Is there a difference in accordance to the alternate Mediterranean Diet (aMED), intakes of a total alternate aMED score and specific aMED dietary constituents in those diagnosed with asthma compared to those without asthma among a sample of children aged 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012 (2005-2012)?

Sarah Steinmetz
NHANES Research Project
NTR 555 Dr. Tangney
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Research Question

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Objectives

The objectives of this epidemiological, non-conventional cross-sectional analysis are to:

1) To determine if there is a difference in accordance to the Alternate Mediterranean Diet (aMED) using the aMED scoring system in a pediatric sample from the United States ages 2-18 among those diagnosed with asthma compared to those without an asthma diagnosis, stratified by gender as well as gender further stratified by age categories (2-5 years old, 6-11 years old, and 12-18 years old) (NHANES 2005-2012).
2) To determine if there is a difference in the mean and median total aMED score in a pediatric sample from the United States ages 2-18 among those diagnosed with asthma compared to those without an asthma diagnosis, stratified by gender as well as gender further stratified by age categories (2-5 years old, 6-11 years old, and 12-18 years old) (NHANES 2005-2012).
3) To determine if there is a difference in median average dietary intakes of Food Patterns equivalents of vegetables (cup equivalents), fruits (cup equivalents), legumes (cup equivalents), nuts and seeds (ounce equivalents), whole grains (ounce equivalents), fish (ounce equivalents), and red/processed meat (ounce equivalents) from the Food Patterns Equivalents Database (cycles taken from equivalent NHANES cycles), as well as the ratio of total grams of monounsaturated fat:saturated fat (NHANES 2005-2012) in a

pediatric sample from the United States ages 2-18 among those diagnosed with asthma compared to those without an asthma diagnosis, stratified by gender as well as gender further stratified by age categories (2-5 years old, 6-11 years old, and 12-18 years old).

Introduction

Asthma is the most common chronic pediatric health condition in the United States [1]. The prevalence of asthma has been trending upwards since 1980 in children. In 2009, Akinbami et al. (2011) reported that asthma affected 7.1 million children (ages 0-17) in the United States, with four million of these children having asthma attacks in the previous year. It was found that during the ages of 0-17, asthma was more prevalent in males, but during early adolescence its prevalence declined. The prevalence of asthma gradually increased throughout childhood in females, and by the ages of 14-17 the prevalence in females was about equal to that of males, but by adulthood the prevalence of females was higher than males. The overall prevalence of asthma was found to be higher in children than in adults [2].

Asthma was found to have many adverse outcomes; In 2007, 0.64 million children had to go to the emergency room because of asthma, 157,000 children were hospitalized because of asthma, and 185 children died because of asthma [2]. In 2006, Vargas et al. found asthma to have a large effect on children's lives due to exacerbated respiratory function, including limitation of activity, ability to attend school, and ability to sleep through the night [3].

Mechanisms for pediatric asthma development are multifactorial, as it is a heterogeneous disease. Many phenotypic factors contribute to its development in the pediatric population; the most common include transient early wheezing before the age of three (secondary to reduced pulmonary function, prematurity, maternal smoking during pregnancy, and exposure to second hand smoke), non-atopic wheezing secondary to viral infection (most commonly respiratory syncytial virus), and atopic wheezing secondary to genetic predisposition to allergens [4]. Childhood obesity is also a risk factor for pediatric asthma development for many postulated reasons, including decreased lunch mechanics, nitric oxide metabolism, and overall increased inflammation [5]. All of these factors lead to airway inflammation, followed by bronchial hyperresponsiveness and persistent wheeze [4].

Many children go into remission of asthma at a young age, but there is a population of children whose asthma persists into adulthood. Risk factors for this population include diminished airflow, female gender, eosinophilia, and airway hyper-responsiveness [6]. Overall, it is suggested that the development of asthma and its persistence into adulthood is influenced by both genetic and environmental factors, however many of these factors are still unknown [7], warranting research on dietary factors of children with asthma.

In the past few years, studies have specifically been conducted on the association of pediatric asthma prevalence and intake of a Mediterranean diet. A major reason for this is that western diets are low in antioxidants, and also tend to be lower in omega 6 and omega 3 polyunsaturated acids, which may be a cause for pediatric asthma development. The Mediterranean diet, on the other hand, provides a rich source of antioxidants and essential lipids which have shown to be protective of asthma development and symptom exacerbation due to an anti-inflammatory effect [8]. In 2013, a meta-analysis conducted by Garcia-Marcos et al. overall found the Mediterranean diet to be associated with a lower asthma occurrence in children [9]. Just recently In 2015, a Peruvian study found that children who ate above the median Mediterranean score had a decreased odds of asthma prevalence compared to children who ate below the median Mediterranean diet score [10]. Therefore, this study will further assess the prevalence of a pediatric asthma diagnosis and differences to accordance to a validated [11], alternate Mediterranean Diet (aMED) [12] and its specific dietary constituents.

Methods

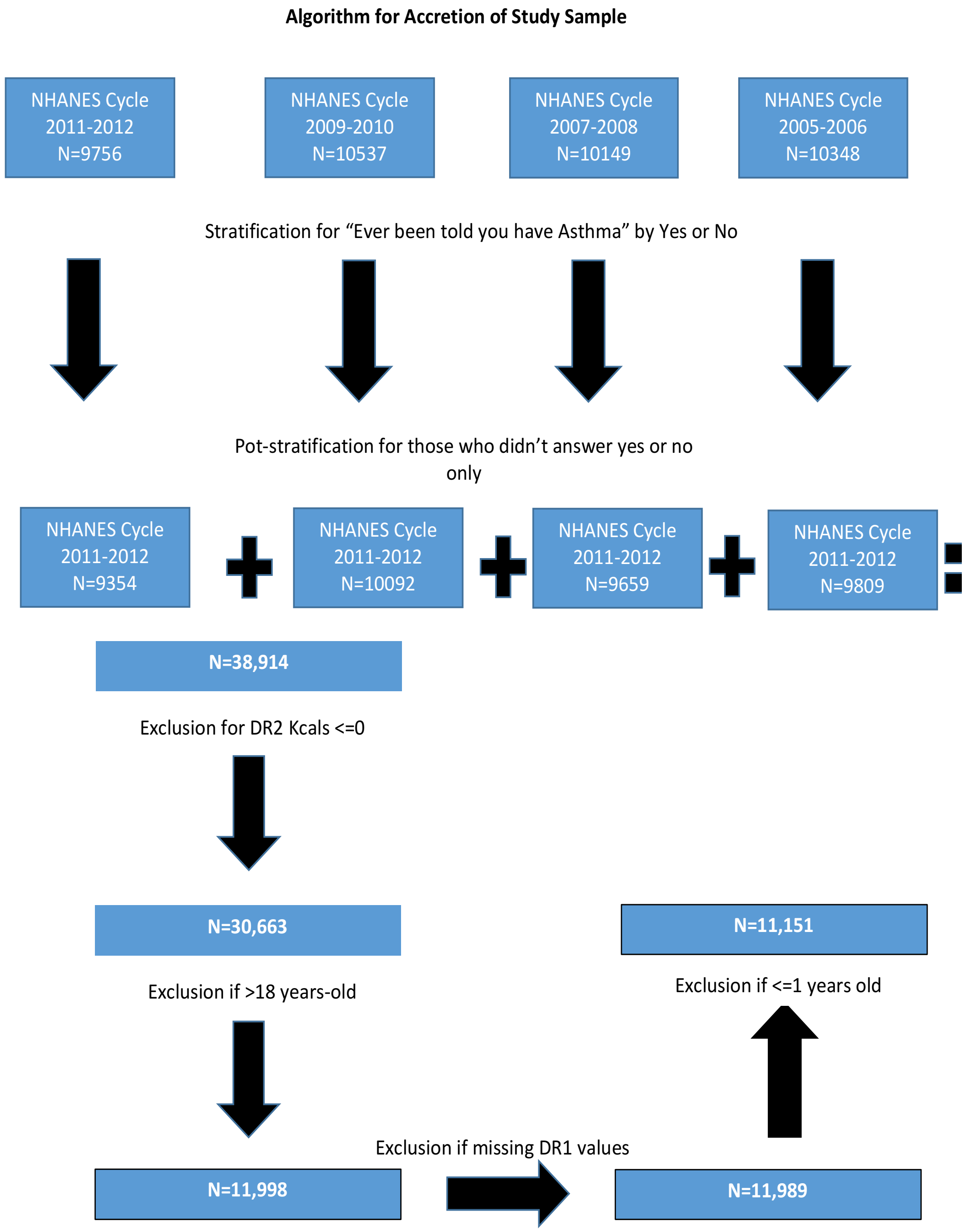
According to the United States Center of Disease Control and Prevention, the Nutritional Health and Examination Survey (NHANES) is both a survey and examination designed to assess demographic, socioeconomic, dietary, and health-related questions, and medical, dental, and physiological measurements, respectively, of both adults and children in the United States. It is annually conducted to a nationally representative sample of 5000 people across the country.

Population Sampling and Exclusions

Subjects were selected from the NHANES database, cycles 2005-2006, 2007-2008, 2009-2010, and 2011-2012. Please see **Figure 1** for the sampling algorithm, and **Appendix A** for the data output. For each individual cycle, components merged by variables were: Demographics, Medical Conditions, Total Nutrient Intakes for dietary recall day 1 and 2, and total Food Pattern Equivalents for dietary recall day 1 and day 2 (data from the dietary recall administered for NHANES). Each cycle yielded a sample size of 10,348, 10,149, 10,537, and 9,756, respectively. The individual cycles were then merged together by cases, yielding 40,790 subjects. Subjects were further excluded if, for the question, "Ever been told you have asthma" answers were 7 (refused to answer), 9 (don't know), or –(missing) i.e. subjects were included only if "yes" or "no" was selected, yielding 38,914 subjects. This served as the context of an asthma diagnosis. Subjects were then excluded if a 0 or less was entered for dietary recall day 2 total calories, or if there was missing data, yielding 30,663 subjects, as it was assumed that if no total calories were recorded for the second day, that the subjects did not complete or did not have total caloric intakes for the first day either. To make the sample a pediatric sample, subjects were excluded if

>18 years old yielding 11,998 subjects. It was discovered that within this sample, though, nine subjects had missing values or <=0 for dietary recall day 1 total calories, therefore those subjects were excluded yielding 11,989 subjects. Given the dietary variability between an infant and a child/adolescent, the sample selection was modeled to mimic other pediatric literature using NHANES that excluded infants, therefore children <=1 years old were excluded [13]. This process yielded a total sample size of 11,151 subjects.

Figure 1. Algorithm for Sampling



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Outcomes

The primary outcome was accordance to aMED, scored using the aMED scoring system (described below). Secondary outcomes included mean/median total aMED scores and median intakes of average aMED Food Pattern Equivalents (vegetables, fruits, nuts and seeds, legumes, whole grains, and red/processed meats) for dietary recall day 1 and day 2 and median intakes of total average monounsaturated fats:saturated fats ratio for dietary recall day 1 and day 2. The secondary outcomes are supported in the literature as the main components of the aMED diet [11], and were created to give potential, specific insight as to differences in dietary intake between children with and without an asthma diagnosis. All outcomes were compared in a pediatric sample ages 2-18 among those with and without asthma asthma diagnoiss, stratified by gender alone and by gender followed by age categories (2-5, 6-11, 12-18) using NHANES 2005-2012.

Computed Variables for Statistical Analysis

Multiple new variables were computed in order to conduct the statistical analyses to assess the outcomes. Please see **Appendix B** for aMED scoring and variable computations.

Alternate Mediterranean Diet Scoring System (aMED)

The original Mediterranean diet is based on the intake of vegetables, legumes, fruit and nuts, dairy, cereals, meat and meat products, fish, alcohol, and the ratio of Monounsatruated fat (MUFAs):saturated fat [14]. The aMED is different than the original Mediterranean diet in that potatoes are excluded from the vegetable group, fruit and nuts are separated into two groups, only whole grain products are included (rather than cereals), only red meat and processed meat are included for the meat group, and alcohol intake is only assessed if consumption is between 5-15 grams/day [11]. For the purposes of this study, alcohol was excluded as its consumption is illegal in the United States in those younger than 21 years old, and all fruit juice was excluded from the fruit category as the literature does not describe if fruit juice normally included in the aMED score is 100% juice, or if it is processed juice with added sugar and flavoring components. Therefore, in this study, categories of the aMED score assessed were MUFAs:saturated fats, vegetables excluding potatoes, fruit excluding fruit juice, legumes, nuts and seeds, whole grains, fish, and red/processed meat; with specifics for each variable computation following.

- Ratio of Monounsaturated Fatty Acids (MUFAS):Saturated Fat: Total MUFAs and saturated fat, expressed as grams per day, were taken from NHANES total nutrient intake for day 1 and 2. An average score was computed by averaging total MUFA consumption for day 1 and 2, then averaging total saturated fat consumption for day 1 and 2. The average for MUFAs was then divided by the average for saturated fat for the average MUFAs:Saturated Fat category.
    - MUFAs=Total monounsaturated fatty acids (g)
    - Saturated Fat=Total saturated fatty acids (g)
- Vegetables: All vegetables, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) were included except for potatoes, expressed as cups per day. The average intake of vegetables minus potatoes between day 1 and 2 was calculated for the average vegetables category.
    - Vegetables= Dark green vegetables + Total red and orange vegetables (tomatoes + other red and orange)+ Other starchy vegetables, excluding potatoes
- Fruits: All fruits, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) were included except for

fruit juice, expressed as cup equivalents per day. The average intake of fruits between day 1 and 2 was calculated for the average vegetables category.

  - Fruits= Intact fruits (whole or cut) of citrus, melons + Berries and Intact fruits (whole or cut) excluding citrus, melons, and berries

- Legumes: All legumes, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) were included and expressed as ounce equivalents per day. The average intake of legumes between day 1 and 2 was calculated for the average legumes category.
  - Legumes= Legumes computed as vegetables + Legumes computed as protein
- Nuts and Seeds: Legumes: All nuts and seeds, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) were included and expressed as cup equivalents per day. The average intake of nuts and seeds between day 1 and 2 was calculated for the average nuts and seeds category.
  - Nuts and Seeds=Peanuts, tree nuts, and seeds, excludes coconut
- Whole grains: All whole grains, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) were included and expressed as ounce equivalents per day. The average intake of whole grains between day 1 and 2 was calculated for the average nuts and seeds category.
  - Whole grains= Whole grains
- Fish: All fish, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) was included and expressed as ounce equivalents per day. The average intake of fish between day 1 and 2 was calculated for the average fish category.

  - Fish= Seafood (finfish, shellfish and other seafood) high in n-3 fatty acids + Seafood (finfish, shellfish and other seafood) low in n-3 fatty acids

- Red/processed meat: All red/processed meat, taken from the total intake of Food Pattern Equivalent database for dietary recall days 1 and 2 (based off of NHANES diet recall) was included and expressed as ounce equivalents per day. The average intake of red/processed meat between day 1 and 2 was calculated for the average red/processed meat category.
  - Red/processed meat= Beef, veal, pork, lamb, game meat, excludes organ meats and cured meats + Cured/luncheon meat made from beef, pork, or poultry + Organ meat from beef, veal, pork, lamb, game, and poultry

The aMED scoring system is based on medians [11]. For all categories except for alcohol and red processed meat, if a subject's average intake (all average intakes are the average between total food pattern equivalents from NHANES dietary recall 1 and 2) was above the median for the specific average intake category he or she received a 1 for "accordant", but if a subject's average intake was below the median for the specific average intake category then he or she received a 0 for "non-accordant". However, the scoring was reversed for red/processed meats, in that if the subject's average intake was above the median he or she received a 0 for "non-accordant", but if the average intake was below the median then a 1 is given for "accordant". In order to obtain median intake for each aMED diet category, frequency tests were conducted on each newly computed average intake variable described above, stratified by gender. The "accordance" variable was then computed per category using this scoring system. To then compute the total aMED score, the accordance variable per aMED category were added together, giving 8 categories total, with a minimum of 0 points and a maximum of 8 points. Overall accordance was then determined by dividing 8 by 2, equating to four, so subjects with a total aMED score in the range of 0-<4 was determined overall non-accordant to the aMED diet, and subjects with a total aMED score in the range of 4-8 was determined overall accordant to the aMED diet.

Secondary and Tertiary Outcome Variable Computations

Secondary outcomes were assessed using average intake variable computations described above.

Demographic Variable Computations

All variables analyzed for demographics, including age at screening adjucated, race/ethnicity, and age when first had asthma were recoded into the same variable to exclude any missing cases, or responses of "don't know".

Data Analysis

Included in the data analysis were 11,151 children, ages 2-18, from NHANES cycles 2005-2012 with or without an asthma diagnosis. All data analyses were stratified by gender and age categories (ages 2-5, 6-11, 12-18), as significant differences were found when a chi-square analyses was performed to analyze differences in sample size by asthma diagnosis, gender, and age. For demographic measurements, categorical variables measured on a nominal scale included race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian), gender, age category (2-5, 6-11, 12-18), and ever been told you have asthma (yes/no). Frequencies [n, (%)] were used to describe these demographic variables. Age at screening and age when first had asthma were continuous variables measured on a ratio scale and were not normally distributed when stratified by gender and gender followed by age category. Therefore, descriptive statistics (median [25^{th}, 75^{th}%]) were used to describe these variables.

Accordance (accordant/non-accordant) to the aMED diet was a categorical variable measured on a nominal scale. A chi-square analysis was conducted in order to assess the difference between accordance in those with and without an asthma diagnosis stratified by gender alone and gender followed by age category (objective 1). The total aMED score can be interpreted as a continuous variable measured on both a ratio scale, as well as an ordinal scale. When stratified by gender and gender followed by age category the data was normally distributed. Therefore, an independent t-test was conducted to determine the difference between mean total aMED score, and a Mann-Whitney U test was conducted to determine the difference between median total aMED score among those with and without asthma stratified by gender alone and gender followed by age category. Average food pattern equivalents and ratio of MUFAs:Saturated fat were continuous variables measured on a ratio scale, however they were not normally distributed, therefore they were described as medians and a Mann-Whitney U test was conducted to determine differences in intakes among those with and without asthma, stratified by gender alone and gender followed by age category (ages 2-5, 6-11, 12-18). All significance was set at $P<0.05$. Please see **Appendix C** for all normality testing.

Results

All data analysis results from SPSS for demographic data are in **Appendix D**. Of the presented demographics (**Table 1**), the only demographic included in this study was number of subjects, therefore significance values for this demographic alone will be reported. A chi-square analysis indicated there were significant differences in number of subjects in all subcategories (gender and age category), indicating significantly more participants were not diagnosed with asthma compared to those with an asthma diagnosis, and certain subcategories had significantly more boys than girls and vice versa [$X^2(1, n=2,870)=11.35$, $p=0.001$ ages 2-5; $X^2(1, n=3,820)=23.59$, $p=0.00$ ages 6-11; [$X^2(1, n=4,461)=8.370$, $p=0.004$].

Table 1. Demographic characteristics measured by prevalence of asthma diagnosis or no asthma diagnosis in a sample of children ages 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, 2011-2012

Characteristic measured by age category (2-5, 6-11, 12-18 years)	**Male:** n=5611		**Female:** n=5540	
	Asthma Diagnosis	**No Asthma Diagnosis**	**Asthma Diagnosis**	**No Asthma Diagnosis**
***Number of Subjects**: n(%)				
2-5	202 (3.6)	1271 (22.3)	135 (2.4)	1262 (22.5)
6-11	386 (6.9)	1529 (27.3)	271 (4.8)	1634 (29.5)
12-18	461 (8.2)	1762 (31.4)	388 (7.0)	1850 (33.4)
Race: n(%)				
Mexican American				
2-5	33 (0.6)	364 (6.5)	26 (0.5)	385 (6.9)
6-11	69 (1.2)	445 (7.9)	48 (0.9)	468 (8.4)
12-18	85 (1.5)	486 (8.7)	76 (1.4)	519 (9.4)
Other Hispanic				
2-5	28 (0.5)	122 (2.2)	10 (0.2)	116 (2.1)
6-11	45 (0.8)	149 (2.7)	26 (0.5)	152 (2.7)
12-18	43 (0.8)	139 (2.5)	41 (0.7)	155 (2.8)
Non-Hispanic White				
2-5	48 (0.9)	414 (7.4)	34 (0.6)	375 (6.8)
6-11	104 (1.9)	458 (8.2)	81 (1.5)	463 (8.4)
12-18	138 (2.5)	513 (9.1)	120 (2.2)	499 (9.0)
Non-Hispanic Black				
2-5	74 (1.3)	273 (4.5)	50 (0.9)	252 (4.5)
6-11	125 (2.2)	349 (6.2)	92 (1.7)	407 (7.3)
12-18	160 (2.9)	473 (8.4)	121 (2.2)	528 (9.5)
Non-Hispanic Asian				
2-5	19 (0.3)	98 (1.7)	15 (0.3)	134 (2.4)
6-11	43 (0.8)	128 (2.3)	24 (0.4)	144 (2.6)
12-18	35 (0.6)	151 (2.7)	30 (0.5)	149 (2.7)
Age when first had asthma (years) (median, IQR)				
2-5	1 (1, 2)		1 (1,2)	
6-11	2 (1,5)		2 (1,5)	
12-18	4 (1, 8)		6 (2, 10)	
Age at screening (years) (median, IQR)				
2-5	4 (2.75, 5)	3 (2, 4)	3 (2,5)	3 (2,4)
6-11	9 (7, 10)	8 (7, 10)	9 (7, 10)	9 (7, 10)
12-18	15 (13,16)	15 (13, 17)	15 (13, 17)	15 (13, 17)

*Statistically significant ($p<0.05$) based on p-value from chi square analysis

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To begin, **Table 2** shows differences in accordance to the aMED diet and prevalence of an asthma diagnosis (all data analysis results from SPSS for demographic data are in **Appendix E**). No significant difference was found among aMED accordance and asthma diagnosis in total males [X^2(1, n=5,611)=0.329, p=0.567] and total females [X^2(1, n=5,540)=3.55, p=0.060]. However, a trend was found for both total genders in that there was a smaller proportion of children diagnosed with asthma who were accordant to the aMED diet, compared to those who were non-accordant (see figures xxx) to the aMED diet and diagnosed with asthma. No significant differences were found among aMED accordance and asthma diagnosis when stratified by gender and age category (please see **Figure 2**) (males ages 2-5 [X^2(1, n=1,473)=2.828, p=0.093]; females ages 2-5 [X^2(1, n=1,397)=0.291, p=0.093]; males ages 6-11 [X^2(1, n=1,915)=0.062, p=0.804]; females ages 6-11 [X^2(1, n=1,905)=2.614, p=0.106]; males ages 12-18 [X^2(1, n=2,223)=1.138, p=0.286]; females ages 12-18 [X^2(1, n=22,38)=0.298, p=0.585]), however in all subcategories there was also a trend in that there was a smaller proportion of children diagnosed with asthma who were accordant to the aMED diet, compared to those who were non-accordant to the aMED diet and diagnosed with asthma.

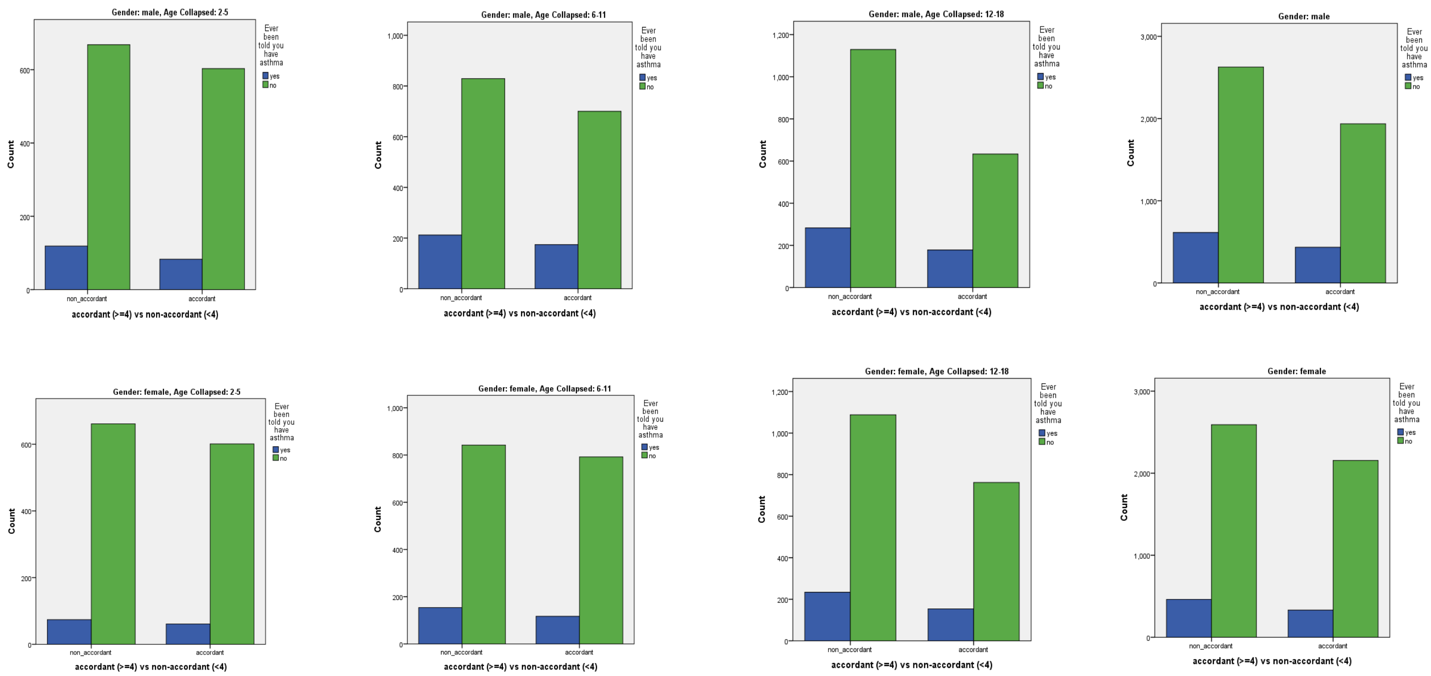
Table 2. Levels of accordance (non-accordant or accordant) to the Alternate Mediterranean Diet and prevalence of an asthma diagnosis (asthma diagnosis or no diagnosis) in a sample of children ages 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, 2011-2012; stratified by specific age category, total ages, and gender

Accordance stratified by age category and total gender	**Male:** n=5611		**P-Value**	**Female:** n=5540		**P-Value**
	Asthma Diagnosis	**No Asthma Diagnosis**		**Asthma Diagnosis**	**No Asthma Diagnosis**	
2-5			.093			.590
Non-Accordant	119 (58.9)	668 (52.6)		74 (54.8)	661 (52.4)	
Accordant	83 (41.1)	603 (47.4)		61 (45.2)	601 (47.6)	
6-11			.804			.106
Non-Accordant	212 (54.9)	829 (54.2)		154 (56.8)	842 (51.5)	
Accordant	174 (45.1)	700 (45.8)		117 (43.2)	792 (48.5)	
12-18			.286			.585
Non-Accordant	283 (61.4)	1129 (64.1)		234 (60.3)	1088 (58.8)	
Accordant	178 (38.6)	633 (35.9)		154 (39.7)	762 (41.2)	
Total Sample			.567			.060
Non-Accordant	614 (58.5)	2626 (57.6)		462 (58.2)	2591 (54.6)	
Accordant	435 (41.5)	1936 (42.4)		332 (41.8)	2155 (45.4)	

A Chi Square analysis was run to assess differences in prevalence of an asthma diagnosis by levels of accordance to the Alternate Mediterranean diet. All data was stratified by gender alone and gender followed by specific age category.
[1]p<0.05=significant
[2]All p-values reported as chi-square test

Figure 2. Differences in levels of accordance (accordant 0-<3) or non-accordant (3-8) in the prevalence of an asthma diagnosis, stratified by gender and specific age category in a sample of children ages 2-18 years old from NHANES cycles 2005-2012

Differences in levels of accordance [(accordant 0-<3) or non-accordant (3-8)] compared to the prevalence of an asthma diagnosis, stratified by number of subjects in gender alone and gender specific age category in a sample of children ages 2-18 years old from NHANES cycles 2005-2012



[1]All results from a chi-square analysis
[2]p<0.05=significant
[3]No significance was found

When the mean total aMED score was compared among those diagnosed with asthma and those without an asthma diagnosis by gender alone (**table 3**) (SPSS results in **Appendix F**, see t-test), no significant difference was found in total males diagnosed with asthma (3.22+/-1.39, n=1049) and without asthma (3.29 +/- 1.43, n=4562);t_{5609}=-1.419, p=0.156. There was a significant difference among females diagnosed with asthma (3.21 +/- 1.50, n=794) compared to those without an asthma diagnosis (3.38 +/- 1.46, n=4746); t_{5538}=-2.90, p=0.004 (effect size of 0.002 indicating a small effect size based on Cohen's r value), indicating those with asthma had a significantly lower mean total aMED score than those without asthma. When gender stratified by age category, the only significant difference was found in females ages 6-11 who were diagnosed with asthma (3.26 +/- 1.52, n=271) compared to those without an asthma diagnosis (3.49 +/- 1.46, n=1634); t_{1903}=-2.36, p=0.19 (effect size of 0.003 indicating a small effect size based on Cohen's r value), indicating those with asthma had a significantly lower mean total aMED score than those without an asthma diagnosis. No significant differences were found for any other subcategories [males ages 2-5 with asthma (3.27 +/- 1.34, n=202) and without asthma (3.45 +/- 3.45, n=1271); t_{1471}=-1.747, p=0.081; females ages 2-5 with asthma (3.31 +/- 1.59, n=135) and without asthma (3.44 +/- 1.43, n=1262); t_{1395}=-0.975, p0.330; males ages 6-11 with asthma (3.31 +/- 1.40, n=386) and without asthma (3.41+/- 1.47, n=1529); t_{1913}=-1.235, p=0.073; males ages 12-18 with asthma (3.13 +/- 1.40, n=461) and without asthma (3.07 +/- 1.40, n=461); t_{2221}=0.794, p=0.427; females ages 12-18 with asthma (3.14 +/- 1.46, n=388) and without asthma (3.23 +/- 1.43, n=1850); t_{2236}=-1.065, p=0.287]. However, trends can be noticed in all subcategories (other than females ages 6-11) of a lower mean total aMED score in those with an asthma diagnosis compared to those without an asthma diagnosis.

When median total aMED scores (**table 4**) (SPSS results in **Appendix F**, Mann Whitney and frequencies) were compared among those diagnosed with asthma and those without an asthma diagnosis by gender alone, no significant differences were found in total males with asthma (median 3, IQR: 2-4) compared to total males without asthma (median 3, IQR 2-4) U=2329886, z=-1.359, p=0.174, but there was a significant difference found in total females with asthma (median 3, IQR: 2-4) compared to total females without asthma (median 3, IQR 2-4) U=1758274.5, z=-3.082, p=0.002. When analysis was further stratified by age categories, a significant difference in median aMED scores was found in males ages 2-5 with asthma (median 3, IQR 2-4) compared to those without an asthma diagnosis (median 3, IQR 2-4) U=117547, z=-1.973, p=0.048 and females ages 6-11 with asthma (median 3, IQR 2-4) compared to those without an asthma diagnosis (median 3, IQR 2-4) U=200366, z=-2.561, p=0.010. No other significant difference in the median total aMED score was found in other subcategories [males with asthma ages 6-11 (median 3, IQR 2-4) and without asthma (median 3, IQR: 2-4) U=285650.5, z=-0.994, p=0.32; males with asthma ages 12-18 (median 3, IQR 2-4) and without asthma (median 3, IQR: 2-4); U=396897, z=-0.772, p=0.440; females with asthma ages 2-5 (median 3, IQR 2-4) and without asthma (median 3, IQR: 2-4) U=80358, z=-1.106, p=0.269; females with asthma ages 12-18 (median 3, IQR 2-4) and without asthma (median 3, IQR: 2-4) U=346853, z=-1.063, p=0.288].

Table 3. Mean Total Alternate Mediterranean Diet Score (0-8) in a sample of children ages 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, 2011-2012 with an asthma diagnosis compared to those without an asthma diagnosis; stratified by specific age category, total ages, and gender

Age Category and Total Ages	**Male:** n=5611 **Mean Total Alternate Mediterranean Diet Score (Mean, +/- SD)**			**Female:** n=5540 **Mean Total Alternate Mediterranean Diet Score (Mean, +/- SD)**		
	Asthma Diagnosis	**No Asthma Diagnosis**	**P-Value**	**Asthma Diagnosis**	**No Asthma Diagnosis**	**P-Value**
2-5	3.27 +/-1.34	3.45+/-1.38	0.081	3.31+/-1.59	3.44+/-1.43	0.330
6-11	3.31+/-1.40	3.41+/-1.47	0.217	3.26+/-1.52	3.49+/-1.46	**0.019**
12-18	3.13+/-1.40	3.07+/-1.40	0.427	3.15+/-1.46	3.23+/-1.43	0.287
Total Sample	3.22 (+/-1.39)	3.29 (+/-1.43)	0.16	3.21 (+/-1.50)	3.36(+/-1.44)	**0.004**

An independent t-test was run to determine differences in mean total Alternate Mediterranean Diet scores in those with an asthma diagnosis and those without an asthma diagnosis. All data was stratified by gender alone and gender with specific age category.
[1]p<0.05=significant
[2]All p-values reported as independent t-tests

Table 4. Median Total Alternate Mediterranean Diet Score (0-8) in a sample of children ages 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, 2011-2012 with an asthma diagnosis compared to those without an asthma diagnosis; stratified by specific age category, total ages, and gender

Age Category and Total Ages	**Male:** n=5611 **Median Total aMED score (Median, IQR)**			**Female:** n=5540 **Median Intake (Median,IQR)**		
	Asthma Diagnosis	**No Asthma Diagnosis**	**P-Value**	**Asthma Diagnosis**	**No Asthma Diagnosis**	**P-Value**
2-5	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	**.048**	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.269
6-11	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.320	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	**0.010**
12-18	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.440	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.288
Total Sample	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.174	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	**0.002**

A Mann Whitney U test was run to determine differences in mean total Alternate Mediterranean Diet scores in those with an asthma diagnosis and those without an asthma diagnosis. All data was stratified by gender alone and gender with specific age category.
[1]p<0.05=significant
[2]All p-values reported as Mann Whitney U tests

When median intakes of specific aMED diet constituents were compared (**Table 5**) (SPSS data analysis output **Appendix G**) among those with an asthma diagnosis and those without an asthma diagnosis in gender alone, total males diagnosed with asthma had significantly different medians than those without asthma in the categories of average MUFA:saturated fat and fruits [(median 0.52, IQR: 0.46-0.61) vs (median 0.51, IQR: 0.44-0.59) U=22255157, z=-2.909, p=0.004 respectively; (median 0.00, IQR: 0.00-0.40) vs (median 0.00, IQR: 0.00-0.16), U=2269641.50, z=02.929, p=0.003 respectively] while total woman diagnosed with asthma had significantly different medians than those without asthma in the categories of MUFA:saturated fat, fruits, and red/processed meats. [U=1765328.00, z=-2.849, p=0.004; U=1781007.50, z=-2.717, p=0.007; U=1753071.50, z=-3.15, p=0.002, respectively]. When stratified by age group, significant differences in medians were found in males ages 2-5; those diagnosed with asthma had significantly different medians of fruits, nuts and seeds, and red/processed meats compared to those without asthma [(median 0.51, IQR=0.43, 0.58) vs (median 0.49, IQR 0.43, 0.58) U=110085, z=-3.450, p=0.001; (median 0.00, IQR 0.00, 0.17) vs (median 0.00 (0.00, 0.34) U=117709.50, z=-2.08, p=0.038; (median 1.00, IQR 0.00-1.00) vs (median 1.00, IQR 0.00-1.00) U=116713, z=-2.08, p=0.038]. Significant differences in medians were found in females ages 2-5; those diagnosed with asthma had significantly different medians of MUFAs:saturated fat, whole grains, and red/processed meats compared to those without asthma [median 0.51, IQR 0.42-0.60) vs (median 0.48, IQR: 0.41-0.55)U=74114.00, z=-2.49, p=0.013; (median=0.25, IQR 0.00-0.69) vs (median 0.38, IQR 0.13-0.76) U=75133.00, z=02.26, 0=0.024; (median 1.00, IQR: 0.00-1.00) vs (median 1.00, IQR: 0.00-1.00) U=75754.00, z=-2.12, p=0.034, respectively]. Significant differences in medians were found in males ages 6-11; those diagnosed with asthma had significantly different medians of MUFAs:saturated fat compared to those without asthma (median 0.52, IQR 0.46-0.60) vs (median 0.51, IQR 0.44-0.59) U=270202, z—2.565, p=0.010, respectively. Significant differences in medians were found in females ages 6-11; those diagnosed with asthma had significantly different medians of vegetables and nuts and seeds compared to those without asthma [(median 0.47, IQR 0.23-0.77) vs (median 0.54, IQR 0.27-0.87) U=204711.500, z=-1.991, p=0.047; (median 0.00, IWUR 0.00-0.17) vs (median 0.00, IWUR 0.00-0.32) U=205252, z=-2.085, p=0.037, respectively]. Significant differences in medians were found in males ages 12-18; those diagnosed with asthma had significantly different medians of red/processed meats compared to those without asthma (median 0.00, IQR 0.00-1.00) vs (median 0.00, IQR 0.00-1.00) U=381794.50, z=-1.95, p=0.047, respectively.

Table 5. Median intakes of Alternate Mediterranean Diet specific dietary constituents in a sample of children ages 2-18 from NHANES cycles 2005-2006, 2007-2008, 2009-2010, 2011-2012 with an asthma diagnosis compared to those without an asthma diagnosis; stratified by specific age category, total ages, and gender

Alternate Mediterranean diet specific dietary constituents, stratified by age category and total ages per gender	**Male:** n=5611 **Median Total Intake(Median, IQR)**			**Female:** n=5540 **Median Total Intake (Median, IQR)**		
	Asthma Diagnosis	**No Asthma Diagnosis**	**P-Value**	**Asthma Diagnosis**	**No Asthma Diagnosis**	**P-Value**
2-5						
Mufa: Saturated Fat	0.51 (0.43, 0.58)	0.49 (0.43, 0.58)	0.540	0.51 (0.42, 0.60)	0.48 (0.41, 0.55)	**0.013**
Vegetables	0.36 (0.19, 0.67)	0.37 (0.18, 0.65)	0.656	0.39 (0.22, 0.61)	0.40 (0.20, 0.68)	0.853
Fruits	0.00 (0.00, 0.08)	0.15 (0.00, 0.26)	**0.001**	0.00 (0.00, 0.17)	0.00 (0.00, 0.24)	0.215
Legumes	0.00 (0.00, 0.00)	0.00 (0.00, 0.14)	0.469	0.00 (0.00, 0.34)	0.00 (0.00, 0.20)	0.738
Nuts and seeds	0.00 (0.00, 0.17)	0.00 (0.00, 0.34)	**0.038**	0.00 (0.00, 0.28)	0.00 (0.00, 0.22)	0.810
Whole grains	0.47 (0.13, 0.94)	0.43 (0.15, 0.90)	0.669	0.25 (0.00, 0.69)	0.38 (0.13, 0.76)	**0.024**
Fish	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.479	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.433
Red/processed meat	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	**0.038**	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	**0.034**
6-11						
Mufa: Saturated Fat	0.52 (0.46, 0.60)	0.51 (0.44, 0.59)	**0.010**	0.52 (0.46, 0.59)	0.51 (0.44, 0.59)	0.292
Vegetables	0.48 (0.25, 0.87)	0.52 (0.27, 0.88)	0.246	0.47 (0.23, 0.77)	0.54 (0.27, 0.87)	**0.047**
Fruits	0.00 (0.00, 0.08)	0.00 (0.00, 0.19)	0.667	0.00 (0.00, 0.25)	0.00 (0.00, 0.26)	0.141
Legumes	0.00 (0.00, 0.16)	0.00 (0.00, 0.00)	0.121	0.00 (0.00, 0.00)	0.00 (0.00, 0.13)	0.185
Nuts and seeds	0.00 (0.00, 0.34)	0.00 (0.00, 0.32)	0.772	0.00 (0.00, 0.17)	0.00 (0.00, 0.32)	**0.037**
Whole grains	0.39 (0.11, 0.92)	0.42 (0.07, 0.92)	0.959	0.39 (0.04, 0.93)	0.38 (0.08, 0.84)	0.981
Fish	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.766	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.443
Red/processed meat	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.486	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.138
12-18						
Mufa: Saturated Fat	0.53 (0.46, 0.12)	0.53 (0.46, 0.01)	0.377	0.53 (0.45, 0.63)	0.54 (0.46, 0.62)	0.927
Vegetables	0.59 (0.29, 1.1)	0.60 (0.30, 1.1)	0.830	0.52 (0.26, 0.93)	0.54 (0.27, 0.96)	0.337
Fruits	0.00 (0.00, 0.03)	0.00 (0.00, 0.04)	0.703	0.00 (0.00, 0.05)	0.00 (0.00, 0.09)	0.568
Legumes	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.908	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.167
Nuts and seeds	0.00 (0.00, 0.24)	0.00 (0.00, 0.27)	0.830	0.00 (0.00, 0.16)	0.00 (0.00, 0.19)	0.999
Whole grains	0.31 (0.00, 1.02)	0.30 (0.00, 0.89)	0.557	0.26 (0.00, 0.74)	0.26 (0.00, 0.74)	0.667
Fish	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.261	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.474
Red/processed meat	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	**0.047**	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.450
Total Sample						
Mufa: Saturated Fat	0.52 (0.46, 0.61)	0.51 (0.44, 0.59)	**0.004**	0.52 (0.45, 0.61)	0.51 (0.44, 0.59)	**0.004**
Vegetables	0.49 (0.25, 0.89)	0.49 (0.25, 0.87)	0.687	0.48 (0.24, 0.83)	0.50 (0.24, 0.86)	0.293
Fruits	0.00 (0.00, 0.7)	0.00 (0.00, 0.16)	**0.003**	0.00 (0.00, 0.11)	0.00 (0.00, 0.20)	**0.007**
Legumes	0.00 (0.00, 0.00)	0.00 (0.00, 0.08)	0.233	0.00 (0.00, 0.00)	0.00 (0.00, 0.08)	0.036
Nuts and seeds	0.00 (0.00, 0.25)	0.00 (0.00, 0.32)	0.176	0.00 (0.00, 0.17)	0.00 (0.00, 0.24)	0.132
Whole grains	0.38 (0.00, 0.94)	0.39 (0.01, 0.91)	0.836	0.30 (0.00, 0.79)	0.33 (0.01, 0.785)	0.077
Fish	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.607	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.796
Red/processed meat	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.113	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	**0.002**

A Mann Whitney U was run to determine differences in median intakes of Alternate Mediterranean diet specific dietary constituents in children diagnosed with asthma compared to children without an asthma diagnosis. All data was stratified by gender alone and gender with specific age category.
[1]p<0.05=significant
[2]All p-values reported as Mann Whitney U

Discussion

No statistically significant differences were found when comparing accordance to the aMED diet and prevalence of asthma diagnosis in a population of children ages 2-18 from NHANES 2005-2012, when stratified by gender alone and gender by age categories. The lack of significant difference is supported by a cross-sectional study conducted in Spain by Gonzales Barcala et al., examining the association of Mediterranean diet and asthma prevalence in 14,700 school children and adolescents. It was found that the Mediterranean diet did not have a protective effect on asthma prevalence or severity, and specifically in girls ages six to seven it actually was significantly associated with a higher risk of severe asthma [15]. However, in both total genders, as well as all gender/age subcategories, there is a consistent trend in that there is a higher proportion of those who are accordant to the aMED diet in those without asthma compared to those with asthma, however this is likely due to a significantly larger sample size in those without asthma. The most notable trend, though, is that for both total genders and all gender/age subcategories, there is a smaller proportion of those with asthma who are accordant to the aMED diet, whereas there is a higher proportion of those with asthma who are non-accordant to the aMED diet, postulating that accordance to the aMED diet may exert a protective effect on asthma prevalence. This trend is supported by several cross-sectional epidemiological studies conducted internationally that have found inverse relationships between Mediterranean diet accordance and asthma prevalence. [16 17 9 10]

When assessing the average total aMED score by total gender followed by gender stratified by age category, females ages 6-11 and total females who did not have asthma had a higher mean total aMED score than those with asthma. This was then further supported by the Mann Whitney U, which showed significantly higher median total aMED scores in females without asthma ages 6-11 as well as total females compared to those with asthma. This is important, as asthma becomes more apparent in female children as they get older, rather than early in life, and a later onset incidence of asthma is associated with persistence into adulthood [6]. Unfortunately, no significant differences in total aMED score were found in total males or specific male age categories in those with and without asthma. The Mann Whitney U, however, did pick up on a difference in median total aMED score among males ages 2-5 in those with asthma and without asthma, though a direction cannot be distinguished as the median and interquartile ranges were the same in both of those with and without asthma. These results are supported by a cross-sectional study conducted by Garcio-Marcos et al. (2007) which examined the prevalence of current occasional asthma and current severe asthma and accordance to the Mediterranean diet, and found accordance to the Mediterranean diet to have a small but protective effect in only girls with current severe asthma only, but not in boys nor both boys and girls with current occasional asthma [9]. Interestingly, when trends in mean total aMED scores were examined, in all categories except total males and males 12-18 years old, males and females without asthma had a higher total aMED score than those with asthma. As mentioned before, though, this could be due to the large differences in sample sizes.

When median specific constituents of the aMED diet were analyzed among those with and without asthma, the majority of the medians for both total males and females, as well as subcategories, were zero, and the majority of the interquartile ranges were zero as well, or a minimal 75th percentile. All median aMED constituents, for both genders and age categories, that were not zero were minimal (less than zero). The only median aMED constituent that was greater than zero is in males and females ages 2-5, for red/processed meat (median 1, IQR: 0-1 for both genders). It is concerning that this category is the highest among this age group, as this food category should be the lowest of the dietary constituents (based on aMED recommendations) for all age groups. In 2010, a cross sectional study conducted by Nagel et al. found a lower lifetime prevalence of asthma with a frequent consumption of fruit, vegetables, and fish, but a higher lifetime prevalence of asthma with high burger consumption [18]. If children are being exposed to red/processed meat being a major dietary component at this young of an age, it would be interesting to follow dietary patterns as they get older, as well as health-related outcomes. Notable significant median differences (that have not already been discussed) started in age categories of 2-5; males with asthma had had a lower median fruit intake compared to those without asthma, while females had a lower median whole grain without asthma. A common significant trend was found in females ages 2-5, males ages 6-11, total females, and total males in that those with asthma had significantly higher median intakes of MUFAs:saturated fats compared to those without asthma. These results can be supported by data from a cross-sectional study by Woods et al. (2003) which found the intake of apples and pears to be protective against current asthma, doctor-diagnosed asthma, and bronchial hyperreactivity, whereas intake of soy beverages (which contain moderate amounts of MUFAS) was found to be associated with an increased risk of current asthma, doctor-diagnosed asthma, and bronchial hyperreactivity [19]. Perhaps MUFAs interact differently with asthmatics compared to those without asthma, especially in a pediatric population. It is also possible that for MUFAs to exert a beneficial effect in those with asthma, they need to be accompanied by other essential fatty acids, like omega 3s, which are an essential component of the Mediterranean diet. This theory could make sense in this study, as subjects classified as "non-accordant" to the aMED indicates a minimal to lack of intake of PUFAs. A study conducted by Yang ZH et al. (2015) found when diet-induced obese mice were fed a 28% lard diet plus 4% EPA or a 20% lard diet plus 12% LCMUFAs, compared to the controls (32% lard diet) mice fed the diet with EPA or LCMUFAs both had increased organ levels of EPA and LCMUFA and decreased inflammatory markers of metabolic syndrome, indicating that although each of these fatty acids are beneficial, there may be a synergistic relationship between the two [20]. However, the discrepancies found in this study are quite possibly due to the differences in sample size.

This study had many limitations. First, although the aMED score is validated, it was modified for this study, and this modification was not validated. Second, aMED specific dietary constituents were not adjusted for energy. It is possible that median intakes for all aMED specific dietary constituents were so low because of this, and as the aMED score was based on the total medians of all these constituents, it could be the reason why subjects who were classified as "accordant" were so minimally accordant. If energy were adjusted, perhaps larger differences between median aMED constituents, as well as median and mean total aMED scores, and overall accordance could have been detected. However, data was stratified by gender and age categories to try to capture the difference in energy intakes, as the energy needs of a two-year old are completely different than that of an 18-year old. Other studies have stratified dietary parameters by similar age categories for this reason [13]. A major limitation was that the sample size among gender and gender/age categories was not adjusted, which most likely skewed the results. Furthermore, for the statistical analysis, Mann-Whitney U tests have less power, and are less likely to pick up on potential differences in data than the parametric equivalent t-test. Also, chi-squares are sensitive to sample size, and because of the irregular sample sizes among those with and without asthma (in both gender alone and gender/age category), a difference in accordance was not detected when there really could have been. Also, they do not give information on the strength of a relationship or its significance, so originally when differences in sample sizes were first detected, it was impossible to know statistically where the differences were and how data should have actually been stratified; only judgment could determine this. Lastly, an asthma diagnosis was based on the question "Ever been told you have asthma" from NHANES, and NHANES does not explain if this was an official medical diagnosis made by a doctor, because it is self-report (in this case the majority of the parents report for the children). It is also possible that children with an asthma diagnosis may have gone into remission, and those without an asthma diagnosis could have developed asthma, which the analysis in this study would not have captured.

This study has many implications for research. First of all, based on analysis of the current literature, it is the only epidemiological study to examine asthma prevalence and accordance to the Mediterranean diet in the United States. The next study to assess the outcomes of this study would be more accurate if energy and sample size were adjusted for. Second, it would be interesting to asses all dietary intake in children with asthma compared to those without asthma, as the aMED diet does not encompass all food, and it is possible that food not included in the aMED diet can improve or exacerbate asthma occurrence and asthma symptoms. The effects of diet on the different types of asthma and respiratory measures in the United States should also be examined. A quintessential aspect of this study is that it showed how few children in this country are accordant to the aMED diet, and even children who are accordant to the aMED diet are minimally accordant to it, which in itself warrants much research. A subset analysis of this study could be conducted to examine differences in specific nutrients in the aMED diet in children with and without asthma, as it is not known if the aMED diet as a whole is potentially protective of asthma, or if it is specific nutrients within the aMED diet that is protective.

Conclusion

In conclusion, there was no difference in accordance to the aMED diet in children ages 2-18 from NHANES 2005-2012 with asthma and without asthma. However, noticeable trends were found for decreased proportions of children with an asthma diagnosis who were accordant to the aMED compared to children with an asthma diagnosis who were not accordant to the aMED diet. Total females and females ages 6-11 with an asthma diagnosis had lower total mean and median aMED scores than females without asthma; and males ages 2-5 with an asthma diagnosis had a lower total median aMED score than those without an asthma diagnosis, indicating in certain genders and age categories, a higher aMED score is preventative of an asthma diagnosis. Among males with and without an asthma diagnosis, median intakes of fruits, nuts and seeds, average MUFA:saturated fat ratio, and red/processed meats differed; among females with and without an asthma diagnosis, median intakes of average MUFA:saturated fat ratio, whole grains, red/processed meat, vegetables and fruits differed. This indicates that male and female children in the United States may have different dietary patterns, which may result in different outcome parameters of an asthma diagnosis. Although not statistically significant, overall trends showed a higher mean and median total aMED score, as well as higher median intakes of aMED dietary constituents, was inversely related to an asthma diagnosis. However, more research is warranted to assess as to whether or not accordance to the Alternate Mediterranean diet and consumption of its specific constituents are effective in preventing or ameliorating asthma in a pediatric population in the United States.

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