FACTORS AFFECTING RESPIRATORY SYNCYTIAL VIRUS POSITIVE WHEEZING ILLNESSES IN INFANTS

by

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A Research Paper

Submitted in Partial Fulfillment of the
Requirements for the
Master of Science Degree
With a Major in

Human Nutrition

Approved: 6 Semester Credits

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April, 2002

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ABSTRACT

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Factors Affecting Respiratory Syncytial Virus Positive Wheezing Illnesses in Infants
(Title)

Human Nutrition Dr. Esther Fahm April 2002 86 pgs.
(Graduate Major) (Research Advisor) (Month/Year) (No. of Pages)

American Psychological Association
(Name of Manual Style Used)

Objective

Respiratory Syncytial Virus or RSV is the most common cause of lower respiratory tract infections in infants and young children. Often, the more severe the episode of RSV, the more likely wheezing will be present with the illness. Infants who experience wheezing with a viral infection may develop asthma in the future. The purpose of this study, therefore, is to determine if there is a difference in the incidence of RSV positive wheezing illnesses during infancy among infants who differ in length of exclusive breast or formula feeding. Extraneous variables such as gender of the infant, maternal history of allergy and asthma, smoking in the infant's environment, and ethnicity of the infant are also thought to play a role in the development of respiratory illnesses. These variables will be examined in addition to breastfeeding to determine if they have an effect on the incidence of RSV positive wheezing illnesses, and counteract, conceal, or augment any protective effects of breastfeeding.

Subjects

The subjects for this project included the 287 infants participating in the Childhood Origins of Asthma (COAST) project, a prospective, longitudinal study at the University of Wisconsin Asthma and Allergy Clinical Research Unit in Madison, Wisconsin being conducted to elucidate possible causes for asthma.

Procedures

The Statistical Package for Social Sciences (SPSS) version 10.0 was utilized for data analysis. The Chi-Square procedure was employed to determine if length of exclusive breastfeeding is independent of gender, ethnicity, smoke exposure, and maternal history of allergy and/or asthma. Binary logistic regression analysis was applied to determine if a relationship exists among RSV and RSV positive wheezing illnesses and length of exclusive breastfeeding, gender of the infant, ethnicity of the infant, smoke exposure, and maternal history of allergy and/or asthma. Finally, multivariate logistic regression analysis was carried out to determine if the incidence of RSV and RSV positive wheezing illnesses were affected when examining all of the variables in combination with each other.

Results

Neither formula feeding nor length of exclusive breastfeeding was associated with gender, ethnicity, or maternal history of allergy and/or asthma. Infants exposed to smoke were significantly less likely, however, to have been breastfed or were breastfed for shorter time periods ($p = 0.043$). With exclusive breastfeeding greater than or equal to six months serving as the reference category, no significant relationship was found between presence of RSV and never breastfeeding or exclusive breastfeeding less than six months. No

significant connection was revealed between RSV positive wheezing illnesses and never breastfeeding or exclusive breastfeeding less than six months. Infants with a maternal history of both allergy and asthma were significantly more likely to have RSV positive wheezing illnesses when examined alone ($p = 0.036$) and while controlling for feeding history, gender, ethnicity, and smoke exposure ($p = 0.032$).

Conclusions

As established by the results, this study demonstrates that breastfeeding, even for prolonged periods of time, does not seem to protect against wheezing illnesses in children with a maternal history of allergy and/or asthma. However, there is no reason to discourage families from this method of feeding. The general benefits of breastfeeding for both infants and mothers are simply too great to ignore.

Acknowledgements

I deeply appreciate Dr. Robert Lemanske sharing both his expertise in the area of pediatric respiratory illnesses as well as the data collected for the COAST study. Without his help, generosity, wisdom, and patience this study would not have been possible. I also greatly valued the opportunity of having Dr. Esther Fahm serve as my research advisor. Her experience, knowledge, and guidance were invaluable. Additionally, I am pleased that Dr. Janice Coker and Dr. Ann Parsons served as my committee members and offered their support, insight, and encouragement. I would also like to thank Ron Gangnon for his assistance with the statistical analyses. He took time out of his day to meet with me on a regular basis and explain the statistical procedures and results to me. Without his advice and supervision, this study would have never come to a close. Finally, I would like to thank the entire COAST research team for their help.

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CHAPTER 1

Definition of Terms

Apgar score-a measure of an infant's color, heart beat, respiration, response to stimuli, and muscle tone five minutes after birth in order to determine his or her health status. A score of seven to ten is considered normal.

Atopy-refers to a variety of disorders such as asthma, eczema, allergic rhinitis, and food allergy that is associated with an elevated level of IgE antibodies. The amount of IgE antibody that individuals make can be assessed through skin or radioallergosorbent (RAST) testing (tests to measure allergy).

Bronchiolitis-inflammation of the bronchioles, the smallest branches of the air passages in the lungs through which air flows.

Colostrum-the thin, watery fluid produced in the mother during the first few days of an infant's life to provide nourishment prior to the production of mature breast milk. It is rich in proteins, especially antibodies, and is low in carbohydrates and fats.

Cytokines-cellular messengers, some of which may play a role in asthma development.

Immunoglobulin A-a plasma protein (antibody) that is also found in both the respiratory and gastrointestinal tracts; it plays a role in immunity by acting against bacterial cells and viruses as a first line of defense.

Immunoglobulin E-a plasma protein (antibody) that serves as a marker of allergic response (the so-called "allergic antibody").

Infancy-the period from birth until 12 months of age.

Lactoferrin-protein found in breast milk that prevents bacterial growth by binding available iron.

Oligosaccharides-carbohydrates that bind harmful microorganisms in the body.

Respiratory syncytial virus or RSV-virus that attacks the mucous membranes of the upper and lower respiratory tract causing symptoms ranging from mild cold symptoms to severe respiratory distress that may result in death. The virus is the most frequent cause of wheezing illnesses in the first two years of life.

Introduction

Asthma is a chronic lung disease characterized by shortness of breath, wheezing, and inflammation leading to airway obstruction (Morgan & Martinez, 1992). As noted by Anderson, Butland, and Strachan (1994), asthma prevalence has increased in industrialized nations over the past several decades. According to the American Lung Association (2001), approximately 4.8 million children are affected by asthma with the highest number of new cases diagnosed in children less than five years of age. Furthermore, the American Lung Association (2001) estimates that the cost of asthma totals approximately 3.2 billion dollars, and that 10.1 million school days are missed each year due to this disease; thus, indirectly raising the cost of asthma even further. Although there are numerous environmental risk factors for asthma, the disease itself may be manifested in infancy.

Respiratory Syncytial Virus or RSV is the most common cause of lower respiratory tract infections in infants and young children (Glezen, Taber, Frank, & Kasel, 1986). According to the American Lung Association (2001), RSV results in 90,000 hospitalizations and 4,500 deaths a year in this population. Additionally, roughly 60% of children will have an RSV positive lower respiratory tract infection during infancy, most likely of a more severe nature than at other times in the life span (Glezen et al., 1986; Openshaw, 1995). RSV can be associated with coughing, wheezing, bluish skin, shortness of breath, nasal

flaring, and rapid breathing. The symptoms appear similar in nature to childhood and adult asthma (Landau, 1994). Often, the more severe the episode of RSV, the more likely wheezing will be present with the illness (Morgan & Martinez, 1992). Therefore, children who experience wheezing with a viral infection before the age of three years are thought to be more likely to develop asthma in the future (Martinez et al., 1995).

The timing of this illness is important for many reasons. First of all, as found from a study using animal models, a respiratory viral infection in the early stages of life may produce long lasting, adverse effects in the respiratory tract (Strachan, 1992). For example, one side effect is an increased number of bronchiolar mast cells (Castleman, Sorkness, Lemanske, & McAllister, 1990). In turn, these bronchiolar mast cells produce histamine, a substance that plays a role in the inflammatory process. These early viral respiratory infections also result in airway hyperresponsiveness or spasms in the respiratory tract (Castleman et al., 1990). Since infancy is an important time for lung development, these damaging results are not surprising. Moreover, infancy is also a time for bolstering the otherwise immature immune system. Therefore, if an infant contracts a respiratory virus while both the respiratory and immune systems are still in the process of developing, permanent damage, such as narrowed, swollen, spasmodic airways causing labored breathing and thick mucous formation in the lungs, may result. What if there was a way, however, to reduce the number of wheezing episodes

associated with or severity of RSV during infancy? Would this lead to a decreased risk of childhood asthma for susceptible individuals?

Over the years, much research has been done regarding the causes of respiratory tract infections during infancy. One area in particular that has received a great deal of attention is the role of breastfeeding in relation to respiratory illnesses. Strong evidence exists that breastfeeding reduces incidence of respiratory illnesses during infancy in developing countries or communities (Brown, Black, Lopez de Romana, & Creed de Kanashiro, 1989; Cesar, Victora, Barros, Santos, & Flores, 1999; Forman, Graubard, Hoffman, Beren, Harley, & Bennett, 1984; Lopez-Alarcon, Villalpando, & Fajardo 1997; Victora, Smith, Barros, Vaughn, & Fuchs, 1989). As a case in point, Cesar et al. (1999) observed that infants from an urban area of Brazil who did not receive breast milk had a 17 times greater risk of being admitted to the hospital for pneumonia than infants who were exclusively breastfed. The effects were especially prominent during the first three months of life. In a study carried out in a slum neighborhood near Mexico City, Lopez-Alarcon et al. (1997) discovered that infants who were exclusively breastfed had less acute respiratory infections and acute respiratory infections of shorter duration until four months of age. As a final point, Cunningham, Jelliffe, and Jelliffe (1991) reported that infants from urban areas of developing nations experience a fourfold increase in deaths from lower respiratory tract infections when they were not breastfed.

The protective effects of breastfeeding in relation to respiratory illnesses in infants from industrialized societies are less clear. Frank et al. (1982) conducted a study in the U.S. and found that breastfeeding did not reduce the occurrence of upper and lower viral respiratory tract infections in the first year of life. Many other studies in developed areas have initially found an association between breastfeeding and reduced incidence of respiratory tract illnesses. After controlling for other factors in the statistical analysis such as maternal smoking, socioeconomic status, and infant birth weight, however, these other factors have been found to play more of a role in respiratory illnesses than breastfeeding (Fergusson, Horwood, Shannon, & Taylor, 1981; Pullan et al., 1980; Taylor, Golding, Wadsworth, & Butler, 1982). Furthermore, in an analysis conducted by Bauchner, Leventhal, and Shapiro (1986) to examine the quality of breastfeeding research based on certain standards, it was found that most early studies supporting breastfeeding did not meet the standards for validity and generalizability. Kovar, Serdula, Marks, and Fraser (1984) also came up with conflicting information about the protective properties of breastfeeding in relation to respiratory illnesses in an early literature review. They found that many of the studies conducted up until that point were poorly designed and failed to account for the impact of confounding variables, length of breastfeeding, and exclusivity of breastfeeding.

More recently, however, many of the studies conducted in developed countries on breastfeeding and infectious disease have followed some of the more stringent standards set forth by Bauchner et al. (1986) and Kramer (1988) that include the following: 1). Defining outcomes (i.e. respiratory tract infections) more clearly, 2). Controlling for extraneous variables such as sex of the child, smoking, ethnicity, socioeconomic status, and parental history of allergy and asthma, 3). Ensuring the length of time during which breastfeeding is studied is of adequate duration, 4). Examining breastfeeding in terms of exclusivity, and 5). Avoiding detection bias by conducting prospective analysis of illness. After implementing the standards into the research protocol, several studies have then found an inverse relationship between duration of breastfeeding and the incidence of respiratory illnesses, particularly in the early months of life (Baker, Taylor, & Henderson,1998; Beaudry, Dufor, & Marcoux, 1995; Cunningham, 1979; Cushing et al. 1998; Howie, Forsyth, Ogston, Clark, & du V Florey, 1990; Nafstad, Jaakkola, Hagen, Botten, & Konegerud, 1996; Pisacane, et al., 1994; Raisler, Alexander, & O'Campo, 1999; Wright et al., 1989; Wright, Bauer, Naylor, Sutcliffe, & Clark, 1998). Other studies have even found the benefits to extend into childhood (Burr et al., 1993; Dell & To, 2001; Oddy et al., 1999; Rylander, Pershagen, Eriksson, & Nordvall, 1993; Saarinen, & Kajosaari, 1995; Wright, Holberg, Taussig, &Martinez, 1995; Wilson et al., 1998; Wright, Holberg, Taussig, & Martinez, 2001b).

Breastfeeding could potentially reduce the incidence or severity of respiratory illnesses for many reasons. First of all, colostrum (or "first" milk) is thought to contain properties that reduce the severity of RSV (Downham, Scott, Sims, Webb, & Gardner, 1976). Secondly, breast milk is believed to contain an array of factors to enhance immunity (Pabst, 1997). Finally, breast milk may even aid in the development of the immature lungs (Martinez, Morgan, Wright, & Taussig, 1988).

In conclusion, numerous discrepancies exist among studies examining infant feeding practices and respiratory illnesses. A great deal of current research points to a positive association between breastfeeding and reduced incidence and severity of respiratory illnesses, particularly in the early months of life. Research also shows that breast milk may contain antibodies as well as other compounds that enhance immune function. However, many other studies have found that breastfeeding is simply not as protective against respiratory illnesses in well-developed areas due to variables such as environmental and social factors. Therefore, the controversy remains.

Statement of the Problem

Currently, a prospective, longitudinal study is underway at the University of Wisconsin Asthma and Allergy Clinical Research Unit located in Madison, Wisconsin. The Childhood Origins of Asthma [COAST] study is following a group of 287 infants from the Madison area community with a family history of allergy and/or asthma to elucidate possible causes for the disease. The principal investigators of this study postulate that asthma will develop if a child has the genetic predisposition for the disease and is exposed to a particular environmental factor at a certain point in time during infancy. The environmental factor in question is RSV. Therefore, if the COAST hypothesis is accepted, an infant who has the genetic potential for asthma and experiences an RSV positive wheezing illness at a crucial point in time during infancy may develop recurrent wheezing or asthma later in life.

The purpose of this subsidiary study, therefore, is to determine if there is a difference in the incidence of RSV positive wheezing illnesses during the first year of life among the infants participating in the COAST study who differ in length of exclusive breast or formula feeding. Extraneous variables such as gender of the infant, maternal history of allergy and asthma, smoking in the infant's environment, and ethnicity of the infant are also thought to play a role in the development of respiratory illnesses. These variables will be examined in addition to breastfeeding to determine if they have an effect on the incidence of RSV

positive wheezing illnesses, and negate, mask, or amplify any protective effects of breastfeeding.

The research hypothesis for this study is that a significant relationship exists in the incidence of RSV positive wheezing illnesses among a group of 287 infants from the Madison, Wisconsin area community who differ in terms of feeding mode. It remains unclear whether or not the relationship will remain significant after controlling for sex of the infant, ethnicity of the infant, smoking in the infant's environment, and maternal history of allergy and asthma.

The null hypothesis for this study is that there is no statistically significant relationship in the incidence of RSV positive wheezing illnesses during infancy for a group of infants who differ in mode of feeding, even while controlling for extraneous variables such as gender, maternal history of allergy and/or asthma, smoke exposure, and ethnicity.

If exclusive breastfeeding is found to reduce the incidence of RSV positive wheezing illnesses, it will provide evidence that this method of feeding may be associated with decreased severity of these infections, since wheezing is associated with lower respiratory tract infections of greater seriousness. Therefore, the infant's respiratory system will have time to develop properly so that adverse, long-term complications such as asthma can be reduced. Acceptance of the hypothesis will also offer further support to encourage exclusive breastfeeding for at least the first six months of life in addition to supplemental

breastfeeding alongside cereals, fruits, vegetables, and meats until one year of age as advised by the American Academy of Pediatrics (1997) and the American Dietetic Association (Dobson & Murtaugh, 2001). It will also help meet the goals set forth by the US Department of Health and Human Services in Healthy People 2010 that include increasing the rate of initial breastfeeding to 75%, increasing the rate of breastfeeding at 6 months to 50%, and increasing the rate of breastfeeding at 12 months to 25% (http://www.health.gov/healthypeople). Currently, only 64% of US women breastfeed at birth, only 29% continue to breastfeed until six months post partum, and only 16% continue to breastfeed at 12 months post partum (Abbott Laboratories, 2001).

CHAPTER 2

Review of Literature

Breastfeeding and its relation to occurrence of disease in both infancy and childhood is a controversial topic. Several studies have found a positive association between breastfeeding and a reduced occurrence of many acute and chronic illnesses, while other studies have appeared in the literature and refuted those findings. In this review, the functional properties of breast milk that may assist in promoting health are outlined. Additionally, a description of the studies that have found varying conclusions when examining the role of breastfeeding in regard to disease prevention during different stages of the life cycle is included, along with speculations as to why some studies are more convincing than others. A discussion on the importance of examining breastfeeding from the angle of exclusivity is also provided. Finally, a debate over the impact that potential confounding variables may have in the relationship between breastfeeding and respiratory illnesses is included. These extraneous variables include sex of the infant, ethnicity of the infant, smoking in the infant's environment, and maternal history of allergy and/or asthma.

The Benefits of Breast Milk

It is a well known fact that breastfeeding affords numerous benefits to both the mother and child. Some of the more commonly known benefits of breastfeeding include strengthening of the mother/child bond, providing the infant

with the perfect composition of nutrients to meet his or her changing needs during growth and development, assisting in development of cognitive function, aiding in digestion, and decreasing costs associated with infant feeding. Additionally, breastfeeding reduces an infant's contact with harmful pathogens in the environment (Heinig, 2001). For instance, an infant who is breastfeeding may spend more time with his or her mother and less time in the presence of strangers where exposure to illnesses is increased. Also, an infant who is breastfeeding is less likely to come into contact with contaminated water or food, a situation that is of concern particularly in developing countries as it can lead to severe diarrhea, emesis, dehydration, and death.

Other than these well-known benefits of breastfeeding, there are many compounds found in breast milk that play important and somewhat complex roles in human development, disease prevention, and illness reduction. Although infant formulas that are cow's milk or soy based are designed to mimic the composition of breast milk as closely as possible, they do not contain factors that strengthen the infant's immune system. For instance, "first milk" or colostrum, as documented by Pabst (1997), contains beneficial components, such as neutrophils and mononuclear cells. The mononuclear cells assist in the development of the immune system by inducing IgA production, and the neutrophils help reduce inflammation. Moreover, Lawrence (2001) and Hanson (1998) both noted that the secretory IgA, that increases in breast milk as maternal exposure to certain

pathogens in the environment increases, acts against respiratory viruses and bacteria that the infant has come into contact with to prevent them from attaching to mucous membranes. Downham et al. (1976) also believed that the secretory IgA found in the colostrum may act specifically against RSV and reduce the severity of the illness. Finally, Sarfati, Vanderbeeken, Rubio-Trujillo, Duncan, and Delespesse (1986) pointed out that colostrum contains components that control IgE, an antibody that promotes allergic reaction and inflammation.

As emphasized by Peat, Allen, and Oddy (1999) and Pabst (1997), breast milk also contains oligosaccharides that inhibit pathogens from affixing to the walls of the respiratory tract, lipids that impart an antibacterial action, and growth factors that enable the immature immune system to develop. Martinez et al. (1988) postulated that breast milk plays a role in enabling lung tissue to mature as well. Breast milk may also contain particles that regulate the immune response by decreasing inflammation and the risk of an allergic reaction, two factors of great importance in the development of asthma (Heinig, 2001). Such a protective factor found in human milk is lactoferrin. This compound may provide antibacterial, antiviral, and anti-inflammatory protection through control of cytokine production (Hamosh, 2001). Prolactin and nucleotides that enhance immune function have also been discovered in human milk (Hamosh, 2001). In fact, prolactin's role in tissue development may be the reason why the thymus, an organ that plays a role in immunity, is found to be larger in breastfed infants (Pabst, 1997).

The exact ways in which all or some of these factors may contribute to a reduced incidence of respiratory illnesses in each individual is not entirely clear. However, the knowledge surrounding the composition of breast milk helps provide support to the belief that breast milk, unlike formula, has the potential to confer numerous beneficial properties to infants to enhance their health status and prevent or reduce acute and chronic illnesses (Oddy, W. H., 2001).

Breastfeeding and respiratory illnesses during infancy

When taking into account the current knowledge surrounding the makeup of breast milk, it is easy to realize why so many studies have been conducted on breastfeeding and illnesses. It seems logical to assume that it would offer protection against a host of diseases. However, the answers about the potential benefits are not always lucid making it difficult to make the aforementioned assumption. This is due to the fact that respiratory infections such as RSV positive wheezing illnesses are associated with numerous risk factors that may be both independent of and related to breastfeeding. Holberg et al. (1991) proposed risk factors such as sex of the infant, overcrowding, ethnicity, smoke exposure, socioeconomic status, birth weight, and birth month. In fact, when Holberg et al. (1991) looked at the relationship among the duration and exclusivity of formula feeding and breastfeeding for less than one month, one to three months, four to six months, and greater than six months, and RSV associated lower respiratory tract infections during the first year of life, they discovered that although breastfeeding

was protective in and of itself, the protective effects of this feeding method on reducing incidence of illness were more profound among infants of lower socioeconomic status. On a similar note, Rubin et al. (1990) studied a group of infants living in Coppenhagen, Denmark who came from small, middle class families and were born to older mothers. They found the number of gastrointestinal, upper respiratory, and lower respiratory illnesses occurring each month to be similar in infants receiving either 100% breast milk or a greater amount of breast milk than formula compared to those infants receiving equal amounts of formula and breast milk, more formula than breast milk, or formula only. Once again, any defensive assets of breast milk may have been diluted in the midst of a middle to upper class environment.

Porro, Indinnimeo, Antognoni, Midulla, and Criscione (1993) examined both the severity of wheezing illnesses and the onset of wheezing illnesses. They reported that exclusive breastfeeding delayed the onset and reduced the severity of wheezing, but that other factors such as family history of atopy and smoking in the household played a larger role in the development of wheezing. Both Fergusson et al. (1981) and Taylor at al. (1982) initially observed a significant decrease in respiratory illnesses among breastfed infants but observed that the significance disappeared after controlling for certain environmental, social, and economic factors. Finally, in a case-control study conducted by Leventhal, Shapiro, Aten, Berg, and Egerter (1986) it was found that, in general,

breastfeeding reduced infectious illnesses such as bronchiolitis, pneumonia, gastroenteritis, and meningitis. However, after stratifying the illnesses based on severity, it was discovered that breastfeeding did not alter the severity of the illness. Thus, Leventhal et al. (1986) speculated that hospitalizations are reduced in breastfed infants most likely because of a "physician's unwillingness to separate a nursing mother and her infant and the belief that a nursing mother is more competent than a non-nursing mother and, therefore, more capable of taking care of the sick child at home" (p. 899). These results point to the notion that the benefits of breastfeeding can be masked when other factors are taken into consideration.

A growing number of studies, nonetheless, have controlled for these extraneous variables in the statistical analysis and have still found protective effects of breastfeeding against respiratory illnesses. Cushing et al. (1998) examined incidence of lower respiratory tract illnesses among a group of infants from a middle class, well-educated population born into non-smoking households in Albequerque, New Mexico. After controlling for birth order, sex, ethnicity, parental history of asthma or atopy, income, and maternal education through multivariate analysis, they found an inverse relationship between the number of lower respiratory tract illnesses and length of exclusive breastfeeding in addition to an inverse relationship between the duration of upper and lower respiratory tract illnesses combined and length of exclusive breastfeeding during the first six

months of life. In summary, they claimed this shorter period of both illnesses as well as the reduced occurrence of lower respiratory tract illnesses suggests that exclusive breastfeeding leads to reduced respiratory illness severity. In an additional study by Howie et al. (1990), a protective effect of exclusive breastfeeding compared to bottle feeding against cough and wheezing between zero to three months and 9 to 12 months was observed among a group of infants in an urban area of Scotland. They concluded that breastfeeding might play an overall role in reducing the severity of the illnesses. Finally, Pisacane et al. (1994) carried out a case-control study in Italy and revealed that breastfeeding lowers the risk of hospital admission for pneumonia and bronchiolitis during the first six months of life. In conclusion, the researchers determined that detection and selection bias were not the reasons for decreased hospital admissions as Leventhal et al. (1986) argued because breast-fed and bottle-fed infants were afforded equal chances to be classified as cases.

On top of decreasing the severity, breastfeeding has also been noted to reduce the incidence of respiratory illnesses. In a study conducted by Nafstad et al. (1996) among a highly educated upper income group in Norway, the researchers found that breastfeeding for more than six months imposed a protective effect against physician diagnosed lower respiratory tract illnesses, specifically pneumonia, bronchitis, and bronchiolitis, in the first year of life, despite the presence of maternal smoking. Beaudry et al. (1995) also studied the

effect of breastfeeding on respiratory illnesses [defined as influenza, colds, ear infections, pneumonia, bronchitis, throat infections, tonsillitis, pharyngitis, whooping cough, croup, and wheezing illnesses] among a group of infants from Canada and discovered that any amount of breastfeeding resulted in both a lower incidence and a reduced number of hospitalizations for respiratory illnesses in the first six months of life. In fact, the bottle-fed group experienced approximately 80% more respiratory infections than the breastfed group when examining feeding status without controlling for extraneous variables. Nevertheless, this protective effect persisted even when age of the infant, maternal age, smoking, and socioeconomic status were included in the statistical analysis.

In a study conducted in England by Baker et al. (1998), it was found that breastfeeding for three months or longer decreased both the prevalence and severity of wheezing during the first six months of life even after controlling for household crowding and maternal smoking. Among a group of infants participating in the Tucson Children's Respiratory Study in Arizona, Wright et al. (1989) examined breastfeeding status and number of lower respiratory tract illnesses in the first year of life and discovered that breastfed infants, regardless of the length of breastfeeding, had a reduced number of wheezing illnesses in the first four months of life. They concluded, however, that the protection did not last past the breastfeeding period. Wright et al. (1998) also examined incidence of certain respiratory illnesses and length of breastfeeding among infants born into a

Navajo Community. The study was designed in such a manner as to limit recall problems by collecting data recorded prospectively in the medical record, to limit surveillance bias by analyzing the incidence of illnesses rather than hospitalizations, and to limit detection bias. The researches found an inverse relationship between the length of breastfeeding and frequency of many illnesses, including bronchiolitis, pneumonia, and croup.

Finally, in an early study carried out by Cunningham (1979), it was determined that any amount of breastfeeding resulted in a decreased risk of certain diseases, including lower respiratory illnesses, as well as hospital admissions while controlling for parental education, maternal age, number of siblings, low birth weight, and sex. Cunningham et al. (1991) then compiled a review of the major studies dealing with breastfeeding and infant health during the 1980s and surmised that breastfeeding offers protection against lower respiratory tract infections such as wheezing, bronchiolitis, and pneumonia among infants from developed countries. Cunningham et al. (1991) also found that the benefits of breastfeeding appear to be most significant during the first six months of life. Wright, Bauer, Naylor, Sutcliffe, and Clark (1998) stated as well that "the evidence of a protective effect of breastfeeding is strongest for this period [the first year of life]" (p. 839).

Breastfeeding and respiratory illnesses during childhood

Although the majority of the evidence shows the strongest effects of breastfeeding to exist during the early months of life, other studies have shown the effects to extend into childhood. Subsequent to Dell and To's (2001) examination of data collected on children from Canada through the first two years of life, the researchers found that breastfeeding, without regard to exclusivity, for greater than nine months resulted in a decreased risk of asthma during these early years of life. Rylander et al. (1993) studied factors related to the development of wheezing bronchitis and asthma up until the age of four years and found, among other things, that breastfeeding for less than three months increased the risk of these respiratory illnesses.

Additional researchers have studied children further along in the life cycle and have reported that breastfeeding during infancy confers protection against a number of respiratory illnesses. Oddy et al. (1999) examined the relationship between length of exclusive breastfeeding and development of asthma in six year-old children in Western Australia while controlling for sex of the child, gestational age, smoking in the household, and day care. They discovered that exclusive breastfeeding for at least the first four months of life resulted in both a lower risk of asthma and atopy by age six as well as a delay in the onset of wheezing and asthma. Wilson et al. (1998) studied a group of children from Dundee, Scotland until seven years of age and concluded that children who were

exclusively breastfed for at least three and one-half months experience a decreased number of respiratory illnesses in childhood. Respiratory illnesses were defined as persistent coughing, wheezing, and breathlessness. After following a group of infants in Helsinki, Finland until 17 years of age, Saarinen and Kajosaari (1995) determined that exclusive breastfeeding, especially for six months or longer and despite a family history of atopy, afforded a significant protective effect against atopic diseases, including respiratory allergies such as allergic asthma. It is important to note, though, that although respiratory allergy includes wheezing associated with respiratory infections, the authors did not include wheezing in their definition of respiratory allergy when examining these young adults.

Regardless of the abovementioned evidence, the relationship between breastfeeding and the protective effects lasting into childhood remains controversial. While observing a group of children in South Wales with a family history of allergic disease until seven years of age, Burr et al. (1993) established that length of breastfeeding was protective against wheezing in atopic children until two years of age. Thereafter, it was only protective in non-atopic children; however, only a small percentage of the study population exclusively breastfed. In a case-control study including approximately 23,800 students enrolled in the public school system in a suburban residential area near Tokyo, Japan carried out by Takemura et al. (2001), the results revealed that breastfeeding significantly

increased the risk for asthma; yet data was collected retrospectively and information to complete the questionnaires was supplied exclusively from parental report. As part of a prospective study conducted on a group of subjects from Britain, Lewis et al. (1996) reported that breastfeeding did not result in a decreased incidence of wheezy bronchitis or asthma at the age of 16; however, asthma and wheezing were once again based on parental report.

On two occasions, Wright, Holberg, Taussig, and Martinez (2000 & 2001b) reported no protective effect between breastfeeding and incidence of asthma in childhood. In this earlier study, the researchers found no significant relationship between the length of exclusive breastfeeding and the number of cases of physician diagnosed asthma by the age of 11 years among children with non-asthmatic mothers. Among the children with asthmatic mothers, there was a significantly higher rate of asthma by 11 years of age the longer the children were exclusively breastfed as infants. More recently, Wright, Holberg, Taussig, and Martinez (2001b) noted that exclusive breastfeeding for at least four months reduced the frequency of recurrent wheezing in the first few years of life despite a maternal history of asthma or the presence of atopy in the child. Wright et al. (2001b) did go on to notice, though, that exclusive breastfeeding greater than four months increased the risk of asthma and recurrent wheezing between the ages of six and 13 years in atopic children born to asthmatic mothers. Nonetheless, as Peat and Li (1999) noted in a review about potential causes of asthma, it is not

clear if interventions, such as promoting breastfeeding, will reduce the prevalence of asthma in the long run; however, there is strong enough evidence to support the theory that a reduction in asthma occurrence in the short term is possible and any measures to possibly decrease the incidence of this disease are important while more studies are being conducted.

Exclusivity of breastfeeding

One reason for the discrepancies surrounding the protective effects of breastfeeding is because of the fact that different studies use different terms to define breastfeeding. Some studies may consider breastfeeding to include any amount of breast milk regardless of supplementation with formula. Other studies divide subjects into groups receiving only breast milk, a combination of breast milk and formula, and no breast milk. As Bauchner et al. (1986) noted, many of the problems inherent with early studies regarding breastfeeding and illness were due to the fact that breastfeeding was not well defined. For example, a study by Pullan et al. (1980) failed to show an association between breastfeeding and reduction in hospital admissions for RSV after controlling for extraneous variables. However, the study failed to provide a definition of the term breastfeeding. Additionally, Dewey et al. (1993) found no significant relationship between breastfeeding and respiratory illnesses, although they did not base breastfeeding entirely on exclusivity and studied a group primarily with mild upper respiratory illnesses instead of more severe lower respiratory tract illnesses.

Similarly, the studies by Fergusson et al. (1981) and Taylor et al. (1982) failed to show an association between breastfeeding and respiratory illnesses after controlling for socioeconomic factors, but did not classify feeding groups according to exclusivity.

Another study by Margolis et al. (1992) found that breastfeeding, when examined in conjunction with other risk factors for respiratory problems, did not result in reduced occurrence of respiratory illnesses. Then again, breastfeeding was defined as receiving any breast milk, despite the amount of formula given. The study by Rubin et al. (1990), described previously, also found no significant association between breastfeeding and illness. Yet, the researchers used mixed feeding groups when drawing conclusions.

The outcomes of previous studies could have potentially been influenced by the lack of a clear definition of breastfeeding (Kovar et al., 1984). In some of the studies in which breastfeeding has been categorized based on exclusivity, significant protective effects of breastfeeding have resulted. For example, Raisler et al. (1999) classified infants based on varying doses of breast milk that they received and found that exclusive breastfeeding was associated with a reduction in cough, wheezing, vomiting, and diarrhea during the first six months of life while minimal breastfeeding was not. The inverse relationship remained while controlling for socioeconomic conditions. When Cesar et al. (1999) examined the relation between infant feeding and hospital admission for pneumonia, an inverse

relationship was found between incidence of pneumonia and exclusivity of breastfeeding, especially during the first three months of life. In a study by Wright et al. (1998), it was determined that exclusive breastfeeding reduced incidence of bronchiolitis, pneumonia, and croup. Finally, in an extensive review by Cunningham et al (1991), it was also noted that protection from breastfeeding increased relative to the exclusivity of breastfeeding, further substantiating the necessity of defining breastfeeding based on exclusivity to optimize outcomes.

Extraneous Variables

Due to ethical issues, it is impossible to set up an experiment on infant feeding by randomly assigning the infants to various feeding groups and then drawing definitive conclusions from the study. However, by not randomly assigning infants to feeding groups, causality may not be derived from the results, and the results may be falsely negative or positive based on other socio-demographic or physical characteristics. Thus, in addition to the necessity of distinguishing between exclusive and partial breastfeeding, it has been well recognized that the way to strengthen the results of studies on infant feeding is to control for potential variables that may confound the benefits of breastfeeding in relation to respiratory illnesses and various other diseases. As noted by Takemura et al. (2001), “Many risk factors for asthma have been proposed including age, gender (male), smoking and family history of asthma” (p.115). Additionally, in a report detailing the 12 necessary standards of infant feeding and illness studies,

age ranges of the infant, ethnic origin, family history of atopic disease, and smoke exposure were listed as the largest sources of confounding variables in infant feeding studies (Kramer, 1988).

Sex of the child is considered a confounding variable due to its well-documented association with respiratory illnesses. As a matter of fact, when considering the effects of sex of the child on the outcome variable, Burr et al. (1993), Rylander et al. (1993), and Takemura et al. (2001) established that both wheezing and asthma occurred more frequently in boys than in girls. A significantly higher prevalence of atopic disorders, such as asthma, in males from birth to seven years of age has also been reported by Zeiger & Heller (1995). In addition to asthma, it has been found that boys experience lower respiratory tract infections more often than girls (Nafstad et al., 1996). Holberg et al. (1991) reported that males had significantly more RSV positive lower respiratory illnesses in the first one to three months of life than females. Their speculation in regards to this discrepancy was that "Males are likely to have smaller airways for their lung size than females." (Holberg et al., 1991, p. 1149). Thus, when lungs are still developing during the first few months of life, males may be at a disadvantage due to this structural difference and any possible benefits of breastfeeding may be masked by this difference.

On top of controlling for sex, researchers have also agreed that it is vital to control for ethnicity of the child. In a study conducted by Zeiger and Heller

(1995), the prevalence of atopy was reported to be higher among the non-white population. The rate of RSV positive lower respiratory illnesses was also found to be significantly higher among the Hispanic population in the first one to three months of life (Holberg et al., 1991). In fact, Wright et al. (1989) even found that being a male and of Hispanic origin intensified the protective effects of breastfeeding even more. Additionally, asthma prevalence is found to be higher among African American children, even among those of higher socioeconomic status (Morgan & Martinez, 1992).

While conducting a study using data gathered from the National Survey of Family Growth, Forste, Weiss, and Lippincott (2001) discovered that African Americans were 2 ½ times less likely to breastfeed than Caucasian women, and that this lack of breastfeeding contributes to the higher infant mortality rate among African American infants. Thus, according to that study, the effects of breastfeeding may actually become increasingly beneficial, rather than masked, when accounting for ethnicity of the child. If rates of respiratory illnesses are noted to be higher among the non-white population, and the protective effects are more pronounced in certain ethnic groups, the actual role of breastfeeding in relation to respiratory illnesses may be slanted.

As well as ethnicity of the child possibly skewing the benefits of breastfeeding in a positive or negative manner, researchers have also found that parental history of allergy and asthma may impact the profitable aspects of

breastfeeding. In fact, one of the risk factors for wheezing illnesses and asthma is a parental history of atopic disease (Burr et al., 1993; Takemura et al., 2001), particularly if maternal asthma is present (Litonjua, Carey, Burge, Weiss, & Gold, 1998; Martinez et al., 1995; Wright et al., 2000; Wright et al., 1995) and the child is greater than 18 months of age (Rylander et al., 1993). The incidence of maternal asthma has been shown to triple the risk for asthma in children less than five years of age when compared to paternal asthma (Litonjua, Carey, Burge, Weiss, & Gold, 1998). Furthermore, Porro et al. (1993) reported that "the greatest influence on wheezing is exerted by a positive family history of atopy and that a mother's positive history alone has the same value" (p. 24). Another important reason to differentiate between maternal and paternal atopic status is due to the notion that breast milk composition may be affected by atopy (Wright et al., 1999).

Due to the strong evidence that family history of atopic disease, particularly maternal history of atopy, has on infants and children, numerous studies have been conducted in recent years on breastfeeding and maternal and child IgE levels. Once again, increasing IgE levels often serve as an indicator of various atopic conditions. If there is a maternal history of allergy and allergy/asthma, it has been hypothesized that this may actually negate some of the protective effects of breastfeeding. For instance, Wright, Sherrill, Holberg, Halonen, and Martinez (1999) found that as maternal levels of IgE increased, so

did infant IgE levels, especially in those infants breastfed greater than four months. When the IgE levels of the children were tested at ages six and 11, IgE levels remained significantly higher among this group. Infants who were breastfed less than four months did not exhibit elevated IgE levels. Among the infants of mothers with low IgE levels, breastfeeding greater than four months was not associated with higher IgE levels during childhood. The researchers observed no relation between paternal IgE and child IgE levels. In a study published in 1995, Wright et al. found that recurrent wheezing, defined as four or more episodes in the past year, was significantly decreased at six years of age in non-atopic children who were breastfed during infancy for any period of time regardless of presence of wheezing during infancy. These results did not hold true for atopic children, however. In a more recent study by Wright, Holberg, Taussig, and Martinez (2001b), it was discovered that atopic children who were exclusively breastfed by asthmatic mothers had a higher risk of asthma and persistent wheeze after six years of age but a lower risk of wheeze through two years of age, despite maternal atopy or asthma. Thus, breastfeeding may offer some initial protection, but that protection may decrease with age.

On a different note, Duchen and Bjorksten (1996) reported low levels of IgE in colostrum, and found the levels to be similar between atopic and non-atopic mothers. They concluded that the low IgE levels found in colostrum most likely do not have a significant relationship to the IgE levels of the infant. To help

clarify these conflicting results in regard to IgE levels in mothers, breast milk, and children, Peat, Allen, & Oddy (1999) posed an alternate explanation stating that atopic mothers may produce breast milk that is composed of different nutrients than that of a non-atopic mother. For example, omega-3 fatty acids, which play a role in reducing inflammation, are reduced in highly allergic mothers. Once again, after considering these abovementioned findings, it becomes necessary to control for this maternal history of allergy and/or asthma in order to provide further clarification regarding the valuable aspects of breastfeeding.

Finally, on top of family history of allergy and asthma confounding any protective effects of breastfeeding, there is a strong belief that smoke exposure may counteract any benefits that breastfeeding confers. In fact, there does appear to be an increase in respiratory illnesses among children that are exposed to a smoke-filled environment (Peat & Li, 1998). Strachan (1992) noted that "the most remedial cause of chest illness in the first year of life currently is parental (particularly maternal) smoking" (p. 178). Smoking in the household has also been shown to be significantly associated with wheezing in the early years of life (Burr et al., 1993; Martinez et al., 1995; Porro et al., 1993; Rylander et al., 1993; Stoddard & Miller, 1995) as well as asthma later in life (Martinez, Cline, & Burrows, 1992). Additionally, it has been reported that infants of mothers who smoked during pregnancy have smaller lungs and diminished lung function (Gern, Lemanske, & Busse, 1999). "Maternal smoking seems to modify lung

development so that the infant will have diminished lower airway function and, as a result, be at increased risk for developing wheezing upon viral infection of the bronchial tree" (Morgan & Martinez, 1998, p. 689). Finally, Becker et al. (1999) also discussed the fact that tobacco smoke exposure is correlated with an increased risk of respiratory illnesses, diminished lung function, and bronchial hyperresponsiveness.

In addition to smoking leading to increased rates of respiratory illnesses among children, it may also have an impact on breast milk. Lawrence (2001) found that cigarette smoking might actually decrease levels of breast milk produced. This could possibly decrease an infant's exposure to the beneficial compounds found in breast milk as well as affect their nutritional status and subsequent growth and development.

Some researchers, on the other hand, have found that breastfeeding may actually bestow supplementary protection on infants exposed to smoke in their environment. Nafstad et al. (1996) reported that infants who were breastfed longer than six months did not have a higher risk of lower respiratory tract infections. Thus, the researchers felt that the outcomes did not back previous beliefs that by products of tobacco smoke are passed to the child through breast milk and cancel out any protective effects. In fact, breastfeeding was more protective among infants of smoking mothers than non-smoking mothers. On top of that, Holberg et al. (1991) observed that smoking had no correlation with the frequency of RSV

positive lower respiratory tract infections during the first 12 months of life. Likewise, Takemura et al. (2001) reported no significant difference in rates of asthma among children with and without parents who smoke. Finally, Woodward, Douglas, Graham, and Miles (1990), reported that although maternal smoking resulted in a greater risk for respiratory illnesses during the first year of life, this risk was seven times higher in those infants who were not breastfed. In summary, since it appears that smoking may or may not reduce or strengthen the protective effects of breastfeeding, it is important to control for it during the statistical analysis due to some inconsistencies on its influence that have been reported previously.

CHAPTER 3

Methodology

Overview

The purpose of this study was to determine if there is a relationship between the incidence of RSV positive wheezing illnesses during infancy among the infants participating in the COAST study due to the length of exclusive breast or formula feeding. Extraneous variables such as gender of the infant, maternal history of allergy and/or asthma, smoke exposure, and ethnicity of the infant are also thought to play a role in the development of respiratory illnesses. These variables were examined in addition to breastfeeding to determine if they have an effect on the incidence of RSV positive wheezing illnesses, and negate, mask, or amplify any protective effects of breastfeeding.

Data utilized for this study on factors affecting RSV positive wheezing illnesses in the first year of life was obtained from the COAST project that began in October 1998. This subsidiary study received approval by the Institutional Review Board at the University of Wisconsin-Stout, Menomonie, Wisconsin. Approval for the COAST project was granted by the Institutional Review Boards at University of Wisconsin-Madison, Meriter Hospital in Madison, WI, and St. Mary's Hospital Medical Center in Madison, WI. Re-approval was granted when the original documents expired in 2001.

Subjects

The subjects for this project included the 287 infants participating in the COAST study that were at least one year of age by May 2001. All of the infants were recruited from one of the following hospitals in south central Wisconsin: Meriter, St. Mary's, UW Hospital, Baraboo, Fort Atkinson, Portage, and Reedsburg. Subjects were enrolled in the COAST study at birth. To be eligible for study entry, at least one of the biological parents had to have allergies (defined as one or more positive allergy skin tests to aeroallergens), asthma or both. Informed consent was obtained from the parents or guardians of the infants prior to their enrollment in the study. A copy of the informed consent document was provided to the University of Wisconsin–Stout and is located in Appendix A.

In order to protect their confidentiality, the subjects were given an identification number upon enrollment in the study at birth. Additionally, in the original study's Patient Information and Consent Form, a section entitled "Voluntary Participation/Withdrawal from Study" explains the fact that participation is voluntary and subjects can withdraw from the study at any point in time. Parents signed the form as subjects were less than one year of age.

Since RSV is epidemic in nature and occurs more frequently during certain seasons, subjects were recruited on a quarterly basis with approximately 40 subjects each quarter. All subjects were required to have an Apgar score over

six at five minutes of age, to be born between 38 and 42 weeks of gestation, and to be free of birth defects or illnesses at birth. This eligibility requirement eliminated the possibility of seriously ill children from confounding the results as they may be more prone to respiratory illnesses.

Parents of subjects were self-selected and learned of the study through several means: newspaper, radio, and/or television advertisements; brochures obtained from LaMaze classes, local obstetric, family practice, pediatric, immunization, and/or women's clinics; letters mailed to families in the community informing them of upcoming studies; community baby supply retail stores; pharmacies; health fairs; word of mouth. The subjects were representative of the Madison area community. Of the study population, approximately 56% were male and 44% female. According to the Wisconsin Department of Health and Human Services (2000), about 51% of the population in the zero to fourteen years age bracket in the Madison area community is male and 48% is female. The ethnic distribution of the subjects was as follows: 87% Caucasian, 8% African American, 3% Hispanic/Latino, 1% Asian/Pacific Islander, and 1% American Indian/Eskimo. This is similar to the ethnic distribution of the Madison area community which is roughly 89% Caucasian, 4% African American, 3% Hispanic, 4% Asian/Pacific Islander, and 0.3% American Indian/Eskimo according to the U. S. Census Bureau (2000).

Procedures

Data utilized for this secondary study was obtained from several different questionnaires designed specifically for the COAST study by a group of physicians and their associates at University of Wisconsin Asthma and Allergy Clinical Research Unit in Madison. A paper copy of all the questionnaires and original data was kept in individual subject binders in the COAST laboratory. There was one binder for each subject. It was labeled on the outside with subject identification number only. The majority of the data for this study was obtained from the computerized COAST database, however. The paper copy of the questionnaires was utilized only when a certain piece of information was missing on a subject from the computerized database. This occurred in nine different cases in regard to feeding history.

Entry of information into the computerized database was completed by COAST research assistants. Consent was granted before accessing the computerized database to protect all subjects since they can be identified by both name and identification number in the computer. However, no names were utilized in this study, only identification numbers.

Table I lists the source, question number, and an *abbreviated* (i.e. only the questions utilized from the questionnaires are listed) version of the questions/items utilized in this study to determine the following variables: infant

feeding history, sex of the infant, ethnicity of the infant, smoke exposure, maternal history of allergy and/or asthma, and RSV positive wheezing illnesses.

Table 1: The COAST documents and a shortened version of questionnaire items utilized to define variables in the study

VARIABLE	DOCUMENT	QUESTION NUMBER	QUESTION
Feeding history	Data Base Additions March, 2000	# 1 item 17	Did not breastfeed (i.e. this item was checked if the mother did not ever breastfeed)
		# 3 items 1-12	At what age (in months) did you start supplementing with formula: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12
		# 3 item 13	Never used formula
Sex of the child	Child Questionnaire One	A items 1 and 2	Sex of your child: male or female
Ethnicity	Personal Data Form 1/9/99	# 16 item 1-5, 99	Race: Mother – Caucasian, African American, Asian/Pacific Islander, American Indian/Eskimo, Hispanic/Latino, Other
		# 25 item 1-5, 99	Race: Father – Caucasian, African American, Asian/Pacific Islander, American Indian/Eskimo, Hispanic/Latino, Other
Smoke Exposure	Parent Questionnaire 1	# 45 item b # 47	If you started smoking cigarettes at a certain age, do you still smoke? Do you smoke a pipe or cigar?
	Parent Questionnaire 2-10 (same questionnaires completed at visits 2-10)	# 46 # 47	Has there been a change in your smoking status? Do you now smoke a pipe or cigar?
	Child Questionnaire 2-9 (same questionnaires completed at visits 2-9)	# 117 # 120 # 123 # 124	Does the child's mother smoke? Does the child's father smoke? How many people who live in the child's home smoke? Does anyone who cares for the child smoke?
	Daycare Questionnaire	# 4	Is child exposed to passive smoke while at day care?
	Residential Questionnaire	# 4	Is child exposed to passive smoke in your home?
Maternal History of Allergy and/or Asthma	Allergy Skin Test Form	# 2-13	Have you had a positive allergy skin test to any of the allergens listed?
	Data Base Additions November, 1999	# 5	Has your asthma diagnosis been confirmed by an MD. If yes, provide date and name of MD.
	Parent Questionnaire 1	# 1 #2 # 4	Have you ever had allergies or asthma ? Have you ever had an asthmatic attack? Was asthma confirmed by a doctor?
	Parent Questionnaire 2-10	# 1 # 4	Have you developed allergies or asthma ? Was asthma confirmed by a physician?
Wheezing Status	Respiratory Illness History	# 4 and # 3, 7, 8, 9, 11, or 12	Parental report that child has used bronchodilators, prednisone, or asthma controllers
	Respiratory Illness Assessment	#5 item j #8 item a, d, f, g #9 item d, e, h, i	Symptomatic for wheezing Indicate treatment options for respiratory illnesses Indicate bronchiolitis, wheezing illness, reactive airway disease, or asthma
	Childrens' Questionnaire Source Document	# 10 # 11 item 2	Indicates treatment options for respiratory illnesses Wheezing on inspiration or expiration

Infant Feeding History

One questionnaire was designed to collect information regarding length of exclusive breastfeeding or formula feeding for each infant. When infants were one year of age, their parents filled out the questionnaire in the presence of a COAST nurse stating the age in months that breastfeeding was supplemented with any amount of formula (one month, two months, three months, and so forth until twelve months of age). Thus, from this question it is possible to derive when exclusive breastfeeding was stopped. If breastfeeding was never initiated, parents checked "did not breastfeed." If formula was never used, parents checked "never used formula." An abbreviated copy of the questionnaire can be found in Appendix B.

The feeding data being analyzed in this study was collected retrospectively. Although feeding data was collected retrospectively, this method meets Kramer's (1988) standards as it did not rely "on prolonged maternal recall" (p. 182) since it was collected at one year of age. Furthermore, Wright et al. (2001) found over 90% agreement after comparing infant feeding data collected both prospectively and retrospectively in their most recent published study.

Subjects were divided into three groups and data was analyzed separately for each group. The groups were based on feeding history as follows: 1) never breastfed (i.e. only formula), 2) exclusively breastfed (i.e. no formula) less than six months, or 3) exclusively breastfed (i.e. no formula) greater than or equal to

six months. The exclusively breastfed infants were divided into two groups at the six-month period since only about 20% of the population still breastfeeds at this six month point (Abbot Laboratories, 2001). Thus, it was important to determine whether breastfeeding in the early months of life, when it is the most common time to employ this method of feeding, was more, equally, or less beneficial as breastfeeding for six months or longer, defined by Saarinen and Kajosaari (1995), as "prolonged breastfeeding" (p. 1066). Moreover, there has been some controversy over whether or not breastfeeding is only protective during the period of utilization and in the earlier months of life or whether the effects extend beyond that early period. Additionally, six month intervals help provide adequate time to reap any protective effects of breastfeeding as recommended by Kramer (1988). Finally, it was important to base the feeding categories on exclusivity because the length of exclusive breastfeeding is a better predictor of the dependent variable than breastfeeding in general (Oddy et al., 1999).

Sex of the Infant

The sex of the infant, classified as either male or female, was obtained from a questionnaire that was completed at the infant's first check-up two months after birth. An abbreviated copy of the form can be found in Appendix C.

Ethnicity of the Infant

The ethnicity of the infant was derived from information on the ethnic background of his or her parents. Parents had the option of selecting one of the following races: Caucasian, African American, Asian/Pacific Islander, American Indian/Eskimo, Hispanic/Latino, or Other. If each parent was of a different ethnic background, the child's ethnicity was listed as the minority race. For example, if the child's mother was Caucasian and the child's father was African American, the child would be listed as an African American. Since approximately 90% of the subjects were Caucasian, they were classified as Caucasian or non-Caucasian for analytical purposes rather than grouped into separate categories for each individual race. Of the 287 infants in the study, parents provided complete information to classify the race/ethnicity of 282 subjects. An abbreviated copy of the form used to determine ethnicity can be found in Appendix D.

Smoke Exposure

For a subject to qualify as having been exposed to smoke in the environment, a parent would have to have smoked at any time during the child's life, a mother would have to have smoked during pregnancy, or the subject would have to be exposed to smoke on a regular basis outside of the home, such as in daycare. For analytical purposes, subjects were labeled as having a positive or negative history of environmental smoke exposure. This method was preferred over categorizing the subjects as positive to maternal smoking, paternal smoking,

or smoke outside of the home since the percentage of subjects falling into each of these individual categories was quite small. Useable responses on smoke exposure were obtained for 284 of the 287 infants in the study . An abbreviated copy of each of the forms utilized to determine if the child was exposed to smoke is located in Appendix E.

Maternal History of Allergy and/or Asthma

Maternal history of allergy was determined based on a positive response to the allergy skin test form. Maternal history of allergy as well as asthma was also ascertained from questions about the development of allergy and asthma, the diagnosis of asthma by a physician, and the presence of asthmatic attacks. The total number of infants included in the analysis of maternal history of allergy and/or asthma was less than 287 because not all of the mothers stated if they had a history of asthma and/or allergies or not. Abbreviated copies of each questionnaire can be found in Appendix F.

RSV and RSV Positive Wheezing Illnesses

The number and type of RSV positive or negative respiratory illnesses each infant experienced was obtained from the COAST database. The respiratory illness data was collected prospectively. The infant's age in months was also documented when the illness was diagnosed. The following protocol for collecting virus data was designed prior to the start of the COAST study by a group of physicians and their associates at University of Wisconsin Asthma and

Allergy Clinical Research Unit in Madison. Diagnosis of a RSV positive illness was based on the following procedure:

Parents were provided with the phone number and pager number of COAST personnel. They were instructed to phone the clinic at the first sign of a lower respiratory tract illness (such as wheezing, coughing, chest rattling, and fever). The COAST personnel then reviewed the signs and symptoms using a virus severity scorecard. On the scorecard, each symptom of a respiratory illness is listed along with a point value according to the severity of the symptom. For example a child with a fever receives one point, a severe cough three points, or wheezing five points.

A child scoring greater than or equal to a score of five was presumed to have a respiratory illness. If the child was thought to have a respiratory illness, he or she was instructed to come to the clinic for a physical exam at which point a nasopharyngeal mucus sample and throat swab were taken to confirm or reject a diagnosis of a RSV positive illness. The RSV positive status was determined by analysis of the samples sent to the Wisconsin State Laboratory of Hygiene, Madison, Wisconsin.

Well-child visits were conducted at two, four, six, nine, and twelve months of age at which time nasopharyngeal mucus testing was done to detect the presence or absence of respiratory viral pathogens. The sample was analyzed by the Wisconsin State Laboratory of Hygiene. The person making the diagnosis of

RSV illnesses was not aware of the child's feeding history. This meets Kramer's (1988) standard of "blind ascertainment of feeding history" (p. 182).

When studying the respiratory illness data, it was necessary to distinguish RSV positive wheezing illnesses from RSV positive illnesses in general, regardless of the presence of wheezing, among those infants who experienced an RSV positive infection during infancy. The necessity of determining whether or not the illness occurred in association with wheezing was due to the notion that analyzing respiratory illnesses both with and without wheezing together may mask any protective effects of breastfeeding (Wright et al., 1989). Additionally, wheezing helps determine the severity of the illness, not just its occurrence.

Several different factors were considered to determine if a physician diagnosed wheezing illness occurred. The child was recorded as having a wheezing illness if he or she used bronchodilators, prednisone, or asthma controllers, experienced wheezing on inspiration or expiration, or experienced bronchiolitis, reactive airway disease, or asthma. Abbreviated copies of all questionnaires that helped determine the diagnosis of RSV positive illnesses as well as wheezing can be found in Appendix G.

Data Treatment and Analysis

The Statistical Package for Social Sciences (SPSS) version 10.0 was utilized for data analysis. The data was entered into a spreadsheet created in SPSS and coded into numerical format on the basis of the following: 1). Presence or absence of RSV infections during infancy, 2). Presence or absence of wheezing with RSV infections, 3). Child's gender (male or female), 4). Maternal history of allergy, asthma, and/or allergy accompanied with asthma, 5). Ethnicity of the child (Caucasian or non-Caucasian), 6). Smoke exposure (positive or negative), and 7). Infant feeding category (never breastfed, exclusively breastfed less than six months, or exclusively breastfed greater than or equal to six months).

Frequency analyses were conducted in order to determine the percentage distribution for each variable studied. The Chi-Square procedure was utilized to test the hypothesis that length of exclusive breastfeeding and formula feeding are independent of gender, ethnicity, smoke exposure, and maternal history of allergy and/or asthma. The Pearson chi-square statistic was employed to determine significance of the results. In order to determine if an individual association exists between RSV/RSV positive wheezing illnesses and length of exclusive breastfeeding, gender, ethnicity, smoking, and maternal history of allergy and/or asthma, binary logistic regression analysis was applied. Binary logistic regression analysis is useful for determining the odds of an event occurring in the presence of certain independent variables. Confidence intervals were also estimated.

It was necessary to use binary logistic regression analysis because the dependent variable was dichotomous nominal and there was no statement regarding the linearity of the relationship between the independent and dependent variables. Finally, using multivariate logistic regression analysis, length of exclusive breastfeeding, gender, ethnicity, smoke exposure, and maternal history of allergy and/or asthma were all factored into the equation using the block entry method to determine any associations among variables and RSV/RSV positive wheezing illnesses when examined in combination with each other rather than separately.

CHAPTER 4

Results

Population Characteristics

A study was conducted on a sample of 287 infants to determine the relationship, if any, among breastfeeding, gender of the child, ethnicity of the child, smoke exposure, and maternal history of allergy and/or asthma in conjunction with RSV positive wheezing illnesses. Table 2 presents the characteristics of the sample population. Approximately 56% of the subjects were male and 44% female. The majority of the population was Caucasian (87%) compared to non-Caucasian (13%). Subjects were much more likely to have been exclusively breastfed than never breastfed at all. Roughly 43% of the subjects were exclusively breastfed for six months or longer, 48% were exclusively breastfed for less than six months, and the remaining subjects were never breastfed. Additionally, subjects were much less likely to be exposed to smoke in their environment (76%). Only one-fourth of the population (24%) came into contact with smoke on a routine basis. Many of the subjects had mothers with a history of allergies alone (47%) or allergies in conjunction with asthma (37.6%). Subjects without a maternal history of allergy and/or asthma comprised about 12% of the study population although they did have a paternal history of allergy and/or asthma. The remaining subjects had a maternal history of asthma alone.

TABLE 2: Population Characteristics

Characteristic	Infants n (%)	
Feeding Method (N=287)		
Never Breastfed	26	(9.1%)
Exclusively Breastfed < 6 months	139	(48.4%)
Exclusively Breastfed ≥ 6 months	122	(42.5%)
Gender of child (N=287)		
Male	162	(56.4%)
Female	125	(43.6%)
Ethnicity of child (N=282)¤		
Caucasian	245	(87%)
Non-Caucasian	37	(13%)
Smoke Exposure (N=284)¤		
Positive	68	(24%)
Negative	216	(76%)
Maternal History (N=276)		
Allergy	130	(7%)
Allergy and Asthma/Asthma alone	114	(41.5%)
Neither	32	(11.5%)
Presence of RSV (N=287)		
Positive	102	(35.5%)
Negative	185	(64.5%)
Presence of RSV with Wheezing (N=102)		
Positive	45	(44.1%)
Negative	57	(55.9%)

¤N = less than 287 due to missing data for this category

The presence of RSV was detected in about one-third of the subjects during infancy while the remaining subjects did not have an RSV positive illness. This finding is lower than the average occurrence of RSV in infants which is around 60% (Glezen et al., 1986 & Openshaw, 1995). Of the subjects in this study who experienced an RSV positive illness, approximately 44% had physician diagnosed wheezing with the illness, indicating greater severity of the illness, while 56% did not have wheezing with RSV.

Factors Associated with Breastfeeding

Certain factors are thought to be associated with breastfeeding during infancy. Results of this study showed that breastfed infants were significantly ($p = 0.043$) less likely to have come in contact with smoke than infants who were exclusively formula fed. No significant associations ($p > 0.05$) were found between method of infant feeding and, gender, race, and maternal history of allergy and/or asthma. A tendency toward an association was observed between race of the infant and method of feeding. Non-Caucasian infants seemed more likely than Caucasian infants to have never been breastfed or exclusively breastfed for a shorter period of time (Table 3).

TABLE 3: Factors Associated with Breastfeeding

Characteristic	Length of Exclusive Breastfeeding			P Value of X^2
	Never	<6 mos	≥ 6 mos	
	N = 26	N = 139	N = 122	
	n (%)	n (%)	n (%)	
Gender of Child				
Male	11 (42%)	78 (56%)	73 (60%)	0.260
Female	15 (58%)	61 (44%)	49 (40%)	
Ethnicity of Child				
Caucasian	21 (80%)	117 (84%)	112 (92%)	0.106
Non-Caucasian	5 (20%)	22 (16%)	10 (8%)	
Smoke Exposure				
Positive	9 (35%)	38 (27%)	19 (16%)	†0.043
Negative	17 (65%)	101 (73%)	103 (84%)	
Maternal History				
Allergy	15 (56%)	70 (50%)	56 (46%)	0.615
Asthma/Allergy	9 (36%)	50 (36%)	54 (44%)	
Neither	2 (8%)	19 (14%)	12 (10%)	

†$p < 0.05$

RSV Illnesses

Binary logistic regression analysis was used to examine the individual association among infant feeding method, gender, ethnicity, smoking, and maternal history of allergy and/or asthma on the occurrence of RSV in infants. Using exclusive breastfeeding greater than or equal to six months as the reference category, no significant relationship ($p > 0.05$) was found between presence of RSV and never breastfeeding or exclusive breastfeeding less than six months. However, those infants who were never breastfed tended to have higher odds of contracting RSV. Additionally, no significant association ($p > 0.05$) was found between presence of RSV and sex of the infant, ethnicity of the infant, smoke exposure, maternal history of allergy, and maternal history of neither allergy nor asthma. In the latter two cases, maternal history of both allergy and asthma was used as the reference category. Although non-significant, there was a trend for infants exposed to smoke to have more RSV infections as well as a trend for infants of non-Caucasian origin to have fewer RSV infections (Table 4).

TABLE 4: RSV Illnesses

Characteristic	°OR	°95% CI	Significance
Feeding Method			
Never Breastfed	1.575	0.669-3.706	0.298
Breastfed < 6 months	0.939	0.563-1.565	0.808
*Breastfed ≥ 6 months			
Gender of Child			
*Male			
Female	1.102	0.677-1.793	0.695
Ethnicity of Child			
*Caucasian			
Non-Caucasian	0.616	0.285-1.331	0.218
Smoke Exposure			
Positive	1.434	0.817-2.517	0.210
*Negative			
Maternal History			
Allergy	1.118	0.661-1.893	0.677
*Asthma/Allergy			
Neither	1.053	0.467-2.370	0.901

°OR=Odds ratio, CI=Confidence Interval

*Served as reference category in the analysis

RSV Positive Wheezing Illnesses

No significant connection ($p > 0.05$) was found between RSV positive wheezing illnesses and never breastfeeding or exclusive breastfeeding less than six months when using exclusive breastfeeding six months or longer as the reference category. Furthermore, no significant association ($p > 0.05$) was found between sex of the child, ethnicity of the child, and maternal history of neither allergy nor asthma (Table 5).

There was, however, a significant relationship ($p = 0.036$) between RSV positive wheezing illnesses and maternal history of allergy alone compared to a history of both allergy and asthma. Infants of mothers with both allergies and asthma compared to mothers with allergies alone were more likely to get RSV positive wheezing illnesses during infancy. Although contradictory to the majority of the available research, there was a weak inverse trend between RSV positive wheezing illnesses and smoke exposure. Infants exposed to smoke appeared to have fewer RSV positive wheezing illnesses (Table 5).

TABLE 5: RSV Positive Wheezing Illnesses

Characteristic	°OR	°95% CI	Significance
Feeding Method			
Never Breastfed	0.695	0.181-2.664	0.595
Breastfed < 6 months	1.331	0.579-3.062	0.501
*Breastfed ≥ 6 months			
Gender of Child			
*Male			
Female	0.954	0.435-2.093	0.906
Ethnicity of Child			
*Caucasian			
Non-Caucasian	0.829	0.219-3.136	0.783
Smoke Exposure			
Positive	0.500	0.200-1.248	0.138
*Negative			
Maternal History			
Allergy	0.397	0.167-0.940	†0.036
*Asthma/Allergy			
Neither	0.519	0.139-1.937	0.329

°OR=Odds ratio, CI=Confidence Interval

*Served as reference category in the analysis

†$p < 0.05$

Multiple Logistic Regression Analysis and RSV Illnesses

Multiple logistic regression analysis was utilized to find an association between feeding method, gender, ethnicity, smoke exposure, and maternal history of allergy and/or asthma in conjunction with RSV positive illnesses. All of the causal variables were entered into the equation in one step. There was no significant relationship ($p > 0.05$) between presence of RSV and gender of the infant, ethnicity of the infant, maternal history of allergy, maternal history of neither allergy nor asthma, never breastfeeding, or exclusive breastfeeding less than six months. However, when examining the odds of developing RSV after comparing never breastfeeding to exclusive breastfeeding greater than or equal to six months, those infants who were never breastfed seemed more likely to get RSV. Also, there was a tendency toward an association between smoke exposure and presence of RSV and ethnicity of the infant and presence of RSV. Infants exposed to smoke tended to have more RSV infections than those not exposed to smoke. Infants of non-Caucasian origin tended to be less inclined than Caucasian infants to have RSV (Table 6).

TABLE 6: Multiple Logistic Regression Analysis and RSV Illnesses

Characteristic	°OR	°95% CI	Significance
Feeding Method			
Never Breastfed	1.723	0.697-4.262	0.239
Breastfed < 6 months	0.958	0.563-1.628	0.873
*Breastfed ≥ 6 months			
Gender of Child			
*Male			
Female	1.064	0.639-1.770	0.812
Ethnicity of Child			
*Caucasian			
Non-Caucasian	0.513	0.221-1.191	0.120
Smoke Exposure			
Positive	1.664	0.902-3.068	0.103
*Negative			
Maternal History			
Allergy	1.134	0.662-1.943	0.647
*Asthma/Allergy			
Neither	1.022	0.447-2.334	0.960

°OR=Odds ratio, CI=Confidence Interval

*Served as reference category in the analysis

Multiple Logistic Regression Analysis and RSV Positive Wheezing Illnesses

Table 7 displays the results when comparing the causal variables with RSV positive wheezing illnesses. The findings for infant smoke exposure and presence of RSV positive wheezing illnesses were somewhat confusing. Infants who were exposed to smoke seemed more likely to get RSV, but less likely to have wheezing with the illness. A significant relationship ($p = 0.032$) did appear between RSV positive wheezing illnesses when comparing maternal history of allergies alone to maternal history of allergy and asthma. Again, maternal history of both allergy and asthma was more indicative of RSV positive wheezing illnesses than maternal history of allergy alone. No significant relationship ($p > 0.05$) was discovered between maternal history of neither allergy nor asthma and RSV positive wheezing illnesses. Furthermore, no significant relationship ($p > 0.05$) was found between RSV positive wheezing illnesses and never breastfeeding, exclusive breastfeeding less than six months, gender of the infant, and ethnicity of the infant (Table 7).

TABLE 7: Multiple Logistic Regression Analysis and RSV Positive Wheezing Illnesses

Characteristic	°OR	°95% CI	Significance
Feeding Method			
Never Breastfed	0.714	0.174-2.931	0.640
Breastfed < 6 months	1.482	0.605-3.632	0.389
*Breastfed ≥ 6 months			
Gender of Child			
*Male			
Female	1.046	0.450-2.432	0.917
Ethnicity of Child			
*Caucasian			
Non-Caucasian	0.933	0.191-4.568	0.932
Smoke Exposure			
Positive	0.425	0.150-1.202	0.107
*Negative			
Maternal History			
Allergy	0.372	0.151-0.917	†0.032
*Asthma/Allergy			
Neither	0.530	0.137-2.043	0.356

°OR=Odds ratio, CI=Confidence Interval

*Served as reference category in the analysis

†$p < 0.05$

Exclusive Breastfeeding and RSV/RSV Positive Wheezing Illnesses

The majority of the subjects were exclusively breastfed for any amount of time (90.9%) during the first year of life. Since the "never breastfed" group was so small in sample size, both binary logistic regression analysis and multiple logistic regression analysis were conducted after eliminating this category from the analysis. This analysis was done in order to determine if breastfeeding would show an alternate association with RSV and RSV positive wheezing illnesses. Results showed no significant relationship ($p > 0.05$) between the number of RSV positive illnesses experienced by infants who were exclusively breastfed less than six months compared to the infants who were exclusively breastfed greater than or equal to six months when examining breastfeeding alone with RSV and when controlling for the extraneous variables. In terms of RSV positive wheezing illnesses, the results were similar. No significant association ($p > 0.05$) appeared between length of exclusive breastfeeding and RSV positive wheezing illnesses. These results held true when adjusting for confounding variables (Table 8).

TABLE 8: Exclusive Breastfeeding and RSV/RSV Positive Wheezing Illnesses

Category	°OR	°95%CI	Significance
Presence of RSV	0.939	0.563-1.565	0.808
Presence of RSV (MLR) ∏	0.945	0.554-1.612	0.836
Presence of RSV with Wheezing	1.331	0.579-3.062	0.501
Presence of RSV with Wheezing (MLR)†	1.578	0.637-3.906	0.324

°OR=Odds ratio, CI=Confidence Interval

∏ MLR = Multiple Logistic Regression Analysis

CHAPTER 5
Discussion

This investigation was carried out to determine if a relationship exists between RSV positive wheezing illnesses and breastfeeding during infancy, as this is a highly controversial area of research (Kramer, 1988 & Cunningham et al., 1991). As established by the results, this study demonstrates that breastfeeding, even for prolonged periods of time, does not seem to protect against wheezing illnesses in infants with a maternal history of allergy and/or asthma.

During infancy, the presence of RSV as well as wheezing illnesses associated with RSV among infants who were never breastfed was not significantly different from infants who were exclusively breastfed for any amount of time. There was a trend for infants to have more RSV positive illnesses in general if never breastfed even when controlling for gender of the infant, ethnicity of the infant, smoke exposure, and maternal history of allergy and asthma. However, these results were not significant, and the trend was not repeated when wheezing was taken into consideration. Even after removing the small group of infants who were never breastfed from the analysis, no inclination was detectable between length of exclusive breastfeeding and RSV positive wheezing illnesses. These results are similar to findings from previous studies that

did not show a relationship between respiratory illnesses and breastfeeding (Dewey et al., 1993; Rubin et al., 1990).

Additionally, no associations were discovered between infant feeding history and gender of the infant or maternal history of allergy and/or asthma. There was a slight, non-significant tendency for non-Caucasian infants to have never been breastfed or breastfed for shorter periods of time. Although consistent with previous findings (Weiss & Lippincott, 2001), the result was not significant. There was a significant association between smoke exposure and method of infant feeding. Those infants who were exposed to smoke were significantly less likely to have been breastfed or were breastfed for shorter periods of time. This finding is similar to the results obtained by Piscaine et al. (1994). As found previously, those infants who are exposed to smoke tend to acquire greater compensation from breastfeeding (Nafstad et al., 1996). Thus, breastfeeding may be particularly important in smoke filled environments. Furthermore, although ethnicity and smoke exposure were controlled for in the multiple logistic regression analysis, the fact that these groups were so small in sample size may have not allowed for adequate analysis and may have affected the outcome.

Since it is unethical to randomly assign infants to a feeding category, other factors present among the infants that could not be controlled for in this study population may have also confounded the results. For instance, part of the lack of association between breastfeeding, RSV, and RSV positive wheezing illnesses

may be due to the fact that the outcome variables were being studied among infants from an urban, middle to upper class environment. First of all, the breastfeeding rates were quite high, even higher than the average for the state of Wisconsin. In this study population, approximately 9% of the infants were never breastfed and 43% were breastfed greater than or equal to six months. In regards to breastfeeding rates for the entire state of Wisconsin, only 22% of infants are breastfed after five to six months of age (Wisconsin Breastfeeding Coalition, 1999). Moreover, the subjects were primarily Caucasian, born into families with a high median income and a high level of education. Approximately 73% of the mother's and 70% of the fathers had a college degree or higher. The median annual income for this area is ~$50,000 compared to a national average of ~$37,000 (U. S. Census Bureau, 2000).

As noted in previous studies, the protective effects of breastfeeding appear to be much stronger among infants from developing countries than those from industrialized nations (Brown et al., 1989; Cesar et al., 1999; Forman et al., 1984; Lopez-Alarcon et al., 1997; Victora et al., 1989). Additionally, breastfeeding has been shown to be more beneficial among infants of lower socioeconomic status, including low levels of parental education, low income, and unsanitary, crowded living conditions, than those of higher socioeconomic status. Several studies have initially found an association between breastfeeding and respiratory illness; however, that relationship often disappears when socioeconomic status is

incorporated into the analysis. (Fergusson et al., 1981; Holberg et al., 1991; Margolis et al., 1992; Pullan et al., 1980; Rubin et al., 1990; Taylor et al., 1982).

There are numerous reasons for this distinction. Often, infants born into families of low socioeconomic status are at increased risk of infection just because of the environment in which they live (Morgan & Martinez, 1992). For example, as income levels decline, access to health care and a clean environment may also decrease. These infants may be more likely to live in crowded, unsanitary environments and be exposed to pollutants and experience a subsequent increase in virus related respiratory illnesses (Morgan & Martinez, 1992). Less educated mothers may also be less knowledgeable about appropriate infant care in general. In an article discussing current statistics on breastfeeding rates as well as influences on the decision to breastfeed or formula feed, Wright observed that "women with less education and lower household incomes were also less likely to breastfeed" (2001a, p. 3). It is also commonly observed that women with low levels of education do not prepare infant formula to the appropriate concentrations. Thus, if infants from low socioeconomic groups are more prone to respiratory illnesses and wheezing (Baker et al., 1997) and are less likely to breastfeed, any beneficial effects of breastfeeding would be amplified in this group. In fact, Holberg et al. (1991) and Cunningham (1979) found that infants of mothers with 12 years of education or less appeared to experience a greater benefit from exclusive breastfeeding.

Decreased lung function may also share a relationship with low socioeconomic status as many mothers in this group do not receive adequate prenatal care. As Martinez et al. (1995) pointed out, infants with small airways and decreased lung function may be more likely to wheeze during a viral infection. If they were breastfed, they may improve lung function through adequate nutrition and thereby decrease the risk of wheezing. Therefore, this may be another one of the reasons breastfeeding was not protective against RSV positive wheezing illnesses in the affluent COAST population. However, lung function was not measured among this group of infants so an analysis of this factor was not possible.

The most important determinant in regards to wheezing with an RSV positive illness in this study was a maternal history of both allergy and asthma. A significant relationship appeared between maternal history of allergy and asthma and wheezing with an RSV positive illness during infancy. The results were significant both when examining maternal history alone with RSV positive wheezing illnesses and when adjusting for feeding method, gender of the infant, ethnicity of the infant, and smoke exposure.

These results are in line with recent studies related to asthma and allergy during infancy and childhood and a maternal history of atopy (Wright et al., 1999). As a matter of fact, although a parental history of allergy and asthma is considered one of the possible factors in the etiology of wheezing illnesses and

asthma in children (Burr et al., 1993; Porro et al., 1993; Takemura et al., 2001), maternal asthma in particular is highly associated with wheezing in children. (Litonjua et al., 1998; Martinez et al., 1995; Wright et al., 2000).

One of the conceivable explanations for the lack of association between mode of infant feeding and RSV positive wheezing illnesses might be due to this maternal history of allergy and asthma. IgE levels are elevated in mothers with allergy and/or asthma. It has been discovered that infants born to mothers with high IgE levels also have elevated IgE levels at nine months, six years, and eleven years of age when breastfed greater than or equal to four months (Wright et al., 1999). Therefore, the high IgE levels may predispose the infants to illness. These markers of allergic disease might be passed through the breast milk itself making breastfed infants more prone to atopic disease.

In an additional study, Wright et al. (2000) found that infants born to asthmatic mothers were more likely to have asthma the longer they were exclusively breastfed during infancy. For example, 57% of the infants born to mothers with asthma who were breastfed at least four months had asthma by age 11 compared to 9% of the infants who received formula starting at birth. Furthermore, in a more recent study, Wright et al. (2001b) again found that breastfed atopic children born to asthmatic mothers were at a greater risk for wheezing and asthma by age 6 years. As noted in an earlier study, a family

history of allergy may so greatly bias children to wheeze that the benefits of breastfeeding are outweighed (Wright et al., 1995).

The slight trend between exclusive breastfeeding and decreased incidence of RSV positive illnesses but no association between exclusive breastfeeding and wheezing illnesses associated with RSV might also be explained by this maternal history of allergy and asthma. Since RSV is caused by infection, breastfeeding is often thought to confer some protection against it (Wright et al., 1999). However, wheezing may be immune to any protective effects of breastfeeding since high IgE levels have been found to share an association with the presence of wheezing.

Although the results of this study may not be generalizable due to the characteristics of the study population, several factors were taken into consideration to strengthen the validity of the study. Kramer (1988) defined several standards to improve the legitimacy of breastfeeding and illness studies. The following standards suggested by Kramer (1988) were applied. First of all, subjects were divided into groups based on exclusivity of breastfeeding rather than any duration of breastfeeding. Breastfeeding has often been shown to be more beneficial when examined in terms of exclusivity rather than any amount of breastfeeding mixed with formula feeding (Raisler et al., 1999 & Wright et al., 1998). Second, exclusive breastfeeding was examined at intervals throughout the first year of life since the positive effects of breastfeeding may or may not be delayed and because the protective effects of breastfeeding have been shown to be

dose responsive (Dell & To, 2001). Third, infant feeding data was collected during a routine clinic visit without knowledge of the infant's disease state to prevent bias. Feeding data was also collected at the end of the child's first year of life rather than after the elapse of several years in hopes of obtaining a more accurate recall from the infants' parents or caregivers. Fourth, the outcome variable, physician diagnosed RSV positive wheezing illnesses, was clearly defined and was ascertained prospectively. The infants were examined by a physician at two, four, six, nine, and twelve months of age during the first year of life. This helped to lessen detection bias. Fifth, the severity, rather than just the presence, of the outcome variable was assessed by looking at the occurrence of wheezing in addition to an RSV positive illness. Sixth, subjects were classified based on maternal history of allergy and/or asthma as this factor can influence the results. Finally, extraneous variables were controlled for in the analysis to help prevent certain sources of confounding, and the seasonal nature of certain respiratory illnesses was accounted for by enrolling equal numbers of infants from different seasons in the COAST study.

Although the standards were met, certain aspects would need to be improved if a similar study were to be conducted in the future. For example, other potential sources of confounding were not analyzed. One source of confounding may be attendance at day care. Infants placed in day care have been shown to have more respiratory illnesses (Holberg et al., 1991; Rylander et al., 1993). A

more recent study found that exposing infants to viral infections at day care was protective against asthma later in life but not against wheezing type illnesses (Infante-Rivard, Amre, Gautrin, & Malo, 2001). Additionally, maternal education and familial income, two possible confounding variables were not controlled for in the analysis. According to the Wisconsin Department of Health and Family Services, roughly 95% of mother's with an education beyond high school access prenatal care in the first trimester of pregnancy versus 65% of mothers with less than a high school education (2000). Lack of prenatal care could influence the health status of the infant in the long run. Next, the initiation of solid feedings was not examined. Although infants may have been exclusively breastfed throughout the first year of life, the timing and type of solid foods given to the infant may have had an impact on the outcome variable as well. Furthermore, even though infant feeding history was obtained at one year of age, it is known that breastfeeding mothers may overestimate length of exclusive breastfeeding and underestimate length of formula feeding.

The study also failed to have adequate statistical power because many of the comparison groups were small in size. For instance, the results of this study showed that maternal history of allergy *and* asthma were significantly associated with wheezing illnesses and that breastfeeding did not bestow any protective benefits. In the study by Wright et al. (2001b), subjects were grouped by maternal asthma alone and not the combination of allergy and asthma. Thus, that may be

one of the reasons why the study by Wright et al. (2001b) revealed advantageous effects of breastfeeding in infancy and not during childhood whereas this particular study did not show any valuable outcomes in infancy. It was not possible to examine infants with a maternal history of asthma alone, however, as the percentage of mothers with asthma only was quite small.

Finally, exposure to pets and dust mites was not controlled for in the analysis. Having a pet in the home may or may not make a child more susceptible to wheezing or asthma based on such factors as a family history of allergy and/or asthma. For example, are the pets kept outside or are they kept inside and allowed to sleep with the children? Earlier studies have shown a linear relationship between pet exposure (caged birds) and wheezing bronchitis (Rylander et al., 1993) as well as dust mites, cat dander, wheezing and damaged lung tissue (Peat & Li, 1999). Other studies, however, have found cat dander to either have no association with wheezing (Burr et al., 1993), a stronger association with wheezing and asthma primarily in older vs. younger children (Apelberg, Akoi, & Jaakkola, 2001), or an inverse relationship with wheezing and asthma (Platts-Mills, Vaughn, Squillace, Woodfolk, & Sporik, 2001). The latter study postulates, however, that the exposure may or may not be beneficial to some children with a certain genetic makeup. Additionally, the inverse relationship between wheezing and pet exposure in younger children may be due to the fact that families with a history of allergy and/or asthma often refrain from keeping pets in the home

(Apelberg et al., 2001). Regardless, exposure to pets was not included in the analysis and may have confounded the results.

In conclusion, the debate over the role of breastfeeding in relation to respiratory illnesses will most likely continue. Nonetheless, the positive association between maternal history of allergy and/or asthma and increased incidence of wheezing illnesses adds support to the outcomes of previous studies in this area showing increased incidence of wheezing or asthma in childhood with a maternal history of asthma (Wright et al., 2001b; Wright et al., 2000; Wright et al., 1995). After conducting an extensive literature review, this appears to be the only study that reveals that breastfeeding is not protective during infancy when maternal history of allergy and/or asthma is taken into consideration. Thus, additional research needs to be conducted to expand on this notion that infants, in addition to children, with a genetic predisposition for wheezing illnesses are not offered supplementary protection from breastfeeding,

Although this study did not find breastfeeding to be beneficial in reducing the prevalence of RSV positive illnesses both with and without the presence of wheezing among a group of infants with a strong maternal history of allergy and/or asthma, there is no reason to discourage families from this method of feeding. The socioeconomic status of the population under study as well as the small number of infants who never breastfed, who were never exposed to smoke, and who were of non-Caucasian origin could have potentially biased the results.

Numerous other studies have revealed a positive relationship between breastfeeding and a reduction in the number or severity of respiratory illnesses (Baker et al. 1998; Beaudry et a1., 1995; Cunningham, 1979; Cushing et al., 1998; Dell & To, 2001; Downham et al., 1976; Howie et al., 1990; Oddy et al., 1999; Raisler et al., 1999; Rylander et al., 1993; Saarinen, & Kajosaari, 1995; Wilson et al., 1998; Wright et al., 1998; Wright et al., 1989). The general benefits of breastfeeding are also too great to ignore. The infant and mother will increase their bonding while the infant receives a source of nutrition that was specially designed to meet his or her needs for growth and development. It remains important to encourage exclusive breastfeeding for the first six months of life and breastfeeding alongside supplemental foods until at least one year of age as recommended by the American Academy of Pediatrics (1997) and the American Dietetic Association (Dobson & Murtaugh, 2001). These recommendations are also evident through the goals of Healthy People 2010 (U. S. Department of Health and Human Services, 2000).

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Appendix A

COAST Consent Form

Reapproval _____

S. Engelba gh, MS, 101

Chairperson, St. Mary's IRB

Date_____

Version 6(2/23/1999)

PATIENT INFORMATION AND CONSENT FORM

STUDY TITLE: Cytokine Dysregulation, Viruses, and Childhood Asthma

PRINCIPAL INVESTIGATOR: Robert F. Lemanske, Jr., M.D.

CO-INVESTIGATOR: James E. Gem, M.D.

INTRODUCTION:

This informed consent describes the procedures and your role as a participant in this research study. Before agreeing to participate in this research study, it is important that you read and understand the following explanations of the proposed procedures. Please read this information carefully and do not hesitate to ask the study doctor or study coordinator any questions. You must sign this informed consent before you and your child may enter the study.

THE NATURE AND PURPOSE OF THIS STUDY:

Asthma is a growing medical concern particularly in children, causing recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. Although asthma may begin soon afterbirth, the natural history of the disease is poorly understood. Both genetic (one or both parents having a history of allergies or asthma) and environmental (specifically viral respiratory tract Infections) factors have been considered to be important in the development of asthma. Identification of genetic markers of asthma may allow screening of high-risk children, permitting better targeting of avoidance measures. Many young children wheeze during viral respiratory infections, but the relationship of these episodes to the development of asthma later in life is not well understood. Studies of young children are needed to test the suspicion that genetic or inheritable factors, combined with early lower respiratory infections, may predict the future development of asthma. The main purpose of this study is to evaluate whether the development of childhood asthma requires the presence of a genetic component and an environmental component (development of a clinically significant lower respiratory tract infection in the first year of life). If you agree to participate In this study, you will be one of approximately 200 families enrolled. This study is being conducted at this center only and is funded by the National Institutes of Health (NIH).

WHAT DOES STUDY PARTICIPATION INVOLVE?

This study will be conducted over a three year period (approximately). It will begin at the time you sign this consent and will continue until your child is three years old. You may be eligible for this study if you are expectant parents, at least one of which has a history of allergies or asthma. Eligibility will be determined at a prescreen visit before the birth of your baby. If you are eligible and do decide to participate, you will need to visit the study center at least six times during the three years of the study. Three of the study visits will take place at your child's primary care provider's office. Each of these visits will last approximately 1/2 to 1 hour.

Study Procedures

Parent medical and family history (once)
Update parent allergy/asthma/family history (nine times)
Child physical exam (nine times)
Parent allergy skin testing (one time for each parent)
Parent blood draw for laboratory tests (onetime for each parent)
Cord blood sample at birth
Child blood draws for laboratory tests (three times)
Child questionnaire (nine times)
Nasal mucus sampling from child (minimum nine times and with any occurrence of lower respiratory infection)
Nasopharyngeal throat swab samples from child (minimum nine times and with any occurrence of lower respiratory infection symptoms)

Explanation of study procedures

Blood draws To evaluate the possible genetic phenotype (hereditary) and environmental components of asthma, blood samples will need to be obtained from both parents and your child. The blood samples will be obtained from a vein and will be tested for immunologic factors to help us learn more about how heredity influences the development of allergies and asthma. Your child's blood will also be evaluated to see how the type of viral infections he/she may have had has affected these factors. Your baby's blood (approximately 1 tablespoon) will be obtained three times during the three years of the study. One blood sample will be obtained from each parent.

DNA Testing As an additional question, we are asking you to consider permitting us to processes and to store a portion of the blood sample obtained from you and your child for future DNA examination. We anticipate that new knowledge about the asthma and allergy genes may be available in the next several years. Therefore, we are asking you now to consider the storage of blood samples in anticipation of these future scientific discoveries. The blood samples from you and your child could contribute to a better understanding as to how and why asthma and allergies may be inherited.

If you agree to the storage of blood for future DNA research, it is essential that we are able to update your medical history at the time the DNA would be evaluated in the future. Therefore, please let the study coordinator knows if you move or change doctors so that you can provide us with this information. If significant changes in your health do occur in the future, we may ask your permission to obtain a second blood sample to permit a comparison with the sample to be drawn shortly. Dr. Lemanske may also want to use your stored DNA as a shared research effort with other researchers investigating the origins of childhood asthma.

Since this is a research project and not part of your regular medical care, we do not intend to use the results of this study to determine your risk of developing asthma or allergic disease. While we hope this research may help someday lead to a test that will identify people with an increased risk of asthma or allergic disease, we do not know if that will happen. Even if a test is developed, a number of problems may occur that can make it risky to use the test to diagnose patients. The test may not be accurate or reliable for everyone, it may not lead to more effective medical treatment, or it might actually be harmful (see the Risks section). For these reasons, no results from the testing of your blood sample will be shared with you, your doctor, or anyone else. In other words, this part of the study will not help you understand your family's risk of developing asthma or allergies. See the "Alternatives" section for other ways your risk may be determined.

It is important for you to know that if you choose not to have some of your or your child's blood stored for future DNA analysis, you and your child are still eligible to participate fully in this research project.

Let us know whether Dr. Lemanske or others may use you and your child's DNA for future research by putting your initials by as many choices that apply:

MOTHER:

____we may not use you or your child's DNA for any future research or share it with other investigators.

____may use you and your child's DNA for research only as it relates to asthma or allergic disease at our site.

____we may use you and your child's DNA for asthma or allergy research being conducted at other sites. All identifying information will be removed from the specimen prior to sharing with another researcher.

____we may use you and your child's DNA for other asthma and allergy research or share it with other researchers only after contacting you and getting your permission.

FATHER:

____we may not use you or your child's DNA for any future research or share it with other investigators.

____we may use you and your child's DNA for research only as it relates to asthma or allergic disease at our site.

____we may use you and your child's DNA for asthma or allergy research being conducted at other sites. All identifying information will be removed from the specimen prior to sharing with another researcher.

____we may use you and your child's DNA for other asthma and allergy research or share it with other researchers only after contacting you and getting your permission.

Allergy skin testing: Expectant fathers will be skin tested at the pre-screen visit and mothers within the first two months following the birth of your baby. Fourteen drops of dissolved extract of common allergens (such as house dust mite, pollen, grass) will be placed on the skin of your forearm and your underlying skin will be lightly pricked with a sterile disposable needle. Fifteen minutes later, your skin will be inspected for localized redness and swelling.

Nasal mucus sampling: A bulb or regular syringe/tube will be used to collect the mucus from your child's nose. Up to three milliliters (about half a teaspoon-dependant upon size of child) of sterile salt water will be administered to each nostril by squeezing the bulb/regular syringe. The bulb/regular syringe will then be released, suctioning the fluid back into the bulb/syringe to help wash out the small amount of nasal secretions that are normally present in all noses.

Throat swabs: To collect the sample, your child's throat will be swabbed with a cotton- tipped applicator using the normal procedure for throat cultures.

Visits:

Prescreen Visit:

This visit will take approximately 1/2 to 1 hour and must occur before the birth of your baby. It is preferable that both parents be present at this study visit; however, it is not required. During this visit at the study center, the study coordinator will ask you questions about your medical history, particularly your history of allergies and asthma, The study coordinator will also perform allergy skin testing on expectant fathers to help determine whether you are eligible to participate. Mothers will have allergy skin testing and a blood sample obtained after the birth of your child. This visit will be scheduled at the study center within two months after the birth of your child at your convenience. Fathers will have a blood sample drawn after the birth of the baby as well. The blood samples will be tested for immunologic factors to help us learn more about how heredity influences the development of allergies and asthma.

Birth of your baby:

There is a possibility that you may not be eligible for the study even after you have signed the consent form. This may be the case if your infant would have an Apgar score of six or less at five minutes of age. An Apgar score is given at birth and again five minutes after birth by a physician as an indicator of a newborn's health status. If your infant is delivered prematurely (before 37 weeks gestation) or very late in gestation (43 weeks or more) you will not be eligible. Similarly, if your baby is born with any significant birth defects or newborn illnesses, you will not be able to participate. If your family is eligible after the birth of your baby, a sample of your baby's cord blood will be obtained at the hospital. This blood will only be tested for immunologic factors to help us learn more about how heredity influences the development of allergies and asthma. This blood is obtained from the placenta or "afterbirth" tissue and does not involve any discomfort to your newborn baby.

Visits 1 and 2:

These visits will take approximately 1 hour (this includes the exam with your child's MD,

the study portion of the visit will add approximately 15-30 minutes) and will be done when your baby is approximately 2 and 4 months old during scheduled well-baby checks at your child's primary health care provider's office. A brief update of the parental questionnaire completed at the prescreen visit will be done. A child's questionnaire will be completed to evaluate your child's health since birth. Questions about your home environment such as where your child usually sleeps will also be asked to help us evaluate the role of environmental factors on the possible development of allergies of asthma. Your child will be seen by his/her primary care provider and will have a physical examination. To evaluate how viral respiratory infections may impact the development of asthma, nasal mucus/throat swab sampling will be obtained to look for viruses in the samples.

Visit 3:

This visit will be performed when your child is approximately 6 months old. The visit will take approximately 1 hour and will be scheduled at the study center. The procedures at this visit include a physical examination of your child by a physician, parent and child health questionnaires, and nasal mucus/throat swab samples.

Visit 4:

This visit will be performed when your child is approximately 9 months old. The visit will take approximately 1 hour and will be scheduled at either the study center or your child's primary health care provider's office. The procedures at this visit include a physical examination of your child by a physician, parent and child health questionnaires, and nasal mucus/throat swab samples.

Visit 5:

This visit will be completed when your child is approximately one year old and will be scheduled at the study center. Procedures at include a physical examination of your child by a physician, parent and child health questionnaires, nasal mucus/throat swab samples, and blood samples from the child.

Visit 6:

This visit will be done when your child is approximately I Y2 years old. Visit procedures will be the same as at visit 3.

Visit 7:

This visit will be done when your child is two years old and will be identical to visit 5.

Visit 8:

This visit will be performed when your child is 2V years old and will be the same as procedures outlined for visit 3.

Visit 9:

This visit will be done when your child is three years old and is the same as visit 5.

To evaluate how viral respiratory infections may impact the development of asthma, collection of nasal mucus and throat swab samples will also be required when your child becomes ill with certain respiratory infection symptoms. Respiratory infections are characterized by fever, wheezing, and/or coughing, and chest/nasal congestion. The collection of these samples will be done at the time of presentation to your child's physicians clinic for a "sick visit", as a home visit,

or at the study center and should ideally be performed within 72 hours of the onset of his/her symptoms meeting the predetermined criteria for the study.

WHAT ARE THE BENEFITS OF STUDY PARTICIPATION?

There is not likely any direct medical benefit to you or your child for participation in this study. It may be a benefit to you and your child's primary physician to have information regarding virus identification from nasal mucus and throat samples available after sampling. The societal benefits of this study may be invaluable. The information we collect about how hereditary and environmental factors impact on the development of asthma could be helpful in addressing the issues surrounding primary prevention of childhood asthma in the future. Some people also find satisfaction in contributing to scientific knowledge.

WHAT ARE THE RISKS?

Drawing blood from a vein may cause discomfort, possible bruising or swelling at the site of injection, and on rare occasions, a minor infection may result from this procedure. You and your child may have a cream celled EMLA applied to your skin before the needle stick, which can decrease the hurt and may cause a rash. Side effects are unlikely with the use of EMLA® cream due to the small dose absorbed.

DNA will be extracted from your blood and analyzed for possible variations in certain genes related to asthma, allergic disease, and respiratory infections. Should your child develop asthma, and should this research result in the identification of a genetic link to the development of asthma, effect of this genetic knowledge will be irrelevant for your child since the condition has already been diagnosed. Should your child not develop asthma, but through testing it is learned that your child has the genetic makeup that is associated with an increased risk for the development of asthma, there is the remote possibility that this knowledge could affect insurability for your child. However, a number of facts are important for you to know. First, no study records or testing information will be released to insurance carriers unless you so request. Second, your insurance carrier will only know that this information has been collected if you disclose it to them. Finally, it is illegal in the state of Wisconsin for employers to discriminate against you on the basis of this genetic information. Federal law provides limited protection against discrimination by insurance companies based on genetic information, but the law does not apply to every situation.

Your child may experience mild irritation at the opening of the nose where the bulb syringe is placed during the nasal mucus collection, however this is very rare. Instilling sterile buffered saline should not burn, but may feel uncomfortable for a few minutes secondary to a dripping feeling until the solution is auctioned back into the bulb syringe. There could bean extremely rare occurrence of an abrasion to the nasal lining if the child were to suddenly jerk his/her head during attempts to obtain the mucus sample. This is very unlikely since the tip of the bulb syringe is very soft and will not be advanced into the nose to any significant extent.

Allergy skin testing carries the risk of itching and burning at the site of the test, and the discomfort of the needle prick. In extremely rare cases, exposure of allergic people to an allergen can result in "anaphylaxis", a term which describes a serious combination of medical problems including severe asthma (chest tightness, coughing, shortness of breath), hives or a rash on your skin, swelling of your skin or tongue, itchiness of your skin and fall in blood pressure. In very rare instances anaphylactic reactions can result in death. Facilities and medications are available for treatment of severe allergic reactions and anaphylaxis if they should occur and a physician will be nearby when the skin test is performed.

WHAT ALTERNATE THERAPIES TO STUDY PARTICIPATION ARE AVAILABLE?

You do not have to participate in this research. As alternatives to participating in this study, you and your child can choose not to participate or to participate in other investigational studies. You and your child would then receive the usual well baby care and check-ups. It is important to remember that this study will not help you learn your risk of asthma or allergic diseases. If you would be interested in determining your risk of developing asthma or allergic disease once such a test becomes available, reliable, and helpful, you should periodically ask you doctor or a genetic counselor if the test is available, and ask him or her to discuss its advantages and disadvantages with you. (A genetic counselor is professionally trained to help you understand what genetic test results mean and don't mean for you and members of your family).

WILL THERE BE COMPENSATION FOR INJURY?

In the event that physical injury occurs as a result of this research, medical care, including hospitalization, is available; however the University of Wisconsin, Meriter Hospital, and St. Mary's Hospital do not automatically provide reimbursement for medical care or other compensation. If physical injury is suffered in the course of the study or for more information, please notify the investigator in charge, Dr. Robert Lemanske at (608) 263-8539.

WILL THERE BE ANY COSTS TO YOU?

There will be no cost for any study-related visits, procedures, or blood tests at the study center as well as study-related nasal mucus and throat swab samples performed at your child's physician's clinic when your child is ill with certain respiratory infection symptoms.

VOLUNTARY PARTICIPATIONIW1THDRAWAL FROM STUDY:

Participation in this study Is entirely voluntary. You may decide not to participate or to discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. You are encouraged to contact the study doctor or coordinator should you decide not to continue your participation in this study. Deciding not to participate will not affect your baby's medical care in any way. Although it is not anticipated, your participation in this study may be terminated by the study center if you do not follow study Instructions or for administrative reasons. If you allow the storage of blood for DNA testing and once the researchers begin studying your DNA, there are two ways you can withdraw from this aspect of the study. One is to ask Dr. Lemanske and his colleagues to remove all identifying information associated with your sample. The other is to ask them to destroy any of your remaining DNA or tissue. Both of these options (especially the second one) could be damaging to the research project, especially if the information from your sample turns out to be important. Therefore we are asking you to think very carefully about the reasons why you might change your mind, and be as sure as you can that you will not withdraw after your sample is taken. If you initially agree to the storage of blood for DNA testing, and then later decide to not allow the DNA testing to proceed, you may still participate in all other aspects of the study if you wish.

WILL THERE RE ANY COMPENSATION?

Recognizing that this study will require extra time and effort, you will be paid $500.00 for your participation. This amount will be prorated according to the following scale based on study visits completed:

Screening visits:

Father Skin test & blo&1 draw $25.00

Mother Skin test & blood draw

(After birth of baby) $25.00

Visits 1-9: $50.00 each

Total = $500.00

In addition, your child will be paid a total of $15.00 for nasal mucus and throat swab samples that are obtained from your child at the time of illness.

We highly encourage that a portion of this money be used for the betterment of your child's development (i.e. investments, savings, or an educational fund). Usable items that will serve doubly as reminders (such as stickers, medicine droppers, magnet, etc.) will be given after every study visit in appreciation of your commitment to helping us learn more about asthma and allergic disease.

WHO WILL SEE THE STUDY RECORDS?

Your study physician and coordinator will treat your identity with professional standards of confidentiality. Your medical records may be accessed and reviewed by study personnel for the purpose of verifying medical history pertinent to determining your eligibility for study participation. Some aspects of the medical information gathered from this study (for example, the virus identification reports that will be sent to your primary care provider) may become part of your child's permanent medical record. No DNA information collected by the study doctor and staff will become part of your permanent medical record.

Your records regarding this study may be subject to review by appropriate officials of the University of Wisconsin should the need arise. No study records or information will be released to insurance carriers unless you so request. Your insurance carrier will only know that this information has been collected if you disclose it to them. Additionally the medical information and records gathered from this study may be submitted to the National Institutes of Health and their agents. The results of this study may be published in scientific journals or be presented at medical meetings, however you and your child will not be identified by name.

WHO WILL ANSWER QUESTIONS?

Please feel free to ask questions at anytime. You may take as long as necessary to decide whether you wish to participate in this study. In addition, if you have questions concerning your rights as a research subject, you may contact one of the patient representatives at (608) 263-8009.

The doctor in charge of the study is Dr. Robert F. Lemanske, Jr. He is a pediatrician specializing in allergy and immunology and is a Professor at the University of Wisconsin Medical School. If you have any questions about this research or believe you have sustained an injury, you can reach Dr. Lemanske at his office at the University of Wisconsin at (608) 263-6180 or (608) 263-8539.

CONSENT **FOR PARTICIPATION AND FUTURE USE OF DNA SAMPLES**

I have read this consent form. I have voluntarily given permission for myself and my child's participation in this research project. I am aware t will receive a copy of this informed consent.

Signature (mother)_____Date_____

Signature (father)_____Date_____

Signature of person obtaining consent_____Date_____

Baby's full name_____

(To be filled in after birth)

Signature of person recording baby's name after birth_____

If you have any questions or problems please contact:

Robert F. Lemanske, Jr., M.D. (608)263-8539.

Appendix B

Feeding History

COAST **Childhood Origins of ASThma**	**Data Base Additions** **March, 2000**	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

1 If you breast fed your baby, at what age (in months) did you completely stop breast feeding?

_1 1 month
_2 2 months
_3 3 months
_4 4 months
_5 5 months
_6 6 months
_7 7 months
_8 8 months
_9 9 months
_10 10 months
_11 11 months
_12 12 months
_13 Stop when 12-18 mo. of age
_14 Stop when 18-24 mo. of age
_15 Stop when 24-30 mo. of age
_16 Still breast feeding
_17 Did not breast feed.

3. If you supplemented with formula during the time that you breast fed your baby, at what age (in months) did you start supplementing?

_1 1 month
_2 2 months
_3 3 months
_4 4 months
_5 5 months
_6 6 months
_7 7 months
_8 8 months
_9 9 months
_10 10 months
_11 11 months
_12 12 months
_13 Never used formula, started feeding milk about one year

Appendix C

Sex of the Child

COAST Childhood Origins of ASThma	Children's Questionnaire VISIT ONE	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

Please answer the questions as frankly and accurately as possible about your child.

Choose ONE box per question unless otherwise indicated. ALL INFORMATION OBTAINED IN THE STUDY WILL BE KEPT CONFIDENTIAL.

A. Sex of your child _1 Male _2 Female

Appendix D

Ethnicity

COAST Childhood Origins of ASThma	Personal Data Form	Date __ __ __ __ __ __ __ __ Interviewer _____ Interviewee ID # _____

RACE
16. **Mother**

_1 Caucasian
_2 African-American
_3 Asian/Pacific Islander
_4 American Indian/Eskimo
_5 Hispanic / Latino
_99 Other, specify _____

RACE
25. **Father**

_1 Caucasian
_2 African-American
_3 Asian/Pacific Islander
_4 American Indian/Eskimo
_5 Hispanic / Latino
_99 Other, specify _____

Appendix E

Smoke Exposure

COAST Childhood Origins of ASThma	Parental Questionnaire VISIT ONE	Subject ID: _____ Subject Initials __ __ __ Visit date _ _-_ _-_ _ _ _ Month day year Interviewer _____ Interviewee ID # _____

45b. Do you still smoke cigarettes? _1 Yes _2 No

47. Do you now smoke a pipe or cigar? _1 Yes _2 No

COAST Childhood Origins of ASThma	Parental Questionnaire VISIT TWO	Subject ID: _____ Subject Initials __ __ __ Visit date _ _-_ _-_ _ _ _ Month day year Interviewer _____ Interviewee ID # _____

46. Since the last visit, has there been a change in your smoking status? _1 Yes _2 No

46a. If yes, please mark the appropriate box.
_1 Increased _2 Decreased _3 Quit

47. Do you now smoke a pipe or cigar? _1 Yes _2No

COAST Childhood Origins of ASThma	**Day Care Environmental Questionnaire**	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

4. Is your child exposed to passive smoke (cigarette) at day care _1 Yes _2 No

COAST Childhood Origins of ASThma	**Residential Environmental Questionnaire**	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

4. Is your child exposed to passive smoke (cigarette) in your home? _1 Yes _2 No

-COAST Childhood Origins of ASThma	**Children's Questionnaire** **VISIT TWO**	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

SMOKE EXPOSURE

117. Does child's mother smoke? _1 Yes _2 No _3 N/A

120. Does child's father smoke? _1 Yes _2 No _3 N/A

123. How many people who live in child's home smoke? _____

124. Does anyone else who takes care of child smoke? _1 Yes _2 No

Appendix F

Maternal History of Allergy and/or Asthma

COAST Childhood Origins of ASThma	**Children's Questionnaire** **Allergy Skin Test Results**	Subject ID: _____ Subject Initials __ __ __ Test date ___ ___ ___ Month day year test completed by : _____ Interviewee ID # _____

2.	Alternaria	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
3.	Tree Fluid	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____mm
4.	Cladosporium	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
5.	Grass Mix	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
6.	Aspergillus	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
7.	Ragweed	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
8.	D. Farinae	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
9.	Weed Mix	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
10.	D. Pteryn	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
11.	Dogs	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
12	Cockroaches	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm
13	Cats	_1 Yes _2 No	____ mm/ ____ mm____ mm/ ____ mm

COAST Childhood Origins of ASThma	**Data Base Additions** **November, 1999**	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

Questionnaire to be completed by parent regarding self.

5. Has your asthma diagnosis been confirmed by an MD?
   _1 Yes _2 No _3 N/A
   If yes, date (5b) _____ Name of MD (5c)_____

COAST Childhood Origins of ASThma	**Parental Questionnaire** **VISIT ONE**	Subject ID: _____ Subject Initials __ __ __ Visit date _ _-_ _-_ _ _ _ Month day year Interviewer _____ Interviewee ID # _____

ABOUT YOUR HEALTH

1. Have you ever had allergies or asthma? _1 Yes _2 No

2. Have you ever had an asthmatic attack? _1 Yes _2 No

Asthma . . .

3. About what age did the asthma start?
   _1 < 5 years
   _2 5-10 years
   _3 11-20 years
   _4 21-30 years
   _5 31-40 years
   _6 >40 years
   _7 N/A

4. Was asthma confirmed by a doctor? _1 Yes _2 No _3 N/A

COAST Childhood Origins of ASThma	**Parental Questionnaire** **VISIT TWO**	Subject ID: _____ Subject Initials __ __ __ Visit date _ _-_ _-_ _ _ _ Month day year Interviewer _____ Interviewee ID # _____

ABOUT YOUR HEALTH

1. Since the last visit, have you developed allergies or asthma? _1 Yes _2 No

4. Was asthma confirmed by a doctor? _1 Yes _2 No _3 N/A

Appendix G

Wheezing Status

COAST Childhood Origins of ASThma	Respiratory Illness History Interview	**Subject ID:_____** **Subject Initials __ __ __** **Visit date ___ ___ ___** **Month day year** **Interviewer** **_____** **Interviewee ID # _____**

3. How many days ago did the illness begin? (If convalescent follow up, ask:) ***How long did the illness last?***

__1 1-3 days
__2 4-6 days
__3 7-10 days
__4 11-14 days
__5 15-21 days
__6 > 21 days

3a. ONSET DATE:

_____/_____/_____

3b. Have you taken your child to a health care professional for these symptoms at any time during this illness? _1 Yes _2 No

3c. If yes, please list date(s) and location(s):

_____

4.Has your child received any medicine at all since this illness began? *(If convalescent ask:**... since the MD visit**)* __1 Yes __2 No

IF YES, WHAT WAS THE MEDICINE? (Check all that apply)

1. ___ Tylenol/Motrin
2. ___ OTC Antihistamine (Triaminic, benedryl, etc.)
3. ___ Albuterol Elixir
4. ___ Antibiotic _____
5. ___ Anti- fungals (such as Gentian violet or Nystatin)

6. ___ OTC Cough syrup (pediacare, Triaminic)
7. ___ Albuterol Nebulizer treatments/ Albuterol inhaler
8. ___ Oral Steroids (such as prelone, prednisolone or prednisone)
9. ___ Inhaled steroids such as fluticasone, budesonide, triamcinolone, or beclomethasone)
10. ___ Nasal Steroids (such as Flonase)
11. ___ Long term controller medication (other than steroids), such as Cromolyn or Montelukast
12. ___ Other Bronchodilators (such as Serevent)
13. ___ Prescription antihistamine (Zyrtec, Claritin, Allegra)
14. ___ Prescription cough medicine (such as Promethazine with codeine)
15. ___ Other med – gastrointestinal (Zantac, metochlopramide)
16. ___ Other med – skin
17. ___ Other med – ENT (eye and ear drops)
18. ___ OTC cold medicines
19. ___ OTC decongestants
99. ___ Other _____

7. Overall, is your child.....
   - __1 improving
   - __2 continuing to become more sick
   - __3 staying the same for the past 1-2 days
   - __4 staying the same for the past 3-5 days

Did ***(Does)*** your child have any of the following: (check all that apply)

8. General symptoms of.....
   - __1 lethargic, “irritable”, “not feeling well”
   - __2 not eating as well as prior to illness
   - __3 having diarrhea
   - __4 stuffiness, noisy nose breathing
   - __99 other _____

9. wheezing? __1 Yes __2 No
11. turned blue? __1 Yes __2 No
12. Produced phlegm from the chest or had chest congestion? __1 Yes __2 No

COAST Childhood Origins of ASThma	**Respiratory Illness Assessment**	**Subject ID:_____** **Subject Initials __ __ __** **Visit date ___ ___ ___** **Month day year** **Interviewer** **_____** **Interviewer ID # _____**

5. Please check (_) the presence of the following symptoms (_=1 _=0)

a. conjunctivitis		h. rales	
b. otitis		i. rhonchi	
c. rhinorrhea		****j. wheezing**	
d. pharyngitis		k. tachypnea	
e. cough during exam		l. retractions/belly breathing	
f. cyanosis		m. diarrhea	
g. vomiting		z. Other	

8. Treatment: (mark all that apply)

a. _ Bronchodilator nebulizer treatment (in office)-
Improved __1 Not improved __2

d. __ Bronchodilators (such as albuterol)
Oral _____1 Nebulizer_____2

f. __ Corticosteriod
__1 oral (such as prelone or prednisolone)
__2 inhaled (such as fluticasone, budesonide, or beclomethasone)
__3 nasal (such as Flonase)

g. __ Other long-term controllers (non-steroids), including Cromolyn and Montelukast

9. Diagnosis (mark all that apply)

d. ____ Bronchiolitis
e. ____ Wheezing Illness (non-specific)
h. ____ Reactive Airway Disease
i. ____Asthma or Asthma Exacerbation

COAST Childhood Origins of ASThma	**Children's Questionnaire** **Source Document** 6/29/01	Subject ID: _____ Subject Initials __ __ __ Visit date ___ ___ ___ Month day year Interviewer _____ Interviewee ID # _____

10. Current Medication	start date	stop date	last taken	dose time
a.	1	2	3	4
b.	1	2	3	4
c.	1	2	3	4
d.	1	2	3	4

11. Pulmonary Auscultation (check all that apply)

□1 No wheezing
□2 Wheezing on inspiration or expiration
□3 Adventitious sounds other than wheezing:
□a Rales □b Rhonchi
□4 If applicable, describe sounds _____

Physical Exam * **ND** = not done **N** = normal **A** = Abnormal

Systems	**ND**	**N**	**A**	**Description of Abnormalities**
12. Hair and Skin 12a. Atopic Dermatitis/ Eczema __ yes __ no 12b. Uticaria/Angioedema __ yes __ no 12c. Rash (nonspecified) __ yes __ no	1	2	3	4