Dietary sodium intake and asthma: an epidemiological and clinical review

T. D. MICKLEBOROUGH,¹ A. FOGARTY²
¹Department of Kinesiology, Human Performance and Exercise Biochemistry Laboratory, Indiana University, Bloomington, Indiana, USA, ²Division of Epidemiology and Public Health, Clinical Science Building, City Hospital, University of Nottingham, Nottingham, UK

SUMMARY
The changes in diet associated with the development of a more affluent lifestyle have been considered one of the environmental factors that may have contributed to the rise in the prevalence of asthma over the past few decades, and dietary sodium has been considered to be a dietary constituent which may be implicated in this phenomenon. The data presented in this review demonstrate that adoption of a low sodium diet for a period of 2–5 weeks may improve lung function and decrease bronchial reactivity in adults with asthma, while sodium loading appears to have a detrimental effect. Similarly, a low sodium diet maintained for 1–2 weeks decreases bronchoconstriction in response to exercise in individuals with asthma. There is no data as to the longer-term effect of a low sodium diet on either the prevalence or severity of asthma or on exercise-induced bronchoconstriction. As a low sodium diet has other beneficial health effects, it can be considered as a therapeutic option for adults with asthma, although it should be considered as an adjunctive intervention to supplement optimal pharmacological management of asthma and not as an alternative. If the relationship between higher sodium intake and increased prevalence and severity of asthma is causal, then there are potential population benefits for asthma as well as cardiovascular disease to be derived from public health measures to reduce sodium consumption.

Keywords: Exercise-induced asthma; asthma; dietary sodium; bronchial responsiveness; exercise-induced bronchoconstriction; airway hyper-responsiveness; alternative treatment; review

INTRODUCTION
The dramatic increase in the prevalence of asthma in the second half of the 20th Century has led to the search for environmental exposures that have driven this change. Diet is one of the environmental factors that have been considered to be potentially important, as dietary patterns have changed over this period and plausible biological mechanisms exist for many nutrients (1), with dietary sodium being one of the first dietary factors to be considered to possibly modify the risk of asthma. We aim to review the current evidence of the effect of sodium intake on asthma and exercise-induced bronchoconstriction (EIB). The data come from two study designs, observational epidemiology which assesses the association of measures of sodium intake on the risk of asthma, and intervention studies, which look at the effect of manipulating dietary sodium intake on asthma-related outcome measures in participants with and without asthma. Generally, the former investigates the effect of sodium of prevalence of asthma, while the latter assess the effect on severity of asthma or bronchoconstriction.

For this review, the keywords: sodium, dietary salt and sodium chloride were coupled with the keywords: asthma, airway hyper-responsiveness, exercise-induced bronchoconstriction; airway hyper-responsiveness; alternative treatment; review

DEFINITIONS AND PREVALENCE OF ASTHMA
Asthma
Asthma is diagnosed clinically on the basis of symptoms of wheeze, dyspnoea and cough, and by objective evidence of variable airflow obstruction (2). The causes of asthma are unknown, but the prevalence of wheeze has increased over the recent decades in developed countries (3,4), and is consistently higher in countries that have adopted an affluent lifestyle, with 20–30% of children living in USA, UK and

Correspondence to:
Timothy D. Mickleborough, Department of Kinesiology, Indiana University, 1025. E 7th St, HPER 112, Bloomington, IN 47401, USA
Tel.: + 1 812 855 0753
Fax: + 1 812 855 3193
Email: tmickleb@indiana.edu

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Exercise-Induced Bronchoconstriction

Exercise-induced bronchoconstriction is not an isolated disorder or specific disease, but rather part of the spectrum of asthmatic disease where exercise is one of many stimuli that may induce airflow limitation (10). Exercise is a powerful trigger of asthma symptoms, and up to 90% of asthmatics experience EIB (11–13), as defined by a > 10% decrease in postexercise forced expiratory volume in 1 s (FEV₁) of at least 20% at a dose < 16 mg/ml (PD₂₀) inhaled methacholine is considered indicative of airway hyper-responsiveness (9).

DIETARY SODIUM AND ASTHMA

It has been observed that asthma morbidity and mortality are greater in communities adopting a more Western lifestyle and in migrants as they move from rural underdeveloped to urban westernised areas (27, 28). Dietary intake of sodium chloride is typically high (averaging 7–10 g/day; 2.8–4 g/day of sodium) (29) in westernised areas and this excess salt intake is associated with other diseases of smooth muscle constriction such as hypertension (30). The minimum recommended daily allowance for sodium in the USA is 500 mg/day (31), with an upper limit of < 2400 mg of sodium per day considered optimal (31) for health. In the UK, the recommended intake of sodium is < 2.4 g/day (32), a decision made mainly on the basis of the cardiovascular benefits to be derived by the population as a whole.

Stoesser and Cook (33) in 1938 were the first to propose a possible connection between salt consumption and the severity of chronic bronchial asthma. In a study, published in abstract form only, in which the numbers of subjects or other details were not provided, they observed that a low salt diet (LSD) contributed to a decrease in symptoms in children with severe asthma, and high salt diets resulted in an increase of symptoms. This study, while lacking in scientific rigour and pulmonary function data, did provide the first indication that dietary sodium chloride might play a role in modifying the severity of asthma.

Epidemiological Studies

Recognising the possibility that a high salt diet may increase symptoms of asthma (33), Burney (34) hypothesised that increased sodium intake may contribute to the increased morbidity and mortality of asthma observed in westernised cultures. Burney et al. (35) tested the hypothesis using the ecological data on asthma death rates and table salt purchases from regions in England and Wales. They found a strong correlation between table salt purchases and mortality because of asthma in men and in children of both sexes, but not in women. The suggestion from these data was that higher dietary sodium chloride may potentiate asthma severity. One explanation for the absence of an association in women was the possibility of the misclassification of women with bronchitis as asthmatic.

In a subsequent study, Burney et al. (35) conducted a cross sectional survey of the prevalence of asthma in rural and urban areas in the south of England. A random 20% of those men who replied, including all those who responded that they had symptoms of asthma, were tested for airway hyper-responsiveness with histamine challenge. A total of 205 men (aged 18–64 years) underwent bronchial reactivity testing, using the histamine challenge test, and of these 138 provided 24-h urine specimens. Regression analysis found increased 24-h urinary excretion of sodium, but not potassium, to be significantly associated with airway responsiveness to histamine. Thus, the authors concluded that a high sodium diet (HSD) may potentiate bronchial reactivity, although they were unable to exclude the possibility that the association may be a consequence of other unrecognised dietary or lifestyle factors associated with sodium intake. As the lower level of the sodium excretions presented in this study, 3841 mg/day, is typical for the Western diet, it is of some importance that airway responsiveness was increased across this already excessive range of dietary sodium intakes.

Schwartz and Weiss (36) used the information collected in the Second National Health and Nutrition Examination Survey to explore the potential relationships among the
dietary factors and respiratory symptoms. The population examined was 9074 adults aged over 30 years old and dietary intake was derived from 24-h dietary recall questionnaires, yielding an estimated intake for sodium of 2640 mg/day and for potassium of 2334 mg/day. The sodium–potassium ratio was 1.25 on average. The analysis indicated that although neither sodium nor potassium in the diet was individually related to bronchitis or wheezing symptoms, the ratio of sodium to potassium was a significant predictor of bronchitis as reported by these adults. Although limited by the measurement error inherent to self-reported dietary estimates, these data do contribute to the body of evidence suggesting the dietary electrolytes may contribute to airway responsiveness.

Pistelli et al. (37) performed a cross-sectional study in Italy among 2593 subjects aged 9–16 years. Questionnaires were used to determine the table salt use, asthma, and asthma symptoms such as wheezing and coughing. Personal table salt use was reported to be positively correlated with reported symptoms of asthma in boys but not in girls. A subset \( n = 2020 \) of subjects underwent methacholine challenge and electrolyte analysis was conducted on 916 urine samples. Airway responsiveness was positively associated with urinary potassium excretion in boys, but not with urinary sodium excretion. Thus, while self-reported table salt use was related to symptoms of asthma, the more objective measure of urinary sodium concentration was not. There was no correlation in females between asthma symptoms and bronchial reactivity with either table salt usage or urine electrolyte concentration. This study used only a single sample of urine corrected for creatinine, and not a 24-h collection, which is a superior measure of sodium excretion and hence dietary intake. This study suggests that consumption of table salt or something associated with it may be associated with increased symptoms of asthma in boys.

Demissie et al. (38) surveyed children selecting 187 cases with a history of asthma or with EIB, along with 145 controls identified from a larger population of 1274 children in Montreal. The children were ranked for salt intake using an unvalidated food questionnaire, and children who had a FEV\(_1\) value >75% of their forced vital capacity (FVC) underwent methacholine challenge for airway responsiveness. The salt scores did not correlate with asthma (defined as a history of asthma or drop in FEV\(_1\) of >10% postexercise), but comparison of the lowest quartile with the highest quartile of salt intake demonstrated significantly higher airway responsiveness in the latter. Thus, despite the crude measurements used, there remained an increase in airway responsiveness with higher levels of salt intake.

Tribe et al. (39) carried out an investigation to study dietary sodium intake and bronchial reactivity, and how this effect may be mediated by cellular sodium transport mechanisms in men with asthma (39). Asthmatic \( n = 27 \) and non-asthmatic \( n = 25 \) men were tested while on their usual diet. Blood leucocytes were used as a model for sodium transport mechanisms. Average sodium excretion was 3887 mg/day for those with asthma and 3818 mg/day for controls. Regression analysis revealed a significant positive relationship between 24 h sodium excretion and airway responsiveness. Additionally, the result from the leucocyte study suggested that a serum-borne factor found in asthmatic serum caused increased sodium influx into leucocytes and was related to the degree of hyper-responsiveness, but independent of the effect of 24-h sodium excretion on airway responsiveness. Hence, these data do support the concept of a positive association between the increased intake of dietary salt and airway responsiveness, while also suggesting that factors in the serum from men with asthma may be involved in both cellular sodium transport and bronchial hyper-responsiveness.

A case–control study of risk factors in the home environment for asthma in 154 children in Kenya identified supplemental salt intake as an independent risk factor for asthma, with a one SD in salt intake being associated with a 60% increase in risk of asthma (40).

There have been four epidemiological studies, which have failed to demonstrate an association between dietary sodium and measures of asthma activity. The largest, by Britton et al. (41), was a study designed to test the hypothesis that dietary sodium intake is an independent risk factor for bronchial hyper-reactivity in the general population. Airway responsiveness to methacholine, atopy, 24 h urinary sodium excretion, and self-reported smoking and symptom history were measured in a random sample of 1702 adults aged 18–70. The results showed no relation between the relative odds of hyper-reactivity to methacholine and 24 h urinary sodium excretion, either before or after adjusting for age, smoking, allergen skin weal diameter and gender. In addition, no association between 24 h sodium excretion and the magnitude of the mean allergen skin weal response or the PD\(_{20}\) value. The authors conclude that the findings do not support the hypothesis that a high dietary sodium intake is a risk factor for airway hyper-reactivity or atopic disease in the general adult population.

Deveroux et al. (42) used data from two epidemiological studies from the north of England, one of 1059 shipyard workers aged 16–27 years old, and a second of 587 men who lived in either rural or urban environments. Twenty-four hour urine samples were available for 22% and 40% of individuals who participated in the studies, respectively, and they demonstrated that there was no association between 24 h sodium excretion and airways responsiveness in either the shipyard workers or the subgroup of men who lived in a rural environment, but a positive association between 24 h sodium excretion and airways hyper-responsiveness in the subgroup of men who lived in an urban environment.
One limitation of this study is the absence of data from up to 78% of individuals eligible to participate and the inability to exclude the possibility of response bias influencing the results.

Sparrow et al. (43) examined the methacholine airway responsiveness and the 24 h excretion of sodium and potassium. Methacholine airway responsiveness was examined among 273 male participants (age range 44–82 years) using 24 urinary excretion of Na⁺ and K⁺ as a surrogate for intake. A significant relationship between methacholine dose–response slope and potassium excretion was found. However, methacholine airway responsiveness was not correlated with sodium excretion.

Zoia et al. (44) sought to determine the relationship of sodium and potassium intake, assessed by means of a 7-day dietary questionnaire, with bronchial responsiveness in a sample of the general population. Two hundred and five participants completed the dietary and respiratory questionnaires and baseline pulmonary function, while 146 subjects underwent a histamine challenge test. These authors could not demonstrate a relationship between these dietary factors and bronchial responsiveness or respiratory symptoms, although this may be a consequence of the use of dietary questionnaires, which tend to be poor at measuring the sodium intake accurately.

These four studies (41–44) that have not demonstrated an association between sodium intake and asthma are difficult to reconcile with the studies that demonstrate an inverse relation reviewed earlier in this article. In particular, the study by Britton et al. (41) is a large study using the objective measures of both sodium intake and airway reactivity and provides a substantial challenge to the hypothesis that dietary sodium is associated with asthma in the general population. Possible explanations for the inconsistency of the data are that dietary factors may have a different effect in children and young adults, as the age of the individual is an important factor in determining the sensitivity to sodium, thus explaining why studies such as those of Britton et al. (41) and Sparrow et al. (43) that have examined relatively older populations do not observe an effect. Alternatively, dietary sodium may not have an effect on asthma in the general population.

**Interventional Studies**

The work by Stoesser and Cook (33) and the earlier epidemiological and cross-sectional studies (34,35) led to subsequent intervention studies testing the hypothesis that dietary salt was associated with asthma severity. Javaid et al. (45) performed an interventional study to examine the effect of changing dietary salt intake on bronchial reactivity as determined by a histamine challenge test in 10 volunteers with asthma and five controls. Baseline 24 h sodium excretion was 3588 mg/day in those individuals with asthma, and 2369 mg/day in the controls. The dietary salt was then increased for 4 weeks resulting in 24 h urinary sodium excretion of 4958 mg of sodium/day for those with asthma, and 4209 mg/day for the controls. The high salt intake significantly increased the bronchial reactivity when compared with the normal diet in asthmatics, but not for control subjects. This study adds support to the concept that elevating dietary salt from a moderate to a high level will increase airway responsiveness, in individuals with asthma but not healthy controls, although the relatively small numbers studied demand caution when interpreting the results because of the low power of this study to demonstrate an effect.

Burney et al. (46) followed up their original observations with an interventional study using a randomised double-blind cross-over study design comparing the supplementation of the normal diet with 1840 mg sodium per day with placebo supplementation in 36 asthmatic patients on the LSD. Prior to implementation of the LSD, urinary excretion of sodium was 2438 mg/day suggesting that this was a population already consuming a relatively salt-free diet. The LSD and placebo supplements resulted in a decrease of 24 h urinary sodium excretion of 736 mg/day in men and by 805 mg/day in women, while with the LSD and sodium supplementation, sodium excretion increased slightly above the baseline. Compared with baseline, there was a decrease in airway reactivity as measured by histamine challenge in men while on the LSD and taking placebo and an increase after supplementing the LSD with replacement salt. The dose of histamine causing a fall of 20% in FEV₁ (PD20) was 1.51 doubling doses lower (i.e. increased airway responsiveness) when taking the sodium supplementation regimen compared with when taking placebo (LSD). This effect was not observed in asthmatic women. Thus, in asthmatic men, lowering dietary salt intake for 2 weeks reduced their airway hyper-responsiveness. The fact that airway hyper-responsiveness did not change in women with asthma after dietary sodium manipulation was consistent with the researchers’ earlier epidemiological finding (34), although no mechanism is known that explains the possible gender differential in airway responsiveness to dietary salt manipulation.

Carey et al. (47) studied 27 asthmatic men receiving 5 weeks of 4600 mg of slow sodium release capsules or placebo capsules daily in a random order (double-blind, cross-over design), while maintaining the LSD (1840 mg/day of sodium). Pulmonary function testing and methacholine challenge was performed at baseline, then at the end of each 5-week period. Daily peak expiratory flow rates (PEFRs) were recorded by the patients, as was medication use. On the normal diet, sodium excretion was 3657 mg/day. The LSD plus placebo produced a 24 h excretion of sodium of 2029 mg/day; and the LSD plus sodium supplement yielded 6716 mg of sodium per day. The LSD plus placebo
was compared with the LSD plus sodium and was associated with lower methacholine reactivity (a decrease of 0.73 doubling doses), deceased bronchodilator usage, with higher PEFRs (5–8%) and FEV1 values (210 ml). Thus, lower salt intakes were associated with improved pulmonary function, reduced asthmatic symptoms and medication use and reduced airway hyper-responsiveness. This study only used male subjects, so no conclusion with regard to the effect of sodium manipulation in females with asthma can be drawn.

Similarly, Medici et al. (48) studied the effect of dietary salt reduction and supplementation on severity of asthma, and in addition examined the possibility that the chloride ion has an active role in the effect of salt in modifying asthma severity. Using a cross-over design, 14 asthmatics (nine men and five women) were placed on the LSD (5–6 g/d of salt; 1978–2369 mg of sodium) for 2 weeks. Subjects then consumed nine capsules throughout the day containing 1 g of salt or placebo for the first 3 weeks, and then crossed over to the second intervention (salt or placebo) treatments for the second 3 weeks. After this, participants then received 3 weeks of sodium citrate as the supplement (with equivalent sodium to that received with the previous salt supplementation). Finally, subjects returned to their usual diet and were followed for 3 weeks. Medication use and peak expiratory flows (PEF) in the morning, noon and evening were recorded daily. Twenty-four hour urine collections documented electrolyte consumption. Laboratory pulmonary function testing and methacholine challenge were performed at regular intervals throughout the study. The mean values for sodium and chloride consumption in this study were 1817 mg sodium, 2982 mg chloride on the LSD; 3151 mg sodium, 4651 mg chloride on the high salt diet; 3083 mg sodium, 3160 mg chloride on the sodium citrate diet; and 2530 mg sodium, 3905 mg chloride on the patients’ usual diet. Patients reported an increase in increased inhaled steroid use and a decrease in PEFR on the high salt diet, but changes in dietary salt had no demonstrable effect on airway responsiveness as measured by methacholine challenge. Sodium citrate loading did not alter these outcomes, suggesting that the sodium ion is an important contributor to these observed effects of salt loading. It is important to note that normal asthma medications were continued during the study and the medication including inhaled corticosteroids was adjusted if the asthma deteriorated as assessed by an increase in asthma symptoms or a decline in PEFR declined. Thus, it is difficult to interpret the data on airway responsiveness, as titration of the medications potentially would mask any response.

Lieberman et al. (49) examined the hypothesis that the amount of daily salt intake influences the severity of asthma as measured by PEF and the variation in PEF during the day. Seventeen asthmatics (nine men and eight women, 27–62 years of age) were observed on their normal diet, after 2 weeks of the LSD, and after 2 weeks of a high salt diet plus daily salt tablets, and PEF monitored at home. Normal diets resulted in sodium excretion of 3381 mg/day; LSD, 1932 mg/day; and high salt diet, 4623 mg/day. There was no effect on either PEF or PEF variability. While subject numbers were low and hence the study was relatively under-powered, these data do not support the general concept of a relationship between the sodium intake and asthma severity. However, airway responsiveness was not measured and the detail that 10 subjects were on daily oral theophylline which improves asthma control would also reduce the likelihood of seeing a beneficial response.

In a recent Cochrane Database Systematic Review, Arden et al. (50) assessed the effect of dietary sodium reduction in patents with asthma. Only six studies fulfilled the inclusion criteria of being randomised-controlled trials, all of which are also reviewed in detail within this present review (46–49,51,52). A meta-analysis of selected data from four of these studies (48,49,51,52), along with individual study analysis (46,47), indicated that there was a pattern suggestive of a small improvement of pulmonary function with a salt restrictive diet and a small reduction in bronchodilator use. Based on the available evidence at the time of the review and considering the small sample size of these studies, the authors decided that it was not possible to conclude whether dietary sodium reduction is beneficial as a treatment for asthma.

Collectively, the studies to date investigating the potential relationship between dietary sodium and the severity of asthma or airway hyper-responsiveness have provided support for the hypothesis that increased dietary intake of sodium may increase the severity of disease in those with asthma. A large randomised-controlled clinical trial is warranted to fully address this issue and should include individuals with well characterised asthma, data on baseline diet, and be sufficiently powered to permit measurement of both physiological outcomes such as lung function and bronchial reactivity, as well as clinically important measures including the daily symptoms score and medication use.

**DIETARY SODIUM AND EXERCISE-INDUCED BRONCHOCONSTRICTION**

Exercise provides a safe and easily controlled challenge to the Airways that permits the evaluation of potential interventions such as the effects of dietary modulation on asthma and airway hyper-responsiveness. All the subjects in the following studies had mild-to-moderate persistent asthma and exhibited EIB as shown by a >10% decrease in postexercise FEV1 compared with pre-exercise values.

To assess the effect of dietary sodium manipulation on the severity of EIB, an initial study was conducted by...
Mickleborough et al. (53) and utilised a double-blind randomised crossover study design. Fifteen individuals with asthma entered the study on their normal salt diet (NSD), and then were placed on either LSD or HSD for 2 weeks. A 1-week washout period on the NSD was included before crossing over to the second treatment period of 2 weeks. Pre- and postexercise pulmonary function tests were performed following each treatment period. For all three diet treatments, 24-h urinary sodium excretions were significantly different (NSD = 3630 mg/day; LSD = 958 mg/day; HSD = 8133 mg/day). Comparing the change in lung function 5 min after an exercise challenge, FVC and FEV₁ significantly improved by 0.95 L and 0.4 L on the LSD, whereas the HSD induced significant reductions of 0.22 L and 0.37 L in FVC and FEV₁, respectively. The data demonstrated for the first time that 2 weeks of dietary salt loading worsened and 2 weeks of salt restriction improved the postexercise pulmonary function in volunteers with EIB. In addition, the LSD improved and the HSD exacerbated pulmonary function during exercise in EIB subjects (52). Specifically, arterial oxygen saturation during exercise was improved by reducing the dietary sodium and worsened by increasing the dietary sodium. The pattern of ventilation during exercise differed with diet, with the HSD resulting in a higher tidal volume and lower breathing frequency selection; the LSD reversed this pattern, with a lower tidal volume and higher breathing frequency.

Gotshall et al. (51), in a follow-up study, conducted a double-blind randomised crossover study to assess the effect of 2 weeks of dietary salt loading and restriction on eight individuals with asthma and EIB, plus eight non-asthmatic controls. Otherwise, study conditions were identical to the previous study (53). Pulmonary function was assessed pre- and postexercise and before and after each treatment period. Diet had no effect on pre-exercise pulmonary function values in either group and had no effect on postexercise pulmonary function values in control subjects. However, the LSD improved and the HSD worsened postexercise pulmonary function values in EIB subjects. FEV₁ decreased by 14% on the LSD, 20% on the NSD and 24% on the HSD at 15 min postexercise. Dietary goals were achieved as urinary sodium excretion fell significantly on the LSD (1761, 3477 and 6266 mg/day on the LSD, NaHCO₃ diet and 19% on the NSD. Urinary excretion of sodium was 1761, 3477 and 6266 mg/day on the LSD, NSD and NaHCO₃ diet, respectively. There was no significant difference in urinary chloride excretion between the LSD (3043 mg/day) and NaHCO₃ diet (2722 mg/day). These data suggest that both the sodium and chloride ion may contribute to the deterioration of the severity of EIB seen after a NSD or HSD.

Recently, Gotshall et al. (54) conducted a study to determine whether a shorter regimen of dietary sodium restriction (1 week) would prove as effective as 2 weeks of sodium restriction in reducing the severity of EIB. Ten individuals with EIB and 10 controls without EIB participated in a randomised double-blind cross-over trial and were placed either on approximately 1500 mg of sodium for 2 weeks, which constituted the LSD or on their NSD. At baseline (NSD), the EIB subjects demonstrated significant reductions in FEV₁ of −27%, −24% and −20% at 1, 5, and 15 min postexercise, respectively. However, after 1 week on the LSD, postexercise FEV₁ improved significantly to −4.5%, −8.9% and −7.63% and after 2 weeks on the LSD to −3.2%, −8.9% and −7.7% at 1, 5, 15 min postexercise, respectively. Thus, the LSD noticeably reduced the severity of EIB and had a similar effect at both 1 and 2 weeks.

As salt comprises both sodium and chloride, it is possible that the anion, chloride, plays an active role in the effect of salt on EIB. In hypertension research, there have been many studies implicating the chloride ion as the main contributor to elevated blood pressure during dietary salt loading. For example, sodium loading with anions other than chloride has failed to produce the elevated blood pressures in models of salt-sensitive hypertension (55,56). Hence, Mickleborough et al. (57) evaluated the influence of low and high chloride diets on the severity of EIB. The study design and protocol were conducted in a similar fashion as the study performed by Gotshall et al. (51) with the only difference being that upon entering the study on the NSD, all participants (EIB, n = 8, and control, n = 8) were either placed on the LSD (low sodium, low chloride) for 2 weeks or a sodium bicarbonate (NaHCO₃) diet (high sodium, low chloride) for 2 weeks. The data confirmed earlier observations (51–53) that the LSD significantly blunted the decline in postexercise pulmonary function in EIB subjects without any effect in control subjects. Additionally, the data indicated that dietary chloride reduction coupled with dietary sodium elevation (NaHCO₃ loading) also attenuated the decrement in postexercise pulmonary function in EIB subjects, but not to the extent of the LSD (low dietary sodium and chloride). FEV₁ fell 7% on the LSD, 14% on the NaHCO₃ diet and 19% on the NSD. Urinary excretion of sodium was 1761, 3477 and 6266 mg/day on the LSD, NSD and NaHCO₃ diet, respectively. There was no significant difference in urinary chloride excretion between the LSD (3043 mg/day) and NaHCO₃ diet (2722 mg/day). These data suggest that both the sodium and chloride ion may contribute to the deterioration of the severity of EIB seen after a NSD or HSD.

In an attempt to delineate a possible mechanism by which dietary salt loading might exacerbate EIB, Mickleborough et al. (58) used the guinea pig model for EIB. The guinea pig manifests dry-gas hyperpnea-induced airway obstruction (HIAO) that parallels the response seen in human subjects with EIB (59,60). As it has been suggested that EIB and HIAO in guinea pigs are mediated by similar mechanisms (59,60), the purpose of the study conducted by Mickleborough et al. (58) was to determine whether altering dietary salt consumption also exacerbated HIAO in guinea pigs. Furthermore, in order to delineate a possible mechanism by which dietary salt may exert an effect on airway responsiveness, the potential pathway of action of dietary...
salt was investigated by blocking leukotriene (LT) production during HIAO in guinea pigs. Thirty-two guinea pigs were split into two groups. One group (n = 16) of animals consumed the NSD (0.75% salt; which is the normal salt content of guinea pig feed) for 2 weeks, whereas the other group of animals (n = 16) ingested the HSD (2% salt). At the end of each treatment period, the animals were anaesthetised, cannulated, tracheotomised and mechanically ventilated during a baseline period and during two dry gas hyperpnea challenges. After the first challenge, the animals were administered masoprocol (nordihydroguaiaretic acid), which is an LT biosynthesis and lipoxygenase inhibitor. The HSD elicited significantly higher airway inspiratory pressures (Ptr) than the NSD postchallenge. However, following the infusion of masoprocol and a second hyperpnea challenge, Ptr was significantly reduced in both diet groups, although the HSD continued to be associated with a higher Ptr than the NSD. Urinary LTE4 excretion significantly increased in the HSD group compared with the NSD group. This novel study demonstrated, for the first time, that elevated dietary salt increased the HIAO response compared with the NSD, and that this effect may be mediated by changes in LT metabolism. The potential interactions of dietary salt and LT production and release in this animal model have yet to be determined. However, a major limitation in this study is that urinary LTE4 excretion may not be reflective of airway cell activity, but in fact be linked to the influence of dietary salt on the kidneys via changes in osmoreceptor activity or the rennin-angiotensin system during exercise, as the kidneys are rich sources of LTs and prostaglandins.

Recently, Mickleborough et al. (61), using a double-blind placebo-controlled randomised crossover design, attempted to determine a possible mechanism by which dietary salt modification may alter EIB in 24 asthmatic patients. The study design was identical to the previous study performed by Gotshall et al. (51). All subjects were required to consume a base diet of 1500 mg/day of sodium, and approximately 2250 mg/day of chloride, which was provided by a menu plan, whether on the LSD or HSD. For the HSD, the base diet was supplemented with ten 1-g salt capsules per day comprising 4000 mg/day of sodium, and approximately 6000 mg/day of chloride (169 mmol/day). For the LSD, the base diet was supplemented in the same manner but with placebo (sucrose) tablets.

This study (61) demonstrated for the first time that modifying dietary salt intake for 2 weeks alters airway inflammation, diffusion capacity of the lung (DLco), and confirms previous observations that altering dietary salt intake can modify the severity of EIA (51,57) with a concomitant reduction in bronchodilator drug use. Induced sputum differential eosinophil and neutrophil cell counts, eosinophil cationic protein, proinflammatory cytokines interleukin (IL)-1β, IL-8 and eicosanoids LTC4-E4, LTB4 and prostaglandin D2 were significantly higher following exercise on the NSD and HSD compared with the LSD. In addition, the NSD and HSD caused a significant reduction in DLco and an increase in pulmonary capillary blood volume (VC), while the LSD produced a significant increase in DLco and diminution in VC. One potential mechanism is suggested by the observation that dietary salt manipulation modified the induced sputum supernatant IL-1β and IL-8 concentration following the exercise, both cytokines that are associated with neutrophilic inflammation (62), although asthma is characteristically associated with airway eosinophilia. This may be a consequence of hyperosmolarity, which has been shown to stimulate IL-8 production in human bronchial epithelial cells in vitro (62). Alternatively, as the human airway mucosa is a semi-permeable membrane which permits osmotic equilibration, it may be hypothesised that dietary salt loading increases airway osmolarity and enhances the release of other proinflammatory mediators including the prostaglandins and LTs.

In summary, these series of studies have provided convincing evidence that salt intake is inversely related with the severity of the bronchoconstrictor response to exercise in asthmatic subjects with EIB. While there are large variations in individual responses, the LSD (approximately 1500 mg sodium per day) reduces the severity of EIB. As most of the data of the association between dietary sodium and EIB have been published by one research team (led by one of the authors of this article), there is a need for similar studies in other populations to see if this effect is reproducible elsewhere.

**IMPLICATIONS FOR CLINICAL PRACTICE**

The data presented in this review demonstrate that adoption of a low sodium diet for a period of 2–5 weeks may improve lung function in adults with asthma, while sodium loading appears to have a detrimental effect. Similarly, a low sodium diet maintained for 1–2 weeks decreases the bronchoconstrictor response to exercise in asthmatics. There is no data as to the longer-term effect of a low sodium diet on either the prevalence or severity of asthma or on EIB. As a low sodium diet has other beneficial health effects, we acknowledge that while the evidence base is limited, a LSD can be considered as a therapeutic option for adults with asthma, although it should be considered an adjunctive intervention to supplement the optimal pharmacological management of asthma and not as an alternative. If the relationship between higher sodium intake and increased risk of asthma is causal, then there are potential population benefits for asthma as well as cardiovascular disease to be derived from public health measures to reduce sodium consumption.
REFERENCES

1 McKeever TM, Britton J. Diet and Asthma. Am J Respir Crit Care Med 2004; 170: 725–9.
2 Tattersfield AE, Knox AJ, Britton JR, Hall IP. Asthma. Lancet 2002; 360: 1313–22.
3 Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. J Allergy Clin Immunol 2000; 105(2 Pt 2): S466–72.
4 Burney P. The changing prevalence of asthma? Thorax 2002; 57(Suppl. 2): I36–9.
5 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998; 351: 1225–32.
6 Halfon N, Newacheck PW. Trends in the hospitalization for acute childhood asthma, 1970–84. Am J Public Health 1986; 76: 1308–11.
7 Klaukka T, Peura S, Martikainen J. Why has the utilization of antiasthmatics increased in Finland? J Clin Epidemiol 1991; 44: 859–63.
8 Anderson HR. Is the prevalence of asthma changing? Arch Dis Child 1989; 64: 172–5.
9 Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. American thoracic society guidelines for methacholine and exercise challenge testing – 1999. Am J Respir Crit Care Med 2000; 161: 309–29.
10 Anderson SD, Kippelen P. Exercise-induced bronchoconstriction: pathogenesis. Curr Allergy Asthma Rep 2005; 5: 116–22.
11 Jones RS, Busto MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. Brit J Dis Chest 1962; 56: 78–86.
12 Kawabori I, Pierson WE, Conquest LL, Bierman CW. Incidence of exercise-induced asthma in children. J Allergy Clin Immunol 1976; 58: 447–55.
13 Anderson SD. Exercise-induced asthma. The state of the art. Chest 1985; 87: 1915S–55.
14 Gotshall RW. Exercise-induced bronchoconstriction. Drugs 2002; 62: 1725–39.
15 Weller JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. J Allergy Clin Immunol 1998; 102: 722–6.
16 Wilber RL, Rundell KW, Szmedra L, Jenkinson DM, Im J, Drake SD. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. Med Sci Sports Exerc 2000; 32: 732–7.
17 Rundell KW, Spiering BA, Baumann JM, Evans TM. Bronchoconstriction provoked by exercise in a high-particulate-matter environment is attenuated by montelukast. Inhal Toxicol 2005; 17: 99–105.
18 Larsson K, Ohlsen P, Larsson L, Malmberg P, Rydstrom PO, Ulrikson H. High prevalence of asthma in cross-country skiers. BMJ 1993; 307: 1326–9.
19 Heir T, Oseid S. Self-reported asthma and exercise-induced asthma symptoms in high level competitive cross-country skiers. Scand J Med Sci Sports 1994; 4: 128–33.
20 Sue-Chu M, Larsson L, Bjerner L. Prevalence of asthma in young cross-country skiers in central Scandinavia: differences between Norway and Sweden. Respir Med 1996; 90: 99–105.
21 Helenius IJ, Tikkanen HO, Hahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. Br J Sports Med 1998; 32: 125–9.
22 Rupp NT. Diagnosis and management of exercise-induced asthma. Phys Sportsmed 1996; 24: 77–86.
23 Haby MM, Peat JK, Mellis CM, Anderson SD, Woolcock AJ. An exercise challenge for epidemiological studies of childhood asthma: validity and repeatability. Eur Respir J 1995; 8: 729–36.
24 Sue-Chu M, Larsson L, Moen T, Rennard SI, Bjerner L. Bronchoscopy and bronchoalveolar lavage findings in cross-country skiers with and without ‘ski asthma’. Eur Respir J 1999; 13: 626–32.
25 Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjerner L, Laitinen LA. Evidence of airway inflammation and remodelling in ski athletes with and without bronchial hyperresponsiveness to methacholine. Am J Respir Crit Care Med 2000; 161: 2086–91.
26 Barbato A, Turato G, Baraldo S et al. Airway inflammation in childhood asthma. Am J Respir Crit Care Med 2003; 168: 798–803.
27 Waite DA, Eyles EF, Tonkin SL, O’Donnell TV. Asthma prevalence in Tokelauna children in two environments. Clin Allergy 1980; 10: 71–5.
28 Van Niekerk CH. Prevalence of asthma: a community study of urban and rural Xhosa children. Clin Allergy 1979; 9: 319–24.
29 Sanchez-Castillo CP, Warrender S, Whitehead TP, James WP. An assessment of the sources of dietary salt in a British population. Clin Sci (Lond) 1987; 72: 95–102.
30 de Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. J Hum Hypertens 2002; 16: 213–23.
31 Council NR. Water and electrolytes. In: Recommended Dietary Allowances, 10th edn. Washington, D.C.: National Academy Press, 1989: 247–61.
32 Salt and Health. Health SACoNFSAaatDo 31. Salt and Health. Her Majesty’s Stationary Office, 2003.
33 Stoesser A, Cook M. Possible relation between electrolyte balance and bronchial asthma. Am J Dis Child 1938; 56: 943–44.
34 Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. Chest 1987; 91(6 Suppl.): 1435–85.
35 Burney PGJ, Britton JR, Chinn S et al. Response to inhaled histamine and 24 hour sodium excretion. Br Med J 1986; 292: 1483–6.
36 Schwartz J, Weiss ST. Dietary factors and their relation to respiratory symptoms. The Second National Health and Nutrition Examination Survey. Am J Epidemiol 1990; 132: 67–76.
37 Pistelli R, Forastiere F, Corbo GM et al. Respiratory symptoms and bronchial responsiveness are related to dietary salt intake and urinary potassium excretion in male children. Eur Respir J 1993; 6: 517–22.
38 Demissie K, Ernst P, Gray Donald K, Joseph L. Usual dietary salt intake and asthma in children: a case–control study. Thorax 1996; 51: 59–63.

39 Tribe RM, Barton JR, Poston L, Burney PG. Dietary sodium intake, airway responsiveness, and cellular sodium transport. Am J Respir Crit Care Med 1994; 149: 1426–33.

40 Mohamed N, Ng’ang’a L, Odhiambo J, Nyamwaya J, Menzies R. Home environment and asthma in Kenyan schoolchildren: a case–control study. Thorax 1995; 50: 74–8.

41 Britton J, Pavord I, Richards K et al. Dietary sodium intake and the risk of airway hyperreactivity in a random adult population. Thorax 1994; 49: 875–80.

42 Devereux G, Beach JR, Bromly C et al. Effect of dietary sodium on airways responsiveness and its importance in the epidemiology of asthma: an evaluation in three areas of northern England. Thorax 1995; 50: 941–7.

43 Sparrow D, O’Connor GT, Rosner B, Weiss ST. Methacholine airway responsiveness and 24-hour urine excretion of sodium and potassium. The Normative Aging Study. Am Rev Respir Dis 1991; 144(3 Pt 1): 722–5.

44 Zoia MC, Fanfulla F, Bruschi C et al. Chronic respiratory symptoms, bronchial responsiveness and dietary sodium and potassium: a population-based study. Monaldi Arch Chest Dis 1995; 50: 104–8.

45 Javaid A, Cashley MJ, Bone MF. Effect of dietary salt on bronchial reactivity to histamine in asthma. Br Med J 1988; 297: 454.

46 Burney PG, Neild JE, Twort CH et al. Effect of changing dietary sodium on the airway response to histamine. Thorax 1989; 44: 36–41.

47 Carey OJ, Locke C, Cookson JB. Effect of alterations of dietary sodium on the severity of asthma in men. Thorax 1993; 48: 714–8.

48 Medici TC, Schmid AZ, Hacki M, Vetter W. Are asthmatics salt-sensitive? A preliminary controlled study. Chest 1993; 104: 1138–43.

49 Lieberman D, Heimer D. Effect of dietary sodium on the severity of bronchial asthma. Thorax 1992; 47: 360–2.

50 Ram FS, Arderen KD. Dietary salt reduction or exclusion for allergic asthma. Cochrane Database Syst Rev 2005; 3: CD000436.

51 Gotshall RW, Mickleborough TD, Cordain L. Dietary salt restriction improves pulmonary function in exercise-induced asthma. Med Sci Sports Exerc 2000; 32: 1815–9.

52 Mickleborough TD, Gotshall RW, Cordain L, Lindley M. Dietary salt alters pulmonary function during exercise in exercise-induced asthmatics. J Sports Sci 2001; 19: 865–73.

53 Mickleborough TD, Cordain L, Gotshall RW, Tucker A. A low sodium diet improves indices of pulmonary function in exercise-induced asthma. J Exerc Physiol 2000; 3: 46–54.

54 Gotshall RW, Rasmussen JJ, Fedorczak LJ. Effect of one week versus two weeks of dietary NaCl restriction on severity of exercise-induced bronchoconstriction. J Exerc Physiol 2004; 7: 1–7.

55 Kurtz TW, Morris RC. Dietary chloride and bicarbonate as determinants of desoxycortocosterone hypertension. J Hypertens 1984; 2: 371–3.

56 Shore AC, Markandu ND, MacGregor GA. A randomized crossover study to compare the blood pressure response to sodium loading with and without chloride in patients with essential hypertension [published erratum appears in J Hypertens 1988 Nov;6(11):i]. J Hypertens 1988; 6: 613–7.

57 Mickleborough TD, Gotshall RW, Kluka EM, Miller CW, Cordain L. Dietary chloride as a possible determinant of the severity of exercise-induced asthma. Eur J Appl Physiol 2001; 85: 450–6.

58 Mickleborough TD, Gotshall RW, Rhodes J, Tucker A, Cordain L. Elevating dietary salt exacerbates hyperpnea-induced airway obstruction in guinea pigs. J Appl Physiol 2001; 91: 1061–6.

59 Freed AN. Models and mechanisms of exercise-induced asthma. Eur Respir J 1995; 8: 1770–85.

60 Freed AN. Experimental models of exercise-induced asthma. In: McFadden ER, ed. Exercise-Induced Asthma. New York: Marcel Dekker, Inc, 1999: 319–49.

61 Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. Med Sci Sports Exerc 2005; 37: 904–14.

62 Hashimoto S, Matsumoto K, Gon Y, Nakayama T, Takeshita I, Horie T. Hyperosmolarity-induced interleukin-8 expression in human bronchial epithelial cells through p38 mitogen-activated protein kinase. Am J Respir Crit Care Med 1999; 159: 634–40.

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