DIET QUALITY AND NUTRITIONAL INTAKE DIFFERENCES BETWEEN YOUNG ADULT AND MIDDLE AGED WOMEN WITH AND WITHOUT UTERINE FIBROIDS PARTICIPATING IN THE NATIONAL NUTRITION AND HEALTH EXAMINATION SURVEY (NHANES) 2001-2006

by

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Diet Quality and Nutritional Intake Differences Between Young Adult and Middle Aged Women with and Without Uterine Fibroids Participating in the National Nutrition and Health Examination Survey (NHANES) 2001-2006

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DEDICATION

This is dedicated to all women suffering from uterine fibroids in the search to find possible causes and research to help in the prevention. I also dedicate this to my parents who helped fund my graduate studies.

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I would like to thank my committee members for their guidance and support in this thesis. Thank you to Dr. Sina Gallo for patiently guiding me through the process. Special thanks to Debby Kermer in Data Services and Dr. Cara Frankenfeld for helping me understand Stata and statistical analysis. I would like to thank the participants of NHANES for making this study possible and their willingness to contribute to the field of scientific study in nutrition.

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LIST OF ABBREVIATIONS

AMPM, Automated Multiple-Pass Method
aMED, Alternate Mediterranean Diet
BMI, Body Mass Index
CAPI, Computer Assisted Personal Interview Software
CDC, Centers for Disease Control
CI, Confidence Interval
CNPP, Center for Nutrition Policy and Promotion
DASH, Dietary Approaches to Stop Hypertension
DPA, Docosapentaenoic acid
DHA, Docosahexaenoic acid
EPA, Eicosapentaenoic acid
FFQ, Food Frequency Questionnaire
HEI, Healthy Eating Index
IGF, Insulin-like Growth Factor
IRR, Incident Rate Ratio
IUD, Intrauterine Device
LH, Luteinizing Hormone
MEC, Mobile Exam Center
MRI, Magnetic Resonance Imaging
NCHS, National Center for Health Statistics
NHANES, National Health and Nutrition Examination Survey
NIEHS, National Institute for Environmental and Health Sciences
OR, Odds Ratio
PCB, Polychlorinated biphenyls
PCOS, Polycystic Ovary Syndrome
RR, Relative Risk
SOFAAS, Solid Fats, Alcoholic Beverages, and Added Sugars
SNP, Single Nucleotide Polymorphism
UAE, Uterine Artery Embolization
USDA, United States Department of Agriculture
WHI, Women's Health Initiative

ABSTRACT

DIET QUALITY AND NUTRITIONAL INTAKE DIFFERENCES BETWEEN YOUNG ADULT AND MIDDLE AGED WOMEN WITH AND WITHOUT UTERINE FIBROIDS PARTICIPATING IN THE NATIONAL NUTRITION AND HEALTH EXAMINATION SURVEY (NHANES) 2001-2006

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Background: Uterine fibroids are a common condition for many premenopausal women with painful side effects and reproductive ramifications. Treatment options are limited and little is known about prevention. Dietary intake and food patterns are modifiable lifestyle factors which may play a role in this condition.

Objective: To evaluate differences in dietary patterns, as measured using the Healthy Eating Index (HEI)-2010, and macronutrient intake between women with and without uterine fibroids.

Methods: Data from the National Health and Nutrition Examination Survey (NHANES) cycles 2001-2002, 2003-2004, and 2005-2006 was obtained to examine a sample of young adult and middle aged women in the United States, excluding those who were pregnant or breastfeeding. Self-reported dietary intake from one day of 24-hour recalls,

anthropometric measurements, reproductive health, and demographic information was collected as part of NHANES. Demographic and reproductive health characteristics were compared between groups using regression and chi-squared tests. HEI-2010 scores and energy adjusted macronutrient intake differences between groups were compared using linear regression adjusting for covariates of age, BMI, race, smoking status, marital status, and educational level.

Results: This analysis included 87 women reporting previous uterine fibroid diagnosis and 743 women without a previous diagnosis. Women with fibroids were older ($p<0.001$), more likely to be college graduates ($p=0.05$) and be married ($p=0.02$). After adjustment, no differences in HEI-2010 scores or macronutrient intakes were noted between groups. Subgroup analysis, of women diagnosed only within the past five years, found fibroid diagnosis was associated with an increase in empty calories subcomponent score of 2.53 (95% CI: 1.12, 3.93, $p=0.002$)) and a decrease in whole fruit subcomponent score of 0.73 (95% CI: -1.44, -0.028, $p=0.044$) compared to women without a fibroids diagnosis.

Conclusion: Women with fibroids did not have significantly different scores in HEI total and subcomponent scores as well as energy adjusted macronutrient intakes. However, women with fibroids diagnosed within the past five years had different scores suggesting differing dietary patterns may be present in women diagnosed more recently, though the subsample size was limited. Due to limitations in this study of use of 1-day of 24-hour recall data, potential misclassification of fibroids, and not controlling for health

literacy, further research via prospective cohort studies to examine food intake patterns and possible relationships with uterine fibroids is warranted.

CHAPTER 1 . LITERATURE REVIEW

Introduction

Uterine fibroids or "leiomyomas" are a type of tumor, usually benign, commonly found in the uterus of women of reproductive age. Up to 50% of women are asymptomatic but for those with symptoms, fibroids can cause significant morbidity and diminished quality of life.[1] Symptoms include excessive bleeding, pelvic pain unrelated to menstruation, bloating, increased frequency of urination, and bowel disturbances.[2] Uterine fibroids have a negative effect on pregnancies, including early termination, preterm labor, and postpartum hemorrhage, and are a source of infertility.[2] Fibroids can grow and lead to an abnormally large distention of the uterus and are the most common reason for hysterectomy[2]. Severe bleeding due to fibroids can lead to iron deficiency anemia and inadequate oxygenation of the red blood cells.[1] Even if removed by surgery, fibroids can grow back.

Diagnosis and Prevalence

Estimations on prevalence of uterine fibroids are difficult to determine. Some women with fibroids are asymptomatic, or do not seek medical care and are not diagnosed. Diagnosis typically happens when a woman presents with symptoms of fibroids, usually excessive bleeding and pelvic pain. There are differing methods of

diagnosis, from pelvic exam to ultrasound, Magnetic Resonance Imaging (MRI), or examining a specimen of uterine fibroid tissue (biopsy) after a hysterectomy. Ultrasound, abdominal or transvaginal, is the most widely used tool to diagnose uterine fibroids and is the most cost effective.[3]

International research studies estimate a prevalence of uterine fibroids in 65-75% of symptomatic women (asymptomatic women who may have fibroids often do not seek medical attention so the prevalence is unclear).[4] A pilot study of asymptomatic women aged 18-30 years found an overall prevalence of uterine fibroids of 15%, as diagnosed by ultrasound. This rate was nearly four times higher in black women at 26%, vs. 7% in white women.[5] An Italian study with 341 women aged 30-60 years found the incidence of uterine fibroids at 21% in women also diagnosed by ultrasound.[6] Undiagnosed fibroids were found in 22% of a predominantly African American population aged 23-34 years, who initially had reported no fibroid diagnosis.[7] Black women tend to have a higher prevalence of fibroids, larger and more fibroids, are diagnosed at earlier ages, and also tend to have a hysterectomy at an earlier age, compared to white women.[8] The risk of uterine fibroids in black women is estimated at two to three times that of white women.[9] Data from Chinese, Japanese, Italian women as well as white and black women in United States, are cited in the literature but there is a lack of information on prevalence rates of uterine fibroids of Hispanic and Mexican American women, possibly due to decreased access to medical care (such as ultrasounds) to diagnose uterine fibroids.

Risk Factors

The risk of developing uterine fibroids is affected by increased weight gain, age, and parity.[1,10–13] Several studies have found an association between weight gain and higher risk. Data from the Nurses' Health Study, a large prospective cohort study of premenopausal women, found a modest increased risk of developing fibroids in women who gained weight since age 18 years.[14] A large cross over study in Italy found that overweight women had an increased risk of fibroids. The multivariate odds ratio (OR) for a Body Mass Index (BMI) of 26 or more was 1.30 (95% CI: 1.09-1.55) among cases with a clinical diagnosis of fibroids and an OR of 1.29 (95% CI: 1.01-1.45) among cases diagnosed by ultrasound, compared to women with a BMI less than 22.[15] BMI, as an indirect measure of body fat, can reflect changes in steroid hormone metabolism and bioavailability.[10] Uterine fibroids are uncommon in women younger than 20 years of age. Risk increases through premenopausal years, peaks around age 50 years (or when menopause begins), and then declines rapidly.[1] Parity of at least one child decreased risk of uterine fibroids.[15] One cross-sectional study concluded that pregnancy impacted age-related changes in serum estrogen levels.[13] Estrogen levels are known to be higher in women with uterine fibroids.[2] An earlier age at menarche increased the risk of uterine fibroids in one study, attributed to higher circulating estrogen levels starting earlier.[2]

Pathogenesis and Treatment

The pathogenesis of uterine fibroids is not clear. Several theories are discussed in the literature.[2,10,16,17] Dysregulation of the inflammatory process or a chronically active

and inflammatory immune system is thought to be involved in uterine fibroid formation.[13,14] Inflammation is a type of non-specific immune response to infection, irritation or injury.[16] An inflammatory response is started by local blood vessels with plasma proteins and leukocytes, white blood cells, progressing into tissues. Vasodilation occurs and increased vascular permeability decreases blood flow with a cascade of events activating leukocytes on endothelial cells.[17] One researcher proposes inflammation may alter the endometrial activity and may affect uterine tissue repair and remodeling.[17] Another hypothesized model for how inflammation induces uterine fibroid formation: if the uterus has an "insult" (injury, infection, or menses) combined with a chronically inflammatory immune profile, then the overactive immune system may form fibrous tissue. Smooth cell proliferation could possibly lead to development of a uterine fibroid.[16] See **Figure 1** for a proposed model of the relationship between inflammation and uterine fibroid formation. Key cellular events include matrix deposition, cell growth, and angiogenesis along with estrogen and progesterone promoting tumor growth, to form uterine fibroid tumors. These tumors are hormonally dependent, do not occur before menarche, and decrease in size, symptoms, and severity after menopause.[18]

A large amount of data points to estrogen stimulating growth of uterine fibroids by estrogen receptors. Fibroids are dependent on estrogen and progesterone in the uterine cavity. Stem cells in the myometrium may be transformed in the presence of these hormones to lead to growth of uterine fibroids. Other hormones, separate from estrogen, and age may also affect development of fibroids.[19] The National Institute for Environmental and Health Sciences (NIEHS) Uterine Fibroid study found an association

between urinary luteinizing hormone (LH) levels in women aged 35-49 years and risk of uterine fibroids.[20] Elevated LH may be influential in the development of fibroids. The incidence of uterine fibroids was 65% higher in women with polycystic ovary syndrome (PCOS) than women without PCOS, possibly due to higher LH in women with PCOS, [Incident rate ratio (IRR) 1.65, (95% CI: 1.21-2.24)].[21] There are also a small number of genetic defects thought to predispose some women to uterine fibroids. However, the exact cellular origins of fibroids are not known.[19]

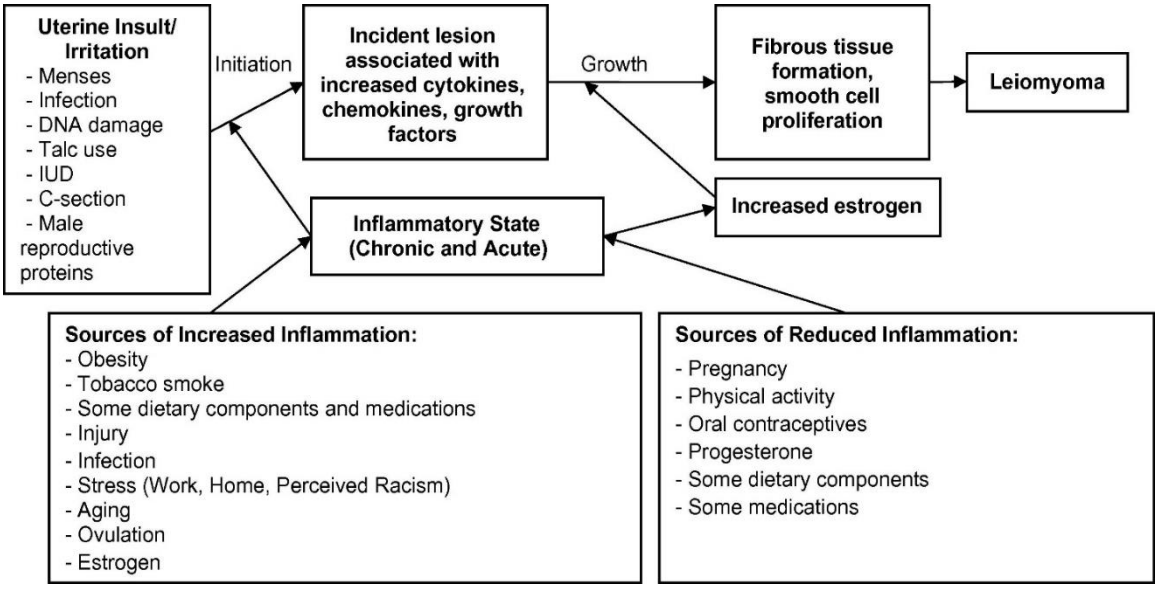

Figure 1 A Hypothetical Causal Model of the Relationship between Inflammation and Uterine Fibroid (leiomyoma) incidence.

Reprinted from Medical Hypotheses, 79, Wegeinka, G, Are Uterine Leiomyoma a consequence of a chronically inflammatory immune system? 226-231, Copyright (2012), with permission from Elsevier

Treatment options vary with the severity of symptoms and whether a woman with fibroids wants to become pregnant. A review of the evidence on treatment options prepared for the Agency for Healthcare Research and Quality, of the Department of Health and Human Services reported that large, well conducted studies in the U.S. population are lacking.[22] Common surgical options include myomectomy (surgical removal of fibroids), uterine artery embolization (UAE), which blocks blood supply to the uterus, and endometrial ablation, which also treats the bleeding. There are many risks to surgery such as the need for blood transfusions, perforation of uterus, and delayed wound healing. Fibroids can continue to grow inside the uterus and can grow back if removed. The leading cause of hysterectomy in the United States is uterine fibroids.[2] Hysterectomy is irreversible and not a feasible option for women wanting to become pregnant. Pharmaceutical options include oral contraceptive agents, non-steroidal anti-inflammatory drugs, and hormonal antagonists that are used for symptom management of pain and decrease in the size of the uterus and fibroids. Negative side effects to these medications and risks make these less preferred treatment options. However, there is evidence that use of oral contraceptive agents for ten years or more decreases risk of fibroids in women by 31%. This points to unopposed estrogen as part of the etiology.[23] There is no clear evidence on best treatments to prevent further growth or regrowth.[22]

Role of Nutrition in Prevention and Treatment

Uterine fibroids are influenced by hormone levels similar to other medical conditions including breast cancer, ovarian cancer, endometrial cancer, and PCOS. The

role of dietary and nutritional factors in uterine fibroids and other hormonally related diseases such as breast cancer and endometrial cancer continues to evolve and points to some associations.[24–26]

Fruits and Vegetables

A protective effect has been observed between fruits and vegetables and hormonally related conditions.[26, 27] Fruits and vegetables contain antioxidants, phytoestrogens, and various phytochemicals that may help lower uterine fibroid risk by working in hormone dependent pathways, by apoptosis (pre-programmed cell death), or by inhibiting proliferation, and therefore lower uterine fibroid risk.[28] A large systematic review, which included 13 studies from around the world, showed a protective effect for fruit and vegetable consumption on uterine fibroids.[4] This review included a case control study from Italy, which showed an inverse association between green vegetable consumption, measured via a food frequency questionnaire (FFQ), and risk of uterine fibroids. Women with the most frequent green vegetable consumption in the upper tertile appeared to have a protective effect on development of fibroids [OR 0.5, 95% CI: 0.4-0.6] vs. those in the lowest tertile. The effect was not significant for fresh fruit intake, [OR 0.8, 95% CI: 0.6-1.0]. A limitation of this study was that it collected information on frequency of fruit and vegetable intake without a quantitative estimation of portion size for fruits and vegetables.[29] The Black Women's Health Study, a prospective cohort study of over 12,000 black women, found a protective effect for both fruits and vegetables. Those who ate four servings of fruits and vegetables per day had a lower risk of uterine fibroids compared with those who consumed one serving per day, assessed

using a FFQ. The multivariate IRR was 0.9, (95% CI: 0.82-0.98).[28] Citrus fruit was inversely associated with uterine fibroid risk. Three or more servings per week was protective compared to less than one serving per week, (IRR 0.92, 95% CI: 0.86-1.0).[28] Three studies in the systematic review showed a stronger association with fruit intake when participants confirmed fibroid diagnosis either by ultrasound or surgery as compared to a self-reported diagnosis.[28–30] A case control study in China found higher fruit and vegetable intake (consumption of fruits and vegetables more than three days per week) significantly decreased the risk of uterine fibroids [OR 0.4, 95% CI: 0.2-0.9] compared to fruit and vegetable intake less than once per week.[30] A cross-sectional analysis of women's diet patterns in the United States looking at fruit and vegetable consumption and uterine fibroids has not been conducted.

Carbohydrates

Carbohydrates may influence the development of hormonally related diseases.[31] Various biological mechanisms could be involved, one of which is related to development of hyperglycemia, insulin resistance, and hyperinsulinemia. Higher estrogen levels may be caused by hyperinsulinemia, which decreases levels of sex hormone binding globulin and increases levels of insulin-like-growth factor (IGF) through decreased levels of IGF binding protein-1.[32] One study which examined IGF-1, found no association with uterine fibroid risk among black women and an inverse association for prevalence among white women.[33] Chronic hyperinsulinemia is one postulated mechanism to explain the development of breast cancer and may be extrapolated to fibroids.[34] Total carbohydrate levels often affect blood sugar levels and

may lead to hyperinsulinemia. Yet, four studies which explored whole grains, dietary fiber, and cereal intake found no associations with uterine fibroids.[28–30,35] A reduced risk of fibroids among people with diabetes was found in the Black Women's Health Study with an OR of 0.77 (95% CI: 0.68-0.98).[21] However, total carbohydrate intake has not been examined in relation to uterine fibroids.

Fat

Several studies have explored total fat and types of fat in relation to uterine fibroids. High fat intake has been linked with higher levels of estradiol, a sex hormone thought to influence uterine fibroid risk.[36] A Japanese cross-sectional study found no association with total fat, saturated fat, monounsaturated fat, and polyunsaturated fats, and uterine fibroids.[35] In a Chinese study and an Italian case control study, eggs, butter, margarine, and oil consumption were not associated with uterine fibroid risk.[29,30] In the Black Women's Health Study, intake of total fat and types of fat was not associated with uterine fibroid risk. However, a small increase in fibroid risk was found among those with intakes of long chain omega-3 fatty acids, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). The IRR for highest vs. lowest quintile of omega-3 fatty acids was 1.18 (95% CI: 1.05-1.34).[36] Supplementation with flax seed oil (a source of omega-3 fatty acids) was associated with increased risk but this was based on a small sample size.[36] However, it is known that many fatty fish contain sources of endocrine-disrupting chemicals such as polychlorinated biphenyls (PCBs), which may increase risk of uterine fibroids. Black women have higher rates of uterine fibroids and national data show that black women

have significantly higher levels of PCBs in their bodies compared to other ethnicities, which suggests PCBs in fatty fish could potentially play a role.[36] The role of PCBs in uterine fibroids is an area of further study. However, total fat intake from the diet has not been studied in relation to uterine fibroids in racial groups other than black women and Japanese women.

Dairy and Calcium

Dairy intake as a food group was examined in a few studies and showed inconsistent associations with uterine fibroids. In an Italian case control study, there was no association between uterine fibroid risk and intake of milk and cheese, but in the Black Women's Health Study, any dairy food was protective, irrespective of fat content.[29,36] The multivariate IRR compared lowest (one serving per day) to highest (four or more servings per day) intake. For the lowest intake, the IRR was 0.94 (95% CI: 0.088-1.00) and for the highest intake was 0.70 (95% CI: 0.58-0.86).[36] Milk consumption was inversely associated with fibroid risk when comparing IRR of more than 14 servings per week to less than one serving per week. The IRR was 0.78 (95% CI: 0.68-0.89) and this association was similar regardless of fat content of the milk.[4] No relation with eggs, butter, margarine, and oil consumption was observed.[29,30] It is worth investigating dairy foods in other ethnic populations for any association with uterine fibroids.

Dairy foods have many components such as calcium, vitamin D, phosphorous, protein, fat, and potassium and each component separately or synergistically may influence a particular disease risk. In the Black Women's Health Study, the calcium to

phosphorous ratio showed the strongest risk of uterine fibroids (IRR: 0.88, and 95% CI: 0.81-0.96, p <0.001) for highest vs. lowest quintile of calcium to phosphorous ratio compared to when the vitamins and minerals in milk were examined separately.[37] However, composition of milk can vary from country to country. For example, high fat dairy products in the United States may contain fat soluble hormones and growth factors that could potentially stimulate the growth of fibroids.[38] Additionally, calcium can increase IGF-1 signaling, which can increase multiplication of cells, a possible risk factor for cancer. In cell culture studies, calcium has both promoted and inhibited various parts of the cancer process. However, in vitro studies are not always able to be replicated in the human body so the effect is not clear.[38]

Vitamin D

A possible protective role of vitamin D and uterine fibroids has been found in research studies.[39–45] The vitamin D receptor is expressed in both the leiomyoma tissue and the myometrial or uterine smooth muscle wall tissue. A study in rats concluded that administering 1,25-dihydroxyvitamin D($1,25(OH)_2$ D), the biologically active form of vitamin D, decreased fibroid tumor size by cell growth and proliferation related genes.[39] Low levels of circulating 25-dihydroxyvitamin D_3 [25 (OH)D], a precursor to $1,25(OH)_2D$ and marker of vitamin D status, are associated with many chronic disease states including cancer, cardiovascular disease, diabetes, autoimmune diseases and several types of infections.[43] The only natural food sources of vitamin D are fatty fish and fortified foods (mostly milk). Therefore, most individuals rely on supplemental sources of vitamin D to meet daily needs. Sun exposure is also a possible source of

circulating 25(OH)D, yet can be affected by a number of factors including latitude, season, skin color, and thus is not a safe nor sustainable source of vitamin D for most people.[41]

Although the Black Women's Health Study did not show an association between dietary or supplemental vitamin D intake and uterine fibroids, three other studies showed a consistently lower level of 25(OH)D in women with fibroids compared to those without fibroids.[42,43,45] Black women in general tend to have lower serum levels of 25(OH)D due to differences in endogenous production from sun exposure.[41,46] One study used cross-sectional data from the Uterine Fibroid Study (NIEHS) in women aged 35-49 years and found that only 10% of black women and 15% of white women with uterine fibroids had sufficient blood levels of vitamin D, defined as 25(OH)D >10 ng/ml. Women with sufficient levels of vitamin D had a 32% lower odds of uterine fibroids compared with those with insufficient levels. The adjusted OR was 0.68 (95% CI: 0.48-0.96).[43] A cross-sectional observational study conducted in Egypt compared 104 women with fibroids (cases) to 50 women without fibroids (controls) and found serum 25(OH)D levels were significantly lower in women with uterine fibroids, 25(OH)D level (19.7 $\pm$ 11.8 ng/ml) vs. those without fibroids (22.3 $\pm$ 6.5 ng/ml, $p \leq 0.01$). After stratifying by race (all subjects were classified as black or white), there was a statistically significant difference between cases and controls within each of the racial groups.[42] A case control study in Italian fertility clinics, showed a higher risk for fibroids among those with low serum vitamin D status (defined as 25(OH)D <10ng/ml), compared to those without fibroids. The adjusted OR in those with fibroids was 2.4 for those women with low serum vitamin

D, (95% CI 1.2-4.9).[45] A study using cross-sectional National Health and Nutrition Examination Survey (NHANES) data, a sample of women living in the United States, did not find a relationship between uterine fibroids and serum 25(OH)D levels when looking at highest to lowest quartiles. However, a probabilistic analysis correcting for potential misclassification, due to self-report of uterine fibroids, showed insufficient 25(OH)D levels (defined as 0-20 ng/ml) was significantly associated with an increased odds of uterine fibroids in white, but not black women [white: OR median estimate: 2.17, (95% CI: 1.26-23.5) vs. black: OR median estimate: 1.70 (95% CI: 0.89-3.51)].[44] The high melanin concentrations in black pigmentation cause decreased absorption of the ultraviolet beta rays from the sun which is necessary for endogenous production of vitamin D.[41] African American women are ten times more likely to have vitamin D deficiency, lower 25(OH)D concentrations, and uterine fibroids as compared to Caucasian women.[42]

Genetic factors may play a role in the relationship between vitamin D and uterine fibroids. Single nucleotide polymorphisms (SNPs) are a common type of genetic variation and can affect how a gene functions and its role in disease based on its location in the gene or nearby.[47] SNPs are associated with levels of 25(OH)D concentrations. Reduced levels of expression of vitamin D receptors are associated with uterine fibroids.[41]

Also, evidence shows an association between vitamin D deficiency and BMI. For each 10% increase in BMI, there is a 4% decrease in 25(OH)D levels.[40] Vitamin D

deficiency and increased risk of uterine fibroids may be partially explained due to its association and high prevalence in those categorized as overweight or obese.[15]

Red Meat and Fowl

"Meat" can be categorized differently within a FFQ depending on which part of the world is being surveyed. The Merriam Webster dictionary defines meat as: 1. Animal tissues considered especially as food. 2. Flesh of a mammal as opposed to fowl or fish.[48] The intake of "meat" can vary in the amounts and types consumed in different countries, and was investigated in China and Italy. The Chinese study asked about consumption of "meat" but did not find any association with uterine fibroids while the Italian study asked specifically about beef and other red meat as well as ham. This latter study reported a moderate association between risk of fibroids and more frequent intake of beef, other red meat, and ham with the multivariate OR of 1.7, (95% CI: 1.4-2.2) for the highest vs. lowest intake of beef and other red meats. In the group with highest consumption of ham, the OR was 1.3, (95% CI: 1.0-1.6).[29,30] A potential explanation of the differing results of these two studies suggests that pork and poultry are the main "meats" in China, while beef and ham are more frequently consumed and considered the main "meats" in Italy.[4] One study on breast cancer, also a hormonally dependent condition, found a direct association with more frequent consumption of meat and ham and breast cancer in the Italian population.[27]

Vitamin A and Carotenoids

Vitamin A is a fat soluble vitamin and is found in foods as either the active vitamin A (retinol) or formed from beta carotene and other carotenoids. Active vitamin

A is found in animal foods such as liver, kidney, fatty fish, and dairy foods. Beta carotene and other carotenoids are found in green leafy vegetables, yellow colored vegetables, and orange fruits and vegetables. Carotenoids, including beta-carotene, also have antioxidant properties that may protect against uterine fibroids and free radical damage.[49] Vitamin A is converted to retinoic acid in the body and a person's diet is the only source of this vitamin.

Some in-vitro research supports involvement of the retinoic acid pathway in uterine fibroid formation.[4] The retinoic acid pathway can affect cell growth, proliferation, and apoptosis. A study involving eight women undergoing hysterectomy for uterine fibroids showed there was a decreased expression of the genes involved in the pathways linked to retinoic acid.[50] One study found the rate of retinoic acid degradation is greater in uterine fibroids cells compared to normal human uterine smooth muscle cells.[51] A potential protective effect of vitamin A has been postulated to increase intracellular retinoic acid and inhibit the growth of leiomyoma cells in-vitro and in animal studies.[4]

Serum levels of vitamin A and beta carotene intake were examined in women with fibroids. A study using NHANES data reported a statistically significant dose response relationship in both white and black women for increasing serum levels of vitamin A and occurrence of uterine fibroids after adjusting for age, race, education, BMI, and oral contraceptive use. Middle vs. low concentrations of vitamin A showed an OR of 2.43 (95% CI: 1.35-4.37) and high vs. low concentrations of vitamin A, OR of 2.66 (95% CI: 1.16-6.10, p=0.02). The authors speculate that some micronutrients may

affect development of uterine fibroids but it is not clear how and what form of ingestion produces these results: food or supplements or both. This may represent diet changes after diagnosis of uterine fibroids, or another possible theory suggests that a group of nuclear receptors might turn on gene expression when attached to retinoid receptors and promote uterine fibroids.[52] A study of dietary and supplement intake of beta carotene was associated with a slightly higher risk of uterine fibroids but only in smokers, looking at highest vs. lowest quintile with relative risk (RR) of 1.36, (95% CI: 1.05-1.76).[53] The role of vitamin A, beta carotene, and food groups containing these, should be studied further for clarity on their associations with uterine fibroids.

Diet Quality

While various vitamins and foods have been studied for associations with uterine fibroids and other hormonally related conditions, it is also worthwhile to examine the context of a whole eating pattern and diet quality. Individuals don't eat single nutrients or foods in isolation. Studying dietary patterns can help understand relationships with disease and nutrients may act synergistically when combined in an eating pattern and provide a more realistic snapshot of food consumption. Therefore, research on diet quality is important.[54] One cross-sectional study in Sweden using a Swedish diet quality tool found that higher diet quality was associated with lower systemic inflammatory markers.[55] Chronic systemic inflammation is a theory for uterine fibroid pathogenesis.

Several studies have looked at relationships between diet quality and hormonally related conditions such as breast cancer, endometrial cancer, and PCOS.[56–60] The Nurses Healthy Study II data compared several tools to measure diet quality including the

Alternate Healthy Eating Index (HEI), the alternate Mediterranean Diet patterns (aMED), and the Dietary Approaches to Stop Hypertension (DASH) patterns and found that diet quality measured by the Alternate HEI was inversely associated with premenopausal estrogen concentrations.[57] The Alternate HEI was developed by the Harvard School of Public Health to better assess chronic disease risk.[61] A study using data from the Women's Health Initiative (WHI) using HEI-2005 showed better diet quality was associated with a decreased risk of all-cause mortality in women with estrogen receptor positive tumors.[58] However, two studies found no association with diet quality, as measured by the HEI-2005 and HEI-2010, and endometrial cancer risk.[56,62] A study in Brazil using the Brazilian HEI found that diet quality was negatively correlated with obesity in women with PCOS.[60] However, there are no studies which examined diet quality using the HEI among women with uterine fibroids.

Healthy Eating Index

The HEI was developed by the United States Department of Agriculture's Center for Nutrition Policy and Promotion (CNPP) as a tool to measure the quality of an individual's diet and is used to look at possible relationships between overall diet and health-related outcomes. It is a useful measure to assess diet quality for the U.S. population by comparing food group and nutrient data against key goals of the Dietary Guidelines.[63,64] The original HEI was developed in 1995 and changes to it have been made to reflect updates to the Dietary Guidelines through the Center for Nutrition Policy and Promotion (CNPP) and the National Cancer Institute.[65]

The HEI-2010 is the most recent version and based on the HEI-2005, but updated to reflect the 2010 Dietary Guidelines and USDA Food Patterns. Some parts of the HEI-2005 were kept in the HEI-2010 such as adequacy (components to increase) and moderation (components to decrease) so that diet quality can be assessed from both perspectives. The HEI-2010 is currently being updated to a newer version to reflect the 2015-2020 Dietary Guidelines but is not yet available for use.[65]

The total HEI-2010 score is the sum of the component scores and has a maximum of 100. There are 12 subcomponents, which each have a score of 5, 10, or 20. Each subcomponent score is based on a standard for a maximum score and density-based, per 1,000 calories, for all subcomponents except fatty acids and empty calories. The scoring is density-based to evaluate the relative mix of foods, which was included as part of the HEI-2005, so that the standards for the maximum scores in each of component areas are easiest to achieve.[63] The intakes of each subcomponent between minimum and maximum scores are scored proportionately. The subcomponents are a set of scores and the maximum points for each subcomponent serves as a weighting factor when calculating the total score.[63] The highest total scores for the HEI-2010 translate into closer adherence to the 2010 Dietary Guidelines.[66] The HEI-2010 scoring system is outlined in **Table 1.1**.

The HEI-2010 subcomponents which are categorized as "adequacy", indicate food groups and nutrients in which higher consumption is recommended. These include the following: total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids. Total fruit includes

fruit juices whereas whole fruit is a sub-category which includes all forms except fruit juice. Beans and peas are included in the total protein component when the total protein component of a participant's food intake is not otherwise met. When total protein subgroup standard is met, beans and peas can be counted in the green vegetable and bean subgroup. Dairy includes all milk products, yogurt, cheese, and fortified soy beverages. Seafood, nuts, seeds, soy products (not beverages) and beans and peas (even though may be in total protein foods category as well) are in the seafood and plant protein category. Fatty acids include the ratio of polyunsaturated fatty acids and monounsaturated fatty acids to saturated fatty acids.[66]

The subcomponents categorized in the "moderation" category indicate food groups and nutrients in which lower consumption is recommended. These include: refined grains, sodium, and empty calories. Empty calories are the percent of total calories from solid fats, alcoholic beverages, and added sugars. For counting alcohol, the threshold is >13 grams per 1000 calories, which is about a 12 oz. beer, 5 ounces of wine or 1.5 oz. of liquor.[66] The USDA food patterns from the 2010 Dietary Guidelines are used as a basis for HEI-2010 scoring standards where mixed foods are broken down into their ingredients consistent with the USDA food patterns. Solid fats and added sugars are counted separately.[67] These food patterns are based on 12 calorie levels and translate the 2010 Dietary Guidelines into set, quantifiable food groups and amounts to consume with a limitation on added sugars and solid fats.[66] **Table 1.2** details these food patterns.

CONCLUSION

Many nutrients and micronutrients have been investigated to ascertain their effect on development of and risk of uterine fibroids. Studies on fruits, vegetables, and dairy found possible protective effects while meat intake had mixed results. These food groupings would be worthwhile to study further, especially in the U.S. population with mixed races since several of these studies were conducted in China or Italy or included solely black women. The HEI-2010 is a helpful tool to assess diet quality in women who have fibroids compared to those who do not have fibroids and should be examined in a sample of young adult and middle aged women in the U.S. Intakes of macronutrients should be investigated for any possible associations with uterine fibroids as well.

Table 1.1 Healthy Eating Index 2010

HEI 2010 component	Maximum	Standard for maximum score	Standard for minimum score
Adequacy (higher score indicates higher consumption)			
Total Fruit[1]	5	≥0.8 cups equiv./1000 kcal [9]	No fruit
Whole Fruit[2]	5	≥0.4 cup equiv./ 1000 kcal	No whole fruit
Total Vegetables[3]	5	≥1.1 cup equiv. / 1000 kcal	No vegetables
Greens and Beans[3]	5	≥0.2 cup equiv. /1000 kcal	No dark-green vegetables, beans, or peas
Whole Grains	10	≥1.5 ounce equiv./1000kcal	No whole grains
Dairy[4]	10	≥1.3 cup equiv./ 1000 kcal	No dairy
Total Protein Foods[5]	5	≥2.5 ounce equiv./1000 kcal	No protein foods
Seafood and Plant Proteins [5,6]	5	≥0.8 ounce equiv./1000 kcal	No seafood or plant proteins
Fatty Acids[7]	10	(PUFAs + MUFAs)/SFA ≥2.5	(PUFAs + MUFAs)/SFAs ≤1.2
Moderation (higher score indicates lower consumption)			
Refined Grains	10	≤1.8 ounce equiv./1000 kcal	≥4.3 ounce equiv./1000 kcal
Sodium	10	≤1.1 gram/1000 kcal	≥2.0 grams/1000 kcal

Empty Calories (solid fats, alcohol, and added sugars) [8]	20	≤19% of energy	≥50% of energy

[1] Includes 100% fruit juice
[2] Includes all forms except juice
[3] Includes any beans and peas not counted as Total Protein Foods
[4] Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages
[5] Beans and peas are included here (not with vegetables) when the Total Protein Foods standard is otherwise not met
[6] Includes seafood, nuts, seeds, soy products (other than beverages) as well as beans and peas counted as Total Protein foods
[7] Ratio of poly-and monounsaturated fatty acids (PUFAs and MUFAs) to saturated fatty acids (SFAs)
[8] Calories from solid fats, alcohol, and added sugars; threshold for counting alcohol is >13 grams/1000 calories.
[9] Equiv. = equivalent, kcal = kilocalories

Source: Center for Nutrition Policy and Promotion CNPP Fact Sheet No. 2 February 2013

Table 1.2 USDA Food Patterns Based on 2010 Dietary Guidelines

Daily Amount of Food From Each Group												
Calorie level[1]	1000	1200	1400	1600	1800	2000	2200	2400	2600	2800	3000	3200
Fruit[2]	1 cup	1 cup	1 ½ cups	1 ½ cups	1 ½ cups	2 cups	2 cups	2 cups	2 cups	2 ½ cups	2 ½ cups	2 ½ cups
Vegetables[3]	1 cup	1 ½ cups	1 ½ cups	2 cups	2 ½ cups	2 ½ cups	3 cups	3 cups	3 ½ cups	3 ½ cups	4 cups	4 cups
Grains[4]	3 oz.-eq	4 oz.-eq.	5 oz.-eq	5 oz.-eq	6oz-eq	6oz-eq	7 oz.-eq	8 oz.-eq	9oz-eq	10 oz.-eq	10 oz.-eq	10 oz.-eq
Protein Foods[5]	2 oz.-eq	3 oz.-eq	4 oz.-eq	5 oz.-eq	5 oz.-eq	5 ½ oz.-eq	6 oz.-eq	6 ½ oz.-eq	6 ½ oz.-eq	7 oz.-eq	7 oz.-eq	7 oz.-eq
Dairy[6]	2 cups	2 ½ cups	2 ½ cups	3 cups	3 cups	3 cups	3 cups	3 cups	3 cups	3 cups	3 cups	3 cups
Oils[7]	15 g	17g	17g	22 g	24 g	27 g	29g	31g	34g	36g	44g	51g
Limit on calories from SOFAAS[8]	137	121	121	121	161	258	266	330	362	395	459	596

[1]Calorie levels are assessed at various levels to accommodate a variety of needs.

[2]Fruit Group includes all fresh, frozen, canned, and dried fruits and fruit juices. In general, 1 cup of fruit or 100% fruit juice, or ½ cup of dried fruit can be considered as 1 cup from the fruit group.

[3]Vegetable Group includes all fresh, frozen, canned, and dried vegetables and vegetable juices. In general, 1 cup of raw or cooked vegetables or vegetable juice, or 2 cup of raw leafy greens can be considered as 1 cup from the vegetable group.

[4]Grains Group includes all foods made from wheat, rice, oats, corn meal, and barley such as bread, pasta, oatmeal, breakfast cereals, tortillas, and grits. In general, 1 slice of bread, 1 cup of ready- to eat- cereal, or grains, ½ cup of cooked rice, pasta, or cooked cereal can be considered as 1 ounce equivalents from the grains group. At least half or all grains consumed should be whole grains.

[5]Protein Foods Group includes meat, poultry, seafood, eggs, processed soy products, and nuts and seeds. In general, 1 ounce of lean meat, poultry, or seafood, 1 egg, 1 Tbsp peanut butter, or ½ ounce of nuts or seeds can be considered as 1 ounce equivalent from the protein foods group. Also, ¼ cup of beans or peas may be counted as 1 ounce- equivalent in this group.

[6]Dairy Group includes all milks, including lactose free products and fortified soymilk (soy beverage) and foods made from milk that retain their calcium content, such as yogurt and cheese. Foods made from milk that have little to no calcium, such as cream cheese, cream, and butter are not part of the group. Most dairy group choices should be low fat or fat free. In general, 1 cup of milk or yogurt, 1 ½ ounces of natural cheese, or 2 ounces of processed cheese can be considered as 1 cup from the dairy group.

[7]Oils include fats from many different plants and from fish that are liquid at room temperature, such as canola, corn, olive, soybean, and sunflower oil. Some foods are naturally high in oils, like nuts, olive, some fish, and avocados. Foods that are mainly oil include mayonnaise, certain salad dressings, and soft margarine.

[8]SOFAAS are solid fats and added sugars. The limits for calories from SoFAS are the remaining amount of calories in each food pattern after selecting t he specified amounts in each food group in nutrient- dense forms (forms that are fat- free or low- fat and with no added sugars).

Adapted from: USDA Center for Nutrition Policy and Promotion, Sept 2011

CHAPTER 2 . RATIONALE, OBJECTIVES, AND HYPOTHESES

RATIONALE

Uterine fibroids are one of the most common gynecological conditions among premenopausal women causing morbidity and diminished quality of life due to excessive bleeding, pelvic pain, and other symptoms. Problems with fertility and pregnancy can occur as well.[1] The prevalence of uterine fibroids is difficult to establish as many women with fibroids can be asymptomatic. Black women have a higher prevalence than white women.[5,8,68]

Several theories on hormonal involvement, inflammation, and genetic defects have been explored in the scientific literature as to the etiology of uterine fibroids.[19] Uterine fibroid pathogenesis theories center on increased unopposed estrogen levels for long periods of time and a chronically active and inflammatory immune system. Inflammation may promote fibrous tissue, change the function of endometrial activity, or alter uterine tissue repair and encourage fibroid formation.[16,17] In fact, a proposed model for inflammation leading to uterine fibroid formation includes possible dietary components that may alter the inflammatory response or interact with hormones, stress, aging, and other factors to influence risk of uterine fibroids.[16] Medications, surgery, and symptom management are not definitive treatment options and all come with risks and

side effects. The exact causes, best treatment options, and steps for prevention are not clear.

Nutrition may provide a possible strategy for prevention and treatment. Food intake of women with fibroids or diagnosed with fibroids may be different than those without fibroids. Added sugar intake may promote inflammation and in one population based cohort study, total sucrose intake was associated with an increased risk of endometrial cancer.[32] Diets with a high glycemic index are also associated with inflammation.[16] A Swedish study found higher diet quality, as measured by adherence to Swedish dietary guidelines, was associated with lower markers of systemic inflammation.[55]

Many studies have shown links between diet quality and other hormonally related conditions such breast cancer, endometrial cancer, and PCOS as measured by various indices.[56–60] Estrogen levels are theorized to promote growth of uterine fibroids so it is possible that hormone levels of women with fibroids can be related to diet, similar to other hormonally influenced conditions.

Various studies on uterine fibroids and specific food and/or nutrient intake have used prospective cohort data and focused on specific populations such as black women and nurses.[28,36,53] However, few studies have been conducted which explored uterine fibroids and dietary intake among a representative sample of the U.S. population. One study examined micronutrient status, measured by serum samples, among premenopausal women in the NHANES.[52] Other nutrients such as vitamins A[52] and D[42,43,45] as well as food groups such as fruits and vegetables[4,28–30] and dairy[36,37] have shown some

associations with risk of fibroids but the data is limited. Macronutrients as a whole, from national data in the U.S., have not been investigated to determine any possible associations with uterine fibroids. No studies have examined diet quality measured by HEI total and subcomponent scores with uterine fibroids. This is important as components of diet quality are modifiable lifestyle factors and may play a role in prevention and treatment of this condition.

Additionally, the costs associated with treatment of fibroids cause significant economic burden. A systematic review of the cost of uterine fibroids from 2000-2013 showed that the average direct costs (medication, hospitalization, surgeries, medical appointments) and indirect costs (loss of work due to disability and absenteeism) totaled between $11,000-$25,000 per patient in the United States in the year following diagnosis of uterine fibroids.[69] In 2000, the direct annual medical costs associated with uterine fibroids were over $2 billion, as estimated by the Centers for Disease Control (CDC).[70]

Given a predicted diminished quality of life for women with fibroids, the high cost of treatment, and the likelihood that fibroids can grow back if removed, women suffering from uterine fibroids do not have many long-term options. Hysterectomy is irreversible and ends a woman's child bearing potential. Research on modifiable risk factors, such as food intake patterns, is needed. Analysis of dietary factors can add to this limited research area by examining food groups as a measure of diet quality along with macronutrient intake. The HEI-2010 is a tool that can be used to compare and contrast any associations of diet quality in women with and without fibroids. Therefore, this study will be conducted to provide data on a subsample of American women with and

without uterine fibroids to find possible associations with diet quality and with macronutrient intake.

OBJECTIVES & HYPOTHESES

Objective 1.1 To compare the HEI–2010 subcomponent and total scores of women aged 20-54 years who self-reported uterine fibroids compared to those who did not.

> **Hypothesis 1.1** There is a difference in HEI-2010 subcomponent and total scores in women aged 20-54 years who self-reported uterine fibroids compared to those who did not.

Objective 1.2 To compare the average macronutrient (carbohydrates, proteins, fats) intakes between women aged 20-54 years who self-reported uterine fibroids compared to those who did not.

> **Hypothesis 1.2** There is a difference in average macronutrient intakes in women aged 20-54 years who self-reported uterine fibroids compared to those who did not.

CHAPTER 3 . NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY DATA (CYCLES 2001-2002, 2003-2004, AND 2005-2006) IN RELATION TO UTERINE FIBROIDS, DIET QUALITY, AND NUTRITIONAL INTAKE

Introduction

Uterine leiomyomas (fibroids) are common estrogen-dependent tumors, usually benign, in reproductive age women.[19] The exact pathogenesis of these tumors is not known but estrogen involvement, inflammation, and genetics are thought to influence formation.[2,10,16,17,19] They are a leading cause of hysterectomy and can lead to diminished quality of life through debilitating signs and symptoms.[2] These include excessive, irregular, and intermenstrual bleeding, pelvic pain unrelated to menstruation, bloating, increased urinary frequency, and bowel disturbance. In addition, reproductive dysfunction may contribute to problems with fertility, early pregnancy loss, and later pregnancy complications such as pain, preterm labor, caesarean section, and post-partum hemorrhage.[1] The estimated cumulative incidence of uterine fibroids is high, with more than 80% of black women and almost 70% of white women reporting fibroids by age 50 with a reported age-specific cumulative incidence, for black and white women combined, of 2.9 (95% CI: 2.5-3.4).[71]

Several studies conducted in the U.S. have focused on black women such as the Black Women's Health Study and the Study of Environment, Lifestyle, and Fibroids, as this is a group at high risk.[7,28,68] The U.S. Nurses Healthy Study II, which also explored uterine fibroids, included women of Hispanic origin, but not Mexican American.[3] Established risk factors for development of uterine fibroids include weight gain, higher

BMI, increasing age in premenopausal years, and women who are black.[1,5,13,68] Conversely, decreased risk of fibroids has been observed in those who smoke and are parous.[11,12]

Treatment and prevention of uterine fibroids is important for researchers to continue to study to better understand this condition. The costs are great to these women, many of whom must have a hysterectomy and child bearing potential ceases. Uterine fibroids can lead to more frequent medical visits, need for more medications, surgeries, and procedures, reduced quality of life, and increased costs due to absenteeism and disability.[69,70] This necessitates finding more evidence for modifiable risk factors.

The role of nutrition and dietary components in the development and prevention of uterine fibroids is a subject investigated in populations all over the world. However, nutrition professionals do not currently have practice guidelines regarding medical nutrition therapy for fibroids. Some research shows a protective effect for fruits and vegetables and uterine fibroids.[4,72] Serum micronutrients were studied in a sample of premenopausal women from NHANES and were found to have a statistically significant positive dose response relationship between vitamin A and uterine fibroids.[52] A study using NHANES data also found a possible association of low serum vitamin D levels and increased risk of uterine fibroids in white women.[44] Data from a 2015 systematic review which included studies conducted around the world, was inconclusive on intakes of fish, meat, and dairy in relation to uterine fibroid risk.[39] Dietary practices, as well as farming and pasture practice and policies, differ in various countries and regions of the world and may explain insignificant results.[4]

A food or nutrient is generally not consumed independently of others and the effect of dietary patterns, which includes the combinations of different foods and beverages in diets, as well as macronutrient intake, could help shed light on inconsistencies found among previous studies. Food and beverage intake is a modifiable risk factor which may also play a role in the treatment for uterine fibroids. Food intake patterns may be one of those factors and one primary tool used to measure diet quality, the Healthy Eating Index (HEI) 2010, has not been previously explored in relation to uterine fibroids. The HEI-2010 measures diet quality of Americans based on the 2010 U.S. Dietary Guidelines.[65] Therefore, in order to examine food patterns more closely, the objectives of this study are to compare overall diet quality, as measured by the HEI-2010, and macronutrient intake among a sample of young and middle aged U.S. women who reported a history of uterine fibroids compared to those who did not.

Methods

This is a cross-sectional analysis using secondary data from the NHANES. The National Center for Health Statistics (NCHS) conducts several major data collection programs as a part of the CDC, one of which is the NHANES. This is a stratified, multistage, probability, cluster sample of non-institutionalized civilians living in the U.S.[73] Sample weighing allows for representativeness of the U.S. population. All protocols in the NHANES have been reviewed and approved by the NCHS Research and Ethics Review.[74] Consent forms were signed by all participants in NHANES and de-identified data is publicly available.

Subjects

A total of 16,128 women participated in NHANES between 2001-2006. This study was limited to women of reproductive age between 20-54 years.[75] Of the 4,953 in the appropriate age range, 319 had missing information on fibroids, 371 were eliminated due to being pregnant or breastfeeding, 714 had gone through menopause, and 2,182 had missing information on macronutrients or BMI. Women reporting calories levels less than 500 or greater than 5,000 calories per day were excluded (n=499).[53,76] Other exclusions included 38 women who had missing data or did not know smoking status, age at menarche, or age at diagnosis of fibroids. A total of 830 women were included in this analysis, 87 with reported fibroids, and 743 women without reported fibroids. Women who had a previous diagnosis of ovarian or uterine cancer on the medical health questionnaire were not excluded as their dietary intake was assumed to not be different for the purpose of this study.

Demographics and Smoking

Demographic data was collected on age, race, educational level, poverty to income ratio, and marital status at an in-person interview using computer-assisted personal interview (CAPI) software. Data on race was re-classified into: "non-Hispanic Black", "non-Hispanic White", combined "Mexican American and Hispanic", and "other" which included multi-racial women. Marital status was re-categorized as "married", which included separated, and "not married" which included divorced, widowed, never married, or living with a partner. Current smoking status has been associated with decreased risk of uterine fibroids[56,57] and therefore included as a covariate

in this analysis and re-categorized as "current/former" and "never". Educational level was re-categorized as "college graduate or higher" vs. "not college graduate" (includes refused or don't know) or "missing". NHANES calculates the poverty to income ratio, which is a measure of family income divided by the poverty level determined by the Department of Health and Human Services' poverty guidelines, specific to family size, year of interview, and state of interview.[77] Poverty to income ratio was grouped into: "below the poverty level" (<1.0), "above the poverty level" ($\geq$1.0), or "missing".

Anthropometrics

Height and weight were collected at the Mobile Examination Center (MEC). Weight was collected using a digital floor scale and measured to 0.1 kg. Standing height was measured to the nearest millimeter using a wall-mounted stadiometer. In order to calculate Body Mass Index (BMI), weight in kilograms was divided by height in meters squared. BMI was categorized as "underweight" (BMI<18.5 kg/m^2), "normal weight" (BMI$\geq$18.5 kg/m^2 and <25.0 kg/m^2), "overweight" (BMI$\geq$25.0 kg/m^2 and <30.0 kg/m^2) and "obese" (BMI$\geq$30.0 kg/m^2) in accordance with National Institutes of Health guidelines.[78]

Reproductive Health Data

Data on uterine fibroids and reproductive health was collected in the NHANES reproductive questionnaire from CAPI. All females aged 20-54 years at the time of the survey were asked two questions on fibroids: "Has a doctor or other health professional ever told you that you had uterine fibroids?", "Yes" answers were considered as having a diagnosis of uterine fibroids and "No" answers were considered as not having fibroids

and included those who answered "refused" or "don't know". Age at diagnosis of fibroids was ascertained from the follow up question: "How old were you when you were first told you had uterine fibroids?" Parity was grouped into the following categories according to number of live births: "0", "1-2", "3+" or "missing". Several studies have reported higher risk of uterine fibroids with not having had any live births and a parity of zero.[57, 59, 60] Some data indicate a reduced risk of uterine fibroids with increased duration of oral contraceptive use.[74] Therefore, data on current oral contraceptive use was categorized as "yes", "no" or "missing". This may be due to unopposed estrogen increasing risk and the effect of both pregnancy and oral contraceptive use decreasing endogenous estrogen and increasing progesterone levels.[29] Age at menarche was presented as a continuous variable as some studies have shown that an earlier age of menarche is associated with higher risk of fibroids.[2, 79]

Nutritional Intake

A 24-hour dietary recall was administered to all participants in the NHANES MEC by an in-person trained interviewer. Interviewers are bilingual in both English and Spanish. This was performed using the USDA's five step Automated Multiple-Pass Method (AMPM) and portion sizes estimated using three dimensional food models.[80] Participants were asked about all foods and beverages consumed during a 24-hour time period and this data was analyzed by the USDA Food and Nutrient Database for Dietary Studies, with each version corresponding to the appropriate cycle year. The 24-hour recall using the AMPM has been shown to be accurate in women, within 10% of actual food intake.[81] This information on food and beverage consumption can be found in the

"What We Eat in America" section of NHANES and was also used to calculate the HEI-2010 subcomponent and total scores. **Table 1.1** details the HEI-2010 scoring and subcomponents. The total HEI-2010 scores and subcomponent scores as well as macronutrients (reported in grams and as percentages of total energy) were analyzed.

Statistical Analysis

Demographic, body measures, and reproductive health data were compared as mean ± standard error for continuous variables and frequency and weighted percentage for categorical variables. Differences between groups were tested using linear regression for continuous variables and chi-squared tests for categorical variables. Linear regression was used to assess differences in HEI-2010 scores and macronutrient intakes between women with fibroids or without fibroids. Regression models were adjusted for race (reference=non-Hispanic white), age, BMI (reference=normal weight), smoking status (reference=never smoked), marital status (reference=married), and educational level (reference=college graduate or higher). Age, race, BMI, and smoking were previously reported in the literature to affect both dietary intake and uterine fibroids and were adjusted for in the analysis as confounders.[10,12,68,79,82] Variables found to be significantly different between groups were included as covariates. As women with a more recent diagnosis of fibroids may possibly reflect different food patterns, a subgroup of women diagnosed in the past five years was compared to women without fibroids and analyzed by using linear regression.

This analysis adjusted for the clustering sample design and sample population weights of NHANES. A p-value of < 0.05 was used for statistical significance and tests

were two tailed. All statistical analyses were conducted using Stata data analysis and statistical software, version 14.2 (College Station, TX).[83]

Results

The demographic characteristics of the women with and without fibroids are reported in **Table 3.1.** Women with fibroids were older with an average age in this study of 41 years old and women without fibroids averaged 33 years old, ($p < 0.001$). Women with uterine fibroids were more likely to be college graduates (28%) than women without fibroids (20%), p=0.05. Married women were significantly more likely to have fibroids (70%) as compared to those without fibroids (57%), p=0.022. There was however, no significant difference in BMI, poverty to income ratio, age at menarche, parity, current birth control use, or smoking status between the two groups. Parity and current birth control use data was missing in 22% and 29% of this subsample respectively. Women who were categorized as obese appeared more likely to have fibroids (42%) than those who did not have fibroids (31%), however, this was not statistically significant. Race was not significantly different between groups. Fibroid prevalence rates by race/ethnicity were as follows: 16% among non-Hispanic black women, 10% among non-Hispanic white, and 8% among Mexican-American and other Hispanic.

Results of multivariate linear regression analyses are reported in **Table 3.2.** Unadjusted total HEI-2010 score was significantly higher among women with fibroids (49.8 ± 1.3) compared with women without fibroids (45.1 ± 0.80, p=0.016). Total HEI score and empty calories subcomponent score were higher for women with fibroids (49.8

± 1.3 and 10.7 ± 0.61 respectively) compared to women without fibroids (45.1 ± 0.8, p=0.016 and 8.5 ± 0.46, p=0.014 respectively). However, these effects disappeared after adjustment for covariates. There was no difference in energy adjusted macronutrient intakes between groups.

The results of a subgroup analysis of women diagnosed within five years are reported in **Table 3.3.** Baseline characteristics for this subgroup are in **Appendix B**. After adjustment, the empty calories subcomponent score remained significantly higher for women with fibroids (11.5 ± 0.64) compared with those without fibroids (8.5 ± 0.46, p=0.002) and being in the fibroids group was associated with a 2.53 higher empty calories subcomponent score (95% CI: 1.12, 3.93). In addition, whole fruit subcomponent score was significantly lower in the women with fibroids (1.7 ± 0.32) vs. those without fibroids (2.4 ± 0.12, p=0.044). Therefore, being in the fibroids group subgroup was associated with a 0.73 lower whole fruit score, (95% CI: -1.44, -0.028) compared to those without fibroids.

Discussion

This study was the first to examine the relationship between diet quality and uterine fibroids in a cross-sectional sample of young to middle aged U.S. women. Our results were in line with previous reports, which showed women with fibroids were significantly older than women without fibroids.[82,84] Additionally, married women and those having higher education were also more likely to have reported a uterine fibroids diagnosis, in line with previous reports.[59,18] However, our results show no differences in

total and subcomponent HEI-2010 scores as well as macronutrient intake between women with or without fibroids after adjustment for age, race, BMI, smoking status, marital status and educational level.

A subgroup analysis of women limited to those diagnosed within the past five years was explored as time since diagnosis may influence dietary intake. Women with fibroids diagnosed within the last five years had lower whole fruit HEI-2010 subcomponent score after adjustment for covariates compared to women without fibroids. The whole fruit subcomponent includes all forms of fruit, except for fruit juice. This finding correlates with studies on the protective effects of higher consumption of fruits and vegetables on uterine fibroid risk. Studies conducted in Italy, China, and the Black Women's Health Study all found a reduced risk of fibroids with consumption of fruit, with higher citrus fruit intake having a protective effect.[28–30] Fruits contain vitamins, minerals, carotenoids, antioxidants and phytoestrogens which may play a role in decreasing uterine fibroid risk at the cellular level. This subgroup was limited but further studies clarifying the role of fruit and its components, in association with risk of uterine fibroids in larger population groups, are warranted.

The results of the subgroup analysis also found higher HEI-2010 subcomponent scores for empty calories among women more recently diagnosed with uterine fibroids vs. those without fibroids, after adjustment for covariates. The empty calories subcomponent score incorporates calories from solids fats, alcohol, and added sugars with higher empty calorie scores translating into lower empty calorie density in the HEI-2010 scoring system. Hence, a total (or best) score for empty calories, with a maximum

being 20, indicates minimal consumption of empty calories. Our finding of higher empty calorie scores in women with fibroids seems counter-intuitive. Added sugars may have inflammatory effects and a main hypothesis for uterine fibroid formation involves inflammation.[13,14,15] In addition, higher fat intake has been linked to higher estradiol, a sex hormone that may influence increased risk of uterine fibroids.[32] Yet, both the Black Women's Health Study and a Japanese cross-sectional study did not show any association with types of fats and uterine fibroid risk.[32, 33] These previous studies examined grams of fat per day, whereas in our current study, solid fats were combined with added sugars and alcohol as a percent of total calories for scoring.

Better empty calories scores among women with fibroids may indicate a focus on a more health oriented lifestyle and higher health literacy level. The women diagnosed with uterine fibroids may reflect women who seek out medical care for signs and symptoms and either take better care of themselves or at least seek out medical care more often or more thoroughly. More studies are needed to further examine solid fats, added sugars, and alcohol separately and as a whole in relation to uterine fibroids in larger populations with medically confirmed diagnoses.

The women with fibroids had a total HEI-2010 score on average of 50 and women without fibroids a total score of 45. Other HEI-2010 total average scores for samples from NHANES populations using adults aged 18-64 years including men and women, show an upward increasing trend each year of average total HEI-2010 scores. Data from 2005-2006 cycle show average total score of 53.7, 2007-2008 of 54.3, 2009-2010 of 57.3, and 2011-2012 of 58.2.[65] High subcomponent scores of the HEI are rare in the United

States except for total protein foods, so comparison to other populations using the HEI-2010 or other diet quality measures can add perspective and is needed for future research.[67]

This study found prevalence of fibroids of 8% among Mexican-American and Hispanic women, an understudied population in terms of fibroid prevalence, and should be explored further. It is unclear whether this lower rate reflects decreased diagnosis due to lack of access to medical care, or a protective role due to cultural or ethnic lifestyle, or genetics. Black women had a higher prevalence of uterine fibroids in this study, 16% vs. 10%, in white women in agreement with other studies.[8,68] Possible reasons include: black women may have different levels of ovarian hormone levels than white women and obesity rates are higher in black women.[83] In fact, the National Center for Health Statistics (NCHS) reports that 57% of black women were categorized as obese and 35.5% of white women, according to research from 2011-2014.[85] Increasing BMI levels in women may cause a decrease in estradiol levels in black, but not white women, which may also be a factor in explaining the higher prevalence of uterine fibroids in black compared to white women.[68]

Strengths and Limitations

The strengths for this study include using NHANES data, a data set that is carefully collected using quality control measures and trained interviewers. The dietary recall method used, the AMPM, has been validated in studies for its accuracy, though any dietary recall is not without flaws as a self-reported measure due to recall bias.[81] Another strength of this study was the uniqueness of comparing HEI-2010 scores in women with

and without fibroids as this has not been researched previously. The HEI-2010 scoring system has been validated and reflects a variety of eating patterns including vegetarian, vegan, and omnivore. The process for scoring is considered valid for a variety of ethnic and cultural groups because mixed dishes can be disaggregated into their ingredients and categorized into food groups that are utilized in the USDA food patterns.[67]

The limitations of this study are the self-reported data. The diagnosis of uterine fibroids was self-reported and not confirmed with medical records, examinations, or testing and should be interpreted with caution. Misclassification of women in the non-fibroids group can occur in both women with either symptomatic or asymptomatic fibroids. Women who are either uninsured or under insured have limited access to medical or gynecological services, do not prioritize the time or have insufficient resources needed for exams or procedures for the appropriate diagnosis, may have been misclassified. A study which examined the accuracy of self-reported uterine fibroids, compared to those whose uterine fibroids were confirmed by ultrasound or medical records in the Nurses' Health Study II cohort, reported about 93% accuracy.[82] The nutritional data are also self-reported so there could be reporting bias and errors in what is reported, frequency, consumption, and intake. Recall bias may cause participants to not fully remember with accuracy the types or amounts of foods and beverages consumed, either accidentally or on purpose. There can be large within-person variability for food intake data and this may decrease statistical power.[86]

Data from this study only examined one 24-hour recall and may not be reflective of a broader picture of one's usual intake and overall dietary patterns. However, day one

of NHANES 24-hour recall is completed in person while day two is via telephone interview. In person 24-hour recall interviews have been shown to generate a greater proportion of responses than phone interviews.[87] Using day one of 24-hour recall data is consistent with other studies.

Another factor that could affect HEI-2010 scores is health literacy level. One study that measured health literacy level found higher HEI scores among those with higher health literacy thus, another element to consider in looking at ways to improve and influence diet quality of a population.[88] One study showed that women who had higher HEI scores were older, married, better educated, and had a higher socioeconomic status or higher income.[89] Cross-sectional studies, such as NHANES, by definition cannot provide information about causality and are limited to associations. Another limitation with cross-sectional investigations is that the disease onset and diagnosis occurred prior to the NHANES data collection and thus temporal order of diet leading to disease or disease leading to diet cannot be established. Those who agreed to participate in NHANES may also be different than those who did not agree to participate.

This sample from NHANES is larger than some,[30,52] yet smaller than other previous studies examining nutritional intake in premenopausal women and uterine fibroids.[12,36,90] The subgroup analysis was not powered to answer the research question, though future prospective studies focusing on women newly or recently diagnosed with fibroids, to help prevent misclassification, combined with a larger sample size are warranted.

Conclusion

This cross-sectional assessment of young adult and middle aged women in the United States provided information on associations between diet quality, food groups (as defined by the HEI-2010 to correspond with the Dietary Guidelines of 2010), and uterine fibroids. Due to limited sample sizes, use of one day of 24-hour recall data, potential for misclassification of fibroids due to self-reporting, and not controlling for health literacy, future prospective cohort studies to explore food intake patterns and associations with uterine fibroids should be explored. One study which examined the number of dietary recalls needed to estimated nutrient intake in overweight and obese adults using the AMPM concluded that three non-consecutive days per month of a 24-hour recall using the AMPM over a 6-month time frame would give an estimation of energy and macronutrient content in overweight and obese people.[91] Methodological problems in nutritional epidemiology studies are present when not accounting for calorie intake, especially given that uterine fibroid risk is increased with higher BMIs and likely higher calorie intakes. Other measures of diet quality such as the Dietary Approaches to Stop Hypertension (DASH) diet or Alternate HEI-2010, or the alternate Mediterranean diet score (aMED) could be investigated in this population as well.[92] More research is needed to better understand any associations between uterine fibroid risk, prevention, types of diets, diet quality, components, and frequencies of intake to find ways to help women with this burdensome medical condition.

Table 3.1 Baseline characteristics of women in NHANES sample 2001-2006 with and without reported uterine fibroids (n=830). Data presented as Mean ± SE for continuous variables and n, (%) for categorical variables.

Characteristic	Women with Fibroids (n=87)	Women without Fibroids (n=743)	P-value
Age (years)	40.8 ± 0.89	33.2 ± 0.43	<0.001
Race [Prevalence]			
Non-Hispanic White	37, (43%) [10%]	347, (47%)	
Non-Hispanic Black	28, (32%) [16%]	147, (20%)	
Mexican American and Hispanic	20, (23%) [8%]	222, (30%)	
Other	2, (2%) [7%]	27, (3%)	0.122
Education			
Not College Graduate	63, (72%)	595, (80%)	0.050
College Graduate or higher	24, (28%)	148, (20%)	
Age at diagnosis (years)	34.1± 0.78	N/A	N/A
Poverty to income ratio			
<1.0	10, (12%)	135, (18%)	
≥1.0	75, (86%)	565, (76%)	0.117
Missing	2 (2%)	43, (6%)	
BMI (kg/m^2)			
≤18.5 (Underweight)	2, (2%)	28, (4%)	
18.6-24.9 (Normal weight)	31, (36%)	273, (37%)	
25.0-29.9 (Overweight)	17, (20%)	209, (28%)	
≥30.0 (Obese)	37, (42%)	233, (31%)	0.107
BMI (kg/m^2)	27.2 ± 0.74	27.5 ± 0.318	0.785
Smoking Status			
Current/Former smoker	33, (38%)	283, (38%)	
Never smoked	54, (62%)	460, (62%)	0.693
Marital Status			
Married	61, (70%)	422, (57%)	0.022
Not Married	26, (30%)	321, (43%)	
Age at menarche (years)	12.5 ± 0.25	12.6 ± 0.05	0.855
Current birth control use			
Yes	13, (15%)	125, (17%)	0.459

No	53, (61%)	392, (53%)	
Missing	21, (24%)	226, (30%)	
Parity			
0	5, (6%)	34, (4%)	
1-2	45, (52%)	317, (43%)	
3 or >	27, (31%)	219, (30%)	0.076
Missing	10, (11%)	173, (23%)	

Table 3.2 HEI scores and macronutrient intakes in women with and without reported uterine fibroids (n =830). Data presented as Mean ± SE and p values for linear regression analyses.

Variable	Women with Fibroids (n=87)	Women without Fibroids (n=743)	Unadjusted	Adjusted[1]
			P value	P value
HEI component (Maximum score)				
Total score (100)	49.8 ± 1.3	45.1 ± 0.80	0.016	0.112
Total vegetables (5)	3.2 ± 0.19	2.9 ± 0.06	0.139	0.443
Greens and beans (5)	1.6 ± 0.27	1.1 ± 0.09	0.067	0.133
Total fruit (5)	2.2 ± 0.24	1.9 ± 0.10	0.348	0.677
Whole fruit (5)	2.5 ± 0.25	2.4 ± 0.12	0.746	0.980
Whole grains (10)	2.0 ± 0.31	2.1 ± 0.12	0.783	0.253
Dairy (10)	5.4 ± 0.41	4.9 ± 0.20	0.164	0.057
Total protein foods (5)	4.1 ± 0.11	3.9 ± 0.07	0.093	0.275
Seafood and plant proteins (5)	2.0 ± 0.29	1.7 ± 0.10	0.423	0.674
Fatty acids (10)	4.4 ± 0.43	4.7 ± 0.12	0.364	0.172
Sodium (10)	5.6 ± 0.29	5.4 ± 0.24	0.639	0.654
Refined grains (10)	6.1 ± 0.31	5.7 ± 0.22	0.278	0.831
Empty calories (20)	10.7 ± 0.61	8.5 ± 0.46	0.014	0.051
Macronutrient Intakes				
Protein (g)	67.4 ± 2.4	71.1 ± 1.6	0.213	0.212
% of calories from protein	15.3 ± 0.51	14.5 ± 0.26	0.162	0.466
Fat (g)	70.4 ± 2.4	74.7 ± 1.4	0.125	0.071

% of calories from fat	35.0 ± 0.90	33.3 ± 0.34	0.120	0.321
Carbohydrate (g)	224.0 ± 10.9	256.7 ± 4.2	0.011	0.041
% of calories from carbohydrate	49.9 ± 1.6	51.7 ± 0.63	0.291	0.685

[1]Adjusted for race, age, BMI, smoking status, marital status, and educational level.

Table 3.3 HEI scores and macronutrient intakes in subgroup analysis of women with fibroids diagnosed within last 5 years, (n =789). Data presented as Mean ± SE and p values for linear regression analyses.

Variable	Women with Fibroids diagnosed in last 5 years (n=46)	Women without Fibroids (n=743)	Unadjusted P value	Adjusted[1] P value
HEI component (Maximum score)				
Total score (100)	48.4 ± 1.7	45.1 ± 0.80	0.119	0.289
Total vegetables (5)	3.2 ± 0.24	2.9 ± 0.06	0.249	0.503
Greens and beans (5)	1.4 ± 0.22	1.1 ± 0.09	0.220	0.356
Total fruit (5)	1.4 ± 0.29	1.9 ± 0.10	0.185	0.082
Whole fruit (5)	1.7 ± 0.32	2.4 ± 0.12	0.095	0.044
Whole grains (10)	1.5 ± 0.55	2.1 ± 0.12	0.281	0.140
Dairy (10)	5.1 ± 0.63	4.9 ± 0.20	0.714	0.509
Total protein foods (5)	4.3 ± 0.17	3.9 ± 0.07	0.043	0.086
Seafood and plant proteins (5)	2.0 ± 0.46	1.7 ± 0.10	0.534	0.697
Fatty acids (10)	5.4 ± 0.62	4.7 ± 0.12	0.287	0.522
Sodium (10)	5.4 ± 0.57	5.4 ± 0.24	0.999	0.970
Refined grains (10)	5.5 ± 0.38	5.7 ± 0.22	0.798	0.395
Empty calories (20)	11.5 ± 0.64	8.5 ± 0.46	0.003	0.002
Macronutrient Intakes				
Protein (g)	69.3 ± 4.0	71.1 ± 1.6	0.698	0.554
% of calories from protein	16.2 ± 0.62	14.5 ± 0.26	0.015	0.055
Fat (g)	71.8 ± 4.4	74.7 ± 1.4	0.567	0.499
% of calories from fat	36.6 ± 1.5	33.3 ± 0.34	0.068	0.088
Carbohydrate (g)	214.4 ± 12.6	256.7 ± 4.2	0.004	0.004
% of calories from carbohydrate	47.9 ± 1.9	51.7 ± 0.63	0.086	0.136

[1]Adjusted for race, age, BMI, smoking status, marital status, and educational level

APPENDIX A

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APPENDIX B

Baseline characteristics of women included in subgroup analysis of women with fibroids diagnosed within last 5 years, (n=789). Data presented as Mean ± SE for continuous variables and n, (%) for categorical variables.

Characteristic	Women with Fibroids diagnosed in last 5 years (n=46)	Women without Fibroids (n=743)	P value
Age (years)	38.8 ± 0.89	33.2 ± 0.43	<0.001
Race			
Non-Hispanic White	20, (44%)	347, (47%)	0.508
Non-Hispanic Black	13, (28%)	147, (20%)	
Mexican American and Hispanic	11, (24%)	222, (30%)	
Other	2, (4%)	27, (3%)	
Education			
Not College Graduate	36, (78%)	595, (80%)	0.159
College Graduate or higher	10, (22%)	148, (20%)	
Age at diagnosis (years)	36.9 ± 0.96	N/A	
Poverty to income ratio			
<1.0	9, (20%)	135, (18%)	0.379
≥1.0	36, (78%)	565, (76%)	
Missing	1 (2%)	43, (6%)	
BMI (kg/m^2)			
≤18.5 (Underweight)	1, (2%)	28, (4%)	
18.6-24.9 (Normal weight)	16, (35%)	273, (37%)	0.428
25.0-29.9 (Overweight)	10, (22%)	209, (28%)	
≥30.0 (Obese)	19, (41%)	233, (31%)	
BMI (mean ± SE)	27.1 ± 0.78	27.5 ± 0.318	0.631
Smoking Status			
Current/Former smoker	18, (39%)	283, (38%)	0.654
Never smoked	28, (61%)	460, (62%)	

Marital Status			0.084
Married	31, (67%)	422, (57%)	
Not Married	15, (33%)	321, (43%)	
Age at menarche (years)	12.3 $\pm$ 0.24	12.6 $\pm$ 0.05	0.303
Current birth control use			0.241
Yes	7, (15%)	125, (17%)	
No	30, (65%)	392, (53%)	
Missing	9, (20%)	226, (30%)	
Parity			0.271
0	2, (4%)	34, (4%)	
1-2	20, (44%)	317, (43%)	
3 or >	17, (37%)	219, (30%)	
Missing	7, (15%)	173, (23%)	

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