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Relationship between dietary antioxidants and childhood asthma: more epidemiological studies are needed

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Summary Approximately 15 million Americans including over 5 million children suffer from asthma, the most common chronic disease in childhood. The prevalence of pediatric asthma has risen sharply over the past four decades, with the sharpest increases occurring in children younger than 6 years and in urban, predominantly minority, populations. The reasons for this dramatic increase are not yet clear. Recent epidemiological studies indicate a higher prevalence of dietary antioxidant deficiency among asthmatics patients. However, the results of these studies are inconsistent or even contradictory. Epidemiological studies with robust design and use of novel epidemiological tools are urgently needed to examine the impact of dietary antioxidants on the incidence of asthma in preschool children. An incidence density case-control study which includes non-atopic controls, who are matched for age, gender, race, study center and sampling time to each asthmatic case will offer a robust study design. A validated food frequency questionnaire and an asthma and atopy severity score can be used to interview the parents of the recruited children. Risk set sampling may enable us to explore possible associations between the type and quantity of dietary antioxidants and the development and severity of asthma in such an epidemiological study.

Bronchial asthma and allergy in adults and children

Bronchial asthma, the most common chronic disease in children, is a hyperactive airway disorder that is associated with recurrent and reversible wheezing episodes and other respiratory symptoms such as cough and shortness of breath [1–3]. The pathophysiology of bronchial asthma is based on the reversible airway obstruction due to bronchospasm, mucus hypersecretion, and mucosal edema. Atopy, the tendency to become allergic, is an important predictor for the development of asthma [2,3]. Anything that contributes to the development of atopy may be crucial to the development of asthma, which per se is often associated with other allergic (atopic) conditions including hay fever (allergic rhino-conjunctivitis) and atopic dermatitis (eczema) [2]. Various allergic and non-specific stimuli, in the presence of hyper-reactive airways, initiate the bronchospasm and inflammatory response seen in asthma [4].

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Epidemiology and burden of disease

Although allergic asthma has its onset at any age, early childhood is thought to be the most critical time for the development of atopy and asthma [3,5]. Almost 30% of asthmatic patients have their first pulmonary symptoms by 2 years of age, but wheezing in many of these infants and toddlers is due to non-asthmatic conditions such as viral diseases (especially respiratory syncytial virus) or gastro-esophageal reflux disease [6]. Nevertheless, 80–90% of true asthmatic children have their first symptoms before the age of 6 years [7] (Fig. 1). The major risk factors for the development of childhood asthma include male gender, African–American race, tobacco smoke exposure, low socioeconomic class, and intense allergenic exposure in infancy (Table 1) [2,8].

Childhood asthma and atopic diseases have large global variation ranging from less than 2% to as high as 33% of the population according to the degree of economic prosperity of the country [9]. The second National Health and Nutrition Examination Surveys (NHANES II) showed that 6.7% of US children 3–17 years of age had asthma. The prevalence in African–American children was greater than in Caucasian children, 9.4% and 6.2%, as was male (7.8%) to female (5.5%), respectively [10]. Currently, there are 15 million Americans including over 5 million asthmatic children in this country [1,2].

Childhood asthma exerts a tremendous burden not only on families but also on healthcare resources [11,12]. The cost for health care of the US asthmatics is estimated to be $5.8 billion annually [11,13]. Almost 30% of asthmatic children have some limitations in activity, compared with 5% of children without asthma [12]. According to a large study that examined over 17,000 asthmatic children in 1988, these children had 10.1 million days missed from school and 200,000 hospitalizations

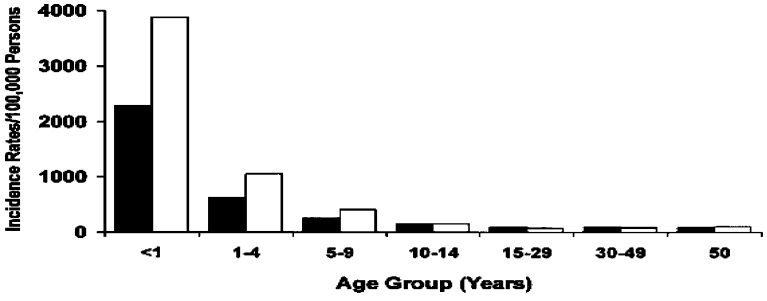

Figure 1 Annual *incidence* rates of wheezing according to age among residents of Rochester, Minnesota, from 1964 to 1983 (unfilled bars: male subjects; filled bars: female subjects) [7].

Table 1 Risk factors for pediatric asthma and atopy.

Risk factors	Possibly environmental	Possibly genetic	Modifiable
Family history of asthma: mother > father		X	
Family history of allergy and/or atopic diseases		X	
Gender: male > female		X	
Race: Black > While		X	
Past history of or coexisting atopy (hay fever, eczema, etc.)	X	X	
Immune system defect or cytokine imbalance (TH_2 to TH_1 transition)	X	X	(X)
Prematurity and/or birth defects	X	X	(X)
Maternal factors during pregnancy (tobacco smoke in utero, etc.)	X	(X)	(X)
Infections (respiratory syncytial virus, parainfluenza, others)[a]	X	(X)	(X)
Seasonal and climate conditions	X		(X)
Socioeconomic status and life style (urban/rural, day-care attendance, etc.)	X		(X)
Exposure to allergens (house dust mite, cockroaches, mold, cat dander, tobacco smoke, air pollution, etc.)[a]	X		X
Food and dietary antioxidants[a]	X		X

[a] Factors likely responsible for the increased rate of asthma in the last four decades.

which resulted in 1.9 million days of inpatient care [14]. Asthmatic children were also noted to have a 1.7 times increased risk of learning disabilities, especially those in fair to poor health, when compared with their non-asthmatic peers [14].

The prevalence of allergic conditions, including asthma, has shown a worldwide consistent pattern of increasing prevalence over the past four decades, particularly among young children (Fig. 2) [2,6,13—16]. During the 1980s, Weitzman et al. [16] found that the prevalence of asthma in the US increased from 3.1% to 4.3%. When evaluated over a 19-year period (1965—1984), the prevalence rate of asthma in children was found to be even more substantially increased (50%) [13—16]. Analysis of a large cohort of 16,381 Spanish individuals with atopic conditions from 1989 to 1999 showed a 7.8% increase in incidence of allergic asthma in the past decade alone [17]. In the US, certain cities such as Chicago or New York appear to be high-risk areas for a number of important epidemiologic trends in pediatric asthma including its recent rise [18].

Gene versus environment

Atopic disease and asthma show a strong hereditary and ethnicity predisposition. A positive family history of atopic disease is observed in 1/3 to over half of all asthmatic children [1—4]. However, the rise in asthma and allergic diseases in association with national prosperity in different countries around the globe in the past four decades speaks for major environmental influences [2,17]. Because the increase in childhood asthma has accompanied social and environmental changes world-wide, it is more likely that a solution to the problem will come from a public health approach than from the discovery of new drugs. Three implicated environmental factors include: (1) air pollution and increased exposure to allergic particles and tobacco smoke, (2) dietary regimen modifications, and (3) a decrease in rate of childhood infections [17]. There is evidence that atopic diseases have increased in spite of no significant rise in grass pollen levels [2,3]. Similarly, urban air pollution or cigarette smoking by parents or young adults have not increased substantially in the industrialized nations, making them very unlikely to be a factor in the rise in allergic diseases [1—3,13]. Other possible causes must therefore be sought, and of these the most plausible are reductions in the incidence of childhood infections and changes in the diet.

Role of diet in asthma and allergic diseases

There is accumulating evidence that diet is the most important factor among the three main environmental factors (air, food and infection) that account for the striking increase in the incidence and prevalence of asthma in the past four decades [19—22]. Recent studies suggest that antioxidant elements and vitamins may confer protection from the development of asthma or may alleviate symptoms in those who have a predisposition to atopy or asthma [19,22]. Available evidence supporting a role for dietary antioxidants in asthma and atopy fall into three broad categories: (1) basic science research denoting the pathophysiology of the association between food antioxidants and airway disease in cell cultures, animal models or in vivo human studies; (2) epidemiological studies

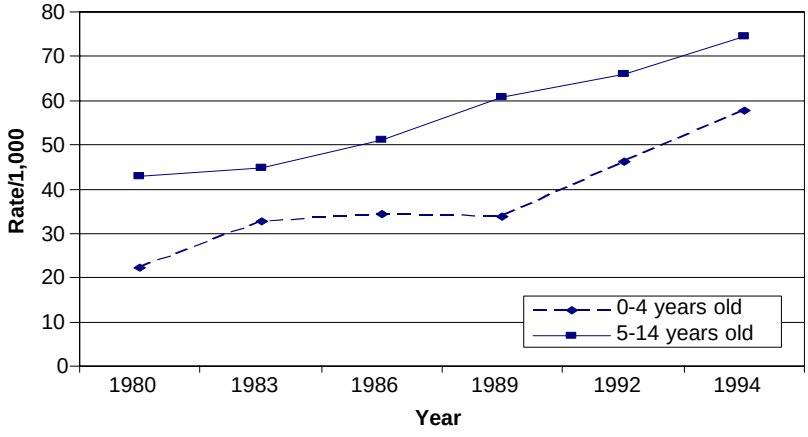

Figure 2 Estimated average annual rate (prevalence) of self-reported pediatric asthma per 1000 of the population. Diamond: 0—4 year old children; square: 5—14 year old children [15].

that examine the role of differences in dietary intake of specific nutrients in explaining the incidence, prevalence and change in the course of asthma and atopy; and (3) clinical trials based on dietary or parenteral supplementation to modify the symptoms or the prevalence or incidence of atopy and asthma.

Role of antioxidants in hyperactive airway disease

Antioxidants are defined by their mechanism of action, i.e. the prevention of the formation of free radicals or the conversion of oxidants to less toxic species. The major natural antioxidants in the diet are water-soluble vitamin C (or ascorbate, mainly derived from fruits, vegetables and potatoes), fat-soluble vitamin E (or tochopherol, mostly from vegetable oils and margarines), and β-carotenes (in fruits and vegetables) [19,22]. Other antioxidants include selenium, manganese, zinc and copper, among others.

Antioxidant—oxidant imbalances in bronchoalveolar fluid may contribute to oxidative stress in respiratory disease, since an excessive free radical generation in the blood of children suffering from asthma has been shown [23]. Schock et al. studied 41 atopic and 83 control children and found that bronchoalveolar alpha-tocopherol (vitamin E) concentration was significantly decreased in the atopic individuals. Moreover, serum and bronchoalveolar ascorbate (vitamin C) concentrations were significantly correlated, which may offer an explanation as to why supplementing the diet with vitamin C might improve asthma symptoms [24]. Fogarty et al. [25] studied the relationship between dietary vitamin E intake and serum IgE concentration and atopy in a random sample of 2633 adults and found that higher levels of vitamin E intake was associated with lower serum IgE level and lower frequency of allergen sensitization. Stone et al. [26] found that patients with symptomatic asthma had a reduced plasma selenium concentration, which is essential in the activity of glutathione peroxidase, the enzymes which is believed to be an important component of pulmonary antioxidant system. Table 2 lists some of the antioxidants that may play a role in the development of atopy or asthma [21,22,26—36].

Antioxidants and asthma and allergy in the adults

Several recent large prospective cohorts have addressed the question concerning the possible role of antioxidants in asthma and allergy but have

Table 2 Antioxidant trace elements and vitamins based on Food and Nutrition Board of the Institute of Medicine [18].

Antioxidant	Daily intake (children)	Daily intake (adults)	Sources of antioxidant	Reference articles for asthma
Vitamin C (mg/day) [ascorbic acid]	15—25	75—90	Citrus fruits, tomatoes, tomato juice, potatoes, brussel sprouts, cauliflower, broccoli, strawberries, cabbage, spinach	[21,22,28—31][a]
Vitamin E (mg/day) [α-tocopherol]	6—7	11—15	Vegetable oils, unprocessed cerealgrains, nuts, fruits, vegetables, meats	[28,29,32,33]
Selenium (mg/day)	20—30	55—60	Organ meats, seafood, plants (depending on soil selenium content)	[26,31,34,35][b]
Manganese (mg/day)	1.2—1.5	1.8—2.3	Nuts, legumes, tea, whole grains, drinking water, supplements	[22]
Copper (mg/day)	0.34—0.44	0.7—0.9	Organ meats, seafood, nuts, seeds, wheat bran, cereals, whole grain products, cocoa products	[36][b]
Zinc (mg/day)	3—5	8—11	Fortified cereals, red meats, certain seafood (vegetarians may have lower GI absorption)	[22,36]

Last column lists relevant studies pertaining to each antioxidant in asthmatic patients.
[a] No association was found explicitly.
[b] Studies that have shown a low, and not a high, intake of this antioxidant may be beneficial in asthmatics.

yielded contradictory results and left significant unanswered questions. The Dutch Zutphen Study [37] showed that fruit intake, thought to be the main source of antioxidants, was inversely related to the subsequent development of chronic non-specific lung disease. In contrast, the Nurses' Health Study [21] showed no relationship between dietary vitamin C intake and subsequent asthma incidence. Nevertheless, the highest quintile of dietary vitamin E intake was protective for incident asthma. Shaheen et al. [34] studied 607 prevalent asthmatic patients and 864 controls in South London, UK, and after controlling for confounders and energy intake found that apple and red wine consumption and intake of selenium were protective. However, in another study on 580 school children, a low, and not a high, selenium intake was found to be protective in those who had asthma [35]. Yet, several other studies showed a low blood level selenium level in asthma [38].

Role of antioxidant intake in childhood asthma and atopy

The role of food intake in the development and persistence of *pediatric* asthma and allergy is even more controversial. In children, a low antioxidant level may lead to a higher susceptibility to the initial exposure of allergens such as mite antigens. The International Study of Asthma and Allergies in Childhood (ISAAC) [9] compared the prevalence rate of pediatric asthma and atopic diseases in approximately 720,000 children from 56 countries and found that the distribution of childhood asthma varied widely with the USA being one of the top 10 countries of asthmatic children. A recent ecological analysis of ISAAC phase I data for 13–14 year old children (463,800 children, 1994/95) and based on data from 1995 Food and Agriculture Organization of the United Nations for 53 countries showed a consistent pattern of decreases in symptoms of wheeze, allergic rhino-conjunctivitis and atopic eczema, associated with an increased per capita consumption of calories from cereal and rice, protein from cereals and nuts, starch, as well as vegetables and vegetable nutrients [20]. Despite known limitations of the ecological studied, this finding is consistent with many other epidemiological studies pertaining to a possible role for diet in asthma. Table 3 summarizes findings from some of relevant epidemiological studies conducted in both children and adults pertaining the possible role of dietary antioxidants in asthma [19–22, 28–35,39–43].

Limitations of the conducted epidemiological studies

Taken together, such studies as listed in Table 3 highlight several important questions that remain unanswered. One of the major limitations of almost all conducted epidemiological studies is that the food intake pattern is studied in "prevalent" asthmatic patients. Hence, the examined associations may not represent a cause–effect relationship. Whereas some of the studies in Table 3 employed case-control analyses, these analyses are performed on cross-sectional data. The outcome of interest, asthma, was present at the time the data were collected, and therefore an assessment of disease status and exposure were at a single point in time, in which case it is not possible to determine whether the exposure preceded or resulted from the disease. The possible impact of the chronic disease on food intake and dietary habit in prevalent patients is not unlikely, since Maffeis et al. [44] found that pre-pubertal males with mild to moderate asthma had a higher metabolic activity per unit fat free mass than non-asthmatic males, and that this increased requirement was apparently well compensated by an increased energy intake. Hence, an optimal epidemiological study should examine the food intake pattern *prior to* the development of asthma. Moreover, with the exception of a recently started clinical trial [41], almost none of the studies were conducted in children younger than 6 years of age, which is the age period where over 80% of asthmatic children have their *first* asthma or allergic manifestation. Therefore, studies on "incident" asthmatic children, 2–6 years, with direct dietary interview and a robust study design are needed.

A proposed epidemiological study: incidence density case-control design

Epidemiological studies should be based on this hypothesis: an inadequate intake of antioxidants in children 2–6 years of age may interact with genetic and environmental risk factors of atopy and asthma and lead to the development and persistence of asthma, associated with other atopic conditions such as hay fever and eczema; the severity and the course of asthma and atopy in these children correlate with the type and degree of dietary antioxidant deficiency (Fig. 3).

We propose an observational study with a matched incidence-density case-control design as its backbone along with cross-sectional and cohort

Table 3 Summary of relevant epidemiological studies concerning the possible role of dietary antioxidants in atopy and asthma [19–22,28–35,39–43].

Authors (publication year)	Study design (sample size)	Subjects (age in years)	Findings (dietary assessment tool)
Schwartz et al. (1990) *NHANES II* [21]	Cross-sectional (9074)	Adults (>30)	Vitamin C intake was protective against wheezing and bronchitis (24-h diet recall)
Shaw et al. (1994) [35]	Cross-sectional (580 → 21% asthma)	Children (8–13)	Low selenium intake was protective
Troisi et al. (1995) [33] *Nurses Health Study*	Cohort (77,866)	Adult females (34–68)	Highest quintile of vitamin E intake was protective for incident asthma
Britton et al. (1995) [29]	Cross-sectional (2633)	Adults (18–70)	High intake of vitamin C and E were protective in functional lung measurements
Cook (1997) [31]	Cross-sectional (2650)	Children (8–11)	Fresh fruit intake was beneficial for lung function. No association with plasma vitamin C found (FFQ)
Soutar et al. (1997) [22]	Case-control (52 vs. 38)	Mixed (16 ± 35)	In atopic persons, low intake of zinc, vitamin C, and manganese led to respiratory symptoms (FFQ)
Fluge et al. (1998) [39]	Cross-sectional (3440)	Adults (20–44)	Fish consumption was NOT a significant predictor of most respiratory symptoms (FFQ)
Bonder et al. (1999) [28]	Nested case-control (94 vs. 203)	Adult (39–45)	Higher vitamin E intake and vitamin C and E blood level were protective in late-onset asthmatics (FFQ)
Forastiere et al. (2000) [30]	Cross-sectional (18,737)	Children (6–7)	Fruits rich in vitamin C, even at a low level of intake, may reduce wheezing in childhood
Hijazi et al. (2000) [32]	Case-control (114 vs. 202)	Children (12 ± 1)	Higher intakes of vitamin E, magnesium and sodium were protective
Picado et al. (2001) [19]	Case-control (118 vs. 121)	Adults (16–74)	No evidence of any association was found (FFQ)
Huang et al. (2001) [40]	Cross-sectional (1166 → 4% asthma)	Adolescents (13–17)	Intake of liver, deep-fried foods and butcher's meat was associated with asthma. No protective effect (FFQ)
Shaheen et al. (2001) [34]	Case-control (697 vs. 864)	Adult (15–60)	High selenium, apple, red wine intake were protective (FFQ)
Takemura et al. (2002) [41]	Case-control (1673 vs. 22,109)	Children (6–15)	Paradoxical finding of increased fish intake in asthmatic children
Ellwood et al. (2002) [20]	Ecological analysis of ISAAC study (463,801 children)	Children (13–14)	Decrease in wheezing and atopic symptoms with increased per capita consumption of cereals, rice and vegetables in 53 countries
Gilliland et al. (2002) [42]	Cross-sectional (2566)	Children (11–19)	Low magnesium and potassium intake were associated with lower lung volumes and flows (FFQ)
Mihrshahi et al.[a] (2001) [43]	Randomized trial (616 births targeted)	Infants (0–5)	A diet supplemented with ω-3-fatty acid is tested in 616 infants with family risk of asthma. Results pending

[a] The recently started study by Mihrshahi et al. [43] is a randomized clinical trial, and not an epidemiological study, but it is listed here due to its potential importance and as the only study on asthmatic children younger than 6 years of age.

components (Fig. 4). In order to examine the hypothesis that an inadequate intake of antioxidants is associated with de novo development of bronchial asthma in children, the quantity and quality of food antioxidants should be studied in a group of (several hundred) children, aged 2—6 years. The study subjects are among those preschool children who are recently diagnosed with bronchial asthma. They will be evaluated by means an interview with their parents based on a food frequency questionnaire (FFQ) designed for this age group. The severity of pulmonary disease and atopy will be assessed by an asthma and allergy questionnaire and review of medical records. The data will be compared to that in the same number of non-asthmatic, non-atopic controls with the same age, gender, ethnicity, study center and recruitment time. Cases and controls can be selected in the emergency room or urgent care centers affiliated to large county hospitals serving inner-city populations, where these centers serve as the main source of medical care for the indigent population with a large number of minority children. The existence of hay fever, atopic dermatitis, and other relevant allergic comobidities will be determined in the asthmatic children via a designated questionnaire as well as medical record evaluation and interview with the physicians. The food intake characteristics of different subgroups of asthmatic patients with different allergic comorbidities will be compared to each other.

In order to examine the hypothesis that the amount or type of antioxidant deficiency in the ingested food correlates with the degree of the severity of asthma and its course over time, the severity and frequency of asthmatic episodes can subsequently be assessed after a 12- to 24-month interval following the first interview by means of an asthma severity questionnaire in most asthmatic children who were recruited for the study, and the association between the amount of antioxidants as obtained by the first FFQ and the severity and frequency of asthma episodes will be evaluated in these children. A second dietary assessment can be obtained 12—24 months after the first one in asthmatic children. The possible impact of changes in quality and quantity of the ingested antioxidants in the improvement or deterioration of asthma and

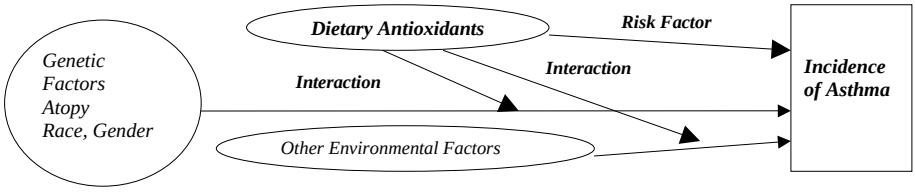

Figure 3 Schematic representation of the hypothesis to be studied.

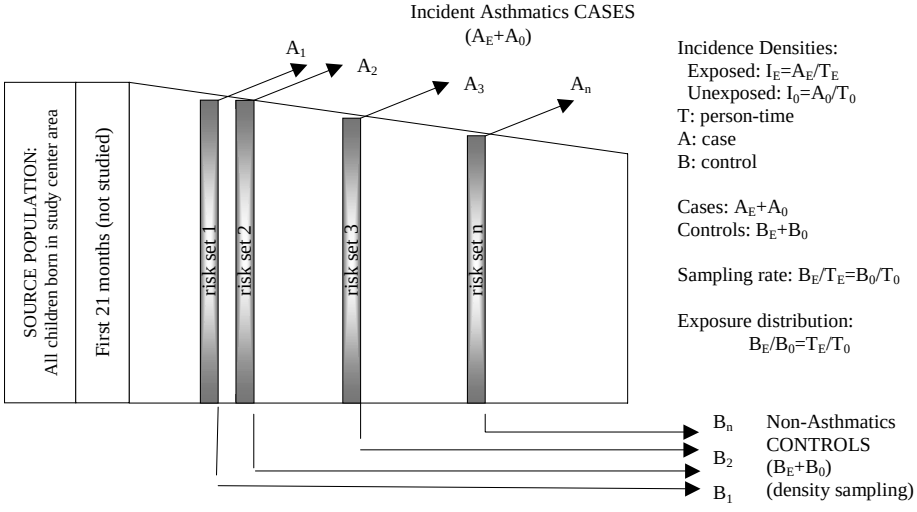

Figure 4 Schematic representation of the "incidence density case-control design" and its analogies to a hypothetical nested case-control study. If the sampling rates for antioxidant deficient (B_E/T_E) and normal nourished children (B_0/T_0) are equal, then the distribution of antioxidant deficiency among controls represent the antioxidant deficiency distribution among the source population ($B_E/B_0 = T_E/T_0$).

atopy will be examined (Fig. 3). This study can also examine a number of other pertinent questions. For example, the impact of other covariates such as family history of asthma, socio-economic status and maternal smoking on the development and persistence of asthma can be examined as well.

Only the newly diagnosed (incident) asthmatic children up to 6 years are proposed to be studied, so that the possible influence of the long-standing (prevalent) asthma on food intake pattern can be avoided and since over 80% of asthmatic children have their first asthma manifestation during their preschool years. Moreover, children with the first diagnosis of asthma prior to 21 months will be excluded, since wheezing episodes in the first 2 years of life may be more often related to infectious or congenital disorders, or even if a child has a true asthma, it may more likely be related to prenatal or other non-nutritional factors. The 12- to 24-month follow-up period serves to assess the severity and frequency of the prevalent disease in the incident patients.

Significance, strengths and unique aspects of the proposed study

Undoubtedly discovering modifiable risk factors of a chronic disease that involves 15 million Americans, including over 5 million children, and consumes almost $6 billion annually in the US is a needed endeavor. The prevalence of pediatric asthma has risen sharply over the past four decades, with the sharpest increases among children younger than 6 years and in urban, predominantly minority, populations [1—5]. Genetic changes are slow and cannot explain the striking increases in asthma and atopy [2]. Although recent epidemiological studies have implicated diet as an important risk factor for the rise in asthma and atopy, many of these studies are not well designed and their findings have many inconsistencies.

The study population we propose includes potentially many African—American and other minority children, in whom the sharpest rise in asthma has been observed. The risk-set sampling is quite feasible, and the required logistics can be arranged easily. There is a wide range of social inequality across population who come to inner-city County hospital based urgent care and emergency rooms. This will increase the chance of detecting associations between dietary antioxidant and asthma, as intake of fruit and vegetables, antioxidant vitamins and selenium rich foods such as fish and whole meal bread vary with income [21,31].

Why not a clinical trial?

Unlike "randomized clinical trials" (RCT), in epidemiological studies control for confounders is limited to those that are recognized and measured, while adjustment for unknown factors is not possible [45]. However, in contrast to RCTs that are very costly (at least several million dollars a year), require excessive expertise and manpower, and can test only one or two main hypotheses, our proposed observational study is by far less costly, can be managed optimally despite limited resources, and can test several already-defined and numerous yet-to-develop hypotheses simultaneously [46]. Furthermore, ethical considerations and social constraints may considerably handicap the implementation of an optimal RCT especially among indigent and minority children younger than 6 years in urban areas, who are at increased risk of atopy and asthma and hence the target of our proposed study.

Why a case-control study with risk set sampling?

We advocate a case-control design despite its known inherent limitations such as a tendency toward selection and information bias. A birth cohort in a designated geographic area would probably yield more accurate information pertaining to the distribution pattern of dietary intake and its risk period. However, a large cohort would redundantly include many non-asthmatic, non-atopic children, would be costly and lengthy, and would involve excessive logistics. Unlike studies performed on some European populations with distinct socioeconomic background [46], the target study population in the proposed study is the US inner-city children mostly with indigent and undereducated parents. Successful cohort subject retention and compliance with longitudinal or periodic assessments would be less likely in such study populations, especially if questionnaires are self-administered and without the interviewer's oversight. Our proposed case-control design is efficient, can be performed in a relatively short period of time, and is less expensive, while the information acquired is comprehensive and the process is closely supervised.

A cumulative incidence case-control study would be done within a shorter period of time, since it did not require ascertainment of incident cases over time. In a cumulative incidence design, however, temporal sequence is difficult to establish, the design is subject more to detection and

survival bias, rare disease and short risk period assumptions and a hypothetically fixed cohort are required, and it is less suitable for chronic disease studies since short risk periods are assumed [47—49]. In the incidence density sampling (Fig. 4) the population can be dynamic, as it is with our reference population of preschool children in the specified geographic areas, unrestricted risk periods such as exposure to antioxidant deficient food are acceptable, and the constancy of the exposure is not required [48].

Another possible limitation is that the association between matching variables and asthma cannot be assessed, while it is known that race/ethnicity (via genetic factors) and place of residence (via environmental and air pollution related factors) have indeed significant bearing on allergy and asthma. Since the independent effect of matching factors on asthma cannot be estimated, as it has been set to null by design, the additive interaction between matching variables and asthma cannot be studied. Moreover, matching on race and study center may increase the potential risk of controls not representing the desired reference population, and hence the observed dietary variations in controls may not represent those in the general population [50]. "Overmatching" and subsequent information loss may ensue if a matching factor is associated with the dietary habit but is not an independent risk factor for asthma [50,51]. However, our proposed matching increases the internal comparability, efficiency and statistical power, since the matching factors, i.e. race and age, are strong confounders and are related to both dietary habits and prevalence of asthma [48,51]. Furthermore, the matched odds ratio is a consistent estimator of incidence density ratio (IDR), with no assumption of the stability of the proportion exposed [48,51]. Matching on time mitigates or even removes its possible bias as a confounder on IDR; hence, no assumption for the stability of asthma incidence in the source population is required [48]. Over-matching is not a concern since the proposed matching factors are all risk factors for asthma. Finally, multiplicative interactions can be studied between matching factors and other confounders.

Is food frequency questionnaire an appropriate tool?

FFQs have been used in major epidemiological studies examining the relation between diet and disease such as Nurses' Health Study [33], in observational studies to compare dietary intake between groups [52], and in interventional studies to assess the composition of total diet and dietary change [53]. In a recently published report of the Food and Nutrition Board of the Institute of Medicine [27], it was acknowledged that FFQ based data were seldom accurate enough to use to assess the adequacy of dietary intakes of either individuals or small groups due to several limitations [27]. However, the same report has also underscored potential limitations of other food intake assessment technologies such as food record or diaries, since in all likelihood, an individual's observed intake during one 7-day period would differ from observed intake in another 7-day period, and both 7-day observed intakes would differ from true usual intake [54].

Another concern is the high degree of collinearity among nutritional components. For instance, vitamin C rich foods are also sources of other components that may be responsible for apparent protective effect of vitamin C on asthma [55]. Notwithstanding the validity of such concerns, the issue of collinearity among dietary components is not specific to this study but an inherent limitation of the field of nutritional epidemiology. Hence the inferences that will be drawn should be all within this context. However, Pearson correlation coefficients will provide a crude measure of the collinearity among antioxidants and other food components, and Eigenvalues and canonic coefficients can be utilized to reveal the degree of collinearity. To minimize the problem of multicollinearity and to allow for an evaluation of the distinct contribution of each antioxidant, residual variables can be defined from linear regression analysis and the residual variable models can be mathematically verified as described recently by Sternfelf et al. [56].

Future steps

Epidemiological studies with robust design and novel approaches in the field of dietary antioxidant and childhood asthma can potentially lead to the generation of many new hypotheses with clinical and public health implications. If significant associations between dietary antioxidants and incidence of asthma in early childhood are found, interventional studies based on direct measurement of blood or bronchial concentrations of antioxidants can then be considered. The impact of atopy can be studied in a more objective way such as by use of measuring serum IgE or skin tests. The emergence of more patient-friendly blood and skin tests [57] in the future may facilitate the imple-

mentation of such interventions in preschool children. Clinical trials can be designed based on one or two single dietary antioxidants that will be shown to have the strongest associations in epidemiological studies. On the other hand, if epidemiological studies fail to show the expected associations, or if they demonstrate contradictory results, more observational studies in different age and race groups are required before interventional studies or clinical trials are considered.

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