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Reversing the trend: Reducing the prevalence of asthma

Jennifer K. Peat, PhD, and Janet Li, MPH *Sydney, Australia*

Background: We urgently need to take steps towards reducing the prevalence of asthma in countries where the prevalence has become unacceptably high in recent years. Because we do not have any good information about causes of the increased prevalence, we cannot act directly to reverse the trend. Therefore we need to take an indirect approach and use known information of etiologic factors to try to reduce asthma in the next generation, while acknowledging that we may be dealing with different factors from those responsible for the increased prevalence. Any successful strategies will also help to ensure that developing countries do not attain such high rates of asthma in their children in coming years.

Objective: This article summarizes the roles of the risk factors that identify "high-risk" children, that provide insights into mechanisms, or that have potential for primary prevention. The factors with the most potential for primary prevention are allergen exposure, parental smoking, breast-feeding, and dietary fatty acids.

Conclusion: In other health models, information about risk factors has been used in successful public health interventions. It is disappointing that the important risk factors for asthma are well documented but that there have been few trials of primary prevention and no changes in public health policies. (*J Allergy Clin Immunol* 1999;103:1-10.)

Key words: Prevalence, risk factors, asthma, diet, allergens, breast-feeding, parental smoking

Abbreviations used

ECRHS: European Community Respiratory Health Survey
ISAAC: International Study of Asthma and Allergy in Children

The prevalence of asthma has been measured in many countries over the last 2 decades,¹⁻⁴ with most researchers concluding that there has been a real increase in the prevalence of both asthma and other allergic symptoms in children and young adults. It can be argued that much of the increase may be explained by measurement error as a result of changes in research methods and in diagnostic labels used by medical practitioners over the years.⁵ On the other hand, the concept of a real increase is validated by studies that have monitored indicators, such as admission rates to hospitals,^{6,7} and objective markers, such as airway hyperresponsiveness.⁸ In essence, the argument is difficult to resolve because any measurement of trends across time will always depend on historical data that are difficult to compare with contemporary data.¹ What is clear is that it is time to take steps to reduce the prevalence of asthma in the many countries in which it is now unacceptably high. It is also important to develop strategies to ensure that developing countries do not attain such high rates of asthma in their children in the coming years.

Because we do not have any good information about the causes of this increase in asthma prevalence, we cannot act directly to reverse the trend. Thus we need to take a less direct approach and use the information on known risk factors to try to prevent asthma from developing in the next generation, while acknowledging that we may be dealing with different factors from those responsible for

From ^athe Department of Paediatrics and Child Health, University of Sydney; and ^bthe Institute of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney.

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Reprint requests: Jennifer K. Peat, PhD, Hospital Statistician, Clinical Epidemiology Unit, New Children's Hospital, NSW 2145 Australia.

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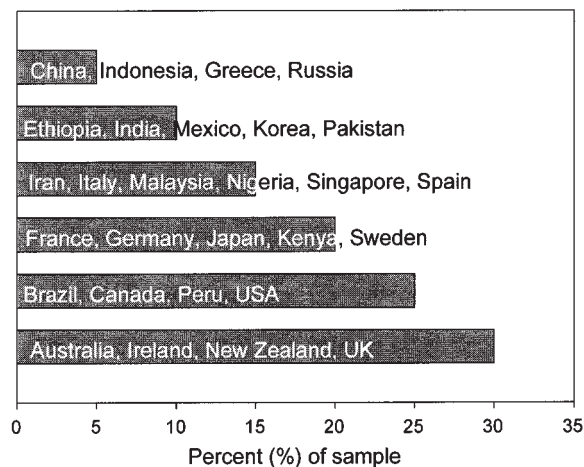


FIG 1. Prevalence of wheeze in the last 12 months as measured in the ISAAC studies.⁹ Only a selection of the 56 participating countries is shown. In the listed countries, prevalence of asthma in children age 13 to 14 years is within the range of the bottom bar on the chart.

the increased prevalence. This article summarizes the roles of factors for which there is evidence of a primary involvement in the etiology of asthma, with particular focus on those with the most potential for immediate use in preventive interventions. Such interventions may also prevent the inception of a trend for increasing asthma in less affluent countries in which a low prevalence has been recorded in recent studies.

PREVALENCE

Studies of the worldwide prevalence of asthma by the International Study of Asthma and Allergy in Children (ISAAC)⁹ and the European Community Respiratory Health Survey (ECRHS)¹⁰ have been landmark events. Because both collaborations have used standardized study protocols and stringent quality control measures, they have overcome the limitations of numerous previous studies of asthma prevalence so that, for the first time, worldwide data can be reliably compared. Fig 1, which summarizes prevalence rates collected from children in some of the countries involved, shows that symptoms of asthma are infrequent in Eastern Europe and Asia but much higher in the UK, Australia, New Zealand, Ireland, and America. There is a greater than 15-fold difference between countries worldwide. Large differences in the prevalence of asthma in adults were also demonstrated by the ECRHS studies, although fewer countries outside Europe were enrolled and the differences were not so marked as in the ISAAC studies.

MORBIDITY

Because of the large demand that asthma morbidity places on health care services, it is essential that countries in which prevalence is high work toward methods

of primary prevention. The proportion of the population receiving treatment for asthma or being admitted to hospitals for asthma has been documented in many countries.¹ In Australia, up to 1% of children are hospitalized for asthma annually, 10% to 12% have asthma with clinically important symptoms that affect lifestyle, and 25% to 30% have symptoms of wheeze, of whom 80% regularly use an asthma medication.¹¹ In the US, 9% to 16% of children use an asthma medication regularly, and 0.4% are hospitalized for asthma annually.^{12,13} The cost of this level of health care use in the community is large.^{14,15} In the event of this, it seems somewhat irrelevant to debate the extent to which perceived changes in prevalence are due to actual changes or to methodology, recognition, or diagnostic labeling. What is more important is that these rates are unlikely to be reduced unless methods of primary prevention are devised and widely implemented.

BETWEEN-COUNTRY COMPARISONS

It is encouraging that the findings of the ISAAC studies of 13 to 14 year old children verify the results of previous studies of younger children, which have been summarized elsewhere,¹⁶ and that the estimates are broadly consistent within countries. This consistency of evidence validates the beliefs that asthma is more prevalent in some countries than others, that an affluent lifestyle is associated with a higher prevalence, and that there are much greater between-country than within-country differences. The real importance of the ISAAC studies will be in identifying the factors responsible for the high or low prevalence in some countries. Because comparisons of regions with similar prevalence are likely to provide little information if exposures are ubiquitous, the best method to accurately measure the effects of risk factors is to compare countries in which prevalence and exposures differ by an important magnitude. The ISAAC studies will provide an excellent base on which to build such studies, which will be likely to yield fundamental information about asthma causation that could not be obtained in any other way.

RISK FACTORS

Many etiologic factors may be responsible for the differences in the prevalence of asthma between countries highlighted by the ISAAC studies (Fig 1), which range from 2% in Chinese and Indonesian children to 30% in children in the UK and Australia. However, it is important to recognize that the primary risk factors that determine why asthma develops in an individual may not be the same as those that determine why this disease develops in so many individuals in a population. Thus 2 possibilities could explain increases in the prevalence of asthma or differences between countries. These are that there has been a *period effect* (an increase in exposure to environmental factors that has increased the risk of asthma developing in the entire population of susceptible subjects) or a *cohort*

effect (changes in environmental exposures have increased the incidence of disease in each subsequent generation of children). There is some evidence that the latter effect has been more dominant.^{1,4,17}

It is also important to recognize 2 categories of risk factors. The most important are the primary risk factors, which increase an entire cohort's risk to some extent and thereby result in a larger number of individuals who cross the disease threshold. There are also secondary risk factors, which increase the severity of asthma or the rate of exacerbations in those who already have established airway abnormalities.¹⁸ Information of secondary factors is helpful in the clinical management of patients with asthma, but information about primary risk factors, which have a fundamental etiologic role, is crucial for developing interventions to reduce the incidence of disease in populations.¹⁹ Of course for asthma, some factors such as exposure to allergens or tobacco smoke may act in both roles.

Although interventions involving both primary and secondary risk factors will ultimately lead to a reduction in morbidity in the community, only primary risk factors can be used to prevent the onset of asthma and are therefore important in long-term public health policies to reduce illness. For such interventions to be useful at a population level, it is important that they can be easily applied at an individual household level and that information about them can be readily communicated as public health policies.

It is unfortunate that we have no direct and very little indirect knowledge of the primary risk factors responsible for the increases in prevalence in many countries. Thus we can only proceed to testing for changes in exposure to risk factors for which we have good knowledge of their primary involvement in asthma and which may be appropriate for use in public health interventions to prevent this disease from developing in susceptible children. The factors for which there is good evidence of their association with asthma are shown in Table I.

RISK FACTORS THAT IDENTIFY "HIGH-RISK" CHILDREN OR PROVIDE INSIGHT INTO MECHANISMS

Factors such as family history, gender, and ethnicity are important for identifying children who are at high risk for the development of asthma and who are most likely to benefit from the effects of public health interventions. Although genetic factors make a major contribution to the development of asthma and new techniques of gene mapping may improve treatment methods in the long term, it is unlikely that such techniques will have direct applicability for preventive strategies in the short term.

The identification of other factors involved in asthma etiology, such as infections in early life,^{20,21} and perinatal factors, such as low birth weight²²⁻²⁵ and disproportionate fetal growth,^{26,27} is essential because of their potential to identify direct causal mechanisms at a cellular level. The role of reduced or increased exposure to infections as a result of fewer siblings, less room sharing,

TABLE I. Risk factors implicated in the onset of childhood asthma

I. Factors that identify "high-risk" children
Family history/genetic markers
Ethnicity, affluence, socioeconomic status
Sex
II. Factors that provide insight into mechanisms
Early infections
Vaccination status, antibiotic use
Exposure to other children (eg, number of siblings, use of daycare, shared bedroom)
Perinatal status
Preterm birth, head circumference, or weight at birth
Mother's age at time of birth
III. Factors that have potential for primary prevention
Indoor allergens
Beds, pillows, floor coverings, pets
Dampness or mold
Heating, ventilation, house construction, etc.
Parental smoking
Prenatal and postnatal exposures
Lack of breast-feeding
Time of breast-feeding cessation and/or introduction of cow's milk
Dietary fatty acids
Omega fatty acids (eg, fish intake, use of polyunsaturated foods)

or greater use of daycare²⁸⁻³² appears to have a closer relation with atopy than with asthma^{33,34} and thus to have a more fundamental role in the development of asthma. Information about the actions of infections may lead to the development of new vaccines or other innovative treatments to prevent atopy or accurately identify the groups who are most at risk, although it may be some years before such interventions are available for use at a population level.

RISK FACTORS WITH POTENTIAL FOR PRIMARY INTERVENTION

Only the interventions that address the known effects of immediate etiologic exposures will be effective in reducing the prevalence of asthma in the short term. The risk factors that have the most potential in a primary preventive role are shown in Table I and are discussed in more detail below.

INDOOR ALLERGENS

The evidence for risk factors with a direct role in asthma causation is most complete for house dust mite allergens. There is clear biologic plausibility for their role in that the proteolytic activity of their enzymes can actively damage the airway epithelium.³⁵ In addition, a dose-response effect and consistency of evidence have been clearly demonstrated.³⁶ The role of allergen exposure is slightly more complicated than that of risk factors in that a 2-stage process is involved whereby exposure leads to the development of sensitization³⁷ and exposure of sensitized subjects leads to

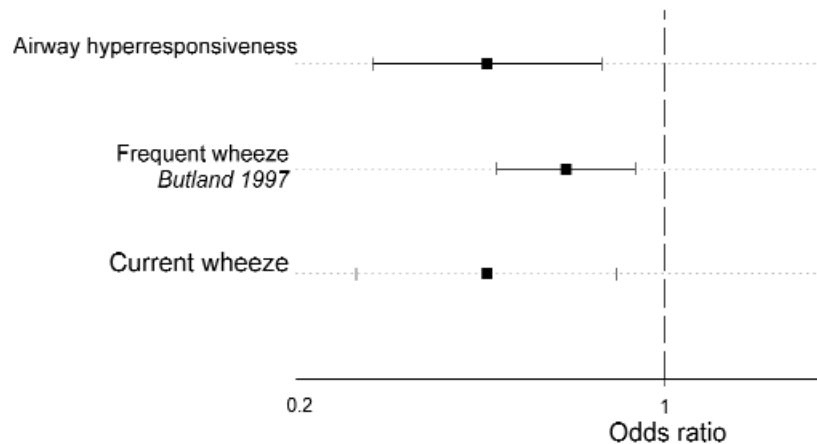


FIG 2. Odds ratio for children to have airway hyperresponsiveness or wheeze if their pillow is synthetic.⁴⁵⁻⁴⁷

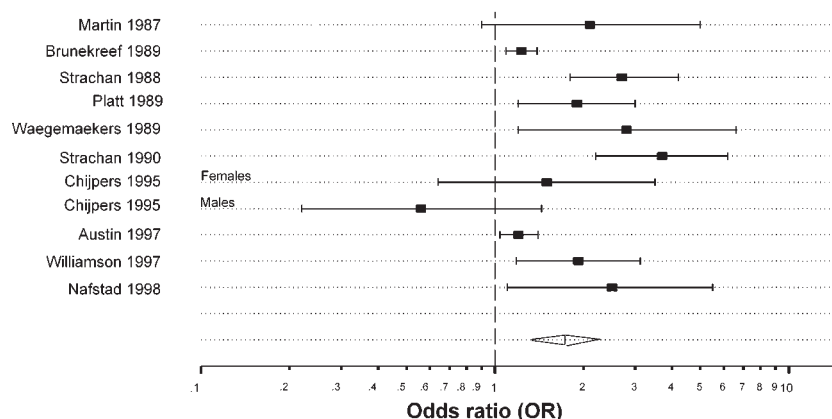


FIG 3. Odds ratios for children to have wheeze if they have dampness or mold in their home.⁹⁶⁻¹⁰⁵ The pooled odds ratio was calculated by means of metaanalysis; a random effects model was used.

the development of asthma.^{38,39} Thus levels of sensitization become more severe in people who live in regions with high exposure levels,⁴⁰ and asthma becomes more severe in people who have become sensitized and who are exposed to high allergen levels.^{41,42}

Epidemiologic studies suggest that a 2-fold reduction of allergen exposure at a community level would significantly reduce rates of sensitization in early childhood,^{37,40} halve the risk of asthma development in sensitized children,⁴³ and similarly reduce asthma severity in clinical terms.⁴¹ The home is thought to be the place of greatest exposure both because numerous sites harbor high house dust mite allergen levels and because this is where people spend most of their time. Bedding, especially the mattress and pillows, are major allergen sources. The role of synthetic pillows has gained interest because these have much higher house dust mite allergen levels⁴⁴ and are associated with higher levels of childhood wheeze and asthma (Fig 2).⁴⁵⁻⁴⁷

Much work has been directed to determining the effectiveness of house dust mite allergen avoidance as a secondary preventive tool. The results from a large number of studies, including a small number of randomized controlled trials, have been reviewed,⁴⁸ and their applicability will be discussed in the next article in this series. These studies have made a vital contribution to the development of effective methods of allergen avoidance that are now available for trial as primary preventive strategies. However, the most effective methods are acknowledged as being quite difficult to achieve because major changes to bedding and washing methods are critical, and the choice and maintenance of floor coverings, furnishings, and ventilation methods is also important.

Although studies to test primary prevention with house dust mite allergen avoidance are now underway in some countries, such studies are necessarily long term, and their results are not yet available. However, 2 randomized controlled trials that have used mixed interventions have pro-

vided very encouraging results.^{49,50} Although the confidence intervals for the difference in the prevalence of asthma between the intervention and control groups in both studies cross the zero line of no effect, an absolute reduction in the prevalence of asthmatic symptoms was achieved at 11% in one trial and 5% in the other, which would be important in population terms. The fact that both studies could be considered to be underpowered in statistical terms highlights the need for a large sample size in such trials and for significant research resources to be invested to establish efficacy.

Many studies have also investigated the relation between dampness or mold in the home and the risk of having asthma.⁵¹ A metaanalysis of the results is shown in Fig 3. Levels of both house dust mite and mold allergens are higher in damp homes,^{52,53} but because none of the studies shown in Fig 3 have included allergen exposure measurements, it is impossible to determine whether health effects can be directly attributed to increased exposure.

Obviously, pets also provide a source of immediate allergen exposure in many homes, and because their allergens are readily transported, significant exposure may also occur in public places.⁵⁴ However, for families whose children are susceptible to the development of asthma and who are serious about using environmental control as a primary preventive strategy, this source of allergens is the most readily preventable of all immediate exposures in the home.

PARENTAL SMOKING

There is an undisputed consensus that parental smoking leads to increased respiratory infections and respiratory illnesses in children. A huge number of studies have demonstrated the effect of parental smoking on childhood illness, and the literature has been reviewed more often and with more rigor than for any other risk factor. Recently, a series of metaanalyses again confirmed that parental smoking increases the risk of children having many respiratory illnesses, including lower respiratory tract infections, asthma, chronic cough, and wheeze.⁵⁵⁻⁵⁸

The pooled odds ratios from these analyses for the occurrence of asthma and wheeze in children exposed to parental smoking were small (ie, in the order of 1.2 to 1.3). However, these risks remain important in population health terms because of the high percentage of children who are exposed to tobacco smoke in their home. For example, in Australia and the US as many as 25% of children have mothers who smoke during pregnancy, and over 40% have a parent who smokes in the home.^{59,60}

Compared with the very large numbers of studies conducted to demonstrate the harm caused by parental smoking, relatively few interventions have tested the beneficial effects of reducing parental smoking. The problems of preventing smoking are complex in that most mothers are aware of the risks of smoking during pregnancy,⁶¹ and pharmacological aids to smoking cessation are contraindicated at this time. Thus smoking cessation interventions during pregnancy have been fairly

modest in that they have centered around educational materials that focus on the negative aspects of continuing to smoke.⁶² It is essential that new interventions are devised to teach behavioral coping strategies and that therefore address the problems caused by acute nicotine symptoms after smoking cessation in a more positive and helpful way. Such strategies are more likely to be effective and, therefore to prevent, a wide range of illnesses, including asthma, that develop in children.

BREAST-FEEDING

Breast-feeding plays a vital role in the development of the immune system.⁵⁹ There is evidence that the antiinflammatory and antiinfective factors in breast milk contribute to the prevention of both allergic illness⁶³ and a wide range of respiratory and gastrointestinal infections.⁶⁴⁻⁶⁶ In addition, breast-feeding reduces exposure to the food allergens contained in cow's milk, whereas bottle-feeding provides regular exposure to many microbial products and foreign proteins that may cause sensitization and other problems in infants, especially those who are at high risk for development of allergic symptoms.⁶⁷

The epidemiologic evidence that breast-feeding protects against the development of asthma is beginning to accumulate, although the process has been slow. Fig 4 shows the odds ratios and 95% confidence intervals from studies that have examined this association. The meta-analysis, which was computed by using a random-effects model, shows that children who are breast-fed to at least 3 months of age are protected from development of asthma with an odds ratio of 0.80 (95% CI: 0.66, 0.97). Other studies show a similar relation between breast-feeding and wheeze in early childhood^{64,68-76} and other atopic symptoms.^{63,77,78} As with parental smoking, the effects demonstrated have been quite small but are of public health importance because a high percentage of infants have ceased to be breast-fed at an early age. In a recent study in Australia we found that over 30% of infants had had cow's milk introduced into their diet by the age of 3 to 4 months (unpublished data).

DIETARY FACTORS

There is both epidemiologic evidence and biologic plausibility that many dietary factors, including omega-3 fatty acids, antioxidants, and sodium, are associated with asthma and reduced lung function.⁷⁹⁻⁸⁴ The evidence for an effect is most complete for the role of omega-3 fatty acids, which are abundant in fish and which prevent airway abnormalities through their antiinflammatory effects in the airway wall.^{85,86} To date, 2 reports from the US^{87,88} and our own studies in Australia^{89,90} show that people who eat fish regularly have fewer asthmatic symptoms. In a recent study of over 600 preschool children, we again found that children with a high level of omega-3 fatty acids in their diet were at a significantly lower risk of having asthma, with an odds ratio of less than 0.5 (unpublished data). In this study over 25% of children had no fresh fish

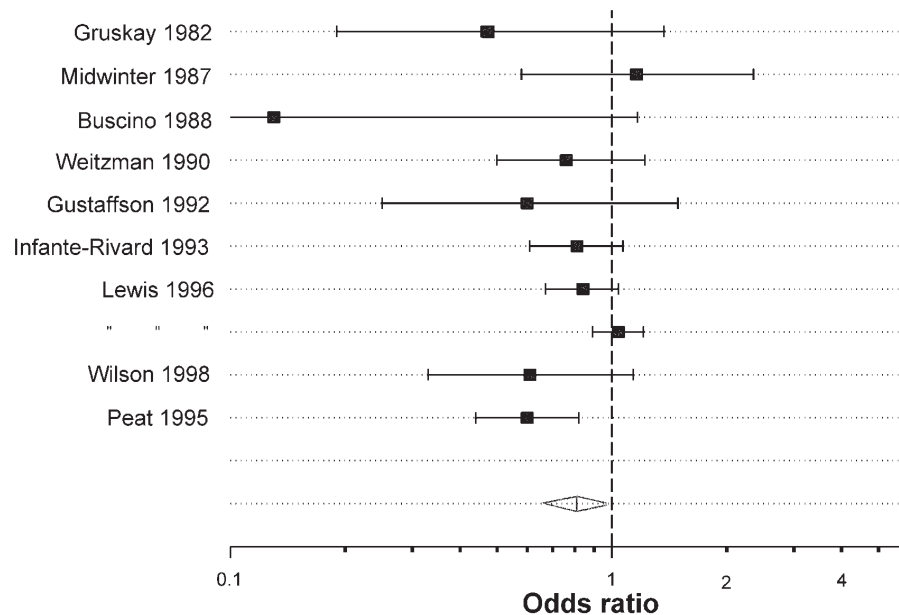


FIG 4. Odds ratios for children to have asthma if they were breast-fed for more than 3 months (Peat, unpublished data).^{78,106-112} The pooled odds ratio was calculated by means of metaanalysis; a random effects model was used.

TABLE II. Evidence for the role of allergens in the etiology and primary prevention of asthma

	House dust mites	Molds	Pets	Cockroach	Pollens
Causality					
Temporality	+	+	—	—	—
Biologic plausibility	+	+	+	+	+
Consistent evidence	+	—	+	—	+
Dose-response relation	+	—	—	—	—
Public health importance					
Size of effect (OR)	3-20	2-10	2-5	?	2-5
Level of exposure	Variable	Variable	Variable	Variable	Variable
Ability to modify	+	—	+	—	—
Effective interventions	+	—	—	—	—

+, Consistent evidence from a number of studies is available; —, evidence is absent, inconsistent, or incomplete.

or omega-3 oils included in their diet, and an even larger percentage had a low intake, which suggests that many children have an inadequate intake of omega-3 fatty acids.

Despite the epidemiologic evidence, supplementation with omega-3 fatty acids has been disappointing as a treatment for established asthma.⁹⁰⁻⁹² However, this would be expected if asthma cannot be reversed once it has developed, if the time of supplementation was too short, or if the dose was too low. To date, no studies have tested whether dietary supplementation with omega-3 fatty acids is effective in the primary prevention of asthma.

ROLE OF RISK FACTORS IN INCREASING PREVALENCE

Because there was no simultaneous monitoring of environmental exposures that may have been responsible for

the increased prevalence of asthma, the only data available are based on speculative or ecologic assumptions. We found some evidence that the numbers of house dust mites increased in 2 regional centers between 1982 and 1992,⁷ but no similar evidence has been reported from other places. In addition, the prevalence of smoking in young women increased in this time period. There is also evidence that improved education levels, increased contraceptive use, and changed family patterns have resulted in more children being born into smaller families or to mothers who typically do not breast-feed.⁹³ In addition, there is some circumstantial evidence that consumption of antioxidants and omega-3 fatty acids has decreased.^{94,95} It is thought that in the last decade the ratio of omega-3 to omega-6 fatty acids changed from 1:5 to 1:25 with the widespread introduction of polyunsaturated oils and spreads, although there is no direct evidence that this change has led to an increased

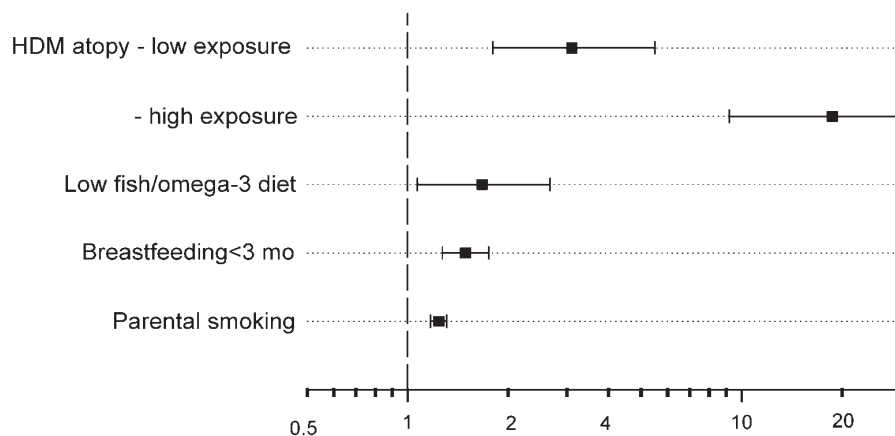


FIG 5. Summary of the magnitude of effects of the “modifiable” risk factors for asthma that have been identified to date for house dust mite allergen (HDM) exposure,⁴² low fish/omega-3 diet,¹¹³ breast-feeding (metaanalysis from Fig 5), and parental smoking.¹¹⁴

prevalence of asthma. Despite the lack of good evidence for a role of any factors in increasing prevalence, it is vital that studies are devised to determine whether reducing exposure to any of the known risk factors can prevent asthma from developing in the next generation of children.

CONCLUSIONS

There is no evidence to suggest that asthma that develops in early life can be reversed by any treatment or environmental intervention. Thus it is important to test whether changes in exposure to the most important environmental risk factors can downregulate the development of allergic sensitization and airway inflammation and thus prevent the asthmatic process from “switching on” in early life. In the search for local exposures that can be manipulated to achieve this goal, it is important that we concentrate on factors for which there is good evidence for causation. We also need to consider their public health importance in terms of the size of effect and our ability to manipulate exposure levels.

The evidence for the known risk factors to date is summarized in Tables II and III, and the size of effect of the most important factors is summarized in Fig 5. Because of overlaps in susceptibility, overlaps in exposure to environmental factors, and the development of different asthma phenotypes in individual children, it is difficult to accurately estimate how far prevalence could be reduced if exposure to all of these factors was prevented. However, a conservative estimate is at least a 50% reduction, with larger benefits expected if any of the interventions prove to have interactive effects.

FUTURE DIRECTIONS

The identification of other potentially preventable risk factors and the confirmation of the roles of known

TABLE III. Evidence for behavioral and diet risk factors in the etiology and primary prevention of asthma

	Parental smoking	Breast-fed less than 3 months	Low omega-3 fatty acid diet
Causality			
Temporality	+	+	—
Biologic plausibility	+	+	+
Consistent evidence	+	+	+
Dose-response relation	+	+	—
Public health importance			
Size of effect	1.3	1.5	2.0
Level of exposure	40%	32%	25%
Ability to modify	—	—	—
Effective interventions	—	—	—

+, Consistent evidence from a number of studies is available, —, evidence is absent, inconsistent, or incomplete.

or suspected risk factors in regions in which their effects are not established will continue to be a slow and painstaking task. This will be especially difficult if reliable tools or questionnaires that are suitable for measuring exposures in epidemiologic studies are not available. In addition, the roles of other risk factors for which exposures can now be measured, such as indoor and outdoor molds, needs better clarification before we can be confident that they will have a productive role in preventive interventions.

Through the ISAAC studies, which have identified regions in which the presence of many potential confounders can be standardized, researchers are now in a better position to measure the effects of risk factors that contribute to the high prevalence of asthma in some countries. Such between-region comparisons, especially of children with similar genetic susceptibility, are likely to provide more comprehensive information about risk factors than has been obtained to date.

However, in affluent countries with a high prevalence of asthma, it is important that we quickly proceed toward testing the effectiveness of interventions, especially those that involve avoiding exposure to factors for which there is evidence to support causation. In other prevalent health problems, such as skin cancer, heart disease, and traffic accidents, mortality rates have been successfully reduced with this approach. It is disappointing that the important risk factors for asthma have been known for some time but that there have been few trials of primary prevention and no changes in public health policies.

In the immediate future, it is crucial that we establish the efficacy of preventive methods in affluent countries in which the prevalence of asthma is high. This will ensure that effective methods can be reliably recommended for developing countries in which the prevalence of asthma is still relatively low and in which resources to treat this disease may not be readily available.

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