal breathing, by increasing NO uptake, may provide clinically meaningful benefits in certain patient populations.

The potential benefit of nasal breathing at rest has led to the suggestion that it may improve physiological responses to exercise. However, what of the feasibility of nasal-only breathing during exercise? Healthy adults spontaneously switch from nasal to oronasal breathing at minute ventilations of 35-45 $L \cdot min^{-1}$ (Niinimaa et al. 1980; Becquemin et al. 1991; Bennett et al. 2003), and without prior habituation, healthy adults even when prompted can only maintain nasal breathing up to ~80% $\dot{V}O_2max$ (LaComb et al. 2017). Nevertheless, when preceded by an extensive training period (>6 months), nasal breathing may be feasible during high-intensity and even maximal exercise without compromising $\dot{V}O_2max$ (Hostetter et al. 2016; Dallam et al. 2018). Thus, after habituation, nasal breathing can probably be sustained during maximal exercise. This leads to the separate question of efficacy: does nasal breathing during exercise provide any physiological advantage over oral or oronasal breathing?

In a mixed-sex cohort of healthy adults, LaComb *et al.* (2017) showed that nasal breathing elicited lower $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ at given submaximal exercise intensities (50%, 65%, and 80% of treadmill-derived $\dot{V}O_2max$) when compared to oral breathing, although the physiological mechanism was unclear. A possible flaw of the study was that exercise bouts lasted only 4 min, whereas a steady state ventilatory response may take considerably longer, particularly in an untrained cohort with a slow kinetic response. The authors also concluded that, when all variables were considered together, “it is likely that oral breathing represents the more efficient mode [of breathing], particularly at higher exercise intensities”. In another study, 10 healthy subjects who were habituated to nasal breathing exhibited lower ventilatory equivalents for $O_2$ and $CO_2$ during nasal-only exercise versus oral-only exercise (differences mediated primarily by significantly lower

$\dot{V}_E$), without a change in $\dot{V}O_2$max or time to exhaustion (Dallam et al. 2018). It is unclear from these studies whether the physiological response to nasal breathing was derived from increased NO uptake or another mechanism. It is possible that healthy subjects will have a blunted ventilatory response at maximal exercise with nasal breathing owing to attenuated tidal volumes and respiratory frequencies (Morton et al. 1995). This may partly explain greater end-tidal $CO_2$ partial pressure ($P_{ET}CO_2$) during nasal versus oral breathing, both at rest and during submaximal exercise (Tanaka et al. 1988; Dallam et al. 2018).

Although oral and nasal breathing evoke similar ratings of perceived exertion during exercise, nasal breathing results in an "unacceptable sensation of air hunger" (Hostetter et al. 2016; Dallam et al. 2018), perhaps associated with the development of hypercapnia (Banzett et al. 2021). In turn, this has the potential to alter breathing patterns and reduce exercise tolerance (Dallam et al. 2018). In patients with COPD, who report pre-existing sensations of "unsatisfied inspiration" (Philips et al. 2021), such air hunger during nasal breathing could exacerbate respiratory symptoms. Nasal breathing during exercise would therefore be inappropriate for COPD patients. Two early studies in patients with asthma (*n*=5 and *n*=12, respectively) reported that nasal breathing during exercise reduced the incidence and/or severity of post-exercise bronchoconstriction relative to oral breathing (Shturman-Ellstein et al. 1978; Mangla and Menon 1981), although it is unclear whether these findings were the result of greater NO intake or also influenced by an increased humidity of inspired air which has also been shown to mitigate the severity of exercise-induced bronchoconstriction EIB (Anderson and Kippelen 2012). In any case, these data support the hypothesis that the nasopharynx and oropharynx play an important role in mediating exercise-induced bronchoconstriction.

*2.2.3 Evidence Summary and Recommendations.* Primary outcomes from the literature on nasal breathing are summarized in **Figure 2**. Data suggest that nasal breathing may improve arterial oxygenation and ventilatory efficiency in critically ill patients at rest, but there is little evidence that such benefits extend to healthy subjects. Nasal breathing is feasible during submaximal exercise and even maximal exercise after extensive habituation, but there is little-to-no data supporting a subsequent benefit on exercise capacity in healthy individuals. There is some evidence of reduced incidence

and/or severity of post-exercise bronchoconstriction with nasal breathing, but due to potential hypoventilation and increased perceptions of “air hunger”, nasal breathing during exercise is not recommended for COPD patients. Its use in patients with other respiratory diseases should be considered on a case-by-case basis.

### 2.3 Generalized and systematized breathing strategies

*2.3.1 Premise and plausibility.* Breathing interventions generally comprise one-or-more of the following techniques: nasal inspiration, deep/slow breathing, breath-hold at end-inspiratory lung volume, prolonged expiration, expiration through pursed lips, and preferential activation of the diaphragm during inspiration. Most breathing interventions encourage inspiration through the nose. This approach may increase the uptake of NO (see Section 2.2) and warm/humidify the inspired air (Naclerio et al. 2007). Inspiration and expiration are usually required to be deep and slow to increase tidal volume and extend the respiratory cycle (Ubolnuar et al. 2019). A prolonged expiration may also help decrease expiratory reserve volume, in turn partially mitigate air trapping and dynamic hyperinflation to reduce respiratory symptoms in certain populations (e.g., COPD). Deep/slow breathing, particularly interventions with prolonged expiration, have also been shown to increase heart rate variability and respiratory sinus arrhythmia through mediating effects on the parasympathetic nervous system (Zaccaro et al. 2018). This is an expanding area of research. Indeed, using functional magnetic resonance imaging, deep/slow breathing was shown to increase cortical and subcortical activity (Critchley et al. 2015), which may partly support improved physical and mental health (Laborde et al. 2022). Pursed-lips breathing typically involves nasal inspiration and prolonged expiration directed through lips that have a “puckered” or “pursed” appearance (see **Figure 3**). Independent of other breathing strategies, expiration through pursed lips may increase expiratory resistance at the mouth, evoking a small positive end-expiratory pressure of ~5 $cmH_2O$ (van der Schans et al. 1997). This can help ameliorate airway compression and expiratory flow limitation in patients with COPD by functionally “stenting” the airways (Marciniuk et al. 2011; Nguyen and Duong 2021). Diaphragmatic breathing comprises many of the aforementioned techniques but with preferential activation of the diaphragm during inspiration. From a practical standpoint, diaphragmatic breathing is achieved by

inspiring with minimal movement of the chest and more pronounced outward abdominal displacement (Cahalin et al. 2002).

*2.3.2 Literature.* The literature on breathing interventions employs inconsistent nomenclature and terms are often used interchangeably. This makes it difficult to discern the efficacy of each technique. Accordingly, we have grouped the literature on breathing interventions and discussed their collective outcomes. The exceptions are pursed-lips breathing (see Section 2.3.3) and the Buteyko Breathing Technique (see Section 2.3.4), which both have a sufficient body of independent research. Most of the literature on breathing interventions has focused on the management of respiratory symptoms in asthma and COPD. Regarding the former, the Cochrane database published a meta-analysis and separate systematic review on breathing exercises in asthmatic adults and children, respectively, with disparate findings. In adults, yoga (including pranayama), breathing retraining, the Buteyko Breathing Technique, the Papworth method, and deep diaphragmatic breathing, all improved quality of life, symptoms and complaints due to hyperventilation, and lung function (forced expiratory volume in 1 second; [$FEV_1$]). However, studies were characterized by poor methodologies and a very low-to-moderate quality of evidence (Santino et al. 2020). The review in children found insufficient data to support the use of breathing techniques for asthma management, owing primarily to a low number of studies (*n*=3, 112 participants) (Macêdo et al. 2016). Another issue impeding interpretation of the pediatric data is that studies generally combined breathing exercises with a comprehensive package of care, thereby precluding any evaluation of breathing exercises alone (Macêdo et al. 2016). As such, due to a low number of studies, limited reporting of data, and variations in reported outcomes, no firm conclusions can be drawn regarding the efficacy of breathing interventions for asthma management. More well-controlled, high-quality studies are needed.

There is a much larger body of work evaluating breathing interventions for improving respiratory symptoms, lung function, and exercise performance and capacity in COPD. In general, long-term breathing interventions including deep breathing with or without preferential activation of the diaphragm, pursed-lips breathing, yoga, singing, and breathing gymnastics, all appear to improve functional exercise performance (mainly 6-min walk test; [6MWT]) (Hamasaki 2020; Lu et al. 2020; Yang et al. 2022), quality of life

(St. George's Respiratory Questionnaire; (Marotta et al. 2020) and stress and anxiety (Hamasaki 2020) in COPD. Several studies also show that pursed-lips breathing, with or without preferential activation of the diaphragm, improves pulmonary function (i.e., forced vital capacity [FVC] and $FEV_1$) (Hamasaki 2020; Lu et al. 2020; see Yang et al. 2022).

The literature on breathing interventions for improving dyspnea in COPD is less consistent. A review of 13 RCTs (998 patients) found that home-based breathing exercises (diaphragmatic breathing, yoga breathing, breathing gymnastics, and singing) improved resting $FEV_1$, 6MWT distance, and ratings of dyspnea (modified Medical Research Council dyspnea scale and St George Respiratory Questionnaire) across the range of disease severity (Lu et al. 2020). By contrast, a Cochrane review of 16 studies (1,233 patients) showed that 15 weeks of breathing retraining (pursed-lips breathing, diaphragmatic breathing, ventilation feedback training, or yoga breathing, both supervised and unsupervised) improved 6MWT distance in COPD but had no consistent effects on dyspnea at rest or health-related quality of life (Holland et al. 2012). Another systematic review and meta-analysis of 19 studies (745 patients) reported that respiratory frequency was significantly reduced at rest and during exercise following a period of dedicated pursed-lips breathing, ventilatory feedback and exercise, diaphragmatic breathing, or combined techniques that lasted between one day and 24 weeks—nevertheless, breathing interventions did not improve ratings of dyspnea relative to controls (Ubolnuar et al. 2019). The reason for the discrepancy in dyspnea-related findings is unclear; however, while Holland *et al.* (2012) and Ubolnuar *et al.* (2019) included studies performed in various environments (including the laboratory and during pulmonary rehabilitation programs in outpatient settings), the review by (Lu et al. 2020) focused exclusively on home-based breathing interventions.

*2.3.3 Pursed-lips breathing (PLB)*. This particular technique has received a great deal of attention as a standalone therapy owing to its effects on dyspnea and exercise tolerance in patients with COPD. The main benefits include reduced respiratory frequency, increased (improved) inspiratory and total respiratory time, and increased tidal volume (Ubolnuar et al. 2019). A bout of PLB has also been shown to reduce resting $CO_2$ retention and increase arterial oxygen tension and oxyhemoglobin saturation in advanced but stable COPD (Thoman et al. 1966; Breslin 1992; Marciniuk et al. 2011). The primary

mechanism by which PLB exerts its effects is by increasing intraluminal airway pressure during exhalation which tends to prevent the airway compression that would otherwise occur as intrapleural pressure increases. In turn, PLB is likely to ameliorate air trapping. Since PLB reduces end-expiratory lung volume and lengthens the diaphragm (thereby improving its tension-generating capacity during inspiration) (Spahija et al. 2005), increased arterial oxygen saturation is likely the result of a more complete, mechanically-efficient respiratory cycle. Pursed-lips breathing has also been used by COPD patients during exercise, with generally favorable outcomes on 6MWT (Bhatt et al. 2013), perhaps mediated by reduced dynamic lung hyperinflation (Cabral et al. 2015), increased arterial oxygen saturation (Cabral et al. 2015), and possible protection against diaphragmatic fatigue (Breslin 1992). Notwithstanding, improvements in exercise capacity with PLB are not a universal finding (Garrod et al. 2005).

Several studies in patients with COPD have tried to distinguish the benefits of PLB from other respiratory interventions or relaxation techniques. Pivotal research by Tiep *et al.* (1986) showed that an acute (15-min) bout of PLB evoked greater increases in $SpO_2$ at rest compared with general relaxation techniques. Others have found that 12 weeks of daily PLB practice was more effective at reducing exertional dyspnea, and increasing 6MWT performance, than expiratory muscle training or a control group that received an educational pamphlet but no intervention (Nield et al. 2007). In another study, a 12-week PLB intervention increased $FEV_1$ and maximal inspiratory pressures by a greater magnitude than diaphragmatic breathing or a no-intervention control (Jansang et al. 2016). One study assessed the effects of an acute bout of diaphragmatic breathing with or without PLB on COPD patients during upright, seated rest (Mendes et al. 2019). Although both interventions increased ribcage and abdominal volumes (measured via respiratory inductive plethysmography), increased arterial oxygen saturation, and decreased respiratory frequency, there were greater reductions in respiratory frequency and longer expiratory times with combined diaphragmatic and pursed-lips breathing. Conversely, neither intervention reduced dyspnea (Medical research Council scale) or end-expiratory chest volume. Thus, the combination of breath control (with preferential activation of the diaphragm) and prolonged expiration through pursed lips may provide several benefits that are distinct from other breathing techniques. Indeed, as an effective

means of managing dyspnea in COPD, PLB has been advocated by the Canadian Thoracic Society in their clinical practice guidelines (Marciniuk et al. 2011) and by the American Thoracic Society in their patient education materials (Lareau et al. 2020).

*2.3.4 The Buteyko Breathing Technique.* This (predominantly) commercial breathing regimen was conceived in the 1950s by Dr Konstantin Pavlovic Buteyko. In its modern form, Buteyko is an amalgam of several breathing techniques which emphasize nasal breathing and periods of breath-hold (referred to as “control pause”). In general, the research on Buteyko is favorable, particularly with respect to asthma management, showing improved quality of life scores (Burgess et al. 2011; Santino et al. 2020). Nevertheless, Buteyko breathing does not appear to be superior to other chronic breathing interventions like yoga, deep/slow breathing, pursed-lips breathing, or diaphragmatic breathing. In addition, several issues cloud the interpretation of the Buteyko literature, potentially undermining its validity.

First, Buteyko breathing is usually administered as a comprehensive package of care that comprises breathing retraining, education, and nutritional advice, making it difficult to discern the isolated benefits of the respiratory intervention (Bruton and Lewith 2005). Second, proponents of Buteyko breathing often extend the claims beyond those supported by the scientific literature. For instance, a major premise of the technique is that breath-hold time predicts alveolar $CO_2$ according to a patented mathematical formula—a claim that has been empirically disproven (Courtney and Cohen 2008). The Buteyko technique also advocates mouth taping as a means of obligating nasal breathing during sleep. However, a randomized, crossover study in patients with symptomatic asthma showed that mouth taping had no effect on asthma control (Cooper et al. 2009). Some proponents even suggest, without evidence, that Buteyko breathing can treat diseases and symptoms (including diabetes, attention-deficit hyperactive disorder, and dental health), claims which undermine the scientific legitimacy of the intervention. It is also worth noting that most clinical studies on Buteyko have assessed outcomes in response to physiotherapy programs that tend to focus on the more conventional, evidence-based aspects of the technique (e.g., deep breathing through the nose).

Another approach of some Buteyko proponents is to associate the technique with unrelated, or tenuously related, research. For example, studies have identified a high

prevalence of allergic rhinitis in children with ADHD (Brawley et al. 2004). By promoting nasal breathing, Buteyko breathing advocates thus imply that the technique can reduce the risk of developing ADHD. Lastly, several commercial incarnations of Buteyko promote long breath holds (>25 s) which may be unsuitable for certain groups (e.g., COPD patients). Accordingly, while the more conventional aspects of Buteyko breathing (nasal inspiration, deep/slow breathing, and breath training) may have benefits for respiratory function, health and exercise professionals should be wary of those claims that are lacking plausibility, currently unproven, and potentially dangerous.

*2.3.5 Additional considerations and conclusions on respiratory interventions.* The literature on breathing techniques for patients with respiratory disease is generally positive. Still, there are subtle nuances in the data that should be highlighted prior to interpretation. For example, research suggests that respiratory physiotherapy using breathing training has the potential to improve inspiratory and expiratory muscle strength following *upper* abdominal surgery (Grams et al. 2012), yet this has questionable utility following *general* abdominal surgery (Pasquina et al. 2006). Physicians and other healthcare professionals must also be conscious of instances where breathing training may be less favorable or even harmful to their patients. Respiratory physiotherapy seems to have limited benefit on lung volume or mortality risk following lung resection (Larsen et al. 2020), and PLB specifically has been shown to increase metabolic demands in patients with interstitial lung disease (Parisien-La Salle et al. 2019). This brings into question the efficacy of PLB for restrictive disorders. Certain breathing techniques may also worsen respiratory symptoms; e.g., several studies show that diaphragmatic breathing may exacerbate dyspnea in patients with severe COPD (Hamasaki 2020), perhaps due to negative effects on the work of breathing and its mechanical efficiency (Gosselink et al. 2012). Anecdotally, the technical demands of preferentially activating the diaphragm during inspiration may render such interventions unsuitable for respiratory patients.

*2.3.6 Evidence Summary and Recommendations.* Primary outcomes from the literature on breathing interventions are summarized in **Figure 3**. Breathing interventions such as deep breathing and pursed-lips breathing may elicit favorable changes in tidal volume, respiratory frequency, respiratory time, and arterial oxygen saturation in patients

with COPD, particularly those with severe or very severe disease. Long-term breathing retraining strategies may improve lung function (mainly lung volumes and capacities), exercise performance, respiratory symptoms, and quality of life in respiratory patients. Pursed-lips breathing, in particular, is an important standalone therapy that should be considered as an adjunct to exercise training and pharmaceutical interventions in pulmonary rehabilitation programs. Breathing interventions should emphasize a deep and slow nasal inspiration followed by a slow and prolonged expiration through pursed lips. Because of possible negative outcomes in patients, breathing interventions should be delivered by experienced therapists with a comprehensive understanding of the benefits and risks of each technique. Patients must also be managed on a case-by-case basis. The benefits of deep/slow breathing in healthy subjects (with normal pulmonary function) are likely limited to changes in parasympathetic activity (and thus heart rate variability) which may support emotional wellbeing rather than other aspects of cardiopulmonary function.

## 2.4 Respiratory muscle training

*2.4.1 Premise and plausibility*. The healthy respiratory system has typically been considered “overbuilt” for the ventilatory demands placed upon it during strenuous exercise. More recently, however, studies have revealed several respiratory constraints that may impede exercise performance in healthy subjects, particularly those who are endurance-trained, and in certain patients with cardiorespiratory disease (Dempsey et al. 2020). When breathing frequency increases during exercise, there is a consequent increase in the resistive loads placed upon the inspiratory and expiratory muscles. In patients with COPD, the resistive loads are exacerbated due to narrowing of peripheral airways. In addition, at lung volumes above relaxation volume, where lung and chest wall compliance are reduced, the inspiratory muscles must overcome increased elastic recoil forces. This increase in elastic loading occurs when tidal volume increases with exercise, and especially in the presence of dynamic lung hyperinflation (i.e., increase in end-expiratory lung volume) consequent to the dynamic compression of airways during forced expiration. Airway narrowing and loss of elastic recoil in COPD give rise to static lung hyperinflation, which further increases the elastic loading on the inspiratory muscles. In

severe COPD, incomplete expiration and inward recoil of the lungs and chest wall result in progressive air trapping and increased alveolar pressure at the end of expiration (i.e., intrinsic positive end-expiratory pressure, PEEPi). To initiate inspiratory airflow, the inspiratory muscles must generate a negative pressure equal in magnitude to PEEPi, subsequently imposing a threshold load on the inspiratory muscles. When the lung is acutely inflated, the pressure-generating capacity of the diaphragm is impaired because the muscle is shortened. At high lung volumes, the pressure-generating capacity of the diaphragm may be further reduced by an increased radius of muscle curvature. Lung inflation also impairs the pressure-generating capacity of the inspiratory intercostal muscles (external intercostals and parasternal intercostals); in contrast to the diaphragm, however, this impairment has been ascribed to changes in the orientation and motion of the ribs (De Troyer and Wilson 2009). In COPD, reductions in the pressure-generating capacity of respiratory muscles may also result from disease-induced changes in respiratory muscle morphology.

Increased loading of the respiratory muscles and/or decreased capacity of the respiratory muscles for pressure generation have direct functional consequences. For instance, an increase in the respiratory muscle load/capacity ratio contributes significantly to the subjective experience of breathing discomfort (i.e., dyspnea) (McConnell and Romer 2004a) and predisposes the respiratory muscles to fatigue. Regarding the latter, decreases in the contractile function of inspiratory and expiratory muscles have been noted following intense, whole-body exercise in healthy young adults (Johnson et al. 1993; Taylor et al. 2006; Tiller et al. 2017) and in select patients with COPD (Hopkinson et al. 2010; Bachasson et al. 2013). This exercise-induced decrease in respiratory muscle capacity further increases the subjective experience of dyspnea. Moreover, the metabolite accumulation associated with fatiguing respiratory muscle work can elicit a sympathetically-mediated vasoconstrictor response in locomotor muscles. This so-called ‘respiratory muscle metaboreflex’ may decrease locomotor muscle blood flow in favor of an increase in blood flow to the respiratory muscles, thereby increasing the fatigability of limb locomotor muscles and reducing central motor output via feedback effects (Sheel et al. 2018). In COPD, excessive loading of the respiratory muscles and activation of the

respiratory muscle metaboreflex may partly contribute to the early development of limb muscle fatigue (Amann et al. 2010).

Respiratory muscle training (RMT) was developed on the premise that enhancing the pressure-generating capacity of respiratory muscles would increase fatigue resistance and/or mechanical efficiency of the respiratory muscles during exercise. Such changes would be expected to prevent or delay the respiratory muscle metaboreflex, thereby improving $O_2$ delivery to working limbs and reducing the intensity of perceived limb discomfort (see **Figure 4**). An increase in the pressure-generating capacity of the respiratory muscles with targeted training would also be expected to reduce the intensity of perceived dyspnea. In health, RMT has been shown to improve the static and dynamic function of respiratory muscles (Romer and McConnell 2003), attenuate fatigability of respiratory (Verges et al. 2007, 2009) and locomotor muscles (McConnell and Lomax 2006), blunt the respiratory muscle metaboreflex (Witt et al. 2007), and attenuate perceptions of respiratory and limb discomfort (McConnell and Romer 2004a). Research pertaining to the influence of RMT on whole-body exercise performance in athletes and patients is somewhat contradictory (see *Literature*).

The three most common approaches to RMT involve flow-resistive loading (high pressure, low flow), pressure-threshold loading (high pressure, moderate flow), and isocapnic voluntary hyperpnea (low pressure, high flow). Devices that impose a resistive or threshold load elicit improvements predominately in respiratory muscle strength, whereas isocapnic voluntary hyperpnea elicits improvements predominantly in respiratory muscle endurance (see McConnell and Romer 2004b for review). More recently, a tapered flow-resistive loading device has been developed to produce a variable load that matches the pressure-volume relationship of inspiratory muscles (Langer et al. 2013). A recent development in the RMT literature pertains to external loading of the respiratory muscles *during* exercise (in-task). So-called “functional” RMT typically involves flow-resistive loading via facemask (Porcari et al. 2016)[1] or nasal restriction (Arnedillo et al. 2020; Gonzalez-Montesinos et al. 2021). Although functional RMT is an attractive proposition due to its specificity of application, the additional loads imposed on the respiratory muscles, and hence the potential training stimulus, are difficult to quantify.

From a practical standpoint, functional RMT may limit the physiological stimulus that can be obtained by applying RMT and exercise independently (Faghy et al. 2021).

*2.4.2 Literature.* In 1976, Leith and Bradley showed that the respiratory muscles of healthy individuals could be trained to increase strength or endurance. Later research sought to evaluate the efficacy of RMT with respect to whole-body exercise performance in healthy individuals and in patients with respiratory disease. Unfortunately, many of the early studies were hampered by methodological shortcomings, including small sample sizes, absence of sham-control groups, unbalanced baseline characteristics, inadequate training intensities, and inappropriate outcome measures (McConnell and Romer 2004b). As such, the ergogenic effect of RMT has been the subject of much debate (e.g., McConnell 2012; Patel et al. 2012). A systematic review and meta-analysis of 46 studies on the effects of RMT in healthy individuals revealed an improvement in endurance performance as assessed using fixed-intensity tests, simulated time-trials, and intermittent incremental tests (Illi et al. 2012). The analysis also showed that resistive/threshold and hyperpnea training did not differ in their effects, that combined inspiratory/expiratory strength training tended to be superior to either intervention alone, and that the greatest improvements with RMT occurred in less-fit subjects and in sports of longer duration (Illi et al. 2012). Another systematic review and meta-analysis, this time on responses in athletes, showed a positive effect of RMT on respiratory muscle function and sport performance outcomes (HajBhanbari et al. 2013). Although the report also noted comparable benefits of RMT for “elite” and “recreational athletes”, the authors classified trained status by whether the subject’s $\dot{V}O_2$max was above or below the minimum, pre-determined requirements for being considered an “athlete”, but without specifically defining “elite”. Thus, the question as to whether training status mediates the efficacy of RMT remains unresolved. More recent studies have shown improvements in repeated-sprint performance (e.g., shorter recovery between sprints or increased number of repetitions) as well as reduced effort perceptions and markers of metabolic stress after resistive RMT (Lorca-Santiago et al. 2020). Collectively, the data show an ergogenic effect of RMT on endurance and repeated-sprint performance in healthy individuals.

The efficacy of RMT in patients with COPD has been studied extensively. While whole-body exercise training is a crucial component of pulmonary rehabilitation in this

population (Casaburi 2008), exercise training does not appear to increase the pressure-generating capacity of the respiratory muscles. Consequently, there has been a great deal of interest in the potential for RMT to increase the capacity of the respiratory muscles and alleviate symptoms. Learned societies, including the American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation (Ries et al. 2007) and the European Respiratory Society/American Thoracic Society (Spruit et al. 2013), have recommended RMT for patients who, despite optimal medical therapy, exhibit dyspnea and reduced respiratory muscle strength. Several systematic reviews and meta-analyses have shown that RMT, when applied as a standalone intervention with controlled training loads in patients with COPD, improves respiratory muscle strength and endurance, exercise capacity, dyspnea, and health-related quality of life (e.g., Gosselink et al. 2011). Adding RMT to a whole-body exercise training program in COPD was shown to have no additive effects on exercise performance or quality of life, suggesting that RMT may only be effective as a standalone treatment in the absence of other interventions (e.g., Gosselink et al. 2011). This notion is corroborated by a recent systematic review and meta-analysis which showed that inspiratory pressure-threshold training in patients with COPD increased inspiratory muscle strength, functional exercise performance, and dyspnea during activities of daily living, but with no additional effect on the intensity of exertional dyspnea when used as an adjunct to pulmonary rehabilitation (Beaumont et al. 2018a). Notwithstanding the limitations of meta-analyses (e.g., poor quality of included studies, heterogeneity, publication bias), recent large-scale RCTs on the effects of RMT in patients with COPD have confirmed that improvements in inspiratory muscle function after adjunctive RMT do not translate to additional improvements in functional exercise capacity, dyspnea, or quality of life (Beaumont et al. 2018b; Schultz et al. 2018; Charususin et al. 2018a). In patients with inspiratory muscle weakness, however, adjunctive RMT during a whole-body exercise training intervention elicited a significant increase in endurance cycling time and a significant reduction in dyspnea intensity at iso-time during the cycling test compared to sham-training (Charususin et al. 2018b).

*2.4.3 Additional applications and population subgroups.* While most studies have investigated the influence of RMT on exercise outcomes in healthy individuals (athletes and non-athletes) and patients with COPD, RMT may also have an application in other

settings where the loads imposed on the respiratory muscles are elevated or the capacity to generate force is reduced. For instance, RMT has been considered in the context of environmental and occupational settings (e.g., altitude and load carriage) (Faghy and Brown 2015; Chambault et al. 2021), and studied in the context of natural aging (Seixas et al. 2020; Manifield et al. 2021). In older adults, exertional dyspnea is consistently elevated at any given intensity of submaximal exercise owing to an increased ventilatory demand (Jensen et al. 2009). Conceivably, RMT might improve exertional dyspnea in older adults through a reduction in the load/capacity ratio of respiratory muscles. In addition to the increase in ventilatory demand, aging is accompanied by a decline in respiratory muscle function which, through a reduction in postural control, has been shown to correlate with impairments in balance performance (Rodrigues et al. 2020). In turn, RMT has been shown to improve balance performance through an increase in the neuromuscular activity of postural muscles (Ferraro et al. 2019, 2020, 2022; Tounsi et al. 2021).

Recent evidence indicates that females have smaller airways than males, and subsequently exhibit greater flow-resistive work of breathing (Peters et al. 2021). There also appears to be a combined influence of age and biological sex on respiratory mechanics which contributes in part to the increased perception of exertional dyspnea noted in older women (Molgat-Seon et al. 2018). Thus, RMT could be an effective intervention to enhance the overall exercise response in young and older women. Other groups with imbalances in the load/capacity ratio of respiratory muscles, and which might therefore benefit from RMT, include: exercise-induced laryngeal obstruction (Sandnes et al. 2022), obstructive sleep apnea (Torres-Castro et al. 2022), cystic fibrosis (Stanford et al. 2020), interstitial lung disease (Zaki et al. 2022), stroke (Fabero-Garrido et al. 2022), hypertension (Craighead et al. 2022), chronic heart failure (Azambuja et al. 2020), pulmonary hypertension (Tran et al. 2021), neurological disorders (He et al. 2021), spinal cord injury (Woods et al. 2022), pre-operative surgery (Dsouza et al. 2021), weaning from mechanical ventilation (Worraphan et al. 2020), ventilator-induced diaphragm dysfunction in the recovery phase (Ahmed et al. 2019), and COVID-19 (e.g., risk reduction, ICU, recovery, and long-COVID) (McNarry et al. 2022). Evidence of the efficacy of RMT in these groups requires further prospective study.

673 *2.4.4 Evidence summary and recommendations.* Primary outcomes from the
674 literature on RMT are summarized in **Figure 4**. If applied with the appropriate frequency,
675 intensity, and duration, RMT can improve specific aspects of respiratory muscle function
676 (e.g., strength and endurance). There is convincing evidence of an ergogenic effect of
677 RMT in healthy individuals (athletes and non-athletes). As a standalone therapy, RMT
678 confers multiple benefits for select patients with COPD. However, the effect of adding
679 RMT to a general exercise program in COPD (including during pulmonary rehabilitation)
680 appears limited. It is conceivable that RMT may be useful for patients with respiratory
681 muscle weakness or those with pre-existing comorbidities who are unable to participate
682 in whole-body exercise training. Further RCTs are needed to ascertain which patients
683 and groups are likely to benefit from RMT.
684
685 **2.5 Canned oxygen**
686 *2.5.1 Premise and plausibility.* Commercial canned oxygen (intended for non-
687 medical use) is a can of hyperoxic gas (~95% $O_2$) equipped with a mask or inhaler cap.
688 The suggested protocol for use differs among manufacturers but typically involves several
689 inhalations, repeated 8-10 times, periodically throughout the day or as needed. Some
690 vendors recommend their product for use immediately before physical activity and/or
691 sporting competition. The ergogenic claims include improved reaction time, “improved
692 breathing” during exposure to heat and pollution, and improved sports performance by
693 delaying onset of fatigue and improving $O_2$ availability for oxidative metabolism. Some
694 brands combine eucalyptus and other oils with the gas mixture which they claim can “relax
695 the nervous system, relax the muscles, and relieve stress”. Despite the extensive claims
696 and widespread and costly prescription of so-called “short burst oxygen therapy” for
697 respiratory patients (e.g., COPD), there is no clear mechanism for the purported
698 physiological benefit. Moreover, in healthy individuals, hemoglobin remains nearly
699 completely saturated with $O_2$ at rest, and exercise-induced arterial $O_2$ desaturation (i.e.,
700 hypoxemia) rarely occurs in healthy (untrained) individuals at sea-level. Consequently,
701 there is little plausibility that acute exposure to concentrated $O_2$ (i.e., several breaths) will
702 influence respiratory outcomes or exercise performance.

*2.5.3 Literature.* The focus of this section is on commercially available canned oxygen and "short burst oxygen" rather than physician-prescribed supplemental oxygen therapy. A systematic review on the efficacy of short-burst oxygen to improve breathlessness, exercise capacity, arterial oxygen saturation, and ventilatory variables in patients with COPD, concluded that its widespread prescription was not evidence-based (O'Neill et al. 2006). Due to a lack of peer-reviewed studies on commercial canned oxygen in particular, most vendors cite clinical literature that is tenuously related (e.g., studies on hyperbaric oxygen therapy or prolonged inhalation of medically certified gas mixtures). Thus, the references provided by manufacturers do not support the claims. One manufacturer published an online press release that mimicked the appearance of a scientific journal article (Elizondo et al. 2019), presumably in an effort to feign scientific legitimacy. On the rare occasion that relevant journal articles were obtained through commercial websites, they were of very low quality and exhibited a high risk of bias. It is worth noting that although gaseous supplemental oxygen (delivered by inhalation) is not prohibited by the World Anti-Doping Agency (WADA 2022), some sports authorities prohibit its use. Athletes should therefore be cognizant of the rules and regulations regarding $O_2$ therapy that govern their sport.

*2.5.4 Evidence Summary and recommendations.* The proposed benefit of acute inhalation of canned oxygen has low plausibility and there is no valid evidence of beneficial effects.

## 2.6 Nutritional interventions

*2.6.1 Premise & plausibility*. Nutrition is a modifiable factor that influences the development and progression of many non-communicable diseases (Cena and Calder 2020; Dominguez et al. 2021). Some nutrients have immunomodulatory, anti-inflammatory, and/or antioxidant effects (Kau et al. 2011; Venter et al. 2020; Gozzi-Silva et al. 2021). Such nutrients may therefore influence respiratory health and disease risk/progression in conditions underpinned by airway and/or systemic inflammation (Berthon and Wood 2015; Hosseini et al. 2017; Parvizian et al. 2020; Heloneida de Araújo Morais et al. 2021). In addition, supplementation with certain nutrients may provide prophylactic and/or therapeutic benefits for certain respiratory patients.

In terms of therapeutic benefits on respiratory health, the bulk of literature focuses on vitamin D, various antioxidants (most commonly vitamin C), omega-3 polyunsaturated fatty acids (n-3 PUFAs), probiotics, and prebiotics. The wealth of literature precludes any detailed discussion of the complex and diverse mechanisms underpinning each nutrient and their independent effects on respiratory health. Instead, the following summary focuses on empirical data regarding the purported antioxidant and immunomodulatory effects and whether they translate to clinically meaningful outcomes.

*2.6.2. Literature on Vitamin $D_3$.* Circulating concentrations of 25(OH)D—a form of vitamin D produced in the liver from hydroxylation of vitamin $D_3$—were found to be inversely associated with the incidence of upper- and/or lower-respiratory tract infection (RTI) (Pham et al. 2019). The incidence of RTI in the general population peaks in the winter (Ginde et al. 2009) when vitamin D deficiency is most common owing to low skin exposure to sunlight ultraviolet B radiation (Farrokhyar et al. 2014; Cashman et al. 2016). Indeed, insufficient circulating concentrations of vitamin D (baseline serum 25(OH)D <50 $nmol \cdot L^{-1}$) have been observed in military personnel (Harrison et al. 2021), athletes (Farrokhyar et al. 2014), and healthy controls (Cashman et al. 2016).

Vitamin D sufficiency can be achieved via oral vitamin $D_3$ supplementation (Carswell et al. 2018; Harrison et al. 2021) and safe exposure to sunlight or simulated sunlight. However, evidence of prophylactic and/or therapeutic effects of vitamin $D_3$ supplementation is confounded by heterogeneity across trials (Jolliffe et al. 2021), with effect-modifiers including dosing regimen and duration, participant age, baseline 25(OH)D, and geographic location (Martineau et al. 2017; Vlieg-Boerstra et al. 2021; Jolliffe et al. 2021; Cho et al. 2022). A recent meta-analysis of 43 RCTs ($n$ = 48,488 mixed-health cohort of children and adults) revealed a modest but overall decreased risk of acute respiratory infection with daily vitamin $D_3$ supplementation of 400-1000 $IU \cdot d^{-1}$ (Jolliffe et al. 2021). A recent RCT reported no change in the incidence of upper-respiratory tract infection following 12 weeks of vitamin $D_3$ supplementation (1,000 $IU \cdot d^{-1}$ for the first four weeks and 400 $IU \cdot d^{-1}$ for eight weeks), but found decreased peak severity and duration of illness (Harrison et al. 2021). Accordingly, irrespective of whether vitamin $D_3$ supplementation influences the incidence of upper-RTI, it may still attenuate the severity and/or duration of illness.

There is a high prevalence of vitamin D deficiency in patients with asthma (Bener et al. 2014) and COPD (Janssens et al. 2011). In fact, in these patients, higher vitamin D concentrations are associated with lower risk, severity, and exacerbation of the primary disease (Gupta et al. 2011; Zhu et al. 2016; Liu et al. 2019). Vitamin D supplementation in these groups has thus been studied for its prophylactic and therapeutic effects. There is insufficient evidence that the prophylactic use of vitamin $D_3$ can prevent asthma in children (Yepes-Nuñez et al. 2018; Luo et al. 2022). In addition, the association between vitamin D status and adult-onset asthma is unclear (Mai et al. 2012; Cheng et al. 2014; Confino-Cohen et al. 2014; Cherrie et al. 2017; Manousaki et al. 2017). The therapeutic effects of vitamin $D_3$ supplementation in children and adults with pre-existing asthma are also equivocal (Jolliffe et al. 2021; Chen et al. 2021). For instance, a recent systematic review (Nitzan et al. 2022) and an independent meta-analysis (Kumar et al. 2021) both concluded that vitamin $D_3$ supplementation did not affect lung function, asthma control, or exacerbation rates in children. Although these studies were not performed in children with pre-existing vitamin D deficiency, findings generally concur with recent RCTs in children with 25(OH)D concentration <50 $nmol \cdot L^{-1}$ (Jat et al. 2021) and <75 $nmol \cdot L^{-1}$ (Forno et al. 2020; Han et al. 2021). By contrast, in asthmatic adults with low vitamin $D_3$ concentration, a meta-analysis of three small trials ($n$ = 92) revealed some protection of vitamin $D_3$ supplementation against exacerbations (Jolliffe et al. 2017). One RCT also showed improved asthma control in 25(OH)D-deficient adults who were supplemented with a weekly dose of 16,000 IU (Andújar-Espinosa et al. 2021).

Based on the aforementioned evidence, vitamin $D_3$ supplementation does not improve lung function in COPD patients (Lehouck et al. 2012; Sluyter et al. 2017; Chen et al. 2019; Foumani et al. 2019), although it may confer improvements in $FEV_1$ in current or former smokers with 25(OH)D <50 $nmol \cdot L^{-1}$ (Sluyter et al. 2017). Data from one meta-analysis of four RCTs ($n$=560) indicate that vitamin $D_3$ supplementation reduces exacerbation rates in vitamin D-deficient patients (Jolliffe et al. 2019). Thus, for COPD patients who are hospitalized for exacerbation, the Global Initiative for Chronic Obstructive Lung Disease recommends vitamin D screening and subsequent supplementation for those found to be deficient (Global Initiative for Chronic Obstructive Lung Disease, 2022).

*2.6.3 Literature on Vitamin C.* In healthy populations, the efficacy of regular vitamin C (ascorbic acid) supplementation on upper-RTI incidence depends on individual physical stress levels and associated immune perturbations. Broadly speaking, the data show no benefit of chronic supplementation. A meta-analysis of 24 trials (>10,000 participants) showed no effect of moderate- or high-dose vitamin C on the incidence of upper-RTI (Hemilä and Chalker 2013). Accordingly, chronic vitamin C supplementation is not justified in normal (vitamin C-replete) populations (Hemilä and Chalker 2013; Gómez et al. 2018). The short-term, therapeutic effects of vitamin C are less conclusive (Hemilä and Chalker 2013), but several reviews report that supplementation shortened the duration of upper-RTI symptoms by ~8-18% (Hemilä and Chalker 2013; Abioye et al. 2021). It may therefore be practical to initiate short-term vitamin C supplementation within 24 h of symptom onset.

There is also evidence that acute supplementation may benefit individuals undergoing periods of extreme physical stress. An analysis of five trials comprising marathon runners, skiers, and soldiers, found that vitamin C supplementation reduced symptoms of the common cold by ~50% following hard exercise (Hemilä and Chalker 2013). Further to moderating viral-mediated respiratory symptoms, the prophylactic effects of vitamin C supplementation in some athletes may result from an attenuation of EIB and associated symptoms (Tecklenburg et al. 2007; Hemilä 2013). Thus, when the risk of infection in athletes is elevated due to a high training/competitive load (Ruuskanen et al. 2022) or extensive travel (Walsh 2019), vitamin C supplementation (0.25-1.0 $g \cdot d^{-1}$) may reduce the severity and/or duration of upper-RTIs (Walsh 2019; Cerullo et al. 2020). An important caveat is that chronic, high-dose (~1 $g \cdot d^{-1}$) vitamin C supplementation may blunt certain training-induced skeletal muscle adaptations (Mason et al. 2020), and is therefore discouraged.

Lastly, there is some evidence that vitamin C may help ameliorate asthma symptoms (Allen et al. 2009; Berthon and Wood 2015). An analysis of three small trials (*n*=40) in asthmatics found that vitamin C supplementation, in various dosing regimens (1.5 $g \cdot d^{-1}$ for two weeks; 2 g ingested 1 h before exercise; 0.5 g ingested 1.5 h before exercise), attenuated the post-exercise fall in $FEV_1$ by 48% (Hemilä 2013). Notwithstanding, there is insufficient evidence to make decisive recommendations

regarding vitamin C supplementation for asthma management, and more RCTs with larger samples are needed.

*2.6.4 Literature on Omega-3 (n-3) poly-unsaturated fatty acids (PUFAs).*

The most abundant PUFA in the Western diet is linoleic acid which is converted to arachidonic acid—a precursor for pro-inflammatory and bronchoconstrictive signaling. By contrast, omega-3 (n-3) PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived primarily from fatty fish, may have anti-inflammatory effects. Specifically, EPA inhibits arachidonic acid, blunts pro-inflammatory signaling, and acts as a precursor for pro-resolving mediators with anti-inflammatory properties (Brannan et al. 2015). Similarly, DHA has been shown to modify gene expression and signaling pathways related to inflammatory mediators (Calder 2010). Dietary supplementation with EPA and DHA has therefore been explored as an adjunct therapy in certain respiratory conditions (Thien et al. 2002; Yang et al. 2013; Stoodley et al. 2019).

Studies show that supplementation with high dose n-3 PUFAs for several weeks mitigates EIB (Mickleborough et al. 2003, 2006; Tecklenburg-Lund et al. 2010; Mickleborough and Lindley 2014; Kumar et al. 2016). Yet, because high dose n-3 PUFA is expensive and may cause gastrointestinal complaints, it is worth noting that both high dose (6.2 g/d) and moderate dose (3.1 g/d) n-3 PUFA appear to exert similar effects on provocation-induced decreases in $FEV_1$ (Williams et al. 2017).

In COPD, studies with n-3 PUFA supplementation show equivocal results. A meta-analysis of eight RCTs found that supplementation increased body mass, increased low-density lipoproteins, and reduced IL-6, but did not influence lung function or quality of life (Yu et al. 2021). These results should be interpreted cautiously because, depending on disease severity and other comorbidities, weight gain may be beneficial for some COPD patients and harmful for others. Moreover, some RCTs provide limited data regarding individual doses of EPA and DHA. For example, an observational cohort study of >120,000 US women and men initially showed that greater consumption of fish (>4 servings per week) was associated with lower risk of newly diagnosed COPD. But subsequent analysis showed that COPD risk was unrelated to total n-3 PUFA intake (Varraso et al. 2015). To date, only one observational cohort study in moderate-to-severe

COPD has shown that high dietary n-3 PUFA reduces risk of severe exacerbations, decreases the number of respiratory symptoms, improves health-related quality of life, and reduces overall morbidity (Lemoine et al. 2020). The same study showed the opposite effects of high dietary n-6 PUFA (linoleic acid) (Lemoine et al. 2020). These data speak to the importance of distinguishing n-3 from n-6 PUFA in supplementation interventions, and the importance of the dietary n-3/n-6 PUFA ratio in respiratory health. More well-controlled RCTs on n-3 PUFA supplementation in current and former smokers with COPD are warranted.

*2.6.5 Literature on Probiotics, Prebiotics, and Synbiotics.*

The microbial profile and gut microbiome have a substantial influence on health and disease (Clemente et al. 2012) and systemic immune function (Roberfroid et al. 2010). Immune function is particularly important for respiratory health, and the “gut-lung axis” represents a promising therapeutic target for the non-pharmacological management of respiratory health and diseases (Marsland et al. 2015). Beneficial changes in the gut microbiota can be achieved through dietary supplementation with probiotics (live microorganisms that confer a health benefit on the host when administered in adequate amounts) (Hill et al. 2014), prebiotics (substrates that are selectively utilized by host microorganisms, conferring a health benefit) (Gibson et al. 2017), and/or synbiotics (a combination of pro- and prebiotics).

In terms of the gut microbiota and its effects on respiratory health in subjects without respiratory disease, the largest body of evidence relates to upper-RTIs, and the data are largely favorable. For example, a 2015 Cochrane review of 10 trials found that probiotics reduced the incidence of upper-RTI relative to placebo (Hao et al. 2015). Other meta-analyses show similar findings in healthy infants, children, and adults after supplementation with probiotics (six studies, $n = 1682$) (Rashidi et al. 2021) and synbiotics (four RCTs, $n = 883$) (Chan et al. 2020). Probiotics may also decrease upper-RTI risk in active individuals and athletes (Cox et al. 2010; West et al. 2011, 2014; Haywood et al. 2014; Strasser et al. 2016).

There is also preliminary data indicating that the gut-lung axis may be a suitable target for managing asthma and related conditions. Prebiotics, probiotics, and synbiotics each reduced airway inflammation and disease severity in rodent models of allergic

asthma (Sagar et al. 2014; Verheijden et al. 2015, 2016). Furthermore, a small-scale, double-blind, placebo-controlled RCT showed potential benefits of prebiotics in adults with EIB (Williams et al. 2016). Specifically, prebiotics reduced serum markers of airway inflammation at baseline and completely abolished the 29% provocation-induced increase in TNF-α (a pro-inflammatory cytokine). Lastly, eight weeks supplementation with probiotics decreased asthma exacerbations in children when compared to placebo (Drago et al. 2022). Although more RCTs in humans are warranted, the pre-clinical rodent data and preliminary human *in-vivo* studies show potential benefits of pre- and/or probiotics as a potential adjunct therapy to support respiratory health.

*2.6.6 Evidence Summary and Recommendations.* Primary outcomes from the literature on nutritional interventions are summarized in **Figure 5**. The effects of chronic vitamin $D_3$ supplementation on the prevalence/severity of upper-RTI are inconsistent. When supplemented prophylactically, there is no evidence of benefits in asthma management. In asthmatics and COPD patients with pre-existing deficiency, vitamin $D_3$ supplementation may confer therapeutic benefits. Long-term, daily supplementation of vitamin C (ascorbic acid) provides little-to-no benefit in those who are vitamin C-replete but may reduce the severity and/or duration of the common cold and symptoms of general RTI when supplemented acutely at symptom onset (0.25-1.0 $g \cdot d^{-1}$), especially in individuals undergoing periods of extreme physical stress. Nevertheless, there is insufficient evidence to support vitamin C supplementation for asthma management. Several weeks of n-3 PUFAs reduce the severity of EIB but similar data in COPD are equivocal, with only one observational cohort study showing reduced risk of exacerbation and benefits to respiratory symptoms and overall morbidity. Daily probiotics and/or prebiotics reduce the incidence of upper-RTI better than placebo in adults, children, active individuals, and athletes. Prebiotics, probiotics, and synbiotics may also reduce airway inflammation and disease severity in rodent models of allergic asthma, with preliminary evidence showing benefits in adults with EIB.

## 2.7 Inhaled L-menthol

*2.7.1 Premise and plausibility*. L-menthol is a cyclic alcohol derived from the oils of various species of *Mentha* (mints) that have been used as medicinal plants for

920 millennia. There is evidence that inhaled or ingested L-menthol triggers a cooling
921 sensation by stimulating sensory nerve endings in the nasal vestibule and mucosa that
922 convey nasal sensation (Aldren and Tolley 1993; Eccles 2003). Because L-menthol has
923 a significant effect on the sensation of nasal airflow, menthol vendors claim that the oil
924 can decongest the upper airways (e.g., during colds and allergies), enhance nasal flow,
925 and improve airway patency. Hence, L-menthol is widely available in lozenges, nasal
926 sprays, vapor rubs, inhalers, cough syrups, mouthwashes, as a scent in aromatherapy
927 oils, and as a flavoring in cigarettes and e-cigarettes. However, the plausibility of L-
928 menthol to improve respiratory function is low because it does not possess the amine
929 group that would be expected of a substance with vasodilator or bronchodilator
930 properties, nor does it have a chemical structure similar to nasal decongestants (Eccles
931 et al. 1988; Eccles 1994). Accordingly, any benefit of L-menthol is likely to be indirect—
932 mediated by cooling sensations that stimulate the nasal trigeminal nerve thereby creating
933 the cognitive illusion of improved inspiratory flow (Kanezaki et al. 2021).
934 *2.7.2 Literature.* Articles were excluded if L-menthol was not inhaled, dissolved and
935 nebulized, ingested orally on a lozenge, rinsed/swilled in the mouth, if the effects of L-
936 menthol could not be distinguished from other substances that were co-administered, or
937 if the article did not assess respiratory function. It is well-established that healthy adults
938 (free from respiratory disorders and the common cold) experience increased sensations
939 of nasal airflow and/or nasal patency after inhaling L-menthol (Eccles et al. 1988; Pereira
940 et al. 2013). Two randomized, placebo-controlled trials showed that inhaling L-menthol
941 reduced sensations of respiratory discomfort during flow-resistive and elastic loading at
942 rest (Nishino et al. 1997) and inspiratory resistive loading during exercise (Kanezaki and
943 Ebihara 2017). Studies in individuals with the common cold also found that a menthol-
944 containing lozenge evoked marked improvements in sensations of nasal airflow and
945 decongestion (Eccles et al. 1990; EccleS et al. 1990). Yet, subjective changes in
946 respiratory perceptions are not reflected in objective changes in breathing patterns (i.e.,
947 respiratory frequency, tidal volume, or inspiratory flow), minute ventilation, or spirometric
948 indices of lung function (Nishino et al. 1997; Kanezaki and Ebihara 2017). Case in point,
949 Köteles *et al*. (2018) showed that nebulized menthol-containing peppermint, rosemary, or
950 eucalyptus oil, inhaled over 15 minutes, had no effect on FVC, $FEV_1$/FVC, or peak

951 expiratory flow (PEF), despite improving the perceptions of spirometric outcomes.
952 Similarly, the only study to assess upper-airway resistance using rhinometry confirmed
953 no effect of menthol on nasal/upper-airway resistance, respiratory frequency, or minute
954 ventilation in healthy adults at rest (Pereira et al. 2013).

955 In obstructive respiratory disorders, the data tend to follow a similar pattern. During
956 inspiratory resistive loading in patients with mild-to-severe COPD, L-menthol significantly
957 improved subjective measures (i.e., physical and mental “breathing effort”, air hunger,
958 breathing discomfort, and anxiety and fear) relative to a non-L-menthol control, but did
959 not influence objective measures (i.e., breathing pattern, respiratory duty cycle, and
960 inspiratory muscle activity) (Kanezaki et al. 2020). Others have observed no difference
961 between nebulized menthol and placebo on FVC or $FEV_1$ in mild asthmatics (Tamaoki et
962 al. 1995). A randomized, double-blind trial in patients with chronic cough found that, in
963 response to a capsaicin provocation test, inhalation of 1 mL nebulized L-menthol (0.5%
964 and 1% concentration) improved peak inspiratory flow relative to placebo, whereas only
965 high-dose L-menthol (1%) attenuated the reduction in forced inspiratory flow at 50% of
966 vital capacity ($FIF_{50}$) and increased the cough threshold (Millqvist et al. 2013). A single-
967 blind (non-placebo-controlled) study of L-menthol-containing “aromatics” observed
968 improved mucous clearance in patients with chronic bronchitis when compared to
969 petroleum jelly, but no effect on lung function (Hasani et al. 2003). Lastly, although studies
970 have generally failed to observe any direct effect of L-menthol on physiological variables
971 during exercise, there is a possible indirect effect of L-menthol on exercise performance
972 in the heat owing to changes in the sensation of oropharyngeal temperature versus
973 placebo (Mündel and Jones 2010).

974 *2.7.3 Evidence Summary and Recommendations.* Primary outcomes from the
975 literature on inhaled L-menthol are summarized in **Figure 6**. By stimulating sensory nerve
976 endings in the nasal vestibule, inhaled L-menthol can augment sensations of nasal
977 airflow, improve respiratory perceptions in both healthy subjects and patients, and
978 potentially relieve dyspnea in COPD. Improved respiratory perceptions may translate to
979 improved exercise performance in the heat. There is some evidence that high-
980 concentration inhaled L-menthol may increase the cough threshold in patients with
981 chronic cough. Nevertheless, L-menthol does not have vasodilator or bronchodilator

properties, and there is little-to-no convincing evidence that L-menthol has direct functional benefits on spirometry-related variables in any population.

## Conclusions

The health and wellness industry is characterized by, and in many cases depends on, lax consumer regulations regarding the products and services sold therein. As a result, interventions are often sold on insufficient evidence, baseless claims, and pseudoscience (Tiller et al. 2022). Not only is there a growing disparity between the substance of commercial claims and the supporting scientific evidence, thereby violating Laplace's principle that "Extraordinary claims require extraordinary evidence", but the legitimate (plausible) and illegitimate (implausible) claims for these interventions are often conflated, obscuring the translation of science to practice. This is a particular problem in the field on respiratory physiology and medicine.

This review is intended as an evidence-based guide to help health and exercise professionals distinguish science from pseudoscience in commercial respiratory interventions and make informed decisions that optimize patient/client outcomes. This review is intended as an evidence-based guide to help health and exercise professionals distinguish science from pseudoscience in commercial respiratory interventions and make informed decisions that optimize patient/client outcomes. In summarizing the recommendations, there are several caveats that should be noted. First, the products/strategies selected for inclusion were commercial interventions (i.e., not controlled drugs or products regulated by the FDA as "medical devices"). The list was delimited to those interventions most prevalent in the health and wellness industry that were coupled to the most conspicuous claims, and there may be prominent, mainstream interventions that were not included.

A second caveat is that the recommendations herein are based on data from controlled laboratory-based studies. The statistical analyses typically used allowed researchers to reject, or fail to reject, the null hypotheses, and subsequently discuss the existence of effects or lack thereof. Yet, such an approach is dichotomous by design, providing little room for nuanced interpretation of differences, potentially overlooking practical or clinical implications. For example, some studies in exercise rehabilitation have

been shown to yield non-significant between-group differences despite moderate-to-large effects that would be deemed meaningful in practice (Zemková 2014). Interventions with moderate-to-large effects, despite lack of statistical significance, may be especially important for high-performance athletes for whom the margins of success are extremely small. The opposite may also be true (i.e., statistical tests may yield highly significant outcomes with trivial effects). To improve external validity in exercise-based studies, researchers have been encouraged to perform robust statistical analyses (e.g., by using appropriate sample sizes, correcting for familywise error rate, etc.) but report them alongside confidence intervals and/or effect sizes as a measure of "practical significance" (Knudson 2009). This might aid in the interpretation of both "statistically significant" and "practically meaningful" outcomes.

In this comprehensive review of literature and expert consensus, overall it was determined that: (1) there is good quality data supporting subjective/perceptual (but not objective) benefits of both nasal dilators and L-menthol; (2) there is some evidence that nasally-derived nitric oxide may benefit critically ill patients but not healthy subjects; (3) there is good evidence that systematized breathing interventions (particularly pursed-lips breathing) can improve exercise performance, respiratory symptoms, and quality of life in COPD and asthma; (4) there is good evidence that respiratory muscle training can improve exercise performance in healthy subjects and respiratory symptoms in some patient populations (e.g., COPD), with benefits for patients with COPD who have respiratory muscle weakness or pre-existing comorbidities precluding them from whole-body exercise training; (5) there is evidence that nutritional interventions including vitamin D and vitamin C may benefit respiratory health in individuals with pre-existing nutrient deficiency and during times of compromised immune function second to increased physical stress, and interesting but inconsistent evidence of benefits of polyunsaturated fatty acids and pre/probiotics/synbiotics; and (6) no evidence that canned oxygen is beneficial for any clinical outcome.

For the interventions aforenoted, we advocate for greater vigilance in determining prior plausibility and evidence for efficacy. We also hope to inspire similar expert reviews that scrutinize interventions stemming from other facets of the commercial health and wellness industry.

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*Authors' contributions.* CRI and NBT conceived the manuscript. All authors drafted, edited, and approved the final version.

## Footnote, page 17

[1]Applied external resistors are intentionally designed to elicit high resistive loads during exercise; thus, they impose considerably greater loads than low-resistance face coverings (e.g., cloth and surgical masks) that might be used for personal protection from airborne pathogens. Indeed, the negative physiological effects of protective face masks have been shown to be negligible when used during physical activity in healthy individuals (Hopkins et al. 2021).

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## FIGURES

**Figure. 1.** Primary outcomes from the literature on internal and external nasal dilators. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change; IND = internal nasal dilator; END = external nasal dilator; OSA = obstructive sleep apnea; $\dot{V}O_{2max}$ = maximal oxygen uptake; HR = heart rate; RPE = ratings of perceived exertion.

**Figure. 2.** Primary outcomes from the literature on nasal breathing. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change; NO = nitric oxide; $\dot{V}O_2$ = oxygen uptake; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$ = end-tidal partial pressure of carbon dioxide; $f_R$ = respiratory frequency; $V_T$ = tidal volume; $\dot{V}O_{2max}$ = maximal oxygen uptake.

**Figure. 3.** Primary outcomes from the literature on systematized breathing interventions. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change; $FEV_1$ = forced expiratory volume in 1 second; COPD = chronic obstructive pulmonary disease; $CO_2$ = carbon dioxide.

**Figure. 4.** Primary outcomes from the literature on respiratory muscle training interventions. One of the putative mechanisms underpinning the effects of respiratory muscle training on exercise tolerance and performance is a possible ‘blunting’ of the respiratory muscle metaboreflex. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change. COPD = chronic obstructive pulmonary disease; $O_2$ = oxygen.

**Figure. 5.** Primary outcomes from the literature on nutritional interventions. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change. RTI = respiratory tract infection; EIB = exercise-induced bronchoconstriction.

**Figure. 6.** Primary outcomes from the literature on inhaled L-menthol. ↑ = evidence of increase; ↓ = evidence of decrease; ↔ = evidence of no change. $FEV_1$ = forced

expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; COPD = chronic obstructive pulmonary disease.

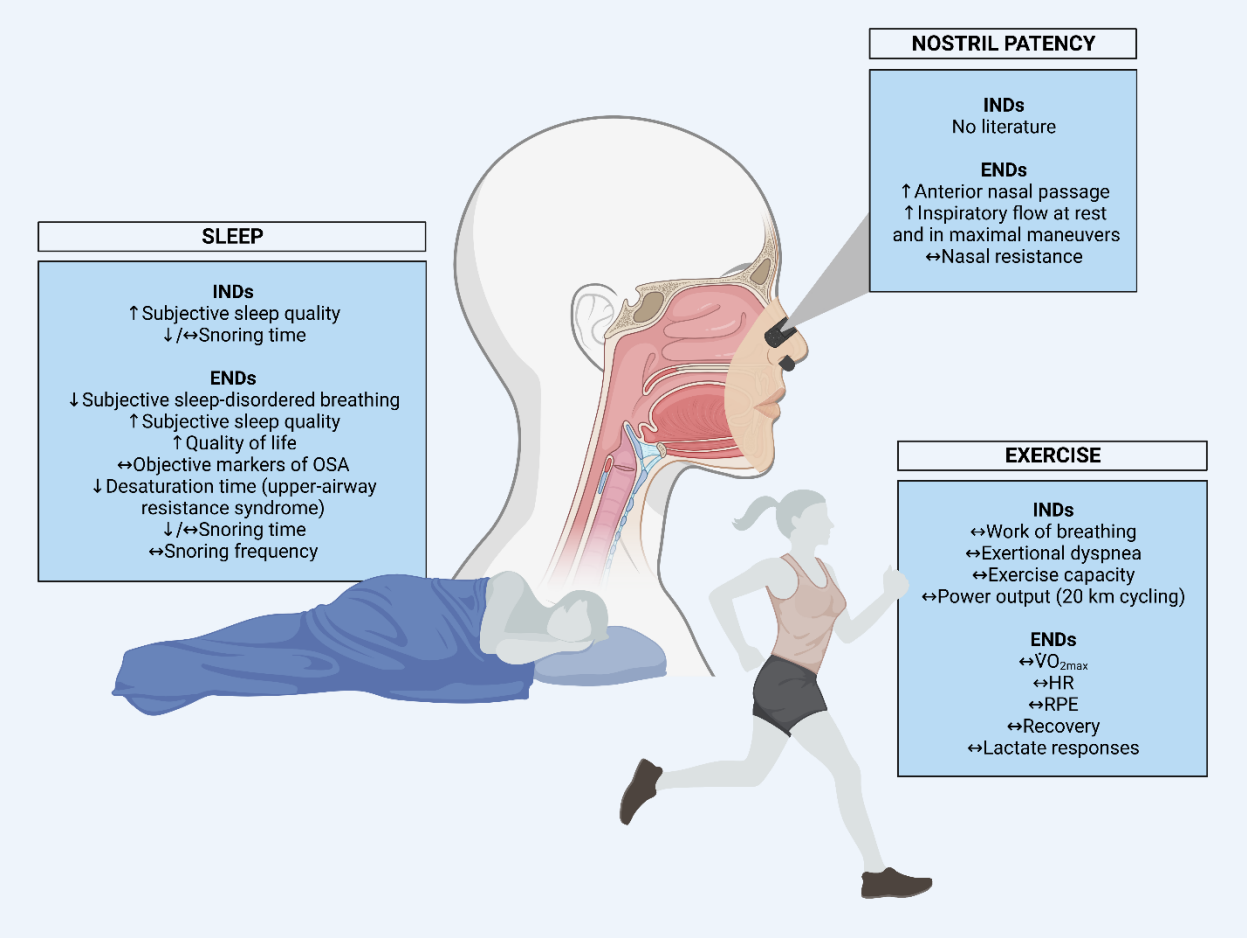
NOSTRIL PATENCY
INDs
No literature
ENDs
↑Anterior nasal passage
↑Inspiratory flow at rest and in maximal maneuvers
↔Nasal resistance
SLEEP
INDs
↑Subjective sleep quality
↓/↔Snoring time
ENDs
↓Subjective sleep-disordered breathing
↑Subjective sleep quality
↑Quality of life
↔Objective markers of OSA
↓Desaturation time (upper-airway resistance syndrome)
↓/↔Snoring time
↔Snoring frequency
EXERCISE
INDs
↔Work of breathing
↔Exertional dyspnea
↔Exercise capacity
↔Power output (20 km cycling)
ENDs
↔$\dot{V}O_{2max}$
↔HR
↔RPE
↔Recovery
↔Lactate responses

**Fig. 1.**

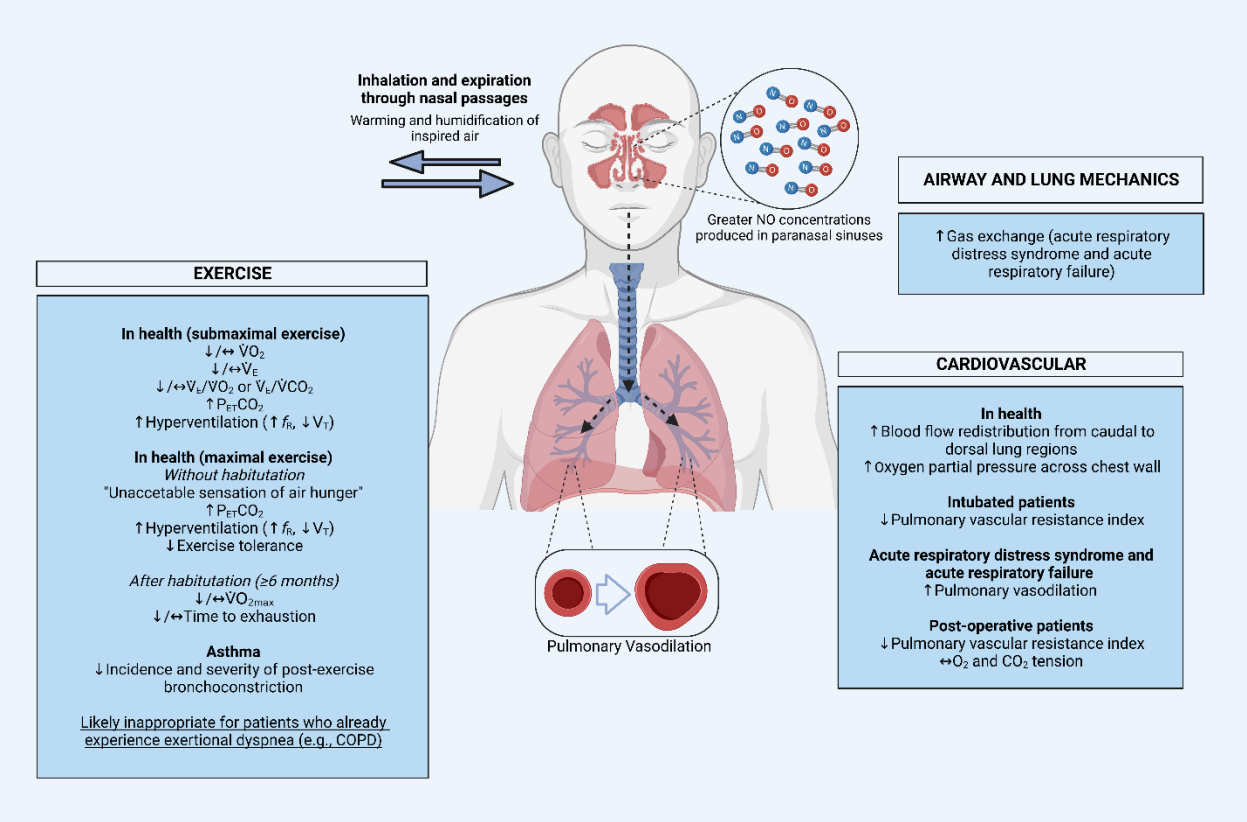
Inhalation and expiration through nasal passages
Warming and humidification of inspired air
Greater NO concentrations produced in paranasal sinuses
AIRWAY AND LUNG MECHANICS
↑ Gas exchange (acute respiratory distress syndrome and acute respiratory failure)
EXERCISE
In health (submaximal exercise)
↓/↔ V̇O2
↓/↔V̇E
↓/↔VE/V̇O2 or VE/V̇CO2
↑ PETCO2
↑ Hyperventilation (↑ fR, ↓ VT)
In health (maximal exercise)
Without habitutation
"Unaccetable sensation of air hunger"
↑ PETCO2
↑ Hyperventilation (↑ fR, ↓ VT)
↓ Exercise tolerance
After habitutation (≥6 months)
↓/↔V̇O2max
↓/↔Time to exhaustion
Asthma
↓ Incidence and severity of post-exercise bronchoconstriction
Likely inappropriate for patients who already experience exertional dyspnea (e.g., COPD)
CARDIOVASCULAR
In health
↑ Blood flow redistribution from caudal to dorsal lung regions
↑ Oxygen partial pressure across chest wall
Intubated patients
↓ Pulmonary vascular resistance index
Acute respiratory distress syndrome and acute respiratory failure
↑ Pulmonary vasodilation
Post-operative patients
↓ Pulmonary vascular resistance index
↔O2 and CO2 tension
Pulmonary Vasodilation

**Fig. 2.**

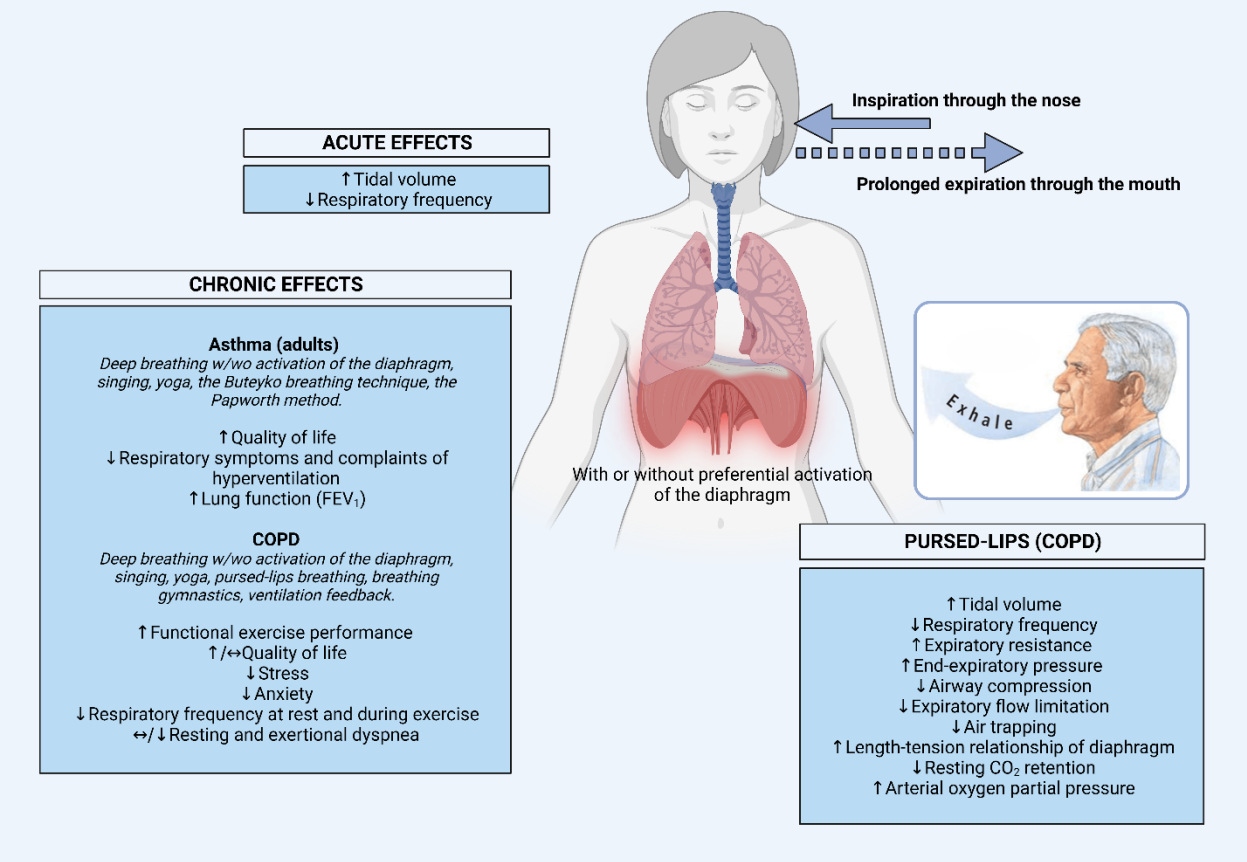
ACUTE EFFECTS
↑Tidal volume
↓Respiratory frequency
Inspiration through the nose
Prolonged expiration through the mouth
CHRONIC EFFECTS
Asthma (adults)
Deep breathing w/wo activation of the diaphragm, singing, yoga, the Buteyko breathing technique, the Papworth method.
↑Quality of life
↓Respiratory symptoms and complaints of hyperventilation
↑Lung function (FEV1)
COPD
Deep breathing w/wo activation of the diaphragm, singing, yoga, pursed-lips breathing, breathing gymnastics, ventilation feedback.
↑Functional exercise performance
↑/↔Quality of life
↓Stress
↓Anxiety
↓Respiratory frequency at rest and during exercise
↔/↓Resting and exertional dyspnea
With or without preferential activation of the diaphragm
Exhale
PURSED-LIPS (COPD)
↑Tidal volume
↓Respiratory frequency
↑Expiratory resistance
↑End-expiratory pressure
↓Airway compression
↓Expiratory flow limitation
↓Air trapping
↑Length-tension relationship of diaphragm
↓Resting CO2 retention
↑Arterial oxygen partial pressure

**Fig. 3.**

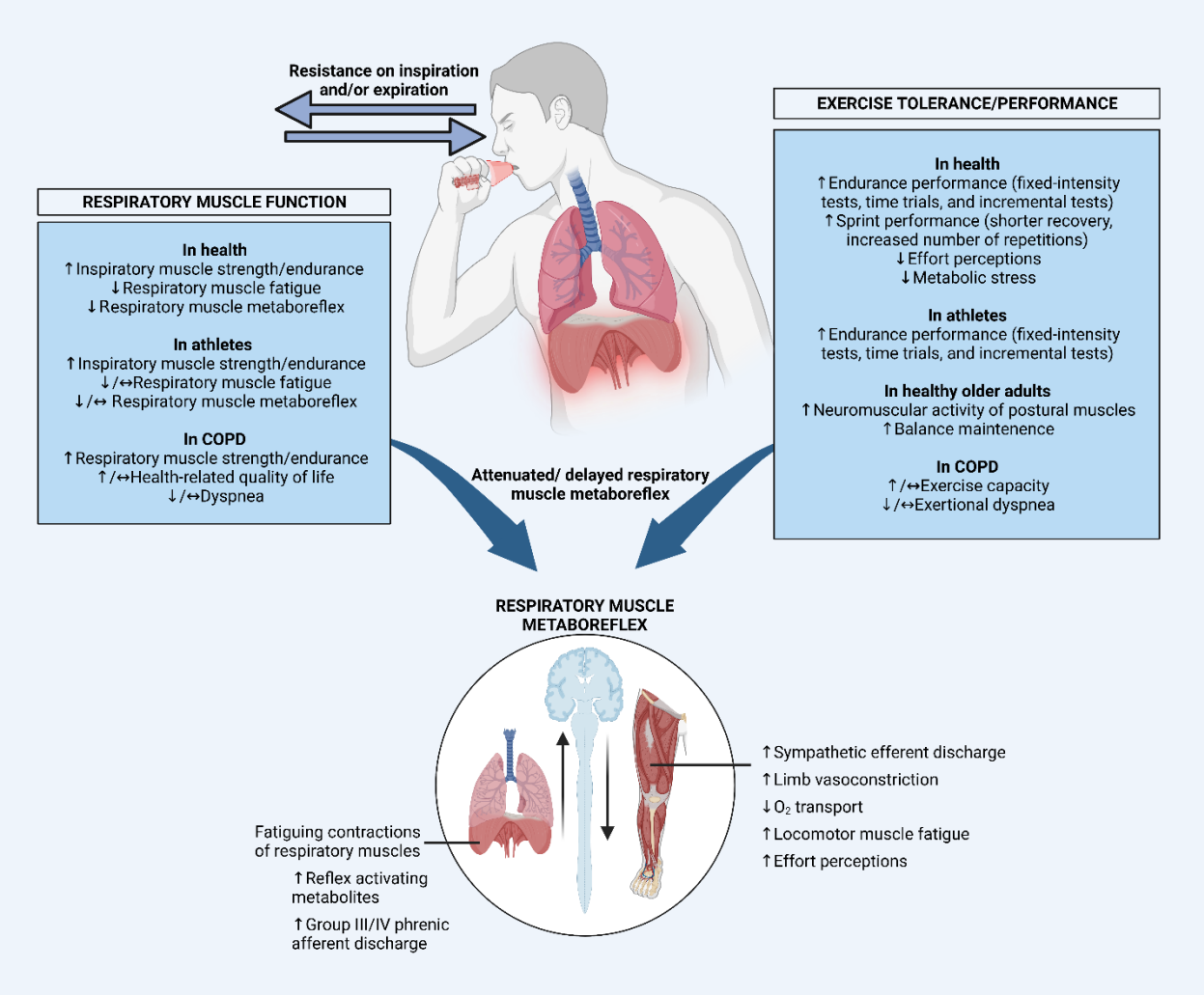
Resistance on inspiration and/or expiration
RESPIRATORY MUSCLE FUNCTION
In health
↑ Inspiratory muscle strength/endurance
↓ Respiratory muscle fatigue
↓ Respiratory muscle metaboreflex
In athletes
↑ Inspiratory muscle strength/endurance
↓/↔ Respiratory muscle fatigue
↓/↔ Respiratory muscle metaboreflex
In COPD
↑ Respiratory muscle strength/endurance
↑/↔ Health-related quality of life
↓/↔ Dyspnea
EXERCISE TOLERANCE/PERFORMANCE
In health
↑ Endurance performance (fixed-intensity tests, time trials, and incremental tests)
↑ Sprint performance (shorter recovery, increased number of repetitions)
↓ Effort perceptions
↓ Metabolic stress
In athletes
↑ Endurance performance (fixed-intensity tests, time trials, and incremental tests)
In healthy older adults
↑ Neuromuscular activity of postural muscles
↑ Balance maintenence
In COPD
↑/↔ Exercise capacity
↓/↔ Exertional dyspnea
Attenuated/ delayed respiratory muscle metaboreflex
RESPIRATORY MUSCLE METABOREFLEX
Fatiguing contractions of respiratory muscles
↑ Reflex activating metabolites
↑ Group III/IV phrenic afferent discharge
↑ Sympathetic efferent discharge
↑ Limb vasoconstriction
↓ $O_2$ transport
↑ Locomotor muscle fatigue
↑ Effort perceptions

**Fig. 4.**

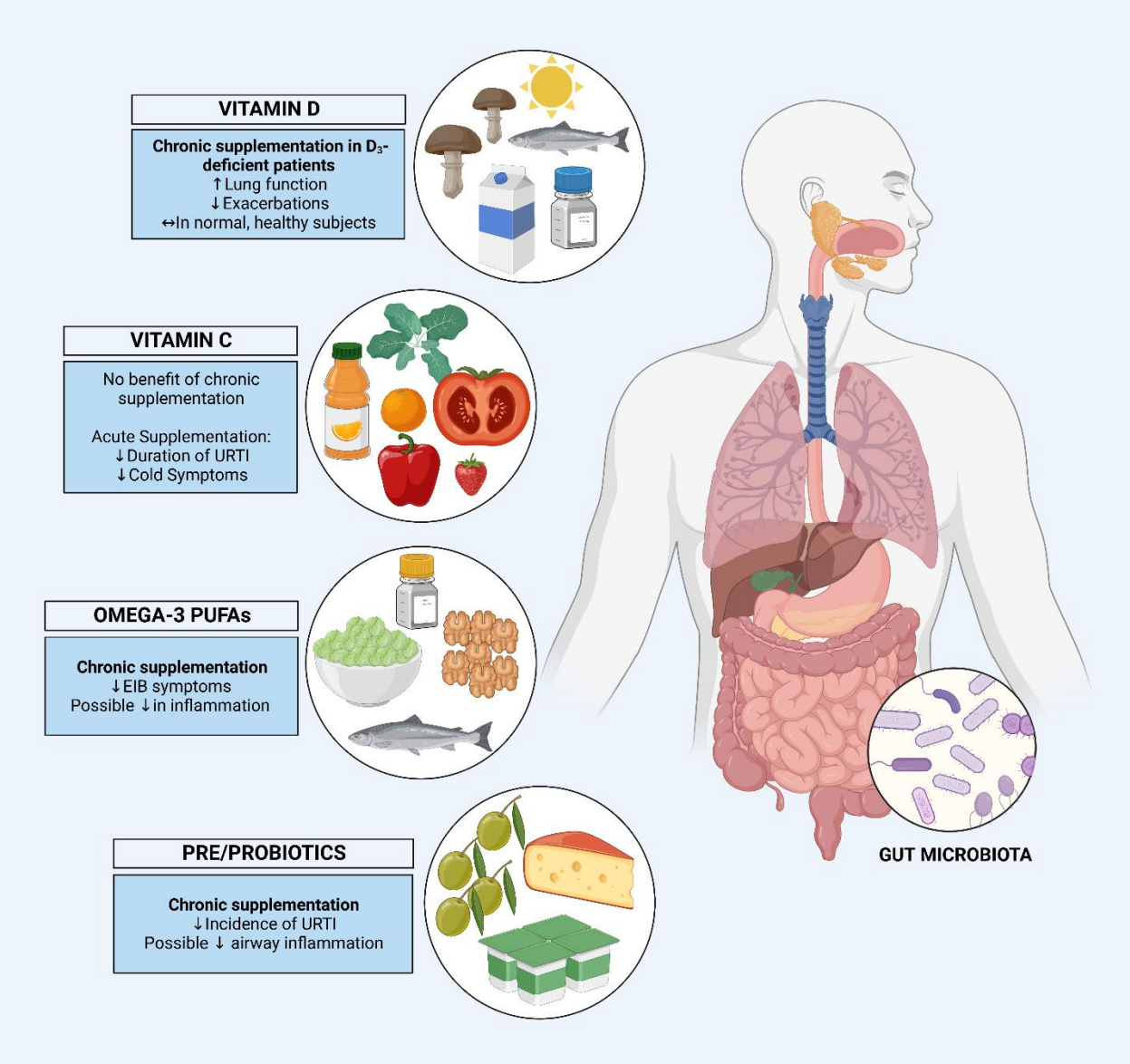
VITAMIN D
Chronic supplementation in $D_3$-deficient patients
↑Lung function
↓Exacerbations
↔In normal, healthy subjects
VITAMIN C
No benefit of chronic supplementation
Acute Supplementation:
↓Duration of URTI
↓Cold Symptoms
OMEGA-3 PUFAs
Chronic supplementation
↓EIB symptoms
Possible ↓in inflammation
PRE/PROBIOTICS
Chronic supplementation
↓Incidence of URTI
Possible ↓ airway inflammation
GUT MICROBIOTA

**Fig. 5.**

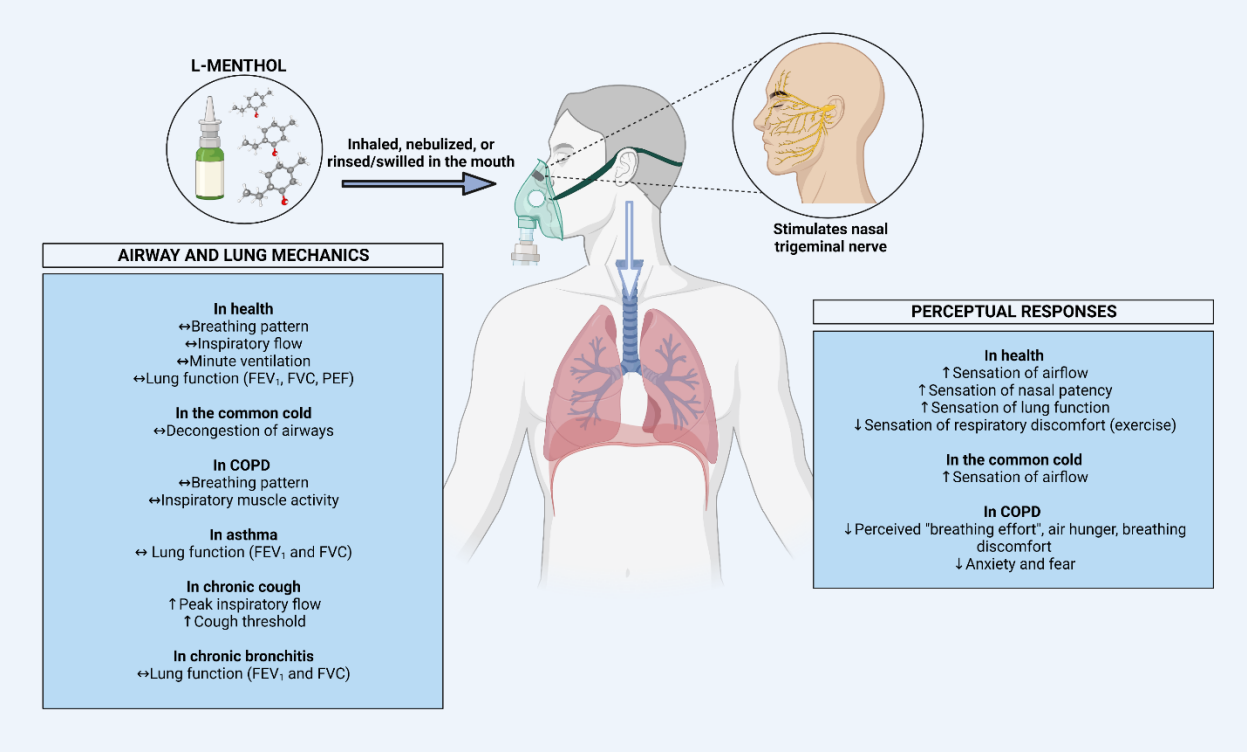
L-MENTHOL
Inhaled, nebulized, or rinsed/swilled in the mouth
Stimulates nasal trigeminal nerve
AIRWAY AND LUNG MECHANICS
In health
↔Breathing pattern
↔Inspiratory flow
↔Minute ventilation
↔Lung function (FEV1, FVC, PEF)
In the common cold
↔Decongestion of airways
In COPD
↔Breathing pattern
↔Inspiratory muscle activity
In asthma
↔ Lung function (FEV1 and FVC)
In chronic cough
↑Peak inspiratory flow
↑Cough threshold
In chronic bronchitis
↔Lung function (FEV1 and FVC)
PERCEPTUAL RESPONSES
In health
↑Sensation of airflow
↑Sensation of nasal patency
↑Sensation of lung function
↓Sensation of respiratory discomfort (exercise)
In the common cold
↑Sensation of airflow
In COPD
↓Perceived "breathing effort", air hunger, breathing discomfort
↓Anxiety and fear

**Fig. 6.**