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Prevalence of metabolic syndrome risk factors in women with PCOS: findings from a multi-ethnic cohort

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PREVALENCE OF METABOLIC SYNDROME RISK FACTORS IN WOMEN WITH PCOS: FINDINGS FROM A MULTI-ETHNIC COHORT

by

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DEDICATION

I would like to dedicate this work to my parents, Cristina and Zé Tomás, my brother, Ricardo, and my sister, Elisabete.

Mãe, obrigada por tude sacrificios que bo faze pa mi e pa nos familia em geral. Nada cum pode dse algum vez ta consegui transmit gratidao cum tem pa bos inumeros eforços. Bo é uma mulher de fibra, de garra e bo ca inchename ser nada menos que isso. Tudo oque mi é, n deve a bo. N'ta espera nunca ca fecob duvida que mi é grata, nha amor pa bo é incondicional. Saber cum pode sempre conta que bos palavras de conforto, mesmo que seja por telephone, da-me segurança cum mestia pa tude es one de aventura fora de casa. Ess mestrado é tanto meu como é teu. Obrigada.

Pai, tu que ensinaste-me a sonhar com os pés fora do chão, obrigada de coração cheio. Eternamente grata no teu voto de confiança em mim e por proporcionares a melhor educação possível. Mas não paraste por ai, também mostraste-me o mundo e uma qualidade de vida que faz-me acordar todos os dias grata. Serás para sempre o meu primeiro amor and I hope to continue making you proud in my future endeavors.

Ricardo, mano, obrigada por ter cuidado de mim em plena adolescência, e por ter ensinado mi cusas sobre mi quin ca sabia man mesteba de prende. Elisabete, viver contigo é um constante aprendizado de como posso ser melhor como pessoa, irmã e figura maternal. À minha familia em geral, Teófilo, Belantina, Maria Jose, Carlos, Becas, Helga, Arnaldo, e a todos os outros obrigada por tudo sem vocês eu não seria quem eu sou hoje. Rafa, obrigada por ter devolvido nha foco, vontade de prospera e tudo apoio qui bu dam.

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PREVALENCE OF METABOLIC SYNDROME RISK FACTORS IN WOMEN WITH PCOS: FINDINGS FROM A MULTI-ETHNIC COHORT

ALEXIS DE FIGUEIREDO VEIGA

ABSTRACT

BACKGROUND Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. It is characterized by oligomenorrhea/menstrual irregularity, androgen excess, and polycystic ovary morphology. Currently there are three distinct diagnostic criteria used to ascertain PCOS in the population: The National Institutes of Health (NIH) criteria created in 1990 and later reviewed in 2012, the Rotterdam criteria established in 2003, and the most recent criteria by the Androgen Excess & PCOS Society (AE-PCOS) criteria developed in 2006. Some prevalence studies suggest that PCOS affects 6.5-8% of the population while others state 10-20% qualify for a PCOS diagnosis. Recent literature shows patients with PCOS have a 43% prevalence rate or 2-fold higher rate than the age-adjusted sample of all ages in the general US population of developing Metabolic Syndrome (Met-S) (Apridonidze et al. 2005; Essah, Wickham, and Nestler 2007). This is important because it can alert physicians to refer their PCOS patients to a nutritionist or endocrinologist as a preventive measurement.

OBJECTIVES This thesis based on The Ovulation and Menstruation Health (OM) Pilot Study, sets out to accomplish the following**:** ascertain the prevalence of PCOS in different

racial/ethnic groups, determine Body-Mass Index (BMI) distribution patterns in PCOS participants based on how they were diagnosed (by a physician/self-diagnosed), and most importantly to determine the prevalence of Met-S risk factors in PCOS vs. Non-PCOS groups.

METHODS The (OM) Pilot Study is an online survey with clinical, community, and online recruitment. After a consent and screening process, the survey asks questions related to demographics, anthropometrics, menstrual cycles, contraceptive history, medications and supplement use, PCOS, reproductive health, general health, diet and lifestyle and lastly, pregnancy and birth history. The questions in this online survey, were designed for an 8th-grade reading level to improve comprehension by a diverse cohort of women. This was done to help address the lack of diversity and PCOS ascertainment in pre-existing cohorts.

RESULTS Following recruitment for The OM Pilot Study, 388 participants completed the consent form and 4 declined consent. 384 completed screener and 34 were deemed not eligible because: 18 were no longer menstruating and 16 were unable/unwilling to provide an email address to the receive survey; thus 350 were eligible. Of those 350 participants that were deemed eligible, only 283 started survey. 283 individuals determined to be eligible based on their gender, capacity to menstruate, and age started the survey. Age eligibility was ≥18 years old. 249 completed the survey through its last section (XIII. Pregnancy & Birth History). Of the 283 participants who enrolled and were eligible to

partake in the study, 177 (64.1%) identified as White, 22 (7.97%) as Hispanic/Latina/Spanish Origin, 34 (12.3%) as Black/African American, 4 (1.4%) as East Asian, 5 (1.8%) as Southeast Asian, 7 (2.5%) as South Asian, 27 (9.8%) selected more than 1 race/ethnicity, and 7 (2.5%) chose not to answer (Table 5).

Participants from the PCOS group had higher prevalence for all the risk factors for Met-S when compared to Non-PCOS group: abdominal fat determined as those who tend to gain weight around stomach/waist (73% versus 60%), abdominal fat ascertained by body figure (33% versus 17%), hypertension (6.9% versus 3.1%), high cholesterol (20.7% versus 8.8%), diabetes (5.3% versus 1.0%), non-alcoholic fatty liver disease (NAFLD) (5.2% versus 0.5%), and lastly sleep apnea (SA) (5.2% versus 2.1%). More noticeably is the absolute difference in prevalence in abdominal fat as determined by the body figure image in which the PCOS group (33%) had a 16% higher prevalence than the Non-PCOS group (17%). Participants that reported having PCOS diagnosed by a physician (37) had a higher prevalence of overweight/obese women (73%) than those that self-diagnosed (23) with PCOS (56.5%).

CONCLUSIONS The OM Pilot Study has demonstrated that it is possible to launch and recruit a diverse sample group representative of the actual population. With this new tool, future studies can better assess risk factors associated with Met-S in PCOS patients taking into consideration their racial/ethnic background.

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LIST OF ABBREVIATIONS

AE-PCOS ..... Androgen Excess & Polycystic Ovary Syndrome Society

AGT ..... Angiotensinogen

Ang 1-7 ..... Angiotensin 1-7

ASRM ..... American Society for Reproductive Medicine

ATP III ..... Adult Treatment Panel Third Report

BMC ..... Boston Medical Center

BMI ..... Body-Mass Index

BUCRC ..... Boston University Charles River Campus

BUMC ..... Boston University Medical Campus

CDC ..... Center for Disease Control and Prevention

ESHRE ..... European Society for Human Reproduction and Embryology

HA ..... Hyperandrogenism

HDL ..... High-Density Lipoprotein

Met-S ..... Metabolic Syndrome

NAFLD ..... Non-Alcoholic Fatty Liver Disease

NIH ..... National Institutes of Health

OA ..... Oligo-Anovulation

OB/GYN ..... Obstetrics/Gynecology

OD ..... Ovarian Dysfunction

OM ..... The Ovulation and Menstruation Health Study

PCOM ..... Polycystic Ovarian Morphology

PCOS ..... Polycystic Ovary Syndrome

SA ..... Sleep Apnea

SAS ..... Statistical Analysis System

WHO ....…… World Health Organization

INTRODUCTION

Racial disparities in health care and sciences

A person's health is influenced by many different factors such as genetics and environment. It is common belief that one's health outcomes are generally related to behavioral lifestyle. However, the World Health Organization (WHO) has found that social determinants of health, such as the type of health care system used and residential location, are what largely contribute to health disparities (Meyer, Yoon, and Kaufmann 2013)

Health disparities are differences in health outcomes observed within populations due to social determinants of health and/or other factors such as: race/ethnicity, gender, and disability (Meyer et al. 2013). Within the female population of the United States, health disparities are visible and alarming. Women who belong to marginalized racial minorities are at an increased risk of developing diseases and being poorly treated. According to a study performed in 2007, African Americans and Hispanics use the health care system less frequently than non-Hispanic Whites. When individuals from these racial and ethnic minorities do use the health care system, the quality of their care is diminished (Robbins and Padavic 2007).

Additionally, research analyzing how often women utilized preventive health services showed that 24% of Hispanic women did not have a medical visit within the last year, followed by 14% of African American women, and 11% of White women. Hispanic women were also more likely to report cost as a key factor in postponing care as compared to White women (Robbins and Padavic 2007). This shows that there are greater barriers

for Hispanic women to access care in contrast to White women, which leaves them more vulnerable to contracting a preventable disease that could be detected during an annual physical appointment. By the time these women seek medical attention, it may be that their disease has progressed to a point where treatment is not as effective or there are no treatment options available.

A study by the Joint Center for Political and Economic Studies in 2009 established that eradicating disparities for minorities would directly lead to a medical expenditure relief of $229.4 billion and would mitigate indirect costs by $1 trillion, during the study period of 2003 to 2006 (Meyer et al. 2013). Thus, there is a direct benefit for treating everyone equally, independent of social determinants, gender, race/ethnicity, and age.

Polycystic Ovary Syndrome (PCOS)

Criteria. Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age. It is characterized by: oligomenorrhea/menstrual irregularity, androgen excess, and polycystic ovary morphology. A syndrome can be defined as a combination of symptoms of unknown etiology associated with a particular abnormality (Azziz 2006). PCOS does not have a singular clearly defined etiology and includes genetic predisposition, environmental exposures, behaviors, and body composition. Its categorization is based on heterogeneous phenotypes, which leads to discrepancies in diagnostic criteria.

Currently there are three distinct diagnostic criteria used to ascertain PCOS in the population: The National Institutes of Health (NIH) criteria created in 1990, the Rotterdam

criteria established in 2003, and the most recent criteria by the Androgen Excess & PCOS Society (AE-PCOS) criteria developed in 2006 (Table 1) (March, Moore et al. 2010). In 2012, a panel sponsored by the NIH concluded that the disorder – PCOS – should be renamed as its current name causes confusion and limits progress in research and patient treatment (National Institutes of Health 2013). PCOS allures to a criterion "ovaries with multiple cysts" that is not sufficient or required for diagnosis and thus it is the sentiment of the NIH and primary care physicians as well as patients that the name should be descriptive of the integral features of the disorder (National Institutes of Health 2013; Teede et al. 2014).

The NIH criteria were created at a conference, where it was determined by participants that the diagnostic features of PCOS were clinical/biochemical hyperandrogenism (HA) and chronic oligo-anovulation (OA), noting that exclusion of associated disorders was necessary (Lizneva et al., 2016). In 2003, a joint conference held by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) congregated 27 PCOS specialists. These experts decided ultrasound evidence of polycystic ovarian morphology (PCOM) should be added to the NIH criteria, which expanded the PCOS phenotypes (Lizneva et al., 2016). This became known as the Rotterdam criteria. Moreover, in 2006, with evidence showing that HA was the strongest indicator of PCOS pathophysiology, the Androgen Excess & PCOS Society (AE-PCOS) sponsored five US and six European and Australian investigators to perform a systematic review of the literature to determine the association between PCOS characteristics and independent morbidity. These investigators found that

HA is the most prominent feature of PCOS and that diagnosis should be based on clinical/biochemical evidence of HA with either ovarian dysfunction (OD) or PCOM (Lizneva et al., 2016).

The variability in diagnostic criteria not only made it difficult to accurately diagnose PCOS patients, but it also created lack in comparability of PCOS research which hindered the progress of understanding the disorder. Thus, in 2012 the NIH created an extension of the Rotterdam criteria that included four practical phenotypes for PCOS diagnosis: 1) phenotype A: HA + OD + PCOM, 2) phenotype B: HA + OD, 3) phenotype C: HA + PCOM, and 4) phenotype D: OD + PCOM. This phenotypic approach to diagnosis of PCOS is highly favored for both the clinical setting and research because it allows for diagnosis based on the presence or absence of crucial features of the disorder (Lizneva et al. 2016).

More recently, a panel of 3,000 health professionals and consumers created an extensive diagnostic guideline book for assessing and treating PCOS – The Monash Guidelines. The Monash Guidelines endorses the Rotterdam PCOS diagnostic criteria in adults. They also made a specific recommendation that when a patient presents irregular menses and hyperandrogenism, an ultrasound evidence of polycystic ovarian morphology is not needed for diagnosis (Teede et al. 2018). Figure 1. illustrates the progression of PCOS diagnostic criteria over time and the required elements for diagnosis as well as specific recommendations made by each institution.

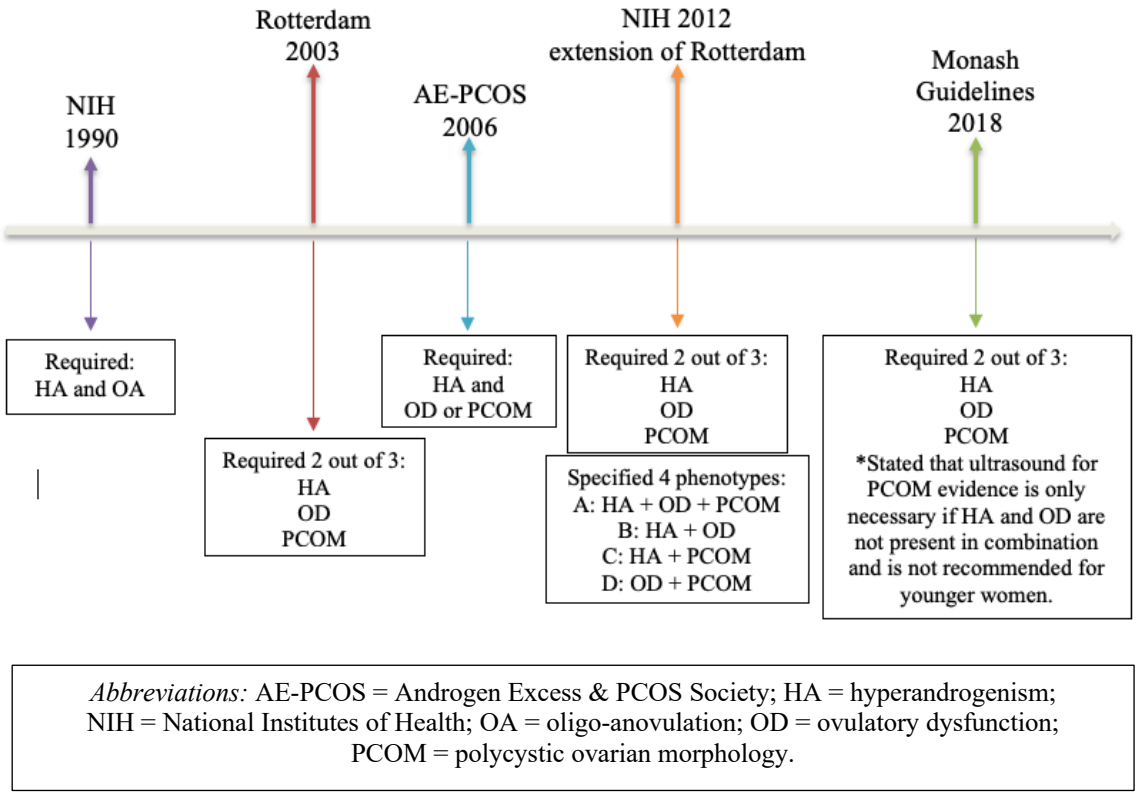

Figure 1. Progression of PCOS diagnostic criteria over time (Lizneva et al. 2016).

Prevalence. Some prevalence studies suggest that PCOS affects 6.5-8% of the population while others state 10-20% qualify for a PCOS diagnosis (March et al. 2010). The variability in percentages stems from the lack of consensus in PCOS diagnosis criteria and because it requires blood work as well as an ultrasound (March et al. 2010). The most conservative criteria are from the NIH 1990 and the least specific criteria are from the Rotterdam which requires that any 2 of the 3 criteria be confirmed (Table 1).

Table 1. The three main diagnostic criteria for PCOS and prevalence (March et al. 2010).

Criteria	Androgen Excess: Clinical or Biochemical	Menstrual Irregularity	Polycystic Ovaries on Ultrasound	Prevalence
National Institutes of Health (NIH) 1990	+	+		6-10%
Androgen Excess & PCOS Society (AE-PCOS) 2006	+	+	**Or** +	10-14%
Rotterdam 2003		Any 2 out of 3		15-20%

Health Implication Across the Lifespan. PCOS is one of the most common causes of infertility in women of reproductive age because the hormonal disruption affects the growth and release of the egg from the ovaries (ovulation). Without the capacity to ovulate, women cannot get pregnant. Even when pregnancy does occur, women with PCOS are at higher risk for: gestational diabetes, miscarriage, preeclampsia, and Cesarean-section surgery. Furthermore, babies of mothers with PCOS are also at an increased risk for being overweight (fetal macrosomia) and spending more time in the Neonatal Intensive Care Unit (NICU) (Plowden, Pal, and Grigorescu 2016).

PCOS related systemic disease severity, including cardiometabolic disease, is exacerbated by obesity and the first line of treatment is weight management. Weight loss helps women reduce central obesity, excess androgen production, improves menstrual cycle irregularities and infertility (Silvestris et al. 2018). In addition, evidence suggests that the use of drug therapy, such as metformin an anti-diabetic medication, during pregnancy

can reduce the risk for pregnancy loss and gestational diabetes, which causes other complications such as pre-eclampsia (Moran et al. 2006; Weissgerber and Mudd 2015). A multifaceted approach to weight loss is proven to be more effective long-term resulting in better health outcomes for women with PCOS. Not only is it important to stick to a strict, restrictive caloric intake nutritional plan and regular physical activity in order to sustain weight loss, it is also crucial to have a supportive system, regular follow-up visits with professionals such as dieticians, and receive encouragement in the adaptation to a healthier lifestyle (Moran et al. 2006).

Metabolic Syndrome (Met-S)

Criteria. Formerly known as Syndrome X, Metabolic Syndrome (Met-S) is a combination of risk factors that increase the risk of developing heart disease and diabetes. To be diagnosed with Met-S, one must have three of the following five metabolic risk factors: high blood pressure, increased abdominal fat, low High-Density Lipoprotein (HDL), high triglycerides level, and high fasting blood sugar (Huang 2009). Other conditions that may play a role in Met-S and PCOS are fatty liver disease, sleep apnea, and gallbladder dysfunction (Chen et al. 2012; Kostoglou-Athanassiou and Athanassiou 2008; Paschos and Paletas 2009) (Figure 2).

Prevalence. The National Health and Nutrition Examination Survey (NHANES) is a longitudinal study to assess health and nutrition amongst children and adults in the United States of America that began in the early 1960s. It is a cross-sectional study that makes use of both surveys and interviews to ascertain the health status of a large cohort of individuals

that are nationally representative of the US population. In the NHANES III cohort (1988-1994), prevalence of metabolic syndrome was calculated using third report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III). The ATP III guidelines for diagnosing Met-S state that one must exhibit 3 or more of the following: waist circumference >102 cm in men and >88 cm in women; high triglycerides (≥150 mg/dL); HDL levels <40 mg/dL in men and <50 mg/dL in women; high blood pressure ≥130/≥85 mmHg; high fasting glucose levels (≥110 mg/dL) (Cleeman 2001). The age-adjusted prevalence of Met-S was 23.7%. The prevalence was found to be similar for men (24%) and women (23.4%). The prevalence of Met-S was found to be higher in women ages 30 to 39 (15%) when compared to ages 20 to 29 years (6%) (Ford, Giles, and Dietz 2002). In women with PCOS, the prevalence of Met-S was 53% from ages 30 to 39 and between ages 20 to 29 it was 45% (Ford et al. 2002). This shows how women with PCOS are more at risk of developing Met-S and thus should be monitored more closely by their primary care physicians and the appropriate specialists for metabolic abnormalities should be included as part of their treatment plan.

Lack of diversity in studies ascertaining the risk of Met-S for patients with PCOS

A recent study found that 46.4% ± 4.2% of patients with PCOS had Met-S (≥3 metabolic abnormalities) compared to 22.8% ± 1.1% of NHANES III women, $P < 0.0001$ (Glueck et al. 2003). Of those women who were diagnosed with Met-S and PCOS, 50 were included in follow-up studies after an average of 6 months on Metformin, an anti-diabetic

medicine that helps with weight loss, and diet. The study found reductions in the following parameters: body weight, triglycerides levels, systolic and diastolic blood pressure, and insulin levels (Glueck et al. 2003). Additionally, there was an increase in HDL cholesterol (Glueck et al. 2003). This is significant because it can alert physicians to refer their PCOS patients to a nutritionist or endocrinologist as a preventive measurement for developing Met-S, as appropriate treatment can have significant effect in ameliorating the symptoms associated with these disorders. However, these studies also highlight the importance of diversifying participant populations as most are performed solely on Caucasian women, as it the case with the study mentioned here. This research is currently limited in accurately assessing the risk of Met-S in PCOS populations of diverse backgrounds such as race/ethnicity.

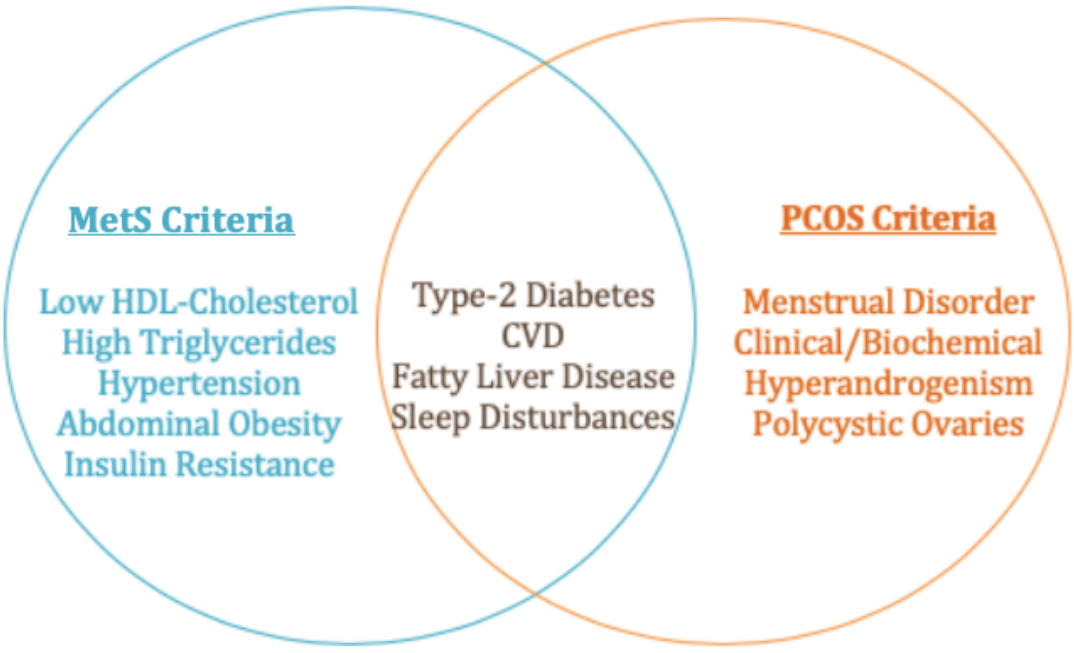

Figure 2. Overlap in diseases/outcomes associated with PCOS and Met-S.

The Ovulation and Menstruation Health (OM) Pilot Study

The OM Pilot Study is a multi-ethnic cohort that aims to collect women's health related information in order to ascertain elements of ovulation and menstruation health across the lifespan. The OM Pilot Study includes questions that assess risk factors and social determinants of PCOS. Additionally, the study captures risk factors associated with gynecologic disorders, such as PCOS, endometriosis, and uterine fibroids. This survey was designed by reproductive endocrinology and infertility specialist, Dr. Shruthi Mahalingaiah, M.D., M.S. The OM Pilot Study address the need for appropriate case ascertainment of PCOS by diagnostic components and the need to capture a diverse sample of the population.

SPECIFIC AIMS

This thesis will focus on the racial/ethnic distribution within OM Pilot Study to assess whether it was able to recruit a diverse sample of participants with PCOS, as it is crucial for the subsequent aims of this paper to be draw conclusions not from a predominantly Caucasian population as other studies have done, but rather from a diverse representative population sample. The three main aims are:

1. Ascertain the prevalence of PCOS in different racial/ethnic groups
2. Determine the prevalence of Met-S risk factors in PCOS vs. Non-PCOS groups
3. Determine Body-Mass Index (BMI) distribution patterns in PCOS participants based on how they were diagnosed (by a physician/self-diagnosed)

METHODS

The OM Pilot Study Design

The OM Pilot Study is an online survey. After a consent and screening process, the survey asks questions related to demographics, anthropometrics, menstrual cycles, contraceptive history, medications and supplement use, PCOS, reproductive health, general health, diet and lifestyle and lastly, pregnancy and birth history. The questions in this online survey, were designed for an 8th-grade reading level to improve comprehension and underwent cognitive testing to validate usability of survey on a diverse cohort of women (Mahalingaiah 2020). Previous cohorts such as Nurses' Health Study, were lacking diversity in their sample group so it was the goal of the Mahalingaiah Lab to create a survey that could be interpreted and easily accessible to people from multiple backgrounds. The study was administered through REDCap, a web application that allows for secure handling of online data capture and is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Participants were asked whether they would like to share their medical record in order to verify their responses to the survey, to which 50 participants agreed. This study is IRB approved at BUMC (H-35075).

The OM Pilot Study Recruitment

Recruitment of the study population was done in multiple locations. These include online using the study website (sites.bu.edu/pcos/), via emails sent through Boston Medical Center (BMC)/ Boston University Medical Campus (BUMC) campus-wide communication emails, and social media posts on multiple platforms (Facebook, Twitter,

LinkedIn). In-person recruitment was done in the form of letters sent to clinical patients presenting to the Obstetrics/Gynecology (OB/GYN) clinics at BMC explaining the study as well as at the Boston Women's Market in Jamaica Plain (09/17/2017). Additional recruitment mechanisms include flyers posted at BMC, BUMC, and Boston University Charles River Campus (BUCRC) and through a partnership with DivaCup® later in the recruitment phase.

The goal of the pilot study was to recruit 200 women of reproductive age with the capacity to ovulate/menstruate over a period of one year. The recruitment period for the pilot study was from August 9th, 2017, when the online survey was made public on the study website, through its official close on February 26th, 2018.

Study Population

Women in this study were participants who enrolled from August 2017 until February 2018. A total of 283 women completed the consent form and began the survey. Of those 283 women, two individuals identified as non-binary or gender queer. Trans-males were included if they were still menstruating or were capable of menstruating during the one-year recruitment period. Participants were excluded if they were less than 18 years of age, identified as male, were pregnant at time of survey, had history of hysterectomy, had been exposed to radiation/chemotherapy, or were unwilling/unable to provide an email address. Participant ages ranged from 18 to 53 years. Five women were above 45 years old category but were not excluded in this analysis.

It is important to note that all participants were allowed to leave questions blank/skip them for any reason, including if they made them uncomfortable or did not think they could answer them accurately so those 249 participants that got to the last section of the survey could have still left questions unanswered throughout the survey. The analysis for this thesis will focus on the 259 individuals that responded to some of or the entire 'Polycystic Ovary Syndrome section' of the survey as well as those 253 individuals that reached the 'General Health section'. These criteria were selected because these two sections are where the majority of questions regarding PCOS status and Met-S risk factors are pulled from.

Disease/Disorder Assessment

The OM Pilot Study survey used the following questions to ascertain disorder status.

PCOS

Section X. Polycystic Ovary Syndrome of the survey contained the following brief description of the disorder: "Polycystic Ovary Syndrome is a health condition involving irregular periods, excess testosterone, increased acne, body and facial hair, and many small cysts in the ovaries. Some women also experience hair loss on the scalp."

Following the brief description, participants were asked: "Has a doctor ever diagnosed you with Polycystic Ovary Syndrome or PCOS?" If participant replied **yes**, they were **skipped** to "How were you diagnosed with PCOS? (please check all that apply)". If participant replied **no**, the **next question** was "Do you think you might have PCOS?" A **yes** reply to this question had them **skipped** to "When do you first think you may have PCOS?" If **no**,

they were **skipped** to "Have any of your female relatives been diagnosed with PCOS (polycystic ovary syndrome)? For this question, we only want to know about those related to you by blood."

Body-Mass Index (BMI)

In 'Section VI. Anthropometrics', participants were asked about their weight and height. BMI was calculated – weight/height in meters sq. A summary of the BMI cutoff points used by The National Institute of Health (NIH) and the World Health Organization (WHO) to assess weight and health risk are can be found on Table 2.

Table 2. BMI cutoff points used by the NIH and the WHO (Weir and Jan 2020).

BMI Cutoffs	Categorization
<18.5	underweight
18.5-25	normal
25-30	overweight
30<	*obese with these specific subcategories for obese:*
30-35	Class 1
35-40	Class 2
40<	Class 3

Met-S Risk Factors

In the '*General Health Section'* of the survey, participants were asked about whether or not they had been diagnosed with a variety of conditions. The questions below were chosen to ascertain Met-S risk factors prevalence in accordance with the criteria dictated in the introduction:

- **Hypertension:** "Have you ever been diagnosed with high blood pressure (not during pregnancy)? a) yes, b) no."
- **High Cholesterol:** "Have you ever been diagnosed with high cholesterol? a) yes, b) no."
- **Diabetes:** "Have you ever been diagnosed with diabetes? Do not include diabetes during pregnancy. a) yes, b) no."
- **Non-alcoholic fatty liver disease:** "Have you ever been diagnosed with non-alcoholic fatty liver disease? a) yes, b) no, c) don't know."
- **Sleep apnea:** "Have you ever been diagnosed with sleep apnea? a) yes, b) no."

'Anthropometrics Section'

An apple shaped figure also known as android obesity or someone who tends to have significant waist circumference (greater than 35 inches for women) is considered to be at risk for Met-S as visceral fat/abdominal fat – fat that is localized around internal organs such as pancreas, liver, etc. – because it is metabolized differently by the body as it is found subcutaneously and is suspected to cause inflammatory responses and narrowing of blood vessels (Samsell et al. 2014; Wang and Nakayama 2010). In the anthropometrics

section of The OM Pilot survey, Renee Canon, a medical illustrator, was commissioned to make realistic drawings of varied body shapes for easier selection. The question selected for anthropometric assessment was: “Which image above looks most like your body shape now?”

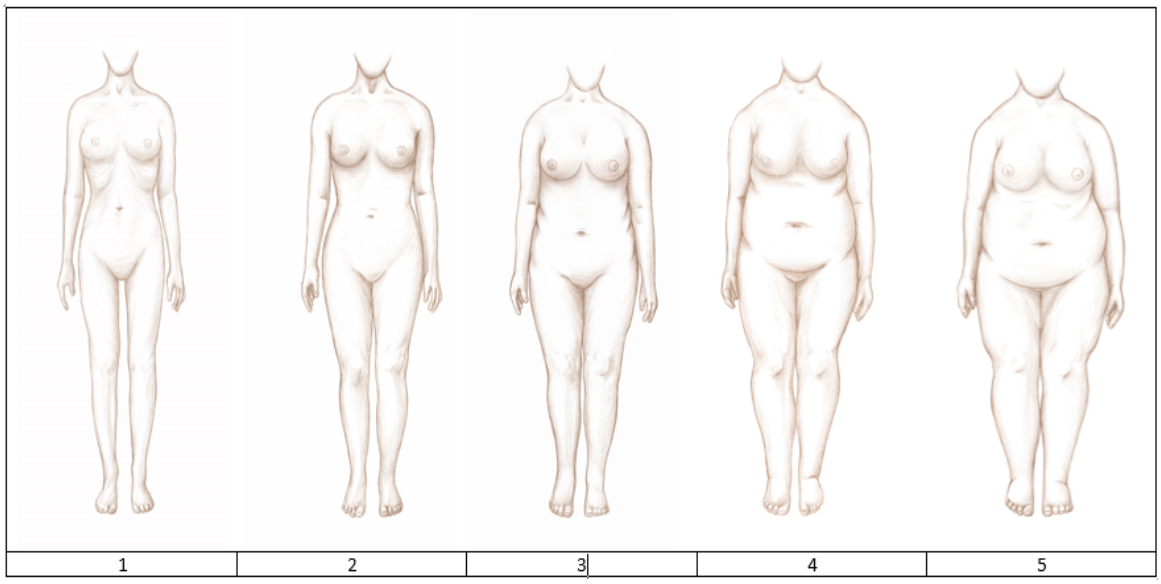

Figure 3. Differentiated Body Shape Illustration by Renee Canon, Medical Illustrator.

However, because the illustrations show an overall weight gain increase from image 1 to 5, to be more precise about abdominal obesity, the responses to one additional question was used to supplement the results from the body shape question of Figure 3.

<u>The question was:</u>

“When you gain weight, where on your body do you mainly tend to add the weight? (check all that apply).

a) Around the waist/stomach

b) Around the hips/thighs

c) Around the chest and shoulders

d) Equally all over

e) Other

f) Don't gain weight

Statistical Analysis

All analyses were performed with SAS (Statistical Analysis System) 9.4 which allows for data management, advanced analytics, multivariate analysis and other manipulations of data.

For prevalence calculations, the following formula was used:

$$Prevalence = \frac{number\ of\ cases}{population}\ x\ 100$$

Due to sample size and scope of this thesis, for comparison of PCOS and Non-PCOS groups prevalence of risk factors for Met-S, the absolute difference between prevalence was used to describe the data. In future studies with larger sample size, a Chi Square analysis should be performed to determine if the difference between prevalence of those two groups is statistically significant.

RESULTS

The OM Pilot Study went live on August 9th, 2017 and it successfully surpassed the 200-women recruitment goal on October 1st, 2017 around 250 women were enrolled by then. 388 participants completed the consent form, 4 declined consent. 384 completed screener and 34 were deemed not eligible because: 18 were no longer menstruating and 16 were unable/unwilling to provide email address to receive survey; thus 350 were eligible. Of those 350 participants that were deemed eligible, only 283 started survey. 283 individuals determined to be eligible based on their gender, capacity to menstruate, and age started the survey. Age eligibility was ≥18 years old. 249 completed the survey through its last section (XIII. Pregnancy & Birth History). Completion of section XIII. was determined by how many participants answered the first question in this section: "Have you ever been pregnant? Please include live births, stillbirths, miscarriages, induced abortions, and tubal and other ectopic pregnancies." With the option of yes or no, and if they answered no, they were skipped to the end of survey. The survey eligibility and completion rates are summarized in Table 3.

Table 3. Survey Eligibility and Completion.

	Initiated Consent Form	Completed Consent Form	Eligible by age/gender/menstrual capacity	Started Survey	Completed Survey
Participants	438	388	350	283	249

This thesis will focus on the 259 individuals that responded to some or the entire 'Polycystic Ovary Syndrome' section of the survey as well as those 253 individuals that reached the 'General Health' section because the questions used to ascertain disorder status were pulled from these sections. Table 4 summarizes how many participants started each part of the survey, and how many moved on to the next section.

Table 4. Breakdown of Completion Rate by Section of Survey.

Sections	*Participants that terminated survey after the last question of a section*	*Participants that went to the next section*
Initial N	283	
About You	5	278
Baseline Questionnaire*	6	272
Anthropometrics	4	268
Menstrual Cycle	0	268
Contraceptive History	6	262
Health and Body	3	259
Polycystic Ovary Syndrome	2	257
Reproductive Health	4	253
General Health	3	250
Diet and Lifestyle	1	249
Pregnancy History**	249	

*Participants demographics related questions.
**End of Survey.

Upon consent and determination of eligibility, participants were asked complete demographic questions. The mean age of participants was 27 years old (Table 5). The categories for race/ethnicity were the following: White, Hispanic/Latina/Spanish Origin, Black/African American, East Asian, Southeast Asian, South Asian, American Indian/Alaskan Native, Middle Eastern/North African, Native Hawaiian/Other Pacific

Islander, and some other race/ethnicity or origin. Participants were allowed to select more than one category. Of the 283 participants who enrolled and were eligible to partake in the study, 177 (64.1%) identified as White, 22 (7.97%) as Hispanic/Latina/Spanish Origin, 34 (12.3%) as Black/African American, 4 (1.4%) as East Asian, 5 (1.8%) as Southeast Asian, 7 (2.5%) as South Asian, 27 (9.8%) selected more than 1 race/ethnicity, and 7 (2.5%) chose not to answer (Table 5).

The level of education of the population was the following: 40.6% completed more than 4-year college degree, 35.7% had a 4-year college degree, 13.4% had some college or 2-year degree, and 7.6% completed 8th grade or less, some high school or high school/GED diploma (Table 5). Also shown in Table 5 is the distribution of the sample population according to their annual household income.

Table 5. Summary of The OM Study Pilot Population Demographics.

Age (years)	
Range	18-53
Mean (SD)	27.2 (6.6)
Median (25th percentile, 75th percentile)	26.0 (23.0, 31.0)
Gender	
Female	280
Other*	3
Race/Ethnicity n, (%)**	
White	177 (64.1)
Hispanic, Latina or Spanish Origin	22 (7.97)
Black of African American	34 (12.3)
East Asian	4 (1.4)
Southeast Asian	5 (1.8)
South Asian	7 (2.5)
>1 Race/Ethnicity	27 (9.8)
Prefer not to respond	7 (2.5)
Level of Education n, (%)	
8th Grade or less, Some high school, High school/GED	21 (7.6)

Some college or 2-year degree	38 (13.4)
4-year college degree	101 (35.7)
More than 4-year college degree	115 (40.6)
Prefer not to respond	8 (2.8)
Annual Household Income n, (%)* **	
Below $15,000	29 (10.2)
$15,000-$24,999	29 (10.2)
$25,000-$49,999	71 (25.1)
$50,000-$124,999	81 (28.7)
$125,000-$149,999	4 (1.4)
$150,000-$199,999	9 (3.2)
$200,000 or more	15 (5.3)
Prefer not to answer	17 (6)
Don't know	20 (7.1)
Declined/Not Available	8 (2.8)

*Trans males that were still able to menstruate were considered eligible to participate in the study. Participants that chose other in gender category identified themselves as non-binary or queer.
**Participants could report more than one race. As a result, the sum of the percent frequencies reported in this section of Table 5 exceeds 100%.
***Individual household income could not be calculated using annual household income and number of individuals per household because annual household income was reported as a range.

Ascertainment of PCOS Prevalence in Different Racial/Ethnic groups of The OM Study Pilot Population

60 out of 256 women who responded to the PCOS diagnosis question, either self-diagnosed or were diagnosed by a doctor as having PCOS. This yields a 23.4% prevalence of PCOS in population sample (Table 6).

Of those 27 participants missing for this specific PCOS ascertainment question, 24 terminated the survey before reaching the 'Polycystic Ovary Syndrome Section' of the survey and 3 participants chose not to respond to this particular question (Table 6).

Table 6. Comprehensive Table of PCOS Status Among 283 Participants.

PCOS Status	N	(%)
Diagnosed by physician	37	13.1%
Self-diagnosis	23	8.1%
PCOS (any)	60	21.2%
No	196	69.3%
****Missing data (did not respond)***	27	9.5%

Of the PCOS participants: 32 (12.5%) were White, 7 (2.7%) identified as Latina/Hispanic, 8 (3.1%) were Black/African American, 6 (2.3%) were Asian, and lastly 7 (2.7%) picked two or more races which put them in the Mixed category. Percentages were calculated among the total number of participants that answered the PCOS ascertainment question (N= 256). Adding these percentages gives the prevalence percentage of PCOS (23.3%) (Table 7), which agrees with the results found on Table 6.

Table 7. Racial Distribution of OM Study Population Based on PCOS Status.

PCOS	White	Latina/Hispanic	Black/African American	Asian	Mixed
Yes	32	7	8	6	7
No	135	11	21	9	20

Total N = 256

The OM Pilot Study was able to recruit a racial/ethnic diverse population sample that is representative of the general US population (Table 8). The only racial/ethnic category significantly lower than the CDC 2018 population census is Latina/Hispanic. However, as explained above Latinas/Hispanic participants may be of any race so they might be represented in the mixed category which could explain why the percentage (9.8%) is significantly higher when compared to CDC US Population Census from 2018 (2.7%) (CDC 2018). Furthermore, this limitation might be circumvented when the Mahalingaiah Lab recruits with the Spanish-language platform.

Table 8. Comparison of OM Health Study Pilot Population Racial Distribution with US population breakdown (CDC July 1st, 2018).*

Race/Ethnicity	OM Study	US Population
White	64.1%	60.4%
Latina/Hispanic*	8.0%	18.3%
Black/African American	12.3%	13.4%
Asian	5.8%	5.9%
Mixed	9.8%	2.7%

*Recruitment for OM Study Pilot was from August 2017 – February 2018, so data from CDC July 1st, 2018 population census was used to compare demographics.
** Latinas/Hispanics may be of any race so they might be represented in the mixed category and not just in the Latina/Hispanic category.
*** Total N here is 276, because there are 7 (2.5%) responses missing.

Further analysis was performed to see the racial/ethnic breakdown within the two PCOS subgroups: those diagnosed with PCOS by a physician versus those that self-

diagnosed with the syndrome. This thesis aims to determine if participants from a specific racial/ethnic background were predominantly more likely to self-diagnose with PCOS than to seek a professional for diagnosis. Out of the 60 participants that reported having PCOS, 37 were diagnosed by a physician while 23 self-diagnosed with the syndrome. Of the 37 individuals that were diagnosed with PCOS by a physician: 16 (43.2%) were white, 6 (16.2%) were Latina/Hispanic, 7 (18.9%) were Black/African American, 4 (10.8%) were Asian, 4 (10.8%) selected two or more races so fell in the Mixed category. Of the remaining 23 participants that self-diagnosed for PCOS: 16 (69.5%) were White, 1 (4.3%) were Latina/Hispanic, 1 (4.3%) were Black/African American, 2 (8.7%) were Asian and 3 (13%) were Mixed (Table 9).

Table 9. Racial Distribution of PCOS Group When Differentiated by Physician Diagnosis and Self-diagnosed.

PCOS Status	**Race/Ethnicity**				
	White	Latina/ Hispanic	Black/African American	Asian	Mixed
Diagnosed by Physician	16	6	7	4	4
Self-Diagnosed	16	1	1	2	3

Total N = 60

Determine prevalence of Met-S risk factors in PCOS vs. Non-PCOS group

In order to determine the prevalence of Met-S risk factors in PCOS participants compared to the controlled group (Non-PCOS group), it was crucial to define Met-S risk factors in the scope of the OM Pilot Study (Table 10). Unfortunately, not all risk factors

used to diagnose Met-S, in accordance with The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III), were ascertained in this pilot cohort study. Participants were not asked specifically about high triglycerides, low HDL levels or high fasting blood sugar. Furthermore, because this survey was designed for an 8th grade reading level, these terms might not have been compatible with the comprehension goals. However, for the two latter components substitutes were included: high cholesterol and diabetes. Understanding that those two risk factors are not exactly what is used to diagnose Met-S, but that they are involved in the same pathways that lead to the outcomes of Met-S which is cardiovascular disease. Shaded in blue are risk factors that are not used in the diagnosis of Met-S but are important to the syndrome as studies have found that there is a degree of influence of these conditions on Met-S (Table 10).

Table 10. Met-S Indicators: Summary Table for Definition of Met-S and How Risk Can Be Assessed in The OM Study Pilot Specifically.

Risk Factors	*Met-S as Defined by ATP III Guidelines**	*Met-S as Defined by The OM Health Study Pilot*
High Triglycerides	X	
Low HDL	X	
High Fasting Blood Sugar	X	
Abdominal Fat	X	X
Hypertension	X	X
High Cholesterol[a]		X
Diabetes[b]		X
Non-Alcoholic Fatty Liver Disease[c]		X
Sleep Apnea[d]		X

*ATP = Adult Treatment Panel III Guidelines was sponsored by NIH in 2001 (Cleeman 2001).

[a]High cholesterol was included because of the assumption that if you have low HDL, the lipoprotein that removes cholesterol from your cells, then you do have high cholesterol.

[b]Diabetes for example is not a risk factor but rather an outcome of Met-S but it was deemed important to report on the findings from this study.

[c]Non-Alcoholic Fatty Liver Disease (NAFLD) and Met-S share common interactions and studies have shown that NAFLD can be an indicator of risk for development of Met-S (Fan et al. 2007).

[d]Sleep Apnea patients have a higher prevalence (6 to 9 times more likely) of Met-S compared to the general population (Gaines et al. 2018).

Abdominal Fat

Table 11 shows that 44 out of 60 participants with PCOS reported that they tend to gain weight around their waist/stomach. This indicates that 73% of those with PCOS in the OM Pilot cohort tend to gain weight around waist and stomach compared to 60% in women without PCOS (117 out of 196) in the OM Pilot cohort.

Table 11. Pattern of weight gain in PCOS vs. Non-PCOS group.

	Tend to gain weight around waist/stomach		*Total*
	Yes ***N (%)***	***No*** ***N (%)***	
PCOS	44 (73)	16 (27)	60
Non-PCOS	117 (60)	79 (40)	196

Images 4 and 5, from Figure 3, were selected for ascertainment of abdominal fat as a risk factor for Met-S because they are most representative of large waist circumference/abdominal fat. Table 12 demonstrates how 19 [(13 chose image 4) + (6 chose image 5)] of PCOS participants selected image 4 or 5 as representative of their current body shape. This means that 33% of the PCOS group identified their body figure as having a significantly large waist circumference/abdominal fat. 34 [27 (image 4) + 7 (image 5)] or 17% of Non-PCOS participants identified their body shape as looking like images 4 and 5. Shaded in blue, are the frequency related to the two images used to determine abdominal fat from Figure 3. N missing was 30 for this question. This is reflective of the 24 participants who did not complete the survey through PCOS section, 3 who did not answer the PCOS diagnosis question, and 3 participants who answered PCOS status but chose not to respond to this particular body shape question.

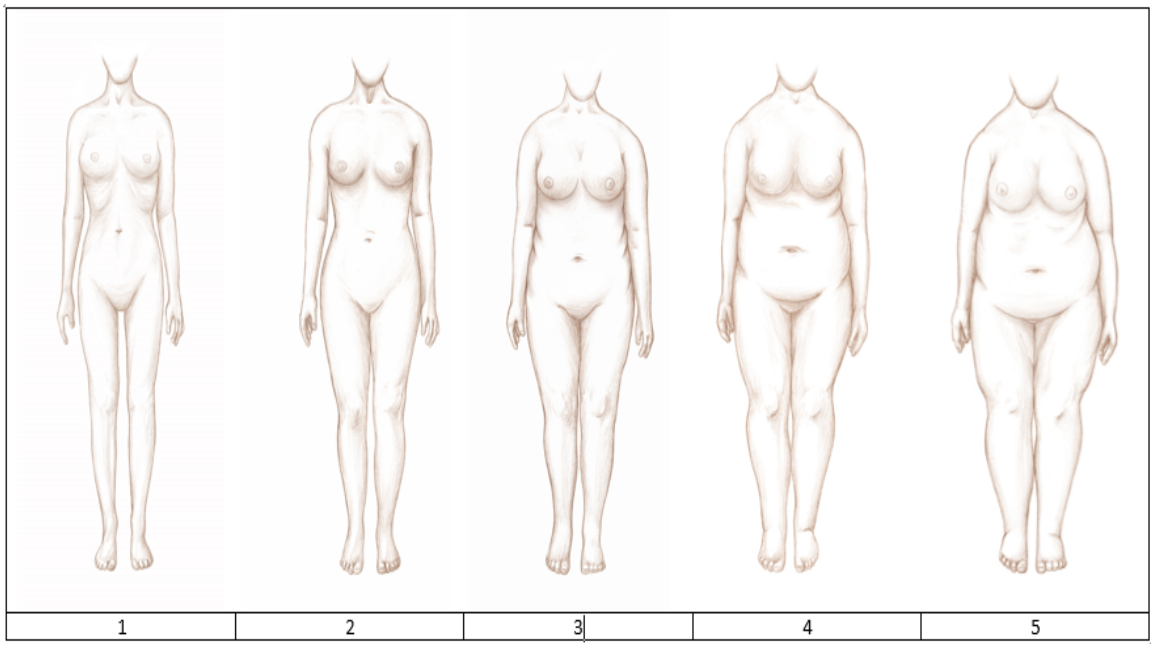

Figure 3. Differentiated Body Shape Illustration by Renee Canon, Medical Illustrator.

Table 12. Summary of body shape distribution within PCOS and Non-PCOS group.

	Which image above looks most like your body shape now? (Figure 3)					
	1 *N (%)*	**2** *N (%)*	**3** *N (%)*	**4** *N (%)*	**5** *N (%)*	**Total**
PCOS	8 (14)	16 (28)	14 (25)	13 (23)	6 (10)	57
Non-PCOS	34 (17)	94 (48)	34 (17)	27 (14)	7 (3)	196

N Missing = 30

Hypertension

Table 13 summarizes the prevalence of hypertension diagnosis for PCOS and non-PCOS participants in the OM Pilot study. 4 PCOS participants said yes to being diagnosed with hypertension, which yields a 6.9% (4/58) prevalence of hypertension in this group. Within the Non-PCOS participants, 6 or 3.1% (6/193) have been diagnosed with hypertension.

Table 13. Prevalence of Hypertension Diagnosis within PCOS and Non-PCOS group.

	Diagnosed with Hypertension		*Total*
	Yes *N (%)*	***No*** *N (%)*	
PCOS	4 (6.9)	54 (93.1)	58
Non-PCOS	6 (3.1)	187 (96.9)	193

N Missing = 32

High Cholesterol

Table 14 shows a comparison of high cholesterol diagnosis amongst participants in the OM Pilot cohort. 20.7% (12/58) of PCOS-diagnosed participants reported having high cholesterol diagnosed by a physician, compared to 8.8% (17/193) of Non-PCOS participants. The 32 missing individuals are comprised of 24 participants who left the survey before the PCOS section, 3 that reached PCOS section but did not respond to the PCOS status question, 2 PCOS and 3 Non-PCOS participants who chose not to respond to the high cholesterol question.

Table 14. Comparison of High Cholesterol Diagnosis Prevalence.

	Diagnosed with High Cholesterol		*Total*
	Yes ***N (%)***	***No*** ***N (%)***	
PCOS	12 (20.7)	46 (79.3)	58
Non-PCOS	17 (8.8)	176 (91.2)	193

N Missing = 32

Diabetes

Table 15 summarizes diabetic status amongst women in the OM Pilot study. 5.3% (3/57) of the PCOS group has been diagnosed with diabetes while 1.0% of Non-PCOS participants from this survey reported to have been diagnosed with diabetes by a physician.

Table 15. Diabetes Ascertainment in two subgroups of the OM Pilot Study.

	Diagnosed with Diabetes		*Total*
	Yes ***N (%)***	***No*** ***N (%)***	
PCOS	3 (5.3)	54 (94.7)	57
Non-PCOS	2 (1.0)	190 (99)	192

N Missing = 34

Non-Alcoholic Fatty Liver Disease (NAFLD)

Table 16 demonstrates those with a NAFLD diagnosis. 3 or 5.2% (3/58) of participants in the PCOS category said yes to being diagnosed with NAFLD while 3 other PCOS participants or 5.2% of this group said they did not know if they had been diagnosed with this condition.

Of the women in the Non-PCOS group, only 1 participant or 0.5% reported diagnosis with NAFLD and 6 or 3.1% said they were unsure of whether they were diagnosed with the condition.

Table 16. Summary of NAFLD prevalence within PCOS and Non-PCOS group.

	Diagnosed with NAFLD			*Total*
	Yes ***N (%)***	***No*** ***N (%)***	***Don't Know*** ***N (%)***	
PCOS	3 (5.2)	52 (89.6)	3 (5.2)	58
Non-PCOS	1 (0.5)	185 (96.4)	6 (3.1)	192

N Missing = 33

Sleep Apnea (SA)

Table 17 summarizes the frequency of sleep apnea diagnosis for women in the OM Pilot study by PCOS status. Of the 58 PCOS participants that responded to this question, 3 (5.2%) said yes to being diagnosed with sleep apnea while 4 out of 193 (2.1%) Non-PCOS participants answered yes for SA diagnosis.

Table 17. Summary of Sleep Apnea Frequency in PCOS vs. Non-PCOS group.

	Diagnosed with Sleep Apnea		*Total*
	Yes ***N (%)***	***No*** ***N (%)***	
PCOS	3 (5.2)	55 (94.8)	58
Non-PCOS	4 (2.1)	189 (97.9)	193

N Missing = 32

Met-S Prevalence

As shown in Table 18, participants from the PCOS group had higher prevalence for all the risk factors for Met-S when compared to Non-PCOS group. More noticeably is the absolute difference in prevalence in abdominal fat as determined by the body figure image (Figure 3) in which the PCOS group had a 16% higher prevalence than the Non-PCOS group. Followed by higher abdominal fat prevalence, as ascertained by whether participants tend to gain weight around waist/stomach, and lastly increased high cholesterol prevalence in PCOS group. The absolute difference in the other Met-S risk factors: hypertension, diabetes, non-alcoholic fatty liver disease and sleep apnea was less than 5%.

Table 18. Summary of the prevalence of Met-S risk factors and PCOS status.

	PCOS	
	Yes	No
Met-S Risk Factors	**Prevalence**	
Abdominal Fat		
1. Tend to gain weight around waist/stomach	73%	60%
2. Body Figure (images 4 and 5)	33%	17%
Hypertension	6.9%	3.1%
High Cholesterol	20.7%	8.8%
Diabetes	5.3%	1.0%
Non-Alcoholic Fatty Liver Disease	5.2%	0.5%
Sleep Apnea	5.2%	2.1%

Determine BMI Pattern Distribution of PCOS participants based on how they were diagnosed

Table 19 illustrates the pattern of distribution of BMI by PCOS status. 27 out of the 37 women that were diagnosed with PCOS by a physician fell in the overweight or obese category. This means that ***73% of women diagnosed with PCOS by a physician*** have an overweight/obese phenotype.

Table 19. BMI distribution of 37 women diagnosed with PCOS by a physician.

Category	BMI range	N
Underweight	17.43 – 18.48	0
Normal	18.77 – 24.96	10
Overweight	25.05 – 29.95	8
Obese class 1	30.03 – 34.94	9
Obese class 2	35.50 – 39.85	5
Obese class 3	40.10 – 54.90	5

Taking a closer look at the 23 participants that self-diagnosed with PCOS, 13 fell in the overweight or obese category (Table 20). This means that ***56.5% of women self-diagnosed with PCOS are part of the overweight/obese phenotype.***

Table 20. BMI distribution of 23 women that self-diagnosed with PCOS.

Category	BMI range	N
Underweight	17.43 – 18.48	1
Normal	18.77 – 24.96	9
Overweight	25.05 – 29.95	6
Obese class 1	30.03 – 34.94	4
Obese class 2	35.50 – 39.85	3
Obese class 3	40.10 – 54.90	0

Based on comparison between the two tables above (Table 19 and Table 20), participants that reported having PCOS diagnosed by a physician had a higher prevalence of overweight/obese women (73%) than those that self-diagnosed with PCOS (56.5%).

DISCUSSION

The association between Polycystic Ovary Syndrome (PCOS) and Metabolic Syndrome (Met-S) has been well established (Pasquali et al. 1999). This thesis sought to ascertain the prevalence of PCOS in the diverse population sample of the OM Pilot Study. The prevalence of PCOS in the sample population was on the higher end of the range because patients were recruited primarily from an Obstetrics/Gynecologic (OB/GYN) clinical setting. The results also indicated that participants that reported being White were more likely to self-diagnose as having PCOS than other races/ethnicities followed by Mixed and Asians. Lastly, no difference was seen between Latina/Hispanic and Black/African American participants in the reporting of self-diagnosis of PCOS.

Previous studies analyzing the association between PCOS and Met-S were done in sample population and compared to large cohorts primarily composed of Caucasian women (Coviello, Legro, and Dunaif 2006; Glueck et al. 2003, 2005). Additionally, one of the goals of this thesis was to determine the prevalence of Met-S risk factors such as: hypertension, high cholesterol, and large waist circumference/abdominal fat in the PCOS group of a multi-ethnic population. Another goal was to analyze distinct BMI distribution patterns in the PCOS group as compared to Non-PCOS participants.

Polycystic Ovary Syndrome is a disorder characterized by "oligo-amenorrhea and clinical and/or chemical hyperandrogenism, accompanied by infertility, obesity, dyslipidemias, hypertension, and impaired glucose tolerance" (Glueck C., Papanna R., Wang P., et al, 2003). Many PCOS patients have metabolic abnormalities used to define Met-S. Met-S, as defined by the Adult Treatment Panel (ATP) III guidelines for women,

is the presence of 3 or more of the following abnormalities: large waist circumference (>88 cm), high triglycerides (≥150 mg/dL when fasting), low HDL cholesterol (<50 mg/dL), hypertension (≥130/85 mm Hg) or high fasting glucose (≥110 mg/dL) (Cleeman, 2001).

Both PCOS and Met-S are syndromes characterized by a combination of symptoms affecting one another. Thus, the mechanism by which the exposure plays into the disease is not always linear and is rather complex. For instance, studies have shown that larger waist circumference/abdominal fat is associated with increased risk for type-2 diabetes mellitus and cardiovascular disease (Cigolini et al. 1996; Goran and Gower 1998). Furthermore, large waist circumference/abdominal fat has been more closely correlated with metabolic syndrome than general obesity as ascertained by BMI (Appel, Jones, and Kennedy-Malone 2004).

It is unclear what the pathway for hypertension is in Met-S but some evidence has shown central/visceral adipose (fat/obesity) tissue promotes the renin-angiotensin system (RAS) (Appel et al. 2004). The RAS is a hormone system that involves many enzymatic pathways and bioactive components that work together to regulate blood pressure (Chappell 2016). Angiotensinogen (AGT) is converted into two bioactive peptides AngII and angiotensin 1-7 (Ang1-7) and these two have opposing effects. AngII is pro-inflammatory, profibrotic and causes vasoconstriction or increased blood pressure, while Ang1-7 is anti-inflammatory, anti-fibrotic and leads to vasodilation or decreased blood pressure (Zhang et al. 2018). Visceral adipose tissue has been shown to increase the expression of AGT and renin which is involved in the multi-step enzymatic pathway that turns AGT into bioactive peptides (Zhang et al. 2018).

Although this pilot baseline ascertainment was not designed to detect the biomarkers of risk for diabetes, that is hyperinsulinemia or insulin resistance beyond what is available on a small subset that agreed to medical record review, it is important to understand how the condition progresses to Met-S. In the beginning stages of Met-S, fasting glucose levels are within normal range because of a state of chronic increased insulin production by the pancreas. As the condition evolves, the pancreas can no longer produce elevated amounts of insulin resulting in impaired glucose tolerance and later hyperglycemia which at this stage one is diagnosed with type-2 diabetes (Appel et al. 2004).

The OM Pilot Study was an online survey taken by participants recruited from multiple locations. One of the limitations of this study is self-reporting bias. Participants are asked to self-report their conditions and if they chose not to share their medical records, which only 50 participants out of the 283 that started the survey gave permission, it is not possible to validate their responses. An additional limitation includes the statistical analysis completed for this thesis. Further statistical analysis, such as a Chi-Square analysis, is necessary to understand whether or not the results are statistically significant. Lastly, the sample size was too small to fully assess the prevalence of Met-S risk factors within the different racial/ethnic PCOS group. Future studies are needed with a larger sample size to fully understand associations between race and ethnicity and Met-S factors.

The strength of this thesis is that the data analysis is performed in a multi-ethnic cohort sample which allows for the results to be generalizable to the whole U.S. population as it is representative. This survey asks important questions related to general health and

reproductive health of women that have not been done before by major studies such as the Nurses' Health Study, NHANES, Cape Cod Cohort. The questions were designed by a board-certified reproductive endocrinology and infertility specialist that has expertise in gynecologic disorders such as PCOS. This unique skillset in conjunction with cognitive testing of the survey questions improves the validity of the questionnaire in ascertaining disease status.

CONCLUSION

This thesis sought to accomplish three aims: ascertain prevalence of Polycystic Ovary Syndrome (PCOS) within the multi-ethnic OM Pilot Study population (Table 6, 7, and 9), determine the Body-Mass Index (BMI) distribution of those PCOS participants (Table 19 and 20), and most importantly to establish the prevalence of risk factors associated with Metabolic Syndrome (Met-S) in PCOS participants (Table 18). The prevalence of PCOS in the OM Pilot Study was found to be 23.4%. The analysis of BMI distribution revealed that 73% PCOS participants diagnosed by a physician were overweight/obese versus 56.5% for PCOS participants that were self-diagnosed. Finally, PCOS participants had higher prevalence for every risk factor associated with Met-S as defined in the OM Pilot Study. More noticeably, was the absolute difference prevalence in abdominal fat as a risk factor for Met-S.

The OM Pilot Study has demonstrated that it is possible to launch and recruit a diverse sample group representative of the actual population. Furthermore, the study highlights the importance of collecting information about disorders such as PCOS as well as risk factors and co-morbidities of gynecologic disease. A future aim of the Mahalingaiah Lab is to recruit at least 10,000 women, with a minimum of 1,000 for each major racial category in the United States as defined by the U.S. Census: Black/African America, White, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Asian. With a diverse sample population, the study team can curate strategies for improved education of populations at high risk of developing gynecologic disease and improve their chances for proper health care.

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