RELATIONSHIP BETWEEN ILLNESS AND ADIPOSITY IN CHILDHOOD

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BY

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ABSTRACT

A relationship between nutrition and survival is deep rooted in history. Presently, there appear to be two primary theories concerning an association between illness and adiposity in childhood. The first theory posits that increased illness is the result of high adiposity. The second theory, “infectobesity”, posits that increased adiposity is virus-induced. Although an association between infection and nutrition is not a novel concept, the focus has now shifted from undernutrition to the impact of overnutrition on childhood illness. Especially in children, studies on this association are sparse.

The aim of this secondary data analysis research project was to investigate the relationship between illness in the first two years of life and percent fat mass at five years of age in a cohort of children who have been studied since birth for the effects of DHA supplementation during pregnancy on childhood cognitive function. Secondary research questions granted further investigation into the relationship between illness in the first two years of life and BMI at four and five years of age. Anthropometric measures were collected at respective biannual study visits. Illness data was collected from the medical record. Only medically documented illnesses were included. Illnesses were categorized into infectious, allergic, unknown, or non-applicable categories. Infectious illnesses were further sub classified according to etiology (viral, bacterial, fungal, or unknown).

Illness in the first two years of life was not found to have a statistically significant association with percent body fat at five years of age. Infectious illness, when combined with the unknown illness category, was found to have a statistically significant association with BMI at four years of age (p-value .025). Despite the 42.5% decrease in sample size from four years to five years, infectious illness was found to be trending toward significance. BMI at five years of age was found to be significantly correlated to percent fat mass at five years of age.

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Chapter One

INTRODUCTION

Presently, there appear to be two primary theories concerning an association between illness and adiposity in childhood. The first theory posits that increased illness is the result of high adiposity. Proponents of this theory claim that the immune system, the protective defense system responsible for the prolonged existence of the human race, is adversely affected by relatively high adiposity (1). The proposed mechanism is that adipose-tissue macrophages (ATMs) can be increased up to three-fold in obese adipose tissue compared to lean adipose tissue. Additionally, mast cells found in subcutaneous fat contribute to inflammation by stimulating the release of the adipocytokines IL-6 and IL-γ. Obesity-associated inflammation is thus linked to metabolic dysfunction. It is hypothesized that the number of ATMs and their polarization status in the adipose tissue is influential in obesity pathogenesis (1). Adipocytes and preadipocytes act similarly to macrophages by showing phagocytic function when exposed to microbes (2). These findings, along with a relatively strong relationship between obesity and C-reactive protein (CRP) levels (3), are the primary basis for this first theory.

The second theory posits that increased adiposity is virus-induced. This theory can be summarized by the term “infectobesity”, or obesity of infectious origin. Proponents of this theory state that obesity could hypothetically be treated with cause-specific approaches such as pathogen-specific vaccines and antimicrobial therapies (2). Evidence for this new approach is embedded in human epidemiological studies and studies of experimentally-induced infection in animal models (2). Longitudinal studies in previously infected humans have been used to observe adiposity alterations following natural infection with a certain microbe, human adenovirus 36 (Ad36). Both kinds of evidence support a causal relationship between viral infection and increased adiposity (2).

Statement of purpose

There is uncertainty about the relationship between illness and adiposity in childhood. The purpose of this project is to evaluate childhood illness during the first two years of life and adiposity at five years of age in a cohort of children who have been studied since birth for the effects of DHA supplementation during pregnancy on childhood cognitive function.

Primary research question

Does illness in the first two years of life relate to percent fat mass at five years of age?

Secondary research questions

Does illness in the first two years of life relate to BMI at four years of age?

Does illness in the first two years of life relate to BMI at five years of age?

Does BMI at five years of age relate to percent fat mass at five years of age?

Chapter Two

LITERATURE REVIEW

Introduction

In the developed and developing world, the prevalence of obesity has been increasing since the 1960's with exponential increases beginning around the 1980s (4). In 2004, children and adolescents today, notably those in the United States, were predicted to be the first generation to not outlive their parents because of childhood obesity (5). The 2007-2008 National Health and Nutrition Examination Survey revealed a 0.6% decline in obesity rates among 2-5 year olds but a 4.5% increase in obesity rates among 6-11 year olds since 2005 (6). Overall, among children aged 2-19 years, obesity rates have increased 1.4% from 2005 to 2007 (6). From this data, one researcher concluded that childhood obesity rates in the United States appear to be plateauing (7). Despite this assertion, the overweight and obese BMIs are still prevalent thereby placing these children at increased risk for acute and chronic disease. Researchers have sought ways to help children avoid obesity. These include behavioral and environmental interventions. There is limited evidence that obesity may itself cause illness; and even more limited evidence that illness can cause obesity. This review of literature discusses childhood adiposity briefly then proceeds into the evidence supporting two hypotheses concerning the relationship between adiposity and illness.

This review of literature used the PubMed and CINAHL electronic databases using the search terms *BMI*, *adipose tissue*, *adiposity*, *body composition*, *body fat*, *health*, *health status*, *child*, *child preschool*, *common cold*, *prevalence*, *incidence*, *Nasopharyngitis*, *immunodeficiency* and *antibodies*. Search results were restricted to articles in English, human studies, studies in children and studies in the United States. The only exception is the latter. Due to limited findings, studies performed outside the United States were included.

Adiposity and Illness

Obesity is a multisystem, multifactorial disorder characterized by adiposity levels in excess of *normal* and adversely affecting health (1, 8, 9). In 2011, the World Health Organization (WHO) estimated the prevalence of childhood obesity to be approximately 43 million children (10). Currently, the childhood obesity rate in the United States is 17% (11).

An association between infection and nutrition is not a new concept. Historically, the association focused on nutrition as a key component in fighting infectious disease conditions such as bacterial infections, tuberculosis and leprosy. The importance of adequate nutrition to keep the immune system strong has not lessened. However, now the question pertains to the association between overnutrition and childhood illness. Although many doctors agree that coughs, colds and related symptoms are usually of no serious concern (12), identifying an association between illness and overnutrition could uncover a key risk factor, or possibly an integral etiology, underlying the childhood obesity epidemic.

Methods used to measure adiposity

Technological advances have allowed for more accurate measures of childhood adiposity. Methods in recent literature include Body Mass Index (BMI), skinfold thickness, dual-energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI), and air displacement plethysmography (BOD POD™ Body Composition System, COSMED USA). Some researchers have also measured serum/plasma adipocytokines, hormones secreted by adipocytes, but these cannot be linked directly to fat mass (8). As is detailed below, some of these options are more accurate and precise than others for determining body composition in children.

Body Mass Index (BMI) is the most common measure to classify a child's weight status due to its low expense and ease of measurement. Calculated by a person's bodyweight in kilograms divided by their height in meters squared, BMI is often used as a surrogate indicator of adiposity status. BMI assesses the presence of excess weight. Therefore, it operates on the assumption that a weight increase unaccompanied by a simultaneous height increase equates to a rise in fat mass. Not only is this not always the case, but also, BMI does not differentiate between lean and fat mass thus it is not a direct measure of adiposity (3, 11). Nonetheless, BMI has been validated as an accurate indicator of increased fat mass in children (13-15).

Skinfold thickness (SKF) is a technique which measures subcutaneous fat to estimate body fat utilizing validated mathematical regression equations. This technique assumes that a direct relationship exists between total body fat and subcutaneous fat. The standardized procedure for measuring skinfold thickness is valid and reliable for estimating body fat; however, accurate measurements are highly dependent on the examiner. Thus, SKF are not always the most reliable option. None the less, SKF is one of the least expensive adiposity measurement techniques and therefore are commonly used by researchers and clinicians alike (16).

Bioelectrical Impedance Analysis (BIA) is another technique used to estimate adiposity. BIA functions on the principle of electrical conductivity speed throughout the different tissues of the body. Fat free mass contains more water, an excellent conductor of electricity, compared to fat tissue. Based on the electrical current speed, BIA is able to calculate an individual's body fat. The price of BIA can vary, but typically resides between SKF and the techniques discussed next.

Although reliable, BIA is not the most accurate measurement technique for one-time body fat measurements. Additionally, BIA results have been found to be influenced by a variety of variables including hydration status, body position, food and beverage consumption, ambient air and skin temperature, recent physical activity, and the electrical conductivity of the examining platform (17).

Dual-energy x-ray absorptiometry (DXA) is a more accurate technique to measure body fat than BMI, SKF and BIA. However, it is also significantly more expensive. DXA is unique in that it utilizes an x-ray to measure fat mass and can then provide regional information for that mass. However, its limited field of view poses a threat to accuracy, especially in obese adults. Beyond cost and it's limited field of view, DXA also exposes the participant to radiation while conducting its measurement (17).

Magnetic Resonance Imaging (MRI) is a technique used to measure organ size, structure, body fat, and regional fat distribution. Although MRI cannot calculate a percent fat mass, it is able to measure the volume of adipose tissue (specifically, subcutaneous adipose tissue (SAT) and intra-abdominal fat or visceral adipose tissue (VAT)) and skeletal muscle. A primary advantage to MRI is that, unlike DXA, MRI does not expose the subject to radiation. However, the long-term safety of MRI (especially in children), the very high cost of the test, and the tediousness of interpreting the test results make MRI an uncommonly used body composition technique (17).

Air Displacement Plethysmography (aka BOD POD™ Body Composition System) is considered one of the most accurate techniques available for body composition determination. Researchers have used the Bod Pod™ (COSMED USA) recently to determine childhood body composition. Operating according to the same principles as hydrostatic weighing, the Bod Pod™ is able to determine the body composition, amount of fat and fat-free mass, of the subject inside. Fat-free mass includes the mass of protein, water, bone, glycogen, and minerals. In approximately five minutes, the Bod Pod™ analyzes the relationship between pressure and volume to determine subject volume and is then able to determine body composition by calculating whole-body density (densitometry). Although the equation used to determine density can vary in adults, the Bod Pod™ utilizes the Lohman equation for all children less than seventeen years of age (18). On average, the Bod Pod™ costs 25-50% less than DXA (17).

Despite the technique of measurement, there are currently no standardized ranges to evaluate the measured adiposity (17).

Health consequences of excess adiposity

Under- and over-nutrition, both types of poor nutritional status, are associated with increased risk of infection. Similarly, infections are positively associated with poorer nutritional status in childhood

(19). Childhood obesity is associated with adult obesity and both are associated with increased risk of chronic disease such as diabetes, cardiovascular disease and cancer (20). Obesity in childhood has been found to increase the risk of respiratory (e.g., obstructive sleep apnea syndrome (OSAS), acute and serious respiratory infections), odontogenic (e.g., gingivitis, dental caries), and dermatological infections. Although no studies have been completed in children, obesity in adulthood has also been suggested to interfere with the pharmacokinetics of various drugs (such as antimicrobial drugs) (9). The implications of the prevalent over- and inappropriate use of antibiotics in childhood (21) on obesity is in need of further exploration (9).

The following sections will focus on two hypotheses regarding an association between adiposity and illness, specifically infection, allergy and asthma.

Adiposity: a cause of illness

Research is now finding that the immune system, the protective defense system by which the existence of the human race today can be largely attributed to, may be the system associated with poor health and disease (1). The following sections discuss the literature on associations between adiposity and common childhood illnesses including allergic conditions (e.g., allergies, asthma) and infectious conditions (such as upper respiratory infections (URI)).

Allergies and asthma

From 1997 to 2011, the prevalence of food and skin allergies in United States children increased 1.7% and 5.1%, respectively (22). In trying to understand the reason for this increase researchers have begun looking into other conditions which have increased as well. One hypothesis is that the increased asthma incidence is the result of increased inflammation, specifically an increase in T helper cell type 2 (Th2) responses. Researchers speculated that allergen exposure, such as to dust mites, would elicit the inflammatory response and cause a cascade of reactions (such as histamine release) resulting in a greater inflammation and asthma prevalence. However, upon investigation into this hypothesis came what is known as the Hygiene Hypothesis. The hygiene hypothesis describes the findings that increased allergen exposure in early life is inversely correlated with allergies later in life. As this is the opposite of the initial speculation, the hygiene hypothesis fails to supply an adequate explanation for recent increase in allergy prevalence. Furthermore, Rotsides et al. concluded that allergy symptoms and asthma in children have a strong, positive association after finding serum immunoglobulin-E (IgE) antibodies in his asthmatic subjects (23). From this finding, asthma and allergy researchers have concluded that the increase is asthma incidence is explained by an ongoing interaction between allergen exposure, hygiene, and lifestyle (24). Specific lifestyle factors currently under investigation include the adoption of the western diet, physical inactivity, and obesity (24).

Physical inactivity is positively correlated with asthma. The hypothetical cause is increased exposure to an indoor air pollutant (25). However, other researchers note a lack of association between physical activity and asthma or medical visits for wheezing (24). More research is necessary before the claim that physical inactivity is responsible for the increase in allergic diseases such as asthma can be definitive.

Similar to physical activity, the association between obesity and allergic diseases (e.g., allergies, asthma) has yielded inconsistent findings. Following interpretation of the NHANES 1999-2006 results, Visness et al. (3) found that, at the 95% confidence level, obese children had a higher risk of asthma and of having had an asthma attack within the last year, 1.68 and 1.97 times respectively, than that of children falling in the normal BMI category. The inconsistent definition of obesity (quartiles versus the AMA-recommended ranges) may explain why some papers based on NHANES data have not found an association (3). However, Scholtens et al. (26) and Porter et al. (27) recently found that children with a high BMI at 8 years of age who had a high BMI since at least the age of 6 years had a higher risk of both childhood and adult asthma, respectively.

Researchers have also found a fairly strong, positive relationship between obesity and C-reactive protein (CRP) levels, a commonly used serum marker to indicate inflammation. In analyzing the relationship of CRP to current asthma among non-atopic children, researchers found that the association between CRP and asthma (OR 1.45; 95% CI: 1.16, 1.18) was confounded by BMI. From the literature, it seems that researchers are suggesting that allergic and systematic inflammation operate independently but that both can lead to asthma (3).

Upper Respiratory Infections (URIs)

Upper respiratory infections (URIs) include nasopharyngitis, sinusitis, pharyngitis, laryngitis, and laryngotracheitis (28). Although common colds can exacerbate asthma (29), researchers suggest that the prevalence of URIs is positively associated with adiposity independent of asthma and allergies (28).

Nasopharyngitis, better known as the *common cold*, is a frequent adverse event in childhood (28). "Frequent colds" was defined as ≥ 4 colds during the previous year (30). Samuel Grief defines the common cold as inflammation of the nasal pathways resulting most often from a respiratory virus. The most likely symptom is nasal congestion or obstruction followed by sneezing, sore or scratchy throat, cough, hoarseness, headache, fatigue/malaise and fever (28). Grief cites Turner's 2011 (31) findings of the following common cold incidence rates in preschool, elementary and adolescent age groups: 6-10 episodes/year, 7-12 episodes/year and 2-4 episodes/year, respectively.

Today, it is recognized that the prevalence of the common cold is influenced by environment and microbial agents. However, the host's inflammatory response holds the greatest responsibility. In other words, although the viral infection may be the primary stimulus, it is the host's immune response that responds with inflammation (30).

One study did suggest that obesity impacts the immune response rate to respiratory syncytial virus (RSV) infection in children. However, the limitations in this study – selection bias, observational bias and recall bias – prevent much weight from being placed on these findings (32).

The proposed mechanism for this first hypothesis, that obesity-induced inflammation is a potential cause of childhood illness, is provided below to aid in hypothesis comprehension. Of note, this article is published by the Department of Immunology at St. Jude Children's Research Hospital; however, it does not specifically state whether it is discussing childhood or adult adipocytes.

"Adipose-tissue macrophages (ATMs)" are increased three fold in obese adipose tissue compared to in lean adipose tissue. This finding combined with the finding that mast cells contribute to inflammation by stimulating the release of the adipocytokines IL-6 and IL-γ, led to the conclusion that the immune system elicited by the adipocytes is responsible for the obesity-associated inflammation linked to metabolic dysfunction. From these findings came the hypothesis that the number of ATMs as well as their polarization status in the adipose tissue are influential in obesity pathogenesis (1). Researchers have also found that adipocytes and preadipocytes act similar to macrophages by showing phagocytic function when exposed to microbes (2).

Adiposity: an effect of illness

Although less research has been conducted on the topic, it has been hypothesized that high adiposity could be the result of illness. "Infectobesity" is the term used to refer to obesity of infectious origin. If true, this concept asserts that obesity could be treated with cause-specific approaches such as pathogen-specific vaccines and antimicrobial therapies. Since these treatment approaches are unconventional when compared to the non-specific lifestyle approaches used today, successful use of these approaches require the adoption of a new understanding of the obesity condition (2, 4, 9). Evidence for this new theory comes from a limited number of human epidemiological studies and experimental studies of infection in animal models (2). Longitudinal studies in humans have been used to observe changes in adiposity following natural infection with a human adenovirus, Ad36. Results of this research provide strong evidence of a causal relationship.

The role of human adenovirus Ad36 in human obesity is the primal finding showing this causal relationship (2). Organized into subgroups, A to F, based on their antigenic similarity, there are presently 51 human adenoviruses that have been identified. As a group, human adenoviruses have been implicated in infections of the upper respiratory and gastrointestinal tracts, and in conjunctivitis. However, human adenoviruses have also been found in asymptomatic patients. Of the 51 human adenoviruses, only Ad36 has been reported to play a role in human adipogenesis (2). Findings come from studies of twins and singletons with and without Ad36 antibodies (4, 33).

Since its initial demonstration in 1982,virus-induced obesity has been suggested to selectively cause a disruption in brain catecholamine pathways (34). The adipogenic role of Ad36 could be tested by exposing Ad36 infected and Ad36 naïve groups to the same microbe and comparing the body weight, body fat, and/or biochemical variables between the two groups (2). However, such studies in humans would not be ethical, therefore studies in animal models and human epidemiological studies are important

In studies on Ad36, its association with BMI and more direct measures of body fat seem to be consistent while its association with the serum lipid profile remains inconsistent. For example, one study found Ad36 to have a positive association with BMI z-score and waist circumference but not with serum lipid concentrations. While another study also found Ad36 to have a positive association with BMI, this study found it associated with increased serum cholesterol and triglycerides concentrations. The hypothesized explanation for this positive association with serum lipids is that Ad36 cells differentiate at a quicker rate thereby accumulating triglycerides at an enhanced rate. The hypothesized explanation for the positive association between Ad36 and BMI is that those who were naturally infected were not physically limited in weight expansion (35).

In one cohort study consisting of 502 adults from the United States, Ad36 antibodies were identified in 30% of the obese participants and in 11% of the non-obese participants. Obese, as measured using BMI, participants with the presence of Ad36 antibodies were found to have significantly higher body weight and the serum lipid profile of Ad36 antibody positive participants (1.29 ± 0.07) was significantly different from Ad36 antibody negative participants (1.70 ± 0.07), $p<0.0001$ (35). When interpreting these findings, it is important to note that many of these studies have not been on children in the United States (2).

Due to the plethora of vaccines available and the lack of support of the hygiene hypothesis (described above), a few explanations have been given for how viruses could be substantial contributors to the rising obesity levels. Regarding the environment, it is postulated that adipogenic microbes are interacting with the obesogenic environment and thus causing the individual to be more susceptible to both the virus and obesogenic behaviors (2). Regarding vaccinations, researchers have found lower levels of anti-tetanus IgG antibodies in vaccinated overweight versus vaccinated normal-weight children. Researchers have hypothesized the cause to be lower generation and/or functioning of the antibody secreting plasma cells, and/or interference of vaccine absorption at the injection site (36).

Conclusion

It is my hypothesis that we will find a positive correlation between childhood illness (i.e., infectious and allergic) and adiposity (i.e., fat mass or percent body fat) by five years of age in a cohort of US children exposed to the US obesogenic environment. A finding of an association between these two variables will be a worthwhile and important scientific finding which could lead to enhanced efforts to improve the health, especially in regards to illness prevalence, of children.

Chapter Three

METHODS

Overview

Due to the uncertainty about the relationship between illness and adiposity in childhood, the purpose of this Masters Thesis research project was to evaluate the association between the prevalence of childhood illness in the first two years of life and percent fat mass at five years of age in a cohort of children who have been studied since birth for the effects of DHA supplementation during pregnancy on childhood cognitive function. Availability of data also allowed for a secondary investigation examining the relationship between BMI and illness at four and five years of age as well as the relationship between BMI and percent fat mass, measured using air displacement plethysmography (aka BOD POD™ Body Composition System), at five years of age.

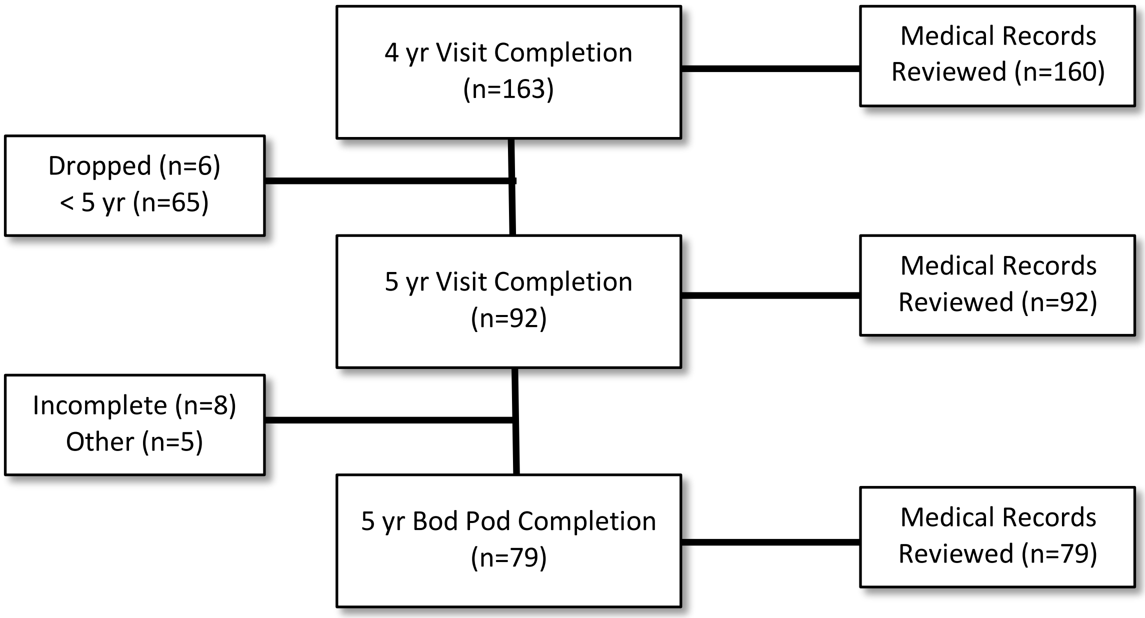
This project utilized data from the KUDOS study (HSC #10186 and #11406).

Sample

The subject sample for this project was drawn from the 301 participants who completed the KUDOS study (see **Appendix A**). The inclusion and exclusion criteria for the parent project are detailed elsewhere (37). Inclusion into this secondary research project required the participant to have complete medical records from birth to twenty-four months and to have completed at least the four year KUDOS study visit. Participants who had completed the five year study visit and the body composition measurement component (see **Appendix B**) were included in the analyses specific to these time points.

As seen in **Figure 1**, by February 1st 2014, 160 participants had completed their four year study visit and had complete medical records, of which 92 participants had also completed their five year study visit, and 79 had completed the body composition measurement component performed at the five year study visit.

Figure 1. Consort Diagram



Setting

All data was collected in the Maternal and Child Nutrition and Development Laboratory at the University of Kansas Medical Center under existing protocols.

Ethics

All aspects of this study, including the data collected, were reviewed and approved by the University of Kansas Medical Center Human Subjects Committee (protocol no. 10186 and 11406).

Procedures / Materials

Study participant medical records were requested (see **Appendix C**) and coded annually. The KUDOS Study ACCESS database was utilized to gather medically documented illnesses for eligible participants. To increase the accuracy of illness reports in this project, the approximately 10% of adverse events not medically documented (parent reported only) were excluded from project inclusion.

Following extraction from the ACCESS database, additional details for each medically documented illness of project participants was confirmed from the medical record directly. Additional details collected from the medical record included medical visit type (e.g., Well Child Check, Sick Visit, Emergency Department), febrile status, specific physical exam findings, any physician commentary regarding illness etiology, and illness treatment. As seen in **Table 1**, medically documented illnesses were objectively categorized as Infectious (I), Allergic (A), Unknown (U), or Non-Applicable (N/A). Categorization required the illness to meet at least one of the criterions for the category.

Illnesses categorized as Infectious required one of the following: presence of a fever (100°F or 37.8°C), as defined by the University of Kansas Hospital; physician findings during physical exam of discolored discharge; physician note of viral, bacterial or fungal etiology; and/or treatment with an antifungal prescription (see **Appendix D**). Although the overuse of antibiotic prescriptions has decreased 36% for acute upper respiratory infections and other conditions in young children (38), antibiotic treatments were not considered substantial evidence for illness categorization due to their continued over- and potentially inappropriate use.

Infectious illnesses were further classified into viral, bacterial and fungal etiologies when possible. Only conditions with a single possible etiology were able to be sub classified (see **Appendix E**).

Illnesses categorized as Allergic required one of the following: physician inclusion of the term "allergy", or one of its derivatives, in the diagnosis or plan section; treatment with an allergy medication; (see **Appendix D**); and/or diagnosis of an evidence-based allergic condition (39).

Illnesses which did not meet criteria for Infectious or Allergic categorization were categorized as Unknown.

Illnesses which do not elicit the immune response were categorized as Non-Applicable.

(See **Appendix F** for examples of illness categorization used specifically for this project.)

Table 1. Criteria for categorization of medically documented adverse events	
Infectious (I)	▪ Presence of a fever (100°F or 37.8°C)[1] ▪ Discolored discharge documented during the physician's physical exam ▪ Physician note of viral, bacterial or fungal etiology ▪ Prescription for Antifungal medication
Allergic (A)	▪ Diagnosis of an "allergy" or an allergic etiology ▪ Treatment with Allergy medication ▪ Diagnosis of evidence-based allergic condition: asthma, eczema, atopic dermatitis, reactive airway disease (RAD), and wheezing (39) (40)
Unknown (U)	▪ Failure to meet criterion for Infectious (I) or Allergic (A) illness categorization
Non-Applicable (N/A)	▪ Adverse Event which does not elicit the immune response (e.g., laceration, teething, infant feeding problems)

[1]per University of Kansas Hospital protocol

Following categorization, illnesses with the same categorization occurring within 30 days (39) were combined into a single Infectious, Allergic, or Unknown category event. There were two exceptions. First was when an Infectious or Allergic illness occurred within 30 days of an Unknown illness. In such a case, the Unknown illness was combined with the Infectious or Allergic illness and collectively considered a single Infectious or Allergic event. The other exception was when an Infectious and Allergic illness occurred within 30 days of one another. In such a case, the separate categorizations remained separate.

Body Mass Index at four and five years of age was calculated based on height and weight measurements taken at the four and five year study visits, respectively. Calculations were performed using the CDC *Children's BMI Tool for Schools* group calculator (41). Height measurements were rounded to a single decimal place before calculating BMI values and percentiles to be used in the data analysis.

Adiposity, fat and fat-free mass, values for each participant was collected from the COSMED USA Bod Pod™ database system. Fat and Fat-Free Mass values were calculated by the system using the evidence-based Lohman (18) equation to calculate densitometry to determine adiposity. Thoracic Gas Volume (TGV) was predicted for each participant based on validated individualized equations built into the software system.

Analysis of Data

Following categorization of all adverse events, only Infectious, Allergic, and Unknown illnesses were analyzed. Non-applicable adverse events were not analyzed due to the lack of elicitation of the immune response. Infectious and Allergic illnesses were analyzed with and without addition of the Unknown illness category. Infectious illness and Allergic illness were the primary datasets comprising the independent variable "illness" mentioned previously in the research question(s), see **Chapter One: Introduction**.

A relationship between the variables of adiposity and illness were analyzed using a linear regression model with illness as the independent variable and adiposity as the dependent variable. Covariates were determined using a linear regression model (for continuous variables) or a One-Way ANOVA (for categorical variables). A Pearson Correlation was used to analyze the third secondary research question investigating the relationship between BMI and percent fat mass at five years of age. Covariates included maternal serum fatty acid status at delivery and maternal pre-pregnancy BMI. These covariates were chosen due to the data used being from a clinical trial on DHA supplementation in utero which was powered for the primary outcomes of increased gestation and consequently greater weight and length at birth (37) and due to the known influence of maternal BMI on child BMI, respectively.

Results were considered statistically significant at a p-value of less than 0.05. Microsoft Excel 2010 and IBM SPSS Statistics version 22 were used to perform the statistical tests. Missing values were managed in a pairwise manner to maximize the sample size for each analysis.

Chapter Four

RESULTS

Subject Characteristics

As illustrated in **Table 2**, there were no significant differences between subject characteristics at any of the three dependent variable time points assessed in this project. The predictor variable of maternal pre-pregnancy BMI has been demonstrated in the literature to have a positive correlation with child BMI. Although maternal pre-pregnancy BMI (MatPrePGBMI) was not found to be significantly related to any of the dependent variables, it did appear to be trending down and therefore was controlled for in the data analysis. Additionally, since this project utilizes a sub population of a larger sample size enrolled in a clinical trial on DHA supplementation in utero, maternal red blood cell phospholipid DHA (22:6n-3, weight percent of total fatty acids) at birth was controlled for in the data analysis even though it was not found to be significantly related to any of the dependent variables.

Table 2. Characteristics of project population at each dependent variable time point						
Variable	4 yr BMI (n=160)	p-value	5 yr BMI (n=92)	p-value	Bod Pod (n=79)	p-value
Gender						
Female*	83 (52%)	.396	52 (57%)	.602	46 (58%)	.316
Male*	77 (48%)		40 (43%)		33 (42%)	
Weight (kg)	17.36 ± 2.16	-	19.83 ± 2.77	-	19.66 ± 2.72	-
Height (cm)	102.95 ± 3.94	-	110.06 ± 4.30	-	109.94 ± 4.37	-
BMI (kg/m^2)	16.34 ± 1.46	-	16.32 ± 1.67	-	16.20 ± 1.47	-
GADel.**	39.50 ± 1.32	.839	39.55 ± 1.26	.454	39.47 ± 1.31	.624
Delivery Type						
1 – vaginal*	114 (71%)	.297	67 (73%)	.759	55 (70%)	.293
2 – cesarean*	46 (29%)		25 (27%)		24 (30%)	
MatPrePGBMI**	22.43 ± 9.72	.145	23.33 ± 9.03	.074	23.57 ± 8.03	.066
Maternal GWG						
1 – inadequate*	25 (16%)	.361	13 (14%)	.126	9 (11%)	.270
2 – adequate*	48 (30%)		24 (26%)		22 (28%)	
3 – excessive*	87 (54%)		55 (60%)		48 (61%)	
Maternal 22:6n3**	6.17 ± 2.20	.188	5.89 ± 2.01	.816	5.28 ± 2.09	.369

GADel: Gestational Age at Delivery; MatPrePGBMI: Maternal Pre-Pregnancy BMI; GWG: Gestational Weight Gain (1-inadequate, 2-adequate, 3-excessive); 22:6n3: Maternal serum DHA levels at time of delivery.
*[n(weight %)]; p-value calculated using a One-Way ANOVA
**Mean ± standard deviation (SD); p-value calculated using a Linear Regression

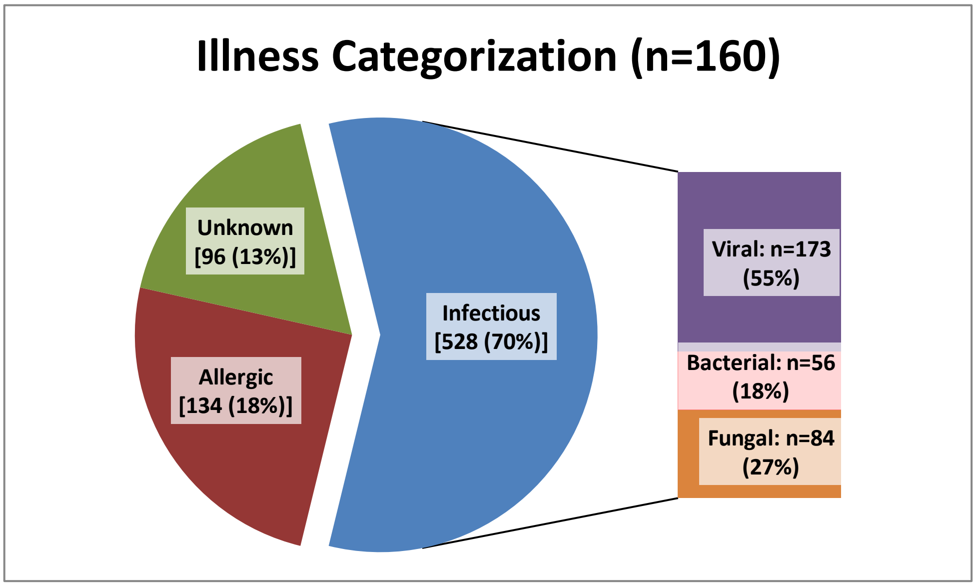
Illness Prevalence

Due to the chronological sequence of the dependent variable time points assessed, this project required a total of 160 subject charts, n=160 completed their four year study visit by February 1st 2014, to be analyzed. There were 1660 adverse events medically documented within the first two years of life (0 to 24 months). All adverse events were categorized, see **Chapter Three: Methods**. Non-illness adverse events were excluded leaving 1130 medically documented illnesses categorized as infectious, allergic or unknown. Illnesses were combined based on the thirty day rule (39), which condensed the number of illnesses to 758 (see **Table 1** for categorization criterion). As seen in **Figure 2**, 70% of illnesses occurring thirty days apart were categorized as infectious, 18% as allergic, and 13% as unknown.

Infectious illnesses were further classified according to a medically confirmed etiology. Due to stringent criteria, only 59% of the infectious illnesses were able to confidently be sub classified according to etiology. See **Chapter Three: Methods** for categorization and sub classification procedures. Of those capable of further categorization (313 infectious illnesses), 173 (55%) were determined to have a viral etiology, 56 (18%) a bacterial etiology, and 84 (27%) a fungal etiology.

The subject sample used to evaluate the correlation between BMI at five years of age and illness (n=92), as well as percent fat mass and illness (n=79) were subsets of this larger, BMI at four years (n=160), sample.

Figure 2.


Illness Categorization (n=160)
Unknown
[96 (13%)]
Allergic
[134 (18%)]
Infectious
[528 (70%)]
Viral: n=173
(55%)
Bacterial: n=56
(18%)
Fungal: n=84
(27%)

Illness Prevalence and Percent Fat Mass

The primary research question for this project was to investigate the relationship between illness in the first two years of life and adiposity, specifically percent fat mass, measured at five years of age. The mean percent fat mass of the subject sample for this analysis was 24.778 ± 5.71. As seen in **Table 3**, illness was not significantly associated with percent fat mass at five years of age. Neither did I find a significant relationship for the two primary illness categories – infectious and allergic – or for their subcategories – viral, bacterial, fungal, and allergic defined as a categorical variable.

Unknown illnesses, those with insufficient evidence to categorize as infectious or allergic, were not found to have a significant association with percent fat mass alone or when combined with either of the primary categorizations – infectious or allergic.

Table 3: Relationship between illness in the first two years of life and percent fat mass at five years of age[1] (n=79)			
	Mean +- SD	Std. β	p-value
Illness, Total	4.11 ± 2.61	.005	.969
Illness, Infectious	2.77 ± 2.00	-.055	.641
Infectious + Unknown	3.33 ± 2.15	-.060	.611
Viral	.92 ± 1.02	-.005	.967
Bacterial	.33 ± .73	.115	.319
Fungal	.51 ± .65	-.135	.239
Illness, Allergic	.78 ± 1.30	.106	.364
Allergic + Unknown	1.34 ± 1.49	.082	.487
None	45 (57%)	-	.342[a]
1+	34 (43%)	-	

[1] Analyzed using a linear regression model, IBM SPSS Statistics 22, using the covariates of maternal serum DHA levels at time of delivery (22:6n3) and maternal pre-pregnancy BMI (MatPrePGBMI)

[a] Categorical variable, analyzed using a One-Way ANOVA.

Illness Prevalence and BMI (4 yr)

A secondary research question for this project was to evaluate the relationship between illness in the first two years of life and BMI at four years of age. The subject sample used in this project had a mean BMI of 16.34 ± 1.46 (**Table 2**). The mean BMI percentile for this group was 65.17 ± 27.05, placing the average in the Normal BMI range. As seen in **Table 4**, 33% of the study population was at the 85^{th} percentile or above and 12% fell into the obese category.

As seen in **Table 5**, when combined with unknown illnesses, infectious illness in the first two years of life was found to be significantly correlated with BMI at four years of age (p-value .025). Infectious illnesses alone, without combining with the unknown illnesses, were very near significance level (p-value .055). No other findings were found to be significant.

Upon removal of all covariates, these findings were still found to be true - p-value .026 and p-value .06, respectively.

Table 4. Summary of participant BMI percentiles at four years of age			
	Females (n=83)	Males (n=77)	Total (n=160)
Underweight (<5th %ile)	4%	0%	2%
Normal BMI (5 – 85th %ile)	63%	68%	65%
Overweight or obese (≥ 85th %ile)[b]	34%	32%	33%
Obese (≥ 95th %ile)	11%	13%	12%

[b] Terminology based on: Barlow SE and the Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 (suppl 4):s164-92.

Table 5: Relationship between illness in the first two years of life and BMI at four years of age[1] (n=160)

	Mean +- SD	Std. β	p-value
Illness, Total	4.74 ± 2.86	-.117	.143
Illness, Infectious	3.30 ± 2.15	-.153	.055
Infectious + Unknown	3.90 ± 2.40	-.179	.025*
Viral	1.08 ± 1.21	-.049	.540
Bacterial	.35 ± .70	-.094	.244
Fungal	.53 ± .718	.014	.865
Illness, Allergic	.84 ± 1.19	.079	.328
Allergic + Unknown	1.44 ± 1.52	-.004	.965
None	81 (51%)	-	.619[a]
1+	79 (49%)	-	

[1] Analyzed using a linear regression model, IBM SPSS Statistics 22, using the covariates of maternal serum DHA levels at time of delivery (22:6n3) and maternal pre-pregnancy BMI (MatPrePGBMI)

[a] Categorical variable, analyzed using a One-Way ANOVA.

* Significant value ($\alpha < 0.05$)

Illness Prevalence and BMI (5 yr)

Another secondary research question for this project was to evaluate the relationship between illness in the first two years of life and BMI at five years of age. The subject sample used to assess this association had a mean BMI of 16.32 ± 1.67 (**Table 2**). The mean BMI percentile was 66.09 ± 26.05, placing the average in the Normal BMI range. As seen in **Table 6**, 28% of this subset population was at the 85th percentile or above and 12% fell into the obese category.

As seen in **Table 7**, illness was not found to be significantly correlated with BMI at five years of age. This remained true for all categories and sub-categories of illness.

Table 6. Summary of participant BMI percentiles at five years of age (n=92)			
	Females (n=52)	Males (n=40)	Total (n=92)
Underweight (<5th %ile)	2%	3%	2%
Normal BMI (5 – 85th %ile)	67%	73%	70%
Overweight or obese (≥ 85th %ile)[b]	31%	25%	28%
Obese (≥ 95th %ile)	10%	15%	12%

[b] Terminology based on: Barlow SE and the Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 (suppl 4):s164-92.

Table 7. Relationship between illness in the first two years of life and BMI at five years of age[1] (n=92)

	Mean +- SD	Std. β	p-value
Illness, Total	4.21 ± 2.70	-.115	.289
Illness, Infectious	2.82 ± 2.07	-.158	.139
Infectious + Unknown	3.38 ± 2.25	-.159	.138
Viral	.87 ± 1.01	-.170	.114
Bacterial	.36 ± .72	.001	.992
Fungal	.49 ± .687	-.016	.881
Illness, Allergic	.83 ± 1.28	.042	.698
Allergic + Unknown	1.39 ± 1.51	.016	.881
None	50 (54%)	-	.382[a]
1+	42 (46%)	-	

[1] Analyzed using a linear regression model, IBM SPSS Statistics 22, using the covariates of maternal serum DHA levels at time of delivery (22:6n3Corr) and maternal pre-pregnancy BMI (MatPrePGBMI)
[a] Categorical variable, analyzed using a One-Way ANOVA.

BMI (5 yr) and Percent Fat Mass

A third and final secondary question for this thesis research project concerned the relationship between BMI at five years of age and percent fat mass measured at five years of age. A Pearson correlation coefficient was computed to assess this relationship. The mean percent fat mass for the participant sample in this analysis was 24.77 ± 5.71. The BMI for this participant sample was 16.20 ± 1.47. The mean BMI percentile was 64.96 ± 26.58, placing the average in the Normal BMI range.

As seen in **Table 8**, BMI at five years of age was found to be significantly correlated to percent fat mass at five years of age (p-value .001). These two variables have a moderate-strength, positive, significant association (r = .353) indicating that as BMI increases percent body fat also increases.

Table 8: Relationship between BMI and percent fat mass at five years of age[1] (n=79)			
	Mean +- SD	Pearson's r	p-value
Fat Mass (%)	24.77 ± 5.71	.353	.001*
BMI, 5 yr (kg/m^2)	16.20 ± 1.47		

[1] Analyzed using a Pearson correlation, IBM SPSS Statistics 22

* Significant value ($\alpha < 0.05$)

Chapter Five

DISCUSSION

This Master's thesis research project sought to investigate the association between illness in the first two years of life and adiposity at five years of age in a cohort of children who have been studied since birth for the effects of DHA supplementation during pregnancy on childhood cognitive function. This project hypothesized that by categorizing illnesses into two broad categories – infectious and allergic - a positive correlation between infection and adiposity, percent fat mass, would be observed at five years of age. As a secondary data analysis, only associations were capable of investigation.

As seen in **Table 3**, illness in the first two years of life and percent fat mass, measured at five years of age, were not found to be significantly associated. Given that the research on this association is limited, and that the limited data is discordant regarding the direction of this association, methodology (especially fat mass measurement technique), population analyzed, etc., my failure to find significance does not necessarily assert that I fail to reject my null hypothesis. Recalling from **Chapter Two: Review of Literature**, obesity is a multisystem, multifactorial disorder with a number of contributing factors including genetic inheritance and behavioral/environmental components (1, 8, 9). Although maternal pre-pregnancy BMI (PrePGBMI) and maternal red blood cell phospholipid DHA (22:6n-3, weight percent of total fatty acids) at birth were controlled for in the data analysis, the cumulative effect of unidentified or seemingly non-significant contributing factors present in this project sample may be skewing the results. Therefore, I investigated this association further through my secondary research questions.

Upon data analysis for the secondary research questions, two significant findings and two noteworthy trends were identified.

The first significant finding was that infectious illness, when combined with the unknown illness category, was significantly correlated with BMI at four years of age (p-value .025). An inverse correlation between these two variables was observed ($\beta = -.179$). BMI was not found to be significantly associated with a specific etiology of infectious illness (viral, bacterial, or fungal). Since BMI is not a direct measure of adiposity, this finding does not confirm a significant relationship between illness and body fat. However, BMI has been validated by researchers and found to be a reasonable, clinically relevant indicator of body fat (13-15). Consequently, BMI has been included in the methodology of the majority of studies on this topic. My identification of a significant association between illness and BMI at four years of age is consistent with the literature (4, 9).

While not statistically significant, when analyzing the association between illness and BMI at five years of age, infectious illness was observed to be trending toward significance (p-value 0.13). Similar to BMI at four years of age, illness was inversely associated with BMI ($\beta = -.15$). This observation is especially noteworthy after consideration of the 42.5% decrease in sample size from the BMI at four years of age dependent variable time point (n=160) and the BMI at five years of age dependent variable time point (n=92). The large sample size reduction questions the statistical power at this time point. Despite this sample size reduction, the sheer observation of an inverse relationship supports the assertion that illness may be one of several contributing factors to the multifactorial condition of obesity, even if not found to be statistically significant in this research project.

Viral infectious illness, when analyzed with the dependent variable of BMI at five years of age, was also found to be trending toward significance (p-value 0.11). Since this project was a secondary data analysis, collecting medical record details retrospectively, this project only had the capability to identify a correlation, not to determine causation. Despite this limitation, this trending inverse correlation ($\beta = -.170$) is noteworthy as it could arguably refute the theory of “infectobesity”, or obesity of infectious origin, as discussed in **Chapter Two: Review of Literature** (9).

A final noteworthy observation concerns the significant and trending associations between illness and BMI at four years of age and between illness and BMI at five years of age, respectively, is the 5% decrease in overweight and obese participants (BMI ≥ 85^{th} %ile) compared to the consistent 12% of obese participants (BMI ≥ 95^{th} %ile) from four to five years of age (see **Table 4** and **Table 6**, respectively). Since BMI is not a measure of adiposity, this observation may be an indication of a cut-off or threshold at which illness has the greatest impact on adiposity. This observation prompts further investigation into the contributing factors associated with a BMI greater than the 85^{th} percentile (e.g., diet quality, physical inactivity, adiposity rebound).

The second significant finding was that BMI at five years of age was significantly correlated with percent fat mass at five years of age (p-value .001). As discussed in **Chapter Two: Review of Literature**, BMI is often used as a surrogate marker for measuring adiposity. BMI has been shown to be correlated with fat mass percentage, most notably in children in the overweight and obese categories (BMI ≥ 85^{th} %ile) (42). The significant finding that BMI at five years of age is positively correlated with percent fat mass, measured by the COSMED USA Bod Pod™ system, (Pearson's r = .353) at five years of age is consistent with the literature. However, with 28% of study participants classified as overweight and/or obese according to their BMI percentiles, this finding does not necessarily support suggestions that BMI at all ranges is significantly correlated with increased adiposity. Given the limitations of this project, this finding can only be used to support the accuracy of BMI measurements at five years of age with percent fat mass at five years of age.

Given the results of this research project - lack of significant findings between illness and percent fat mass, presence of a significant finding with BMI at four years of age, two trending observations with BMI at five years of age, and the significant, positive association between BMI at five years of age and percent fat mass at five years of age - I am unable to reject or fail to reject my null hypothesis. This project does not appear to negate the possibility that a statistically significant relationship between illness and adiposity does indeed exist. The results of this Master's thesis research project reinforce the need for further investigation into this association, especially in children.

Strengths

The strengths of this project include the prospective data collection methods and the stringent criterion for categorizing illness, especially the sub classification of infectious illnesses according to etiology. The stringent criterion was necessary to prevent inaccurate, over categorization. Due to the data collection methods used for this project, this project opens the door to a variety of additional secondary analyses in the future. A few examples of potential future directions utilizing this project's data include an investigation into an association between illness and other body composition measurements (such as absolute fat mass and fat free mass), an investigation into an association between medical visit type prevalence and adiposity or febrile prevalence and adiposity, etc.

Limitations

The limitations of this project include failure to control for the effect of DHA supplementation on immunity, failure to control for the effect of diet on immunity, and the inability to analyze the entire KUDOS cohort. Since the KUDOS study is not yet complete, study personnel are still blinded to subject randomization. Once the study is complete and all staff are unblinded, the analysis from this project could be repeated and DHA supplementation could be analyzed as a possible covariate. Waiting until the KUDOS study is complete would also ameliorate the limitation of having an incomplete study subject sample.

Despite these limitations, the data supporting the theory that obesity may have an infectious origin (infectobesity) are sparse. Although I suspect these limitations to have had a negative impact on identifying the hypothesized positive correlation, I do not suspect that these limitations had a significant impact on the results. In other words, the results of this project are consistent with the literature in that it lends support that a relationship between illness and adiposity in childhood exists. Due to its limitations, this project is unable to support a directional correlation. However, the beta-coefficients appear to refute the infectobesity theory claim. In summary, the results from this thesis research project support the need for further investigation into the additional explanations and theories regarding the illness-adiposity association beyond infectobesity.

As anticipated, this project was a worthwhile personal experience which positively contributed to my personal knowledge base and experience in research.

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Appendix A

Consent Form

CONSENT FORM
The Effects of DHA on Pregnancy and Infant Outcome
(Kansas University DHA Outcomes Study or KUDOS)

Sponsor: NIH (1R01 HD047315)

INTRODUCTION

As a pregnant woman who is between 8 and 20 weeks of gestation, you are being invited to enroll in a research study of a nutrient (DHA) that is a component of normal brain and important for brain development. The centers involved in the study are the University of Kansas Medical Center in Kansas City, Kansas, St. Luke's Hospital in Kansas City Missouri, and Truman Medical Center in Kansas City, Missouri. If you decide to enroll in this study, your baby will participate in research procedures at the University of Kansas Medical Center. Dr. Susan Carlson is the main investigator for this study. A total of 350 pregnant women will be enrolled in this study between October 2005 and January 2010.

You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. You should ask as many questions as you need to understand what will happen if you participate in the study.

BACKGROUND

Docosahexaenoic acid (DHA) is a fat that is found in very large amounts in the brain. DHA is important for how my baby sees and learns. Breast milk and, since 2002, US formulas contain DHA. Many studies have shown that DHA in the diet helps the baby's vision, attention, and ability to learn. In this way, DHA is considered an important nutrient for babies after they are born.

DHA may also be important before babies are born. Four studies found that women's DHA during pregnancy was related to higher infant/child function. These studies are called observational studies, meaning that the women's normal DHA status was studied in relation to development of the baby/child. There is only one study that gave women DHA during pregnancy and measured development of their babies/children. That study showed higher IQ at 4 years of age in children whose mothers took fish oil capsules during the last 6 months of pregnancy. (Fish oil contains a lot of DHA). However, because women in the study also consumed DHA while they were breastfeeding they provided more DHA to their babies after they were born. Therefore, the study does not prove that giving DHA before babies are born will help their development. There are no studies that have varied DHA intake only during pregnancy. You and your child are being asked to participate in such an experimental study.

PURPOSE

The purpose of this study is to determine if a dietary supplement of DHA during pregnancy will help babies be born at the right time and help their development. If you decide to be in the study, you will have a 50-50 chance of receiving capsules with the supplement of DHA or ordinary food oil, which does not contain any DHA.

HSC Submission Date:08/25/2009
HSC Approval Date:12/28/08
HSC Approval (Payment)Date: 2/11/08
HSC Approval (HSC Address) Date: 11/3/05
HSC Approval (Rev CF COI) Date:

HSC #: 10186
Approval Date: 10/07/09 to 05/11/10
Assurance #: FWA00003411

PROCEDURES

If you choose to enroll yourself and your infant in this study, the investigators will record some information from your medical record about your pregnancy and medical history. They will also ask you a few questions about foods that you usually eat. You will have a blood sample collected from a vein in your arm. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA in your blood as well as other nutrients. You will be asked to provide a current address and phone number where you can be contacted. .

During pregnancy: You will be randomly assigned (like flipping a coin) to capsules with DHA-oil or ordinary food oil (which does not contain any DHA). The DHA-oil is the same oil that is used in US infant formulas and has been fed safely to millions of infants.

You will be given enough capsules each month to take 3 capsules each day and you agree to try to consume all 3 capsules. If you consume all 3 capsules, you will consume 600 mg of DHA. The capsules are relatively small and you should find them easier to swallow than many nutrient supplements. They are orange-flavored, so if you burp (common in pregnancy and in the first week of taking any nutrient supplement), the taste should not be unpleasant. You do not need to take the capsules at any specific time as they are a nutrient and not a drug. However, you should decide upon a regular time to take them so that taking the capsules will become a habit and you won't forget. For example, you might wish to take them just before you go to bed or when you have your first beverage of the day.

Neither you nor the investigators will know which capsules you have been assigned to. On the day you enroll for the study, we will send you home with your first bottle of capsules. About 30 days later (early enough so that you do not run out of capsule), you will receive another bottle of capsules in the mail. AT THAT TIME, YOU AGREE TO PLACE THE FIRST BOTTLE WITH ANY REMAINING CAPSULES IN THE ENVELOPE AND DROP IT INTO THE MAIL.

This process will be repeated each month until your baby is born and you will continue to take 3 capsules per day until your baby is born. Each time you receive a new bottle, you will mail back the bottle that you have been using and that day will open and begin using the new bottle.

The investigators will contact you by phone at least once per month. They will ask about capsule intake and they will ask how you are doing. Maintaining contact with our study personnel on a monthly basis is very important.

IF YOUR PHONE NUMBER OR ADDRESS CHANGES AT ANY TIME DURING THE STUDY, YOU WILL LET THE INVESTIGATORS KNOW BY CALLING 913-588-3781 AND LEAVING A MESSAGE.

Delivery: After you are admitted to the hospital to deliver, you should telephone study personnel or ask the person at admitting to telephone them. You will be given a cell phone number today to call. Once you deliver your baby, the investigators will visit you in the hospital to collect data about your delivery and your baby's health. A sample of your baby's cord blood will be collected after delivery by nurses at the hospital and given to the

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investigators. A nurse will also draw a small blood sample (one-half teaspoon) from you while you are in the hospital. The blood samples will be used to measure DHA and other nutrients. The investigators will visit you, and give you an appointment for your baby's first follow-up visit at KUMC.

Visit 1 (6 weeks of age): The investigators will measure how your baby sees using a test that involves placing 3 electrodes directly on your baby's head. The process involves cleaning the area then placing a small amount of paste similar to toothpaste on the head. The electrodes are placed on top of the paste. The electrodes will be used to record your baby's brain waves while he/she is looking at pictures. Your child's weight, height and head circumference will be measured again and you will be asked questions about what your baby eats. If you are breastfeeding your baby, you will be asked to provide a teaspoon of breast milk to the investigator. The sample will be frozen and analyzed for fats that are found in the capsules. The visit should last about 40 minutes. You should arrive on time and allow that amount of time for the visit.

Visit 2 (4 months of age): The investigators will measure how your baby sees using the same test as before and another vision test. Your baby will wear a pair of plastic glasses during the second test. In another test, your child will be given an object to look at several times. The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured and you will be asked about what food your baby eats. Your baby will have a blood sample collected by either heel stick or drawn from a vein. If it is necessary to use a heel stick, the investigator may use a cream or spray that will numb the area before obtaining the sample. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA and other nutrients. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit will take 60-90 minutes.

Visit 3 (6 months of age): The investigators will measure how your baby sees using the test that requires him/her to wear a pair of plastic glasses. In another test, he/she will be given an object to look at several times (just like at 4 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take 40 -60 minutes.

Visit 4 (9 months of age): Your baby will have both tests that measure how he/she sees. In another test, your child will be given an object to look at several times (just like at 4 and 6 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object and your baby's heart rate will be measured during the test. Your child will be video recorded during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take about 40-60 minutes.

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Visit 5 (10 months of age): During this visit your baby will be placed on your lap in front of a small table. A test will be completed with a small toy, foam block and 2 cloths that will be placed in front of your child. You will also take a short language test. The small toy will be given to your child to keep. In another test, your baby will be asked to take turns with the researcher building fun toys. After your baby has played for a moment with the pieces, the researcher will show him or her how to build the toy. Then, your baby will be given a turn to put the toy together. Your baby's turn will happen either immediately or after 10-minutes of play with other things. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child will be video recorded during the tests. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. You will be asked questions about what your baby eats. The entire 10-month visit should last 70 minutes.

Visit 6 (12 months of age): The investigators will measure how your baby sees using both vision tests. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your child has been sick or not acting well since his/her last visit. We will request your child's medical record from his/her doctor. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your baby cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

Visit 7 (18 months of age): The investigators will measure how your child sees using the test that he/she had while wearing plastic glasses. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. Your child will also be given a standardized test to measure mental and physical development. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You will be asked questions about the words your child uses and understands. You should let the investigator know if your child has been sick or not acting well since his/her last visit. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your child cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

RISKS

Some redness, soreness, or bruising may occur at the site of blood sampling. There is also a very slight risk of infection.

You may experience burping from the capsules and find this unpleasant

There are no known risks of consuming the amount of DHA you will be provided if you receive the DHA. Even if you forget to take your capsules for one or two days, there is no known risk of deciding to "catch up" on the third day. The amount is smaller than pregnant women in many countries eat every day. Nevertheless, you could develop a problem that has not been observed before.

NEW FINDINGS STATEMENT

You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate or to allow your child to participate in this study.

BENEFITS

You and your child may or may not benefit from participating in this study. If you receive the supplement, it may help your baby to be born at the right time and your baby's/child's development. If you will not get the supplement, your baby and you will not be getting any of those benefits. It is also possible that all infants/children will get some benefit from being followed closely with developmental testing. It is hoped that additional information gained in this research study may be useful in understanding if DHA can help your baby be born at the right time and help your baby's vision, attention, and learning as he or she grows. You will receive a video recording of your infant doing the 4, 6, and 9 month looking test when the 12 month visit is complete.

ALTERNATIVES

You do not have to participate in this study to be able to take DHA supplements while you are pregnant. You may purchase capsules containing DHA at local stores without a prescription (for example, Osco, Costco, Wal-Mart). There are also several brands of prenatal supplements with DHA available by prescription or over the counter. The prenatal capsules typically contain 200 mg of DHA each and are marketed to take one capsule/day as a DHA supplement.

COSTS

Capsules containing either DHA or food oil will be provided to you at no cost while you are participating in this study. You will not incur any costs because of your or your child's participation

PAYMENT TO SUBJECTS

If study investigators are able to communicate with you each month you will be given 2 bonus gift cards to either Wal-Mart or Target of $25 each. The first gift card will be given to you half way through your treatment phase if communication is maintained at least one time each month during the first half of your treatment. The second gift card will be given at delivery if communication maintained at least one time each month during the second half of your treatment.

Additionally, if the study investigators are called after you are admitted for delivery you will be given your choice of a bonus gift card worth $50 from either Wal-Mart or Target. You may make the call yourself or have someone else call for you. Study personnel will give you the gift card when they come to the hospital after your baby is born.

Once your baby is born,you will receive a check for $50 after your baby completes each of the following visits: 6 weeks, 4 months, 6 months, 9 months, and 10 months. You will receive a check for $100 after your child completes each of the following visits: 12 and 18 months.

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The reimbursements are to cover the costs of transportation and to partially compensate you for your time required to participate in the study.

Your name, address, social security number, and the title of this study will be given to the KUMC Research Institute. This is done so that the Research Institute can write a check for study payments. Payments are taxable income.

IN THE EVENT OF INJURY

In the event you experience any serious health problem (hospitalization, life-threatening illness, or death) for any reason during your pregnancy, you should immediately seek treatment or help in the way you normally would as if you were not in a study. You should let Susan Carlson, Ph.D. know about any of these problems as soon as possible by calling her office (913-588-5359) or the study office (913-588-3781). A message may be left at both numbers. Dr. Carlson may also be reached at home (816-960-1805).

INSTITUTIONAL DISCLAIMER STATEMENT

If you believe you have been injured as a result of participating in research at Kansas University Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Compensation to persons who are injured as a result of participating in research at KUMC may be available, under certain conditions, as determined by state law or the Kansas Tort Claims Act.

Truman Medical Center (TMC) will provide medical attention to you if you suffer any injury or harm as a direct result of participating in this research project. TMC, your study doctor, and the sponsor of this study will decide, at their discretion, who should pay for the medical care. TMC will provide treatment to you in the event of any medical emergency while present at TMC, whatever the cause. Moreover, you will have the benefit of the coverage of any existing healthy insurance you own. Participation in this research study does not take the place of routine physical examinations or clinic visits to your person physician. If you believe you have been injured as a result of participating in this study you are encouraged to contact the study investigator, Dr. Susan Carlson, at her work number, 913-588-5359.

The University of Missouri-Kansas City appreciates the participation of people who help it carry out its function of developing knowledge through research. Although it is not the University's policy to compensate or provide medical treatment for persons who participate in studies, if you think you have been injured as a result of participating in this study, please call the investigator, Dr. Susan Carlson at 913-588-5359 (work) or Sheila Anderman, IRB administrator of UMKC's Adult Health Sciences Institutional Review Board at 816-235-6150

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

Names of subjects or information identifying subjects will not be released without written permission unless required by law. Videotapes of your baby when he/she is looking at pictures and playing with toys will be used only by the investigators and their students and to make a videotape copy for you. The videotapes will be secured under lock and key like all other information that could be linked directly to your child. The videotape of your child will not be shown without specific permission from you and even then would not identify your

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child by name. Efforts will be made to keep you and your child's personal information confidential. Researchers cannot guarantee absolute confidentiality. If the results of this study are published or presented in public, information that identifies you and/or your baby will be removed.

The privacy of you and your child's health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). If you choose to participate in this study, you will be asked to give permission for researchers to use and disclose your and your baby's health information that is relevant to the study.

To perform this study, researchers will collect health information about me and my child from his/her and my medical records and from the study activities that are listed in the Procedures section of this consent form. My and my baby's study-related health information will be used at KU Medical Center by Dr. Carlson, members of the research team, Truman Medical Center, St. Luke's Hospital and the KU Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC and at Truman Medical Center that oversee research, including the KUMC Human Subjects Committee, the IRB that governs St. Luke's Medical Center and Truman Medical Center and other committees and offices that review and monitor research studies.

Dr. Carlson and her team may share information about me and my baby with representatives of Martek Biosciences, the monitoring company who verifies study data, the laboratory that processes study lab samples, other business partners who help with the study, the U.S. Food and Drug Administration (FDA), and U.S. agencies that govern human research (if and when regulatory compliance issues arise). Martek Biosciences (Columbia, MD) donated the capsules for this study that is otherwise supported by the National Institute of Child Health and Human Development.

Some of the persons or groups that receive my and my baby's study information may not be required to comply with HIPAA privacy laws. My and my child's information may lose its federal protection if those persons or groups disclose it.

Permission granted on this date to use and disclose my health information remains in effect indefinitely. By signing this form I give permission for the use and disclosure of my and my child's information for purposes of the study at any time in the future.

If I enroll in the study, the investigators cannot tell me what capsule I was assigned to until the study ends. This may be after I have stopped taking the capsules.

QUESTIONS

I have read the information in this form. Dr. Carlson or her associates have answered my question(s) to my satisfaction. I know if I have any more questions after signing this I may contact Dr. Carlson or one of her associates at (913) 588-5359. If I have any questions about my or my child's rights as a research subject, I may call (913) 588-1240 or write the Human Subjects Committee, University of Kansas Medical Center, 3901 Rainbow Blvd. MSN 1032, Kansas City, KS 66160.

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SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

My and my child's participation in this study is voluntary and the choice to not participate or to quit at any time can be made without penalty or loss of benefits. Not participating or quitting will have no effect upon the medical care of treatment my child receives now or in the future at the University of Kansas Medical center. The entire study may be discontinued for any reason without my consent by the investigator conducting the study, by the sponsor of the study, or the FDA. My child's participation can be discontinued by the investigator or by the sponsor if it is felt to be in my child's best interest or if I do not follow the study requirements. If I choose to withdraw before my child is 18 months of age, I may be asked to answer questions about the study on the telephone.

If I want to cancel permission to use my or my child's health information, I should send a written request to Dr. Carlson. The mailing address is Susan Carlson, Ph.D., Dept. of Dietetics and Nutrition, MS 4013, 4019 Delp, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If I cancel permission to use my child's health information, the research team will stop collecting any additional information about me and my child.

Should the study be terminated prior to the completion of my pregnancy, neither the investigator nor the University of Kansas Medical Center will be under any obligation to provide me with DHA capsules used in the study.

CONSENT

Dr. Carlson or her associates have given me information about this research study. They have explained what will be done and how long it will take. They explained the inconvenience, discomfort and risks that may be experienced during this study.

By signing this form, I give my permission for my and my child's health information to be used and disclosed for the purposes of this research study. If I choose not to sign this form, my child and I will not be able to participate in the study.

I voluntarily consent to my and my child's participation in this research study. I have read the information in this form and have had an opportunity to ask questions and have them answered. ***I will be given a copy of the signed form to keep for my records.***

____
Type/Print Subject's Name

______________________________ _______ ______________
Signature of Subject Time Date

____
Type/Print Name of Person Obtaining Consent

______________________________ ______________
Signature of Person Obtaining Consent Date

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Type/Print Name of Principal Investigator

Signature of Principle Investigator Date

May the investigators contact you after the study is over to ask if you interested in continuing your child's participation? If you agree to be contacted, the investigators would explain any new study to you later and you would have the chance to decide if you wanted to participate at that time (please circle your response).

Yes

No

You may choose not to be contacted in the future and still be able to participate in the main study.

Type/Print Subject's Name

Signature of Subject Time Date

Type/Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent Date

Type/Print Name of Principal Investigator

Signature of Principle Investigator Date

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Appendix B

Consent for Body Composition Assessment

CONSENT FORM
THE EFFECTS OF DHA ON PREGNANCY AND INFANT OUTCOME
(Addendum to HSC #11406)

You have enrolled in the University of Kansas HSC #11406 to evaluate whether taking a supplement of DHA can influence pregnancy and infant outcomes. As part of the study, we are interested in your child's growth, and we have measured his/her weight, length and head circumference at each visit. We have recently obtained an instrument that allows us to obtain information about your child's body fat and muscle mass. Now that your child is 5 years of age, we would like to measure his/her body fat and muscle mass. The results would add to the measures of growth we already have on your child. To complete the test, your child will wear a swimsuit and sit inside an egg shaped pod so the space they take up inside the pod can be measured. The procedure is simple, non-invasive and takes approximately 5 minutes to complete. We can show you the chamber if you would like to see it before you decide to have your child participate. We will keep the data confidential just as we have with all of your other personal information. If you agree to let us measure the body fat and muscle mass of your child, please check the "yes" box; if you do not agree, please check the "no" box.

Yes ☐

No ☐

____
Type/print Subject's Name

Signature of Subject	Time	Date

____
Type/Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent	Date

____
Type/Print Name of Principal Investigator

Signature of Principle Investigator	Date

Appendix C

Consent for Release of Medical Records

THE UNIVERSITY OF KANSAS MEDICAL CENTER
CONSENT FOR THE RELEASE OF CONFIDENTIAL INFORMATION

I, ______________________________ born on ______________________, hereby

authorize ____ to disclose to:

The University of Kansas Medical Center

3901 Rainbow Boulevard MS 4013

Kansas City, Kansas 66160-7200

Attention: Infant/Child Nutrition Research Clinic Phone: (913) 588-5743; **Fax: (913) 945-6621**

the following information: ____

____

____

____

____

I am requesting the release of my health information for the purpose of research use. I understand that my medical records (including any alcohol or drug abuse information) may be protected by Federal Regulations. I also understand that I may revoke this consent at any time except to the extent that action has been taken in reliance on it (e.g., probation, parole, etc.) and that in any event this consent expires automatically as described below.

SPECIFICATION OF THE DATE, EVENT, OR CONDITION UPON WHICH THIS CONSENT EXPIRES (if left blank this consent expires in one year)

____

EXECUTED THIS ______________ DAY OF ______________________, 20____

______________________ (Witness)

______________________ (Printed name of patient, parent, guardian, or authorized representative)

______________________ (Signature of patient, parent, guardian, or authorized representative)

______________________ (Nature of relationship if other than patient)

PROHIBITION ON REDISCLOSURE: THIS INFORMATION HAS BEEN DISCLOSED TO YOU FROM RECORDS WHOSE CONFIDENTIALITY IS PROTECTED BY FEDERAL LAW. FEDERAL REGULATIONS (42O FR PART 2) PROHIBIT YOU FROM MAKING ANY FURTHER DISCLOSURE OF THIS INFORMATION EXCEPT WITH THE SPECIFIC WRITTEN CONSENT OF THE PERSON TO WHOM IT PERTAINS. A GENERAL AUTHORIZATION FOR THE RELEASE OF MEDICAL OR OTHER INFORMATION IF HELD BY ANOTHER PARTY IS NOT SUFFICIENT FOR THIS PURPOSE. FEDERAL REGULATIONS STATE THAT ANY PERSON WHO VIOLATES ANY PROVISION OF THIS LAW SHALL BE FINED NOT MORE THAN $500, IN THE CASE OF A FIRST OFFENSE, AND NOT MORE THAN $5,000, IN THE CASE OF EACH SUBSEQUENT OFFENSE.

Drug Abuse Office and Treatment Act of 1972 (21 USC 1175) Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970 (42 USC 4582)

Appendix D

Classification of commonly used medications

<table>
<tr><th colspan="2">TABLE 9: Classification of commonly used medications in the first two years of life among the KUDOS cohort</th></tr>
<tr><td rowspan="3"><u>Antibiotic</u>
Zithromax
Amoxicillin (Amox)
Omnicef (Cefdinir)
Augmentin
Suprex (Cefixine)
Ciprofloxacin/Dexamethasone (Ciprodex) – steroid and Abx combo
Tobramycin (Tobrex)
Retapamulin
Vigamox (Mofifloxacin)
Trimethoprim – Polymyxin B (Polytrim)
Clindamycin
Gentamicin
Ciprofloxacin (Cloxan)
Ceftriaxone (Rocephin)
Clarithromycin (Biaxin)
Mupirocin (Bactroban)
Sulfamethoxazole/Trimethoprim (Bactrim)
Erythromycin ointment
Ofloxacin otic
Cortisporin
Cefalexin (Keflex)</td><td><u>Antifungal</u>[1]
Nystatin
Nizoral Shampoo
Fluconazole
Clotrimazole
Gentian Violet
Lotrimin (Butenafine)
Ketoconazole cream
Oxiconazole (Oxistat)
Griseofulvin</td></tr>
<tr><td><u>NSAIDS</u>
Aspirin
Ibuprofen
Diclogenac
Naproxen</td></tr>
<tr><td><u>Antacids</u>
Maalox
Zantac (Ranitidine)
Prilosec
Zantac</td></tr>
<tr><td><u>Allergy</u>[1]
Nasonex
Benadryl (Diphenhydramine or DPH-Elixir)
Hydroxyzine (Atarax)
Loratadine (Claritin)
Singular
Cetirizine</td><td><u>Analgesic</u>
Tylenol
Antipyrine/Benzocaine (Auralgan/Aurodex/Auroto)
Oxycodone/Acetaminophen (Roxicet)</td></tr>
<tr><td><u>Corticosteriod</u>
Triamcinolone
Cloderm
Flonase (Fluticasone) (Cutivate)
Prednisolone (Orapred)
Desonide
Dexamethasone (Decadron)
Budesonide/Pulmicort
Hydrocortisone (Westcort)
Ciprodex</td><td><u>Other</u>
Dextromethorphan (Delsym) – cough suppressant
Dr. Smith's OTC Diaper Rash Ointment
Levosalbutamol (Xopenex) – cough suppressant
Albuterol (Proventil)
Bacotracom
Nizatide (Axid)
Selsun Blue – antidandruff shampoo
Tenar DM – cough suppressant
Desitin – diaper rash barrier cream
Bacitracin – specific to staph infections
Acyclovir – Herpes virus</td></tr>
<tr><td colspan="2">[1] Medications used as determining factor in differentiating between illness categories
NOTE: Dx trumps criterion. Ex: Y125 dx Diaper Rash-Candidal but no antifungal Rx → fungal</td></tr>
</table>

Appendix E

Infectious Illness Categorization List

TABLE 10. Infectious Illness Categorization List	
Viral Illness	Hand, foot and mouth disease Conjunctivitis* with clear, thin, white discharge (no itching) Chicken Pox Herpangina RSV Gingivostomatitis Influenza A Coxsackie Virus Roseola Molluscum Contagiosum Any illness in which MD noted viral etiology
Bacterial Illness	Boil Carbuncle Cellulitis Conjunctivitis* with thick, white-yellow or green discharge (aka purulent) Folliculitis, + Staph Impetigo Pertussis Stye Bacterial infection (inc. Streptococcus, MRSA)
Fungal Illness	Dermatophytosis or Tinea Corporis (aka Ringworm) Diaper Dermatitis - Candidal, Rx: Antifungal Otorrhea/OM, fluffy white to off-white discharge Thrush Yeast Infection

*Only illness in which color of discharge can be used to differentiate infectious etiology.
"A green or yellow nasal discharge is not a sign that you need antibiotics."
www.nlm.nih.gov/medlineplus/ency/article/003051.htm

Appendix F

Common examples of illness categorization

Table 11. Common examples of illness categorization in the KUDOS cohort	
Abscess	Infectious --> "An abscess is a collection of pus in any part of the body that, in most cases, causes swelling and inflammation around it. Abscesses occur when an area of tissue becomes infected and the body's immune system tries to fight it...Abscesses may be caused by bacteria, parasites, and foreign substances." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002329/#adam_001353.disease .causes)
Adenoid Hypertrophy	N/A UNLESS meets Infectious criteria → "Enlarged adenoids means this tissue is swollen. Enlarged adenoids may be normal. It may start when the baby grows in the womb. The adenoids help your body prevent or fight infections by removing bacteria and germs…Infections can cause the adenoids to become swollen. The adenoids may stay enlarged even when you are not sick." (http://www.nlm.nih.gov/medlineplus/ency/article/001649.htm)
Alopecia	N/A --> "The cause of alopecia areata is unknown...Alopecia areata is thought to be an autoimmune condition. This occurs when the immune system mistakenly attacks and destroys healthy body tissue." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002421/#adam_001450.disease .causes)
Anemia of prematurity	N/A --> "The anemia of prematurity is caused by untimely birth occurring before placental iron transport and fetal erythropoiesis are complete, by phlebotomy blood losses taken for laboratory testing, by low plasma levels of erythropoietin due to both diminished production and accelerated catabolism, by rapid body growth and need for commensurate increase in red cell volume/mass, and by disorders causing RBC losses due to bleeding and/or hemolysis." (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2981681/)
Ankyloglossia	N/A --> "Tongue-tie (ankyloglossia) is a condition that restricts the tongue's range of motion."
Asthma	Allergic --> Vissing 2012 article categorized asthma under "atopic dz" such as atopic dermatitis (which we categorize as allergic) and allergic rhinitis. Amanda Foiles categorized asthma under "any allergy". Birch 2010 article categorized asthma as allergic disease.
Atopic Dermatitis	Allergic
Blepharitis	N/A --> "In people with blepharitis, too much oil is produced by the glands near the eyelid. The exact reason for this problem is not known. Blepharitis is more likely to be seen with: A skin condition called seborrheic dermatitis or seborrhea, which often involves the scalp, eyebrows, eyelids, behind the ears, and creases of the nose; Allergies and lice that affect the eyelashes (less common); Excess growth of the bacteria that are normally found on the skin; Rosacea -- a skin condition that makes the face turn red" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002586/#adam_001619.disease .causes)
Boil	Infectious - Bacterial --> "Boils and carbuncles are painful, pus-filled bumps that form under your skin when bacteria infect and inflame one or more of your hair follicles." (http://www.mayoclinic.org/diseases-conditions/boils-and-carbuncles/basics/definition/con-20024235)

Bronchiolitis	Infectious --> "Bronchiolitis is swelling and mucus buildup in the smallest air passages in the lungs (bronchioles), usually due to a viral infection." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001970/#adam_000975.disease.causes), Viral Illness per KUH protocol, "Lower Respiratory Infections: Bronchitis, Bronchiolitis and Pneumonia - *Etiology*: Causative agents of lower respiratory infections are viral or bacterial. Viruses cause most cases of bronchitis and bronchiolitis." (http://www.ncbi.nlm.nih.gov/books/NBK8142/)
Bronchitis	Infectious --> "Acute bronchitis is usually caused by viruses, typically the same viruses that cause colds and influenza....The most common cause of chronic bronchitis is smoking cigarettes." (http://www.mayoclinic.org/diseases-conditions/bronchitis/basics/causes/con-20014956) "Lower Respiratory Infections: Bronchitis, Bronchiolitis and Pneumonia - *Etiology*: Causative agents of lower respiratory infections are viral or bacterial. Viruses cause most cases of bronchitis and bronchiolitis." (http://www.ncbi.nlm.nih.gov/books/NBK8142/)
Carbuncle	See boil
Cellulitis	Infectious - "common skin infection caused by bacteria" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001858/#adam_000855.disease.causes)
Chicken Pox	Infectious --> "Chickenpox is a viral infection in which a person develops extremely itchy blisters all over the body." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002559/#adam_001592.disease.causes)
Congestion	Unknown UNLESS meets criteria for Infectious or Allergic --> "In most cases, the nose becomes congested when the tissues lining it become swollen. The swelling is due to inflamed blood vessels…A stuffy nose is usually by a virus or bacteria. Causes include: common cold, flu, sinus infection. Congestion also can be caused by: hay fever or other allergies, use of some nasal sprays or drops for more than 3 days (may make nasal stuffiness worse), nasal polyps, pregnancy, vasomotor rhinitis." (Ex: Chart 106 9/23/2008) (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0003540/#adam_003049.symptoms.causes)
Conjunctivitis	Causes: virus (thin, clear white d/c), bacteria (thick, white-yellow or green d/c, "purulent" per American Family Physician Figure 2; "exudate" – pus or clear liquid → Unknown. http://www.aafp.org/afp/1998/0215/p735.html), irritant, allergy (itching and clear-white d/c) (http://www.aurorahealthcare.org/yourhealth/housecalls/display.asp?Type=EA&ID=142)
Constipation	N/A unless dx at same time as something A or I (example: Constipation & Viral Syndrome --> Infectious) "Constipation is most often caused by: low-fiber diet, lack of physical activity, not drinking enough water, delay in going to the bathroom when you have the urge to move your bowels, stress, travel, colon cancer, disease of the bowel (such as irritable bowel syndrome), mental health disorders, nervous system disorders, pregnancy, underactive thyroid, use of certain medications." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0003612/#adam_003125.sympto

	ms.causes)
Contact Dermatitis	Allergy Rx --> Allergic, Other Tx --> N/A (b/c probably irritant) "Contact dermatitis is a condition in which the skin becomes red, sore, or inflamed after direct contact with a substance. There are two kinds of contact dermatitis: irritant or allergic." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001872/#adam_000869.disease.causes)
Cough	N/A if occurs at same time as other more descriptive AE. If alone then UNKNOWN.
Cradle Cap	N/A UNLESS Tx: Antifungal Rx --> Infectious
Croup	Unknown UNLESS meets infectious or allergic criteria. "may be caused by: viral infection (most common), bacterial infection, allergies, breathing in something that irritates your airway, acid reflux" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001955/#adam_000959.disease.causes)
Cyst	N/A UNLESS meets Infectious criteria --> "Cysts form for a number of different reasons. They can be caused by: infections, inherited diseases, chronic inflammation, and blockages in ducts." (http://www.healthline.com/health/cyst) (Example: 002)
Dacryostenosis	N/A --> "A blocked tear duct is a partial or complete blockage in the pathway that carries tears from the surface of the eye into the nose." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002011/)
Dermatitis	Try to narrow down to specific type! Unknown if cannot narrow down --> "Dermatitis is a general term that describes an inflammation of the skin...A number of health conditions, allergies, genetic factors and irritants can cause different types of dermatitis." (http://www.mayoclinic.org/diseases-conditions/dermatitis-eczema/basics/causes/con-20032183)
Diaper Dermatitis	Antifungal Rx --> Infectious; Other --> N/A (b/c irritant origin) "Diaper rashes caused by infection with a yeast or fungus called Candida are very common in children." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001960/#adam_000964.disease.causes)
Diarrhea	Unknown UNLESS MD note Allergic rxn or meets Infectious criteria --> "The most common cause of diarrhea is the stomach flu (viral gastroenteritis). This mild viral infection goes away on its own within a few days. Eating or drinking food or water that contains certain types of bacteria or parasites can also lead to diarrhea. This problem may be called food poisoning." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0003613/#adam_003126.symptoms.causes)
Dry Skin	N/A
Dysphagia	N/A UNLESS meets Allergic criteria
Dysuria	Unknown --> could be allergic rxn to ointment, etc OR could be infection such as UTI
Eczema	Allergic
Emesis	N/A UNLESS meets Infectious or Allergic criteria and not dx with anything else
Enlarged Lymph Nodes	Unknown UNLESS meet Infectious criteria --> "Infections are the most common cause of swollen lymph nodes. …" Autoimmune disorders, cancer, or certain Rx (seizure Rx or Typhoid immunization) can cause as well. (http://www.nlm.nih.gov/medlineplus/ency/article/003097.htm)

Epistaxis	N/A UNLESS dx with Infectious or Allergic condition -->"Nosebleed. Common causes include: Allergic rhinitis, An object stuck in the nose, Barotrauma, Blowing the nose very hard, Chemical irritants, Direct injury to nose (including a broken nose), Hereditary hemorrhagic telangiectasia, Nose picking, Overuse of decongestant nasal sprays, Repeated sneezing, Surgery on the face or nose, Taking large doses of aspirin or blood-thinning medicine, Upper respiratory infection, Very cold or very dry air" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0003594/#adam_003106.symptoms.causes)
Esophagitis	N/A unless meets Infectious criteria --> "...often caused by fluid that contains acid flowing back from the stomach to the esophagus, a condition called gastroesophageal reflux. An autoimmune disorder called eosinophilic esophagitis also causes this condition. Persons with weakened immune systems due to HIV and certain medications (such as corticosteroids) may develop infections that lead to esophagitis." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002138/#adam_001153.disease.causes)
Exotropia/ Intermittent Divergent Strabismus	N/A --> Exotropia/ Intermittent Divergent Strabismus
Folliculitis	N/A UNLESS found to be +Staph or meets Infectious criteria --> "starts when hair follicles are damaged by rubbing from clothing, blockage of the follicle, or shaving. Most of the time, the damaged follicles become infected with Staphylococcus (staph) bacteria" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001826/#adam_000823.disease.causes)
Gastroenteritis	Unknown UNLESS meets criteria for Infectious or Allergic --> "Gastroenteritis is an inflammation of the lining of the intestines caused by a virus, bacteria or parasites." (http://www.nlm.nih.gov/medlineplus/gastroenteritis.html#cat1)
GERD	Check to make sure not allergic rxn. Generally speaking, will be N/A.
Gingivostomatitis	Infectious --> "Gingivostomatitis is an infection of the mouth and gums that leads to swelling and sores. It may be due to a virus or bacteria." (http://www.nlm.nih.gov/medlineplus/ency/article/001052.htm) (See 070 Y82 dx at 18.4m - CMH documentation says Gingivostomatitis is caused by a virus.)
Hand, Foot & Mouth disease	Infectious --> "Hand-foot-mouth disease is a relatively common infection viral infection that usually begins in the throat." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001961/#adam_000965.disease.causes)
Hemangioma	N/A
Hematochezia	N/A --> "Hematochezia is the passage of fresh blood per anus, usually in or with stools."
Herpangina	Herpangina is a viral illness that involves ulcers and sores (lesions) inside the mouth, a sore throat, and fever. (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001964/#adam_000969.disease.causes)
Hordeolum	see Stye (http://pediatrics.med.nyu.edu/conditions-we-treat/conditions/hordeolum)

Hydroceles	N/A → "During a baby's development in the womb, the testicles descend from the abdomen through tube into the scrotum. Hydroceles occur when this tube does not close. Fluid drains from the abdomen through the open tube and gets trapped in the scrotum. This causes the scrotum to swell." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001546/#adam_000518.disease.causes)
Hypospadias	N/A --> Hypospadias is a birth (congenital) defect in which the opening of the urethra is on the underside of the penis. The urethra is the tube that drains urine from the bladder. In males, the opening of the urethra is normally at the end of the penis. (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002265/#adam_001286.disease.causes)
Impetigo	Infectious --> "Impetigo is caused by streptococcus (strep) or staphylococcus (staph) bacteria. Methicillin-resistant staph aureus (MRSA) is becoming a common cause." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001863/#adam_000860.disease.causes)
Insect Bite	N/A regardless of tx (if infectious or allergic, another AE will occur)
Intertigo	N/A UNLESS meets Infectious criteria --> "Intertrigo is inflammation of the skin. It tends to occur in warm, moist areas of the body where two skin surfaces rub or press against each other. Such areas are called 'skin folds.'…It is caused by moisture, bacteria, yeast, or fungus in the folds of the skin." (http://www.nlm.nih.gov/medlineplus/ency/article/003223.htm)
Jaundice	N/A
Lacrimal Duct Obstruction	N/A UNLESS meets Infectious criteria --> " (Example: 002)
Lymphadenopathy	Infectious --> "Lymphadenopathy is the term for swelling of the lymph nodes...The lymphatic system is part of the immune system and functions to fight disease and infections. As infection-fighting cells and fluid accumulate, the lymph nodes enlarge to many times their normal size. Nearly all children will develop lymphadenopathy at some time, as the condition commonly occurs in response to an infection from a virus, such as an upper respiratory infection. Bacterial infections, such as strep throat caused by the streptococcus bacterium, can also cause lymphadenopathy." (http://www.urmc.rochester.edu/Encyclopedia/Content.aspx?ContentTypeID=90&ContentID=P02044)
Miliaria rubra	N/A --> aka Heat Rash
Molluscum	Infectious --> "Molluscum contagiosum is a viral skin infection that causes raised, pearl-like papules or nodules on the skin." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001829/#adam_000826.disease.causes)
Neonatal Acne	N/A --> "Neonatal acne is thought to result from stimulation of sebaceous glands by maternal or infant androgens." (http://www.aafp.org/afp/2008/0101/p47.html)
Nursemaid's elbow	N/A --> Nursemaid's Elbow

Otitis Externa	Unknown UNLESS meets Infectious or Allergic criteria. "Otitis externa is most commonly caused by infection (usually bacterial, although occasionally fungal), but it may also be associated with a variety of noninfectious systemic or local dermatologic processes." (http://www.aafp.org/afp/2001/0301/p927.html)
Otitis Media	Unknown UNLESS meets Infectious (inc. red and bulging TM) or Allergic criteria --> "Inflammation of the middle ear without reference to etiology or pathogenesis" (http://emedicine.medscape.com/article/994656-overview) "A dull or absent light reflex from the eardrum may be a sign of a middle ear infection or fluid. The eardrum may be red and bulging if there is an infection. Amber liquid or bubbles behind the eardrum are often seen if fluid collects in the middle." (http://www.nlm.nih.gov/medlineplus/ency/article/003340.htm)
Otorrhea OR OM	A scant white mucus discharge indicates acute external ear infection. A fungal infection of the external ear results in a fluffy white to off-white discharge. In some cases however, the discharge may be black, gray, bluish-green or yellow. A white to yellow mucus discharge with pus and deep pain indicates middle ear infection with perforated eardrum A purulent mucus discharge without pain which is present sometimes and absent at other times may indicate chronic middle ear infection. Infection of the bone around the ear results in ear discharge with a bad odor. A clear, thin and watery discharge following head injury could indicate a fracture in the skull. Trauma to the ear may result in a bloody mucus discharge. Read more: Acute Ear Infection / Ear Discharge - Symptom Evaluation http://www.medindia.net/symptoms/acute-ear-infection.htm#ixzz2nOJ2DTXs "Pus" d/c --> Infectious “Exudate” → Unknown - could mean pus or clear fluid
OM c Effusion / Serous OM (SOM) / Secretory OM / Glue Ear	N/A UNLESS meets Allergic or Infectious criteria (shouldn't meet Infectious criteria but if does then trumps N/A categorization; Example: 90 M54 at 15.7m) --> "Otitis media with effusion (OME) is when there is thick or sticky fluid behind the eardrum in the middle ear, but there is no ear infection...The following can cause swelling of the lining of the Eustachian tube, leading to increased fluid: Allergies; Irritants (especially cigarette smoke); Respiratory infections. The following can cause the Eustachian tube to close or become blocked: Drinking while lying on your back; Sudden increases in air pressure (such as descending in an airplane or on a mountain road)." (http://www.nlm.nih.gov/medlineplus/ency/article/007010.htm)
Suppurative Otitis Media	Infectious --> "Acute suppurative otitis media is distinguished from secretory (serous) otitis media by the presence of purulent fluid in the middle ear…Suppurative otitis media can be diagnosed positively only by aspiration of purulent fluid from the middle ear, but this procedure is rarely necessary for initial diagnosis and management." (http://pediatrics.aappublications.org/content/56/2/285)
Papular Rash	N/A UNLESS meets infectious or allergic criteria --> "...papular rash refers to small raised red bumps" (http://www.medicinenet.com/rash/symptoms.htm)

Petechiae	N/A UNLESS meets Infectious criteria --> "Petechiae are pinpoint, round spots that appear on the skin as a result of bleeding under the skin…Caused by prolonged straining, certain medications, infectious diseases, and other medical conditions." (http://www.mayoclinic.org/symptoms/petechiae/basics/causes/sym-20050724)
Pertussis	Infectious --> "Pertussis is a highly contagious bacterial disease that causes uncontrollable, violent coughing. The coughing can make it hard to breathe. A deep "whooping" sound is often heard when the patient tries to take a breath." aka Whooping Cough (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002528/#adam_001561.disease.causes)
Pharyngitis	Unknown UNLESS meets Infectious criteria --> "Pharyngitis is caused by swelling in the back of the throat (pharynx) between the tonsils and the (larynx). Most sore throats are caused by colds or the flu. Coxsackie virus or mononucleosis can also cause sore throat." (http://www.nlm.nih.gov/medlineplus/ency/article/000655.htm).
Pink Eye (Conjunctivitis)	Unknown UNLESS meets Infectious criteria --> (fever, discolored d/c, etc)"Pink eye is commonly caused by a bacterial or viral infection, an allergic reaction, or — in babies — an incompletely opened tear duct." (http://www.mayoclinic.org/diseases-conditions/pink-eye/basics/definition/con-20022732)
Plagiocephaly	N/A --> aka Flat Head Syndrome
Pneumonia	Infectious --> "Pneumonia is an infection that inflames the air sacs in one or both lungs. The air sacs may fill with fluid or pus, causing cough with phlegm or pus, fever, chills and difficulty breathing. A variety of organisms, including bacteria, viruses and fungi, can cause pneumonia." (http://www.mayoclinic.com/health/pneumonia/DS00135) "Lower Respiratory Infections: Bronchitis, Bronchiolitis and Pneumonia - *Etiology*: Causative agents of lower respiratory infections are viral or bacterial." (http://www.ncbi.nlm.nih.gov/books/NBK8142/)
Pneumothorax	N/A --> aka collapsed lung
Post Vaccine Contusion	N/A --> Although post vaccine contusion could be sign of allergic rxn to vaccine, LBP and EK agree on 01/17/2014 that post vaccine contusion is most appropriate to label as "N/A" rather than "U"
Pruritus	N/A --> "Pruritus simply means itching. It can be associated with a number of disorders, including dry skin, skin disease, pregnancy, and rarely, cancer."…These disorders should be coded as separate AEs. (http://www.webmd.com/skin-problems-and-treatments/guide/skin-conditions-pruritus)
Ptosis	N/A --> Drooping of the eyelid (http://www.nlm.nih.gov/medlineplus/ency/article/001018.htm)
Pustules	Infectious → "Pustules are small, inflamed, pus-filled, blister-like lesions on the skin surface." (http://www.nlm.nih.gov/medlineplus/ency/article/003234.htm)
Rash	N/A unless meets Infectious or Allergic criteria…if specific type, see if specific type listed
Reactive Airway Disease (RAD)	Allergic (Birch 2010 article) --> Reactive Airway Dz (RAD)

Respiratory Distress Syndrome	N/A --> "Respiratory distress syndrome (RDS) is a breathing disorder that affects newborns. RDS rarely occurs in full-term infants. The main cause of respiratory distress syndrome (RDS) is a lack of surfactant in the lungs. Surfactant is a liquid that coats the inside of the lungs." (http://www.nhlbi.nih.gov/health/health-topics/topics/rds/)
Rhinorrhea	Unknown --> "Runny nose can be caused by anything that irritates or inflames the nasal tissues. Infections — such as the common cold and influenza — allergies and various irritants may all cause a runny nose." (http://www.mayoclinic.org/symptoms/runny-nose/basics/causes/sym-20050640)
Roseola	Infectious --> "Roseola is a viral infection that commonly affects infants and young children." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001963/#adam_000968.disease.causes)
Rotary Nystagmus	N/A --> Rotary Nystagmus
Scabies	N/A --> "Scabies is an easily spread skin disease caused by a very small type of mite." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001833/#adam_000830.disease.causes)
Seborrheic Dematitis	N/A UNLESS Tx: Antifungal Rx --> Infectious "Seborrheic dermatitis is a common, inflammatory skin condition that causes flaky, white to yellowish scales to form on oily areas such as the scalp, face or inside the ear. It can occur with or without reddened skin. *Cradle cap* is the term used when seborrheic dermatitis affects the scalp of infants. The exact cause of seborrheic dermatitis is unknown. Doctors think it may be due to a combination hormone levels, weakened immune system, lack of certain nutrients, or nervous system problems. Irritation from a yeast called Malassezia may also lead to this condition." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001959/#adam_000963.disease.causes)
Sepsis	Infectious --> "Sepsis is an illness in which the body has a severe response to bacteria or other germs…A bacterial infection anywhere in the body may set off the response that leads to sepsis." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001687/#adam_000666.disease.causes)
Sinusitis	Infectious --> "Sinusitis is inflammation of the sinuses. It occurs as the result of an infection from a virus, bacteria, or fungus." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001670/#adam_000647.disease.causes)

Stomatitis	Most likely Unknown UNLESS find evidence that HSV1 infection --> "Herpes Stomatitis is caused by infection of the HSV1 virus in young children.... Aphthous stomatitis is caused by a variety of problems with oral hygiene or damage to mucous membranes. Some potential causes include: dry tissues from breathing through the mouth due to clogged nasal passages; small injuries due to dental work, accidental cheek bite, etc.; sharp tooth surfaces, dental braces, or retainers; celiac disease (allergy to gluten); food sensitivities to strawberries, citrus fruits, coffee, chocolate, eggs, cheese, or nuts; allergic response to certain bacteria in the mouth; inflammatory bowel diseases; autoimmune disease that attacks cells in the mouth; HIV/AIDS; weakened immune system; deficiency in Vitamin B12, folic acid, iron, or zinc; certain medications; stress." (http://www.healthline.com/health/stomatitis)
Stridor	Unknown UNLESS dx with something else that can be determined to be Infectious or Allergic --> "Stridor is an abnormal, high-pitched, musical breathing sound caused by a blockage in the throat or voice box (larynx). It is usually heard when taking in a breath....Common caused include: Abscess on the tonsils; Airway injury; Allergic reaction; Croup; Diagnostic tests such as bronchoscopy or laryngoscopy; Epiglottitis, inflammation of the cartilage that covers the trachea (windpipe); Inhaling an object such as a peanut or marble (foreign body aspiration); Laryngitis; Neck surgery; Use of a breathing tube for a long time; Secretions such as phlegm (sputum); Smoke inhalation or other inhalation injury; Swelling of the neck or face; Swollen tonsils or adenoids (such as with tonsillitis); Vocal cord cancer" (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0003565/#adam_003074.symptoms.causes)
Stye	Infectious --> "A stye is an inflamed oil gland on the edge of your eyelid, where the lash meets the lid...A stye is caused by bacteria from the skin that get into the oil glands in the eyelids that provide lubrication to the tear film." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002004/#adam_001009.disease.causes)
Teething	N/A
Thrush	Infectious -overgrowth of Candida fungus (only)
Tinea Corporis	Infectious --> "Tinea corporis is a skin infection due to fungi. It is also called ringworm of the body." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001880/#adam_000877.disease.causes)
Tonsillitis	Infectious --> "Tonsillitis is inflammation (swelling) of the tonsils. A bacterial or viral infection can cause tonsillitis. Strep throat is a common cause." (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002038/#adam_001043.disease.causes)
Umbilical Granuloma	N/A --> "An umbilical granuloma is a small nodule of firm pinkish-red tissue (similar to scar tissue) with persistent yellow-green drainage. This is different than an infection because it is not accompanied by swelling, redness, warmth, tenderness, or a fever." (http://americanpregnancy.org/firstyearoflife/umbilicalcord.htm)
URI	Infectious UNLESS Allergic Rx then Unknown → "*Etiology*: Most upper respiratory infections are of viral etiology. Epiglottitis and laryngotracheitis are exceptions with severe cases likely caused by *Haemophilus influenza* type b. Bacterial pharyngitis is often caused by Streptococcus pyogenes." (

Wheezing	Allergic UNLESS dx with URI or other condition which would make breathing difficult (then N/A) (Birch 2010 article)
Xerosis	N/A --> "Xerosis is an abnormal dryness of the skin or mucus membranes." (http://www.nlm.nih.gov/medlineplus/ency/article/000835.htm)

*Rule of thumb: If the condition ends in "-itis" then "unknown unless meets infectious criteria" b/c usually infection