

An Overview of Integrative Therapies in Asthma Treatment

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Abstract Treatment of asthma lends itself to an integrative medicine approach due to the multifactorial nature of the disease. It is well established that asthma has a neuromuscular component (bronchospasm), an immunological component (inflammation), and a psychological component. This encourages the use of diverse approaches to address all avenues of pathophysiology, aiming for the most effective blend of treatment approaches possible. Integrative medicine is defined by NIH NCCAM (<http://nccam.nih.gov>) as medicine that blends the use of evidence-based complementary therapies with conventional medicine. Statistics from the 2007 National Health Interview Survey (NHIS), conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), showed that approximately four out of 10 adults and approximately one in nine children and more than 50 % of children living with chronic illness, including asthma, used complementary therapies in the USA in 2007. Asthma and allergies rank among the top 15 most common medical conditions in which integrative therapies are used in both children and adults. To date, integrative treatment approaches with some evidence for benefit in asthma treatment include the following: nutrition modification, mind-body medicine, physical activity, and certain dietary supplement interventions.

Keywords Integrative medicine · Complementary medicine · Asthma · Nutrition · Mediterranean diet · Mind-body medicine · Environment and health

Introduction

Despite medical advances in the treatment of asthma, prevalence of the disease has continued to increase in both children and adults. Reasons for this are the subject of active study [1]. Asthma treatment is complicated by its heterogeneous nature [2, 3], leaving practitioners, and patients and their families faced with significant challenges in the current medical model.

Surveys indicate that many people turn to integrative medicine to help reduce symptom triggers and dependence on prescription medication. Statistics from the 2007 National Health Interview Survey (NHIS), conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), showed that approximately four out of 10 adults and approximately one in nine children and more than 50 % of children living with chronic illness used complementary therapies in the USA in 2007. Asthma and allergies rank among the top 15 most common medical conditions in which integrative therapies are used in both children and adults [4, 5].

Integrative medicine is an emerging field that blends conventional and evidence-based complementary medicine, with a focus on preventative health. Broad categories for integrative therapies include the following: lifestyle (nutrition, exercise, sleep, environment, mind-body medicine), biochemical (medications, dietary supplements), biomechanical (massage, manual medicine, surgery), and bioenergetics (acupuncture, therapeutic touch, prayer and spirituality, homeopathy) [6] approaches.

Principles of integrative medicine practice include the following:

- Emphasis on family-centered preventative health and lifestyle change
- Support of the individual's innate healing response

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- Focus on the therapeutic relationship between patient and clinician
- Consideration of health in all dimensions (body, mind, and spirit)
- Cultural competency with respect to philosophy and practices
- Use of all appropriate evidence-based therapies [7].

Integrative medicine to treat asthma has been reported in children, adolescents, and adults and spans socioeconomic groups. For example, a study of 160 inner-city high school students with asthma reported that 80 % used integrative therapies, with rubs, herbal teas, massage, prayer, and herbal syrup being the most commonly used [8]. Another study of 151 adolescents with asthma reported that 71 % used integrative medicine in the previous month, with relaxation techniques and prayer being the most frequently used [9].

A 2012 survey study by Shen and Oraka of 5,435 children showed that 26.7 % of those with current asthma had used complementary therapies in the preceding 12 months. The most commonly used therapies included breathing techniques, vitamins, and herbal products. Higher use was reported among children with poorly controlled asthma and in those in lower socioeconomic settings [10]. Use of complementary therapies in adults is also high [11], with up to 60 % prevalence reported in some studies, especially in adults with work-related asthma [12].

High Prevalence of Use, Low Disclosure

The use of integrative therapies is often underreported by patients and may be met with skepticism or alarm by practitioners [13]. Reasons for patient's use of integrative therapies vary. In the treatment of asthma, in addition to a desire to reduce dependence on prescription medication, reasons may include a desire to improve overall health, interest in exploring all treatment options, desire to maximize nutrition, and reduction of caretaker stress. In certain cases, integrative medicine treatments may be perceived as less invasive, more natural, and more cost-effective than comparable conventional medicine approaches [14].

Ethical Concerns

As in any medical encounter, ethical and legal considerations are paramount in integrative medicine. The guiding principles of beneficence (promote the well-being of the patient), nonmaleficence (do no harm), and patient autonomy (does the patient have enough information to make an informed decision) are highly applicable in both routine and complex clinical settings [15]. Historically, progress in the field has been hindered by the commercial promotion of untested and unregulated therapies. The primary goals of this paper are to

convey a balanced approach to the use of integrative medicine in patients with asthma and to stress the importance of well-informed use of evidence-based therapies. Given the high prevalence of use and the advancement of this emerging field, it is important for physicians caring for patients with asthma to ask about the use of integrative therapies at each patient visit and to understand how to locate reputable sources of information on integrative treatments.

Ideally, clinicians would ask about complementary and integrative therapy use in a systematic way in every patient, at each encounter, including inquiring about the patient's reasons for its use, types of therapies, positive effects, and any noted side effects with the goals of:

- Encouraging full disclosure of therapies in use
- Promoting patient-centered care in the context of a trusting relationship
- Decreasing risk of unintended drug-supplement interaction
- Facilitating discussion of all appropriate therapies
- Enhancing the patient's sense of self-efficacy
- Addressing facts as well as uncertainty of treatment options
- Accurately assessing the risk-benefit ratio of the proposed therapy [16].

Challenges in Integrative Medicine

In addition to challenges related to affordability and insurance reimbursement, variability of training, licensing, and credentialing of practitioners in the various modalities can be a cause for concern in integrative medicine. To counteract this, clinicians should familiarize themselves with issues such as:

- Does sufficient evidence exist for therapeutic benefit as primary or adjunct therapy?
- Clinician qualifications, experience, and scope of practice
- Clear understanding of the proposed treatment plan
- Use of informed consent
- Ongoing communication and coordination with conventional practitioner
- Duration of clinical trial
- Importance of comprehensive medical records [17].

Strengths and Benefits

One of the strengths of integrative medicine is its inclusive approach to treatments that may act synergistically, for example the use of a mind-body therapy such as guided imagery to help reduce anxiety or improve sleep quality in the asthmatic patient. Both have potential to reduce the need for anxiolytics

and improve overall well-being. Another strength of integrative medicine is its focus on patient's long-term health goals in addition to the management of their illness.

Rapid Progress

The field is evolving rapidly and is represented at over 50 academic health centers in the USA which participate in the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM). Academic fellowships based on the growing literature in evidence-based integrative medicine are available, and integrative medicine will become a formal medical specialty board in the USA in 2014 (ABPS) [18].

Integrative Medicine and Asthma Treatment

Asthma lends itself to an integrative medicine approach. It is established that asthma has a neuromuscular component (bronchial hyperresponsiveness) [19] and an immunological component (inflammation) [20–22].

In some patients, psychological components exist, which may occur in the form of psychological triggers, such as stress [23], or manifest as the burden of living with a chronic illness [24, 25].

This encourages the use of diverse approaches to address all avenues of pathophysiology, aiming for the most effective blend of treatment approaches possible. One of the most powerful intersections of integrative medicine and asthma treatment is the goal of reducing inflammation. This is addressed in the core topics of integrative medicine: healthy nutrition, physical activity, stress management, healthy relationships, restorative sleep, and the selective use of dietary supplements. The proinflammatory nature of asthma lends itself to a focus on these lifestyle areas, with the added benefit of providing patients the opportunity to gain a greater sense of control over their illness. To date, benefits in asthma treatment have been seen using conventional approaches, nutrition modification, mind-body medicine treatment, physical activity, and certain dietary supplements. Education about the link between a healthy environment and lung function is another important intersection of integrative medicine and asthma treatment.

In-depth discussion of each facet of integrative therapy is beyond the scope of this overview; therefore, a research update will be offered in areas with strongest evidence in asthma treatment.

Nutrition

Nutrition has been shown to influence asthma symptoms [26]. For example, the Mediterranean diet pattern frequently used in

integrative medicine to reduce systemic inflammation cardiovascular risk [27–29] has shown a promise in reducing asthma and allergy prevalence, especially in children [30, 31]. This diet includes a high consumption of fruits and vegetables, olive oil as the principal source of fat, high-quality whole grains, low consumption of meat, low-fat dairy in moderation, and regular fish intake. Teas and spices from around the world (such as green tea, turmeric, and cinnamon) high in phytonutrients are included for their anti-inflammatory and antioxidant effects.

A cross-sectional study of 1,125 10- to 12-year-old children in Greece evaluated the correlation between Mediterranean diet adherence and asthma (defined according to phase II of the International Study on Allergies and Asthma criteria). Each 1-unit increase in Mediterranean diet adherence as measured by the KIDMED score was associated with 16 % lower likelihood of having asthma symptoms (95 % confidence interval (CI), 0.77–0.91) after adjusting for confounders. This association was consistent in both urban and rural areas, although urban dwellers had an overall higher prevalence of asthma symptoms [32].

A study by Chatzi et al. demonstrated an inverse relationship between adherence to the Mediterranean diet in pregnancy and rates of atopy and wheezing in offspring ($n=460$) at age 6.5 years. A high Mediterranean diet score in pregnancy was shown to be protective for persistent wheeze (odds ratio (OR) 0.22; 95 % CI 0.08 to 0.58), atopic wheeze (OR 0.30; 95 % CI 0.10 to 0.90), and atopy (OR 0.55; 95 % CI 0.31 to 0.97) in these children after adjusting for confounding variables [33]. Benefits of prenatal introduction of this anti-inflammatory diet pattern have also been associated with a reduced prevalence of atopy and wheeze in children [34]. Fish consumption, a core element in the Mediterranean diet, has been independently evaluated for its protective effect against atopy risk in children. A review of five studies by Kremmyda et al. on the effect of maternal fish intake during pregnancy indicated a protective effect against atopy and allergy in children [35], and a large longitudinal Danish birth cohort study of 28,936 mothers showed a dose-response correlation for high maternal fish intake (two to three meals/week) with low prevalence of wheeze in offspring ($n \sim 22,000$) at 18 months ($p=0.001$) [36].

Use of the Mediterranean diet as a treatment strategy in adults also has supporting data, although less so than that in the pediatric population. A small 12-week randomized study by Sexton et al. of 38 adults with asthma showed small improvements in spirometry and in quality of life in the treatment group receiving the Mediterranean diet [37]. A larger study of 174 adult asthmatics by Barros et al. showed that controlled asthmatics (23 %) as measured by symptoms, lung function, and exhaled nitric oxide had significantly higher adherence to a Mediterranean diet pattern as opposed to the uncontrolled asthmatic group (77 %) [38, 39].

Overall, it appears that there may be a potential benefit of a Mediterranean diet in patients with asthma; however, a number of unmeasured confounding variables may be influencing the study results. Some evidence supporting its use in the prenatal and childhood time frame exists [31].

Fiber and Inflammation

An emerging topic in nutrition research involves the influence of fiber on inflammatory diseases, including asthma. Recent animal studies have shown that high dietary fiber can regulate the lung's immune system, resulting in a reduction of airway inflammation. Dietary fiber is metabolized by gut microbes into short-chain fatty acids, which attenuate the inflammatory pathways in macrophages and in dendritic cells and promote the development of regulatory T cells along with their actions related to maintaining the integrity of gut epithelium [40]. These studies add to the growing body of research linking the gut microbiome to a variety of inflammatory-driven conditions and are consistent with recommendation of the Mediterranean diet, naturally high in fiber.

Dietary Supplements

The use of dietary supplements, including herbal preparations is prevalent in children and adults with asthma [41]. In spite of this enthusiasm, two large systematic reviews highlight a lack of high-quality randomized controlled studies. For example, a 2008 Cochrane Database Systematic review of 27 studies examining herbal interventions for chronic asthma in adults and children found that while the use of herbals was prevalent, the wide variability of compounds used, poor study quality, and small sample sizes precluded a firm endorsement of any specific herbal intervention for asthma [42]. A 2010 systematic review of 26 studies by Clark et al. drew similar conclusions [43].

Open discussion about integrative therapies in the medical encounter is especially important when considering dietary supplements. In part, this is due to the risk of possible herb-drug interactions or allergic reactions. For example, *Echinacea* and *chamomile* are both members of the ragweed (Compositae) family and may cause allergic reactions in susceptible individuals. Other dietary supplements have been shown to contain naturally occurring substances such as ephedra that can potentiate beta-agonists. Unilateral substitution of prescription drugs with dietary supplements by the patient may also put them at risk for a delay of appropriate medical treatment in acute situations.

Three dietary supplements have garnered particularly active research interest in asthma treatment: omega-3 fatty acids, vitamin D, and vitamin C.

Omega-3 fatty acids have potent anti-inflammatory effects and play a critical role in gene expression and metabolic regulation. They have been shown to have beneficial effects on body weight and insulin resistance [44] and have recognized triglyceride-lowering effects. They are integral to fetal neurodevelopment and have been clearly associated with prolongation of gestation [45]. The use of omega-3 fatty acid supplementation has shown some promising evidence in asthma treatment [46], but conflicting study results, in part due to postulated genetic polymorphisms, indicate a need for larger randomized controlled studies before a definitive recommendation for their use in asthma can be made in both children and adults [47–49]. Although no evidence exists for the use of omega-3 fatty acids in asthma, overall risk of omega-3 fatty acid supplements is low. Avoid high doses in patients on anticoagulants due to synergistic antiplatelet effects.

Vitamin D

Vitamin D is a prohormone that controls calcium, phosphorous, and bone metabolism. It is involved in many cellular processes, including nerve function,

is known to play a significant role in immunomodulation in many illnesses, although questions remain about its specific benefit in asthma. Vitamin D has been associated with normal lung development in the prenatal period [50].

Vitamin D deficiency is widely prevalent even in those with regular sun exposure and has been associated with obesity and the metabolic syndrome in both adults and children [51] and increased risks of breast, prostate, colorectal, and some other cancers [52]. Vitamin D deficiency has been strongly linked to asthma in the pediatric population and correlated with increased severity of symptoms, more frequent exacerbations, reduced lung function, and increased need for medication [53]. However, a recent study in JAMA of 408 adults with persistent asthma and vitamin D deficiency ($n=207$ treatment group) did not show a benefit when receiving vitamin D added to inhaled ciclesonide in prevention of asthma exacerbation or rate of the first treatment failure [54]. Other studies do exist that support the role of vitamin D in improving steroid sensitivity and preventing asthma exacerbation triggered by acute respiratory infection [55].

A protective role for Vitamin D against severe pathology such as recurrent exacerbations and irreversible airway obstruction caused by airway remodeling is also the topic of active research inquiry [55–57].

Vitamin C

A Cochrane review inclusive of 11 studies, $n=419$ (10 adult studies and 1 pediatric study) found insufficient evidence to produce recommendations for the use of vitamin C for management of asthma or exercise-induced bronchoconstriction.

Several small studies have suggested a benefit of vitamin C in exercise-induced bronchoconstriction, but study quality overall was judged to be of low quality. Larger controlled studies are needed to clarify potential benefit [58].

Mind-Body

Mind-body medicine might be defined as the deliberate harnessing of positive interactions between thought, emotion, and human physiology for the specific purpose of enhancing health. An important goal in mind-body medicine is the development of a sense of control and self-efficacy. Mind-body therapies can be used to address fear, anxiety, inflammation, and airway hyperresponsiveness as well as psychological stress, which has been associated with asthma, especially in men [59].

Some of the most commonly used mind-body therapies in children with asthma include breathing exercises [10], prayer, and relaxation [9], which can be used alone or in conjunction with guided imagery or biofeedback [60].

Clinical hypnosis also has a long history of successful use in both pediatric and adult asthmatic patients, dating back in the literature to the early 1960s and early 1970s [61].

A 1986 prospective, randomized, single-blind controlled study in 39 adults showed a 74.9 % improvement ($p < 0.01$) in airway hyperresponsiveness to methacholine challenge in patients with high susceptibility after a 6-week course of hypnotherapy. Significant improvements in peak flow were seen in the treatment group ($p < 0.01$), and bronchodilator use decreased by 26.2 % [62]. Hypnosis has also been used very successfully in the pediatric population; for example, in a study of 505 children by Kohen et al. in which 40 % of participants had asthma, a 50 % reduction in symptoms of asthma and 70 % reduction in school absenteeism were recorded in asthmatic children [63]. Another large study of 303 pediatric respiratory patients by Anbar showed improvement in 80 % of patients with chronic asthma, habit cough, shortness of breath and chest pain/pressure, and hyperventilation with no patients reporting worsening of symptoms [64].

Mindfulness is another mind-body approach with some promise in asthma. Jon Kabat-Zinn, PhD, creator of mindfulness-based stress reduction (MBSR) describes mindfulness practice as “a means to commit fully in each moment to be present; inviting ourselves to interface with this moment in full awareness, with the intention to embody as best we can an orientation of calmness, mindfulness, and equanimity right here and right now” [65].

MBSR has been widely used in medicine for treatment of anxiety and symptoms related to cancer treatment including pain and anxiety. Studies also exist for its efficacy in certain factors in the treatment of asthma. For example, a

randomized controlled trial of an 8-week MBSR program ($n=42$) versus an educational program ($n=41$) in adult patients with asthma showed clinically significant improvements from baseline in quality of life and perceived stress, without demonstrable improvements in lung function [66]. Studies exploring the potential benefit of mindfulness in children and adolescents with asthma are needed. Qi gong and tai chi, prayer, biofeedback, guided imagery and relaxation training, and yoga are other frequently used mind-body therapies in adults [41].

Although a 2013 Cochrane Database Systematic Review found inconclusive evidence to support the use of breathing exercise such as the Buteyko technique, studies do exist demonstrating the benefit of breathing exercises in patients with asthma [67].

The use of acupuncture in asthma has shown equivocal results in improvement in lung function in patients in asthma, although some studies have shown improvement in perceived quality of life [68, 69].

A randomized controlled study by Vempati et al. in 29 adults showed progressive improvement in pulmonary function over the course of an 8-week yoga program compared to a wait-listed control group [70]. Small studies have also shown benefit of yoga on quality of life in asthmatic children, although further studies are needed [71, 72].

Potential downsides to the use of mind-body therapies include possible delay of treatment or exacerbation of preexisting mental illness or trauma. One of the arts and challenges for the clinician is to tailor the mind-body therapy to the patient's needs.

Physical Activity

Regular enjoyable physical activity is fundamental to good health and has benefit in asthma, especially in regard to cardiovascular fitness and improvement in peak expiratory flow [73, 74]. Although people living with asthma may be faced with obstacles such as exercise-induced bronchospasm, exercise is still generally recommended. A training program of at least 3 months that included a minimum of two 60-min training sessions per week at an individualized intensity level was the conclusion of a systematic literature review by Wanrooij et al. [75]. Another consideration related to exercise in asthma is social stigma. For example, children with asthma have been shown to encounter obstacles in the school setting, such as lack of access to medication, teasing or bullying, and embarrassment at their need for medication, and may lack effective asthma action plans [76]. Obese children with asthma can have additional challenges with bullying and social stigma and may need support from the medical team to implement successful physical activities programs [77].

Environment and Health

“Healthy habits in a healthy habitat” is a simple way to summarize core integrative therapies. This includes the impact of environment on lung function. Although detailed discussion of this expansive subject is beyond the scope of this paper and new studies suggest that early exposure to natural allergens and bacteria may convey a protective effect against wheezing [78], it is known that air quality with relation to outdoor air particulate matters, and criteria air pollutants such as ozone, carbon monoxide, and sulfur dioxide [79] can have a detrimental effect on the lungs and affect airway inflammation and remodeling [80]. Exposure to the synthetic chemical bisphenol A, a ubiquitous endocrine disruptor found in plastics and resins, has been correlated with proinflammatory mediators [81] and asthma in animal studies [82] and in a prospective birth cohort study in 568 inner-city children where prenatal urinary spot concentrations were inversely correlated with child’s wheeze at age 5 years ($p=0.02$). Bisphenol A urinary concentrations in the children at age 3, 5, and 7 were positively associated with wheeze, $p=0.005$, 0.03 , and 0.04 , respectively [83]. The possible link between pesticide exposure and asthma is also under active study [84].

The impact of environment on human health is a complex and pressing issue that deserves attention from all members of the health-care team in asthmatic patients.

Conclusion

The use of integrative therapies is common in children and adults with asthma, yet its use may not be disclosed due to fear of a negative reaction by the health-care team. Open and respectful discussion of all therapies will improve patient safety, and the use of evidence-based integrative medicine can allow the clinician to offer new treatment options in asthma. Several integrative medicine therapies reviewed here, including the Mediterranean diet, use of vitamin D supplementation, mind-body medicine therapies, and physical activity, may have potential for improvement in overall quality of life, but lack conclusive evidence of objective benefit in asthma treatment. These approaches may serve as adjuncts to conventional asthma treatment. The positive prenatal effects of the Mediterranean diet on reduction of atopy and wheeze in offspring remain an area of active research investigation.

A healthy environment also has an important impact on lung health and is emphasized in integrative medicine. More studies are needed before recommendations can be made for the majority of dietary supplements in asthma. Clinicians and patients will benefit from staying up-to-date on integrative approaches to asthma and need reliable sources of information to help them do so.

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Compliance with Ethics Guidelines

Conflict of Interest Hilary McClafferty declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

1. Prevention CfDCA. Asthma in the US 2011 [May]. <http://www.cdc.gov/VitalSigns/Asthma/index.html>.
2. Polonikov AV, Ivanov VP, Bogomazov AD, Freidin MB, Illig T, Solodilova MA. Antioxidant defense enzyme genes and asthma susceptibility: gender-specific effects and heterogeneity in gene-gene interactions between pathogenetic variants of the disease. *BioMed Res Int*. 2014;2014:708903.
3. Wade A, Chang C. Evaluation and treatment of critical asthma syndrome in children. *Clin Rev Allergy Immunol*. 2014. doi:10.1007/s12016-014-8408-0
4. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Stat Rep*. 2008;12:1–23.
5. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data*. 2004;343:1–19.
6. Kemper KJ. Separation or synthesis: a holistic approach to therapeutics. *Pediatr Rev/Am Acad Pediatr*. 1996;17(8):279–83.
7. Maizes V, Rakel D, Niemiec C. Integrative medicine and patient-centered care. *Explore*. 2009;5(5):277–89.
8. Reznik M, Ozuah PO, Franco K, Cohen R, Motlow F. Use of complementary therapy by adolescents with asthma. *Arch Pediatr Adolesc Med*. 2002;156(10):1042–4.
9. Cotton S, Luberto CM, Yi MS, Tsevat J. Complementary and alternative medicine behaviors and beliefs in urban adolescents with asthma. *J Asthma Off J Assoc Care of Asthma*. 2011;48(5):531–8.
10. Shen J, Oraka E. Complementary and alternative medicine (CAM) use among children with current asthma. *Prev Med*. 2012;54(1):27–31.
11. Marino LA, Shen J. Characteristics of complementary and alternative medicine use among adults with current asthma, 2006. *J Asthma Off J Assoc Care Asthma*. 2010;47(5):521–5.
12. Knoeller GE, Mazurek JM, Moorman JE. Complementary and alternative medicine use among adults with work-related and non-work-related asthma. *J Asthma Off J Assoc Care of Asthma*. 2012;49(1):107–13.
13. Ball SD, Kertesz D, Moyer-Mileur LJ. Dietary supplement use is prevalent among children with a chronic illness. *J Am Diet Assoc*. 2005;105(1):78–84.
14. George M, Birck K, Hufford DJ, Jemmott LS, Weaver TE. Beliefs about asthma and complementary and alternative medicine in low-income inner-city African-American adults. *J Gen Intern Med*. 2006;21(12):1317–24.
15. Gilmour J, Harrison C, Cohen MH, Vohra S. Pediatric use of complementary and alternative medicine: legal, ethical, and clinical issues in decision-making. *Pediatrics*. 2011;128 Suppl 4:S149–54.
16. Adams D, Dagenais S, Clifford T, Baydala L, King WJ, Hervas-Malo M, et al. Complementary and alternative medicine use by pediatric specialty outpatients. *Pediatrics*. 2013;131(2):225–32.
17. Gilmour J, Harrison C, Asadi L, Cohen MH, Vohra S. Referrals and shared or collaborative care: managing relationships with

- complementary and alternative medicine practitioners. *Pediatrics*. 2011;128 Suppl 4:S181–6.
18. American Board of Physician Specialties. Available from: <http://www.abpsus.org>.
 19. Bell MC, Busse WW. Severe asthma: an expanding and mounting clinical challenge. *J Allergy Clin Immunology Practice*. 2013;1(2):110–21. *quiz* 22.
 20. van Rensen EL, Evertse CE, van Schadewijk WA, van Wijngaarden S, Ayre G, Mauad T, et al. Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment. *Allergy*. 2009;64(1):72–80.
 21. Linares Segovia B, Cortes Sandoval G, Amador Licon N, Guizar Mendoza JM, Nunez Lemus E, Rocha Amador DO, et al. Parameters of lung inflammation in asthmatic as compared to healthy children in a contaminated city. *BMC Pulm Med*. 2014;14(1):111.
 22. Nadeem A, Siddiqui N, Alharbi NO, Alharbi MM. Airway and systemic oxidant-antioxidant dysregulation in asthma: a possible scenario of oxidants spill over from lung into blood. *Pulm Pharmacol Ther*. 2014. doi:10.1016/j.pupt.2014.06.001.
 23. Vliagoftis H. Psychological stress and asthma: a new enemy within. *Int Arch Allergy Immunol*. 2014;164(2):109–11.
 24. Eilayyan O, Gogovor A, Mayo N, Ernst P, Ahmed S. Predictors of perceived asthma control among patients managed in primary care clinics. *Qual Life Res: Int J Qual Life Asp Treat Care Rehabil*. 2014. doi:10.1007/s11136-014-0700-1.
 25. Tapp H, Hebert L, Dulin M. Comparative effectiveness of asthma interventions within a practice based research network. *BMC Health Serv Res*. 2011;11:188.
 26. Scott HA, Jensen ME, Wood LG. Dietary interventions in asthma. *Curr Pharm Des*. 2014;20(6):1003–10.
 27. Tognon G, Lissner L, Saebye D, Walker KZ, Heitmann BL. The Mediterranean diet in relation to mortality and CVD: a Danish cohort study. *Br J Nutr*. 2013;111(1):151–9.
 28. Hoevenaer-Blom MP, Nooyens AC, Kromhout D, Spijkerman AM, Beulens JW, van der Schouw YT, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. *PLoS One*. 2012;7(9):e45458.
 29. Tognon G, Hebestreit A, Lanfer A, Moreno LA, Pala V, Siani A, et al. Mediterranean diet, overweight and body composition in children from eight European countries: cross-sectional and prospective results from the IDEFICS study. *Nutr Metab Cardiovasc Dis*. 2014;24(2):205–13.
 30. Arvaniti F, Piftis KN, Papadimitriou A, Papadopoulos M, Roma E, Kapsokefalou M, et al. Adherence to the Mediterranean type of diet is associated with lower prevalence of asthma symptoms, among 10–12 years old children: the PANACEA study. *Pediatric Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol*. 2011;22(3):283–9.
 31. Saadeh D, Salameh P, Baldi I, Raherison C. Diet and allergic diseases among population aged 0 to 18 years: myth or reality? *Nutrients*. 2013;5(9):3399–423.
 32. Grigoropoulou D, Piftis KN, Yannakoulia M, Papadimitriou A, Anthracopoulos MB, Yfanti K, et al. Urban environment adherence to the Mediterranean diet and prevalence of asthma symptoms among 10- to 12-year-old children: the Physical Activity, Nutrition, and Allergies in Children Examined in Athens study. *Allergy Asthma Proc Off J Reg State Allergy Soc*. 2011;32(5):351–8.
 33. Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*. 2008;63(6):507–13.
 34. Chatzi L, Kogevinas M. Prenatal and childhood Mediterranean diet and the development of asthma and allergies in children. *Public Health Nutr*. 2009;12(9A):1629–34.
 35. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allerg Immunol*. 2011;41(1):36–66.
 36. Maslova E, Strom M, Oken E, Campos H, Lange C, Gold D, et al. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis—longitudinal evidence from the Danish National Birth Cohort. *Br J Nutr*. 2013;110(7):1313–25.
 37. Sexton P, Black P, Metcalf P, Wall CR, Ley S, Wu L, et al. Influence of Mediterranean diet on asthma symptoms, lung function, and systemic inflammation: a randomized controlled trial. *J Asthma Off J Assoc Care of Asthma*. 2013;50(1):75–81.
 38. Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG, et al. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. *Allergy*. 2008;63(7):917–23.
 39. Barros R, Moreira A, Fonseca J, Delgado L, Castel-Branco MG, Hahtela T, et al. Dietary intake of alpha-linolenic acid and low ratio of n-6:n-3 PUFA are associated with decreased exhaled NO and improved asthma control. *Br J Nutr*. 2011;106(3):441–50.
 40. Huffnagle GB. Increase in dietary fiber dampens allergic responses in the lung. *Nat Med*. 2014;20(2):120–1.
 41. George M, Topaz M. A systematic review of complementary and alternative medicine for asthma self-management. *Nursing Clin North Am*. 2013;48(1):53–149.
 42. Arnold E, Clark CE, Lasserson TJ, Wu T. Herbal interventions for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2008;1, CD005989.
 43. Clark CE, Arnold E, Lasserson TJ, Wu T. Herbal interventions for chronic asthma in adults and children: a systematic review and meta-analysis. *Prim Care Respir J: J General Pract Airways Group*. 2010;19(4):307–14.
 44. Innis SM, Novak EM, Keller BO. Long chain omega-3 fatty acids: micronutrients in disguise. *Prostaglandins Leukot Essent Fat Acids*. 2013;88(1):91–5.
 45. Mozurkewich EL, Klemens C. Omega-3 fatty acids and pregnancy: current implications for practice. *Curr Opin Obstet Gynecol*. 2012;24(2):72–7.
 46. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest*. 2006;129(1):39–49.
 47. D'Auria E, Miraglia Del Giudice M, Barberi S, Mandelli M, Verduci E, Leonardi S, et al. Omega-3 fatty acids and asthma in children. *Allergy Asthma Proc Off J Reg State Allergy Soc*. 2014;35(3):233–40.
 48. Yates CM, Calder PC, Ed RG. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther*. 2014;141(3):272–82.
 49. Miles EA, Calder PC. Omega-6 and omega-3 polyunsaturated fatty acids and allergic diseases in infancy and childhood. *Curr Pharm Des*. 2014;20(6):946–53.
 50. Paul G, Brehm JM, Alcorn JF, Holguin F, Aujla SJ, Celedon JC. Vitamin D and asthma. *Am J Respir Crit Care Med*. 2012;185(2):124–32.
 51. Holick MF. The vitamin D epidemic and its health consequences. *J Nutrition*. 2005;135(11):2739S–48S.
 52. Kennel KA, Drake MT. Vitamin D in the cancer patient. *Curr Opin Support Palliat Care*. 2013;7(3):272–7.
 53. Gupta A, Bush A, Hawrylowicz C, Saglani S. Vitamin D and asthma in children. *Paediatr Respir Rev*. 2012;13(4):236–43. *quiz* 43.
 54. Castro M, King TS, Kunselman SJ, Cabana MD, Denlinger L, Holguin F, et al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *JAMA J Am Med Assoc*. 2014;311(20):2083–91.
 55. Berraies A, Hamzaoui K, Hamzaoui A. Link between vitamin D and airway remodeling. *J Asthma allergy*. 2014;7:23–30.

56. Mann EH, Chambers ES, Pfeffer PE, Hawrylowicz CM. Immunoregulatory mechanisms of vitamin D relevant to respiratory health and asthma. *Ann N Y Acad Sci*. 2014;1317(1):57–69.
57. Poon AH, Mahboub B, Hamid Q. Vitamin D deficiency and severe asthma. *Pharmacol Ther*. 2013;140(2):148–55.
58. Milan SJ, Hart A, Wilkinson M. Vitamin C for asthma and exercise-induced bronchoconstriction. *Cochrane Database Syst Rev*. 2013;10, CD010391.
59. Runeson-Broberg R, Norback D. Work-related psychosocial stress as a risk factor for asthma, allergy, and respiratory infections in the Swedish workforce. *Psychol Rep*. 2014;114(2):377–89.
60. Luberto CM, Yi MS, Tsevat J, Leonard AC, Cotton S. Complementary and alternative medicine use and psychosocial outcomes among urban adolescents with asthma. *J Asthma Off J Assoc Care of Asthma*. 2012;49(4):409–15.
61. Maher-Loughnan GP, Mason AA, Macdonald N, Fry L. Controlled trial of hypnosis in the symptomatic treatment of asthma. *Br Med J*. 1962;2(5301):371–6.
62. Ewer TC, Stewart DE. Improvement in bronchial hyper-responsiveness in patients with moderate asthma after treatment with a hypnotic technique: a randomised controlled trial. *Br Med J (Clin Res Ed)*. 1986;293(6555):1129–32.
63. Kohen DP, Olness KN, Colwell SO, Heimel A. The use of relaxation-mental imagery (self-hypnosis) in the management of 505 pediatric behavioral encounters. *J Dev Behav Pediatr JDBP*. 1984;5(1):21–5.
64. Anbar RD. Hypnosis in pediatrics: applications at a pediatric pulmonary center. *BMC Pediatr*. 2002;2:11.
65. Jon Kabat-Zinn P. *Wherever You Go, There you are: mindfulness meditation in everyday life*. New York: Hyperion Books; 1994.
66. Pbert L, Madison JM, Druker S, Olendzki N, Magner R, Reed G, et al. Effect of mindfulness training on asthma quality of life and lung function: a randomised controlled trial. *Thorax*. 2012;67(9):769–76.
67. Cowie RL, Conley DP, Underwood MF, Reader PG. A randomised controlled trial of the Buteyko technique as an adjunct to conventional management of asthma. *Respir Med*. 2008;102(5):726–32.
68. Mehl-Madrona L, Kligler B, Silverman S, Lynton H, Merrell W. The impact of acupuncture and craniosacral therapy interventions on clinical outcomes in adults with asthma. *Explore*. 2007;3(1):28–36.
69. Wechsler ME, Kelley JM, Boyd IO, Dutile S, Marigowda G, Kirsch I, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med*. 2011;365(2):119–26.
70. Vempati R, Bijlani RL, Deepak KK. The efficacy of a comprehensive lifestyle modification programme based on yoga in the management of bronchial asthma: a randomized controlled trial. *BMC Pulmonary Medicine*. 2009;9:37.
71. Tahan F, Eke Gungor H, Bicici E. Is yoga training beneficial for exercise-induced bronchoconstriction? *Alternative Therapies Health Medicine*. 2014;20(2):18–23.
72. Galantino ML, Galbavy R, Quinn L. Therapeutic effects of yoga for children: a systematic review of the literature. *Pediatr Phys Ther Off Publ Sect Pediatr Am Phys Ther Assoc*. 2008;20(1):66–80.
73. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. *Cochrane Database Syst Rev*. 2013;9, CD001116.
74. Beggs S, Foong YC, Le HC, Noor D, Wood-Baker R, Walters JA. Swimming training for asthma in children and adolescents aged 18 years and under. *Cochrane Database Syst Rev*. 2013;4, CD009607.
75. Wanrooij VH, Willeboordse M, Dompeling E, van de Kant KD. Exercise training in children with asthma: a systematic review. *Br J Sports Med*. 2014;48(13):1024–31.
76. Walker TJ, Reznik M. In-school asthma management and physical activity: children's perspectives. *J Asthma: Off J Assoc Care of Asthma* 2014:1–6. doi:10.3109/02770903.2014.920875.
77. Corbo GM, Forastiere F, De Sario M, Brunetti L, Bonci E, Bugiani M, et al. Wheeze and asthma in children: associations with body mass index, sports, television viewing, and diet. *Epidemiology*. 2008;19(5):747–55.
78. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014. doi:10.1016/j.jaci.2014.04.018.
79. Agency USEP. What are the six common air pollutants?
80. Guarneri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014;383(9928):1581–92.
81. O'Brien E, Dolinoy DC, Mancuso P. Perinatal bisphenol A exposures increase production of pro-inflammatory mediators in bone marrow-derived mast cells of adult mice. *J Immunotoxicol*. 2014;11(3):205–12.
82. Nakajima Y, Goldblum RM, Midoro-Horiuti T. Fetal exposure to bisphenol A as a risk factor for the development of childhood asthma: an animal model study. *Environ Health Global Access Sci Source*. 2012;11:8.
83. Donohue KM, Miller RL, Perzanowski MS, Just AC, Hoepner LA, Arunajadai S, et al. Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. *J Allergy Clin Immunol*. 2013;131(3):736–42.
84. Amaral AF. Pesticides and asthma: challenges for epidemiology. *Frontiers in Public Health*. 2014;2:6.